MEDI 1

Neuropathic pain: Overview and therapeutic strategies

***Jeffrey D. Kennedy**, Neuroscience, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4755, kennedj2@wyeth.com*

Among human disease, chronic pain encompasses a collection of conditions that are, in general, greatly underserved by available therapeutic agents. In particular, development of effective treatment options for neuropathic pain, i.e., chronic pain resulting from nerve damage, has proven to be challenging. Although great advances have been made in our understanding of the biology and biophysics of the neural circuitry involved in pain signal transmission and sensation, the continuing unmet medical need surrounding its treatment in part lies with the complexity of etiologies, diverse patient responses to pain, and multiple mechanisms that can lead to the same clinical presentation. Included among the many targets currently being investigated as potential drug discovery candidates, particular interest has focused on a number of ligand- and voltage-gated ion channels. An overview of neuropathic pain mechanisms is presented here, including a discussion of the role of NMDA receptors in driving its initiation and maintenance.

MEDI 2

Carboxylate bioisosteres of gabapentin that target the alpha-2-delta protein

***Jacob B. Schwarz**[1], Carmen E. Burgos-Lepley[1], Lisa R. Thompson[2], Simon A. Osborne[2], Justin S. Bryans[2], Mark J. Field[2], Dic Williams[2], David J. Dooley[1], Ayman El-Kattan[1], Charles P. Taylor[1], and David J. Wustrow[1]. (1) Michigan Laboratories, Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, (2) Sandwich Laboratories, Pfizer Global Research and Development*

A series of carboxylate bioisosteres of structures related to gabapentin were prepared. When the carboxylate was replaced by a phosphinic, sulfinic, or sulfonic acid moiety, no binding of the substrate to the alpha-2-delta subunit of voltage gated calcium channels was observed. However, when a tetrazole was employed as the bioisostere, this group was in fact recognized by the alpha-2-delta protein. Further characterization of amino tetrazoles demonstrating affinity for alpha-2-delta revealed a similar pattern of functional in vitro and in vivo activity to gabapentin. This presentation will detail the pharmacology of these particular bioisosteres in the context of neuropathic pain paradigms.

MEDI 3

Novel series of potent and selective antagonists of mGluR1: Possible use in the treatment of neuropathic pain

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Glutamate is considered to be the major excitatory amino acid in the mammalian brain. To exert its effects, glutamate activates two major receptor classes; the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs). The iGluRs are responsible for fast excitatory effects while the mGluRs typically play a modulatory role on these fast glutamatergic effects. The mGluRs belong to the Type C class of G-protein coupled receptors. Currently eight mGluR subtypes have been cloned and are classified into three groups on the basis of their sequence homology, pharmacology and second messenger transduction mechanisms. Group I mGluRs (mGluR1 and mGluR5) are positively coupled to phospholipase C (PLC) while the Group II mGluRs (mGluR2 and mGluR3) and Group III mGluRs (mGluR4, mGluR6-8) are negatively coupled to adenylyl cyclase. Inhibition of the Group I mGluRs may have potential in the treatment of epilepsy, neurodegeneration and neuropathic pain thus designating these receptors as interesting drug targets. The SAR surrounding a novel class of potent and selective antagonists of mGluR1 will be presented.

MEDI 4

The identification of KCNQ channel modulators and their potential use in disorders associated with excessive neuronal excitability

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The M-current (IM) is a low threshold, slowly activating, non-inactivating voltage-dependent potassium current found in a variety of neurons. This current has been found to play a dominant role in regulating neuronal excitability due to its unique activity in the voltage range of action-potential initiation. Recently the biophysical and pharmacological properties of the heteromultimeric potassium ion channels KCNQ2/Q3 and KCNQ3/Q5 were shown to be essentially identical to that of the M-current. Further investigations have established the presence of KCNQ2 and KCNQ3 potassium channels in many areas of the sensory nervous system including the DRG, thalamus and cortex. Hence, small molecules that activate these KCNQ heteromultimers may be potentially useful for the treatment of epilepsy and pain. We will describe the identification and structure activity relationship of a series of compounds that increase the current flow through these channels. Finally an assessment of their in vivo efficacy in mice and rat models of epilepsy and pain will be presented.

MEDI 5

Novel urea and amide TRPV1 antagonists as potential new therapeutic agents for the treatment of neuropathic pain

***Susan M Westaway**, Neurology & GI CEDD, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow CM19 5AW, United Kingdom, Fax: +44 (0) 1279 627896, sue.m.westaway@gsk.com*

Recent research has generated a wealth of data which define the role of TRPV1 in pain pathways. Activation of this ion channel by noxious stimuli leads to the sensation of pain. These stimuli include heat, low pH and various chemical mediators such as capsaicin (the pungent component of hot chilli peppers), the endogenous cannabinoid anandamide and

arachidonic acid metabolites from the lipoxygenase pathway. Thus, blockade of the response at this channel may offer a new way to treat debilitating conditions such as neuropathic pain for which there is currently a high unmet medical need. At GSK, high throughput screening of our compound collection led to the identification of potent novel series of ureas and amides which antagonise human TRPV1. A lead optimisation programme was undertaken which culminated in the discovery of TRPV1 antagonists with an excellent pre-clinical profile for evaluation as potential therapeutic agents.

MEDI 6

Multiple 5-HT approaches to novel anti-depressants

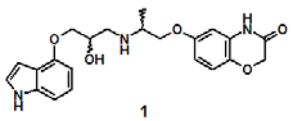
***Simon E Ward**, Psychiatry Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow CM19 5AW, United Kingdom, Fax: +44 (0) 1279 627728, simon_e_ward@gsk.com*

Extensive pre-clinical and clinical data links the enhancement of serotonergic neurotransmission with the anti-depressant action of the both the newer class of selective serotonin reuptake inhibitors (SSRIs) as well as the older classes of monamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. Considerable research has been carried out to investigate other 5-HT targets associated with the disease and studies involving combination treatments with selective serotonin reuptake inhibitors and 5-HT1 receptor ligands have been carried out in the clinic.

Starting from the high throughput screening hit 1 with affinity for the 5-HT1A receptor, a chemical series has been developed which displays a range of affinities across the 5-HT1 receptor subtypes and the serotonin transporter. The chemistry and SAR of this series is presented together with the medicinal chemistry strategies employed.

[1] Middlemiss, D. N., Price, G. W., Watson, J. M. Serotonergic targets in depression. Current Opinion in Pharmacology 2002, 18-22.

[2] Atkinson, P. J., Bromidge, S. M., Coleman, T., Duxon, M. S., Gaster, L. M., Hadley, M. S., Hammond, B., Johnson, C. N., Middlemiss, D. N., North, S. E., Price, G. W., Rami, H. K., Riley, G. J., Scott, C. M., Shaw, T. E., Starr, K. R., Stemp, G., Thewlis, K. M., Thomas, D. R., Thompson, M., Vong, A. K. K., and Watson, J. M. 3,4-Dihydro-2H-benzoxazinones as 5-HT1A receptor ligands with potent 5-HT reuptake inhibitory activity. Bioorganic & Medicinal Chemistry Letters 2005, 737-741.



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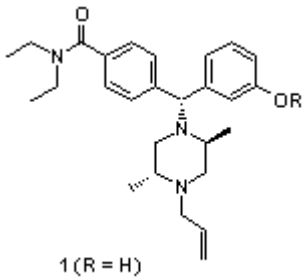
MEDI 7

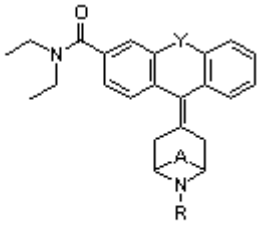
Synthesis and structure-activity relationship of tricyclic piperidinylidenes and tropanylidenes, a novel class of delta opioid agonists

Bart L. De Corte[1], *John R Carson*[1], *Andrea B Works*[1], *Christine M Razler*[1], *Mark E. McDonnell*[1], *James J. McNally*[1], *Li Liu*[2], *Philip M. Pitis*[3], *Laura Andraka*[1], *Christopher A Teleha*[1], *Jef C. Proost*[1], *Sui-Po Zhang*[3], *Ellen E. Codd*[1], *Raymond W. Colburn*[3], *Dennis J. Stone*[1], *Lory J. Molino*[1], *Christopher R. Van Besien*[1], *Christopher M. Flores*[1], *and Scott L. Dax*[1]. *(1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, LLC, Welsh & McKean Roads, P.O. Box 776, Spring House, PA 19477, Fax: 215-628-3297, bdecorte@prdus.jnj.com, (2) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, (3) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C*

The mu, kappa, and delta opioid receptors belong to the G-protein coupled receptor superfamily. Their involvement in the mediation of the perception of pain, pleasure and mood is well documented. Morphine as well as most other marketed opioids attribute their therapeutic effect predominantly through the mu opioid receptor. Although morphine gives rise to potent analgesia, it does so in the context of unwanted clinical effects. In recent years, targeting of the delta opioid receptor has emerged as a potential alternative for the treatment of a variety of painful conditions. Following the discovery of the enkephalin peptides as endogenous ligands for the delta opioid receptor, a number of selective peptidic ligands have been reported. Since then, non-peptide delta-selective opioid agonists such as BW-373U86 (1) and SNC-80 (2) have been studied extensively. We report here the discovery of a series of tricyclic piperidinylidenes (3) and tropanylidenes (4), a novel class of potent delta opioid receptor agonists. The synthesis and structure-activity relationship of this class of compounds will be presented.



1 (R = H)
2 (R = Me)



3 (A = absent)
4 (A = CH_2CH_2)

MEDI 8

Synthesis of small molecules designed to complement disease-associated thyroid hormone receptor mutants

A. Quamrul Hassan *and John T. Koh, Department of Chemistry, University of Delaware, Academy Street, Newark, DE 19711, aqhassan@udel.edu*

TSH-secreting pituitary tumor (TSHoma) and resistance to thyroid hormone (RTH) have been shown to be associated with mutations to the thyroid hormone receptor s(TR). One missense mutation (H435Y) has been found in both TSHoma and RTH. Importantly, His435 is believed to play a key role in ligand-dependant transactivation mechanism of TR. We have synthesized series of novel pyridine-based thyromimetics designed to complement TR? (H435Y). Whereas natural ligand T3 is ~400 fold less potent toward TR?(H435Y) than wild-type TR, the synthetic analog QH13 is a super agonist at nanomolar concentration towards TSHoma-associated mutant. Significantly, QH13 can selectively activate the mutant without affecting the wild-type TR subtypes. Inspired by our success with pyridine-based analogues, we currently are exploring other heterocyclic and fused ring scaffolds to improve potency and selectivity. Similarly, we have developed highly selective and potent compounds that activate the synthetic mutant TR?(H435A), which is not responsive to the endogenous ligands. Such "functionally orthogonal" ligand-receptor pairs are being explored as novel tools to study the genomic versus non-genomic actions of steroid/nuclear hormones.

MEDI 9

CDK2/CyclinA inhibitors: Targeting the cyclinA recruitment site with small molecules derived from peptide leads

Daniel P. Sutherlin[1]*, Georgette M. Castanedo*[1]*, Kevin Clark*[1]*, Shumei Wang*[1]*, Vickie Tsui*[1]*, Mengling Wong*[1]*, John B. Nicholas*[2]*, Dineli Wickramasinghe*[3]*, and James Marsters*[1]*. (1) Department of Medicinal Chemistry, Genentech, Inc, 1 DNA way, South San Francisco, CA 94080, Fax: 650-225-2061, Dans@gene.com, (2) Neurion Pharmaceuticals, (3) Department of Biooncology, Genentech, Inc*

The syntheses of potent small molecule inhibitors of the CDK2/CyclinA recruitment site are described. Where most small molecule drug discovery programs have focused on the active site of the Cyclin Dependent Kinase, we have pursued inhibitors that bind to a substrate recognition groove on the surface of CyclinA distant from the kinase active site. Inhibition of cyclinA with cell penetrating peptides selectively kills cancer cells in vitro and in vivo. Nanomolar octa-peptide leads (40 nM) were initially truncated in order to identify a smaller, albeit significantly less potent, tetrapeptide lead (20 μM). All losses in affinity were recovered by finding new contacts with the protein surface and by rigidification of the peptide backbone using a combination of solid-phase parallel synthesis and structure based design. Finally, two guanidines were eliminated to result in neutral small molecules that are equal to the activity of the starting peptides (21 nM).

MEDI 10

Novel VEGFR-2 kinase inhibitors for the treatment of cancer

Stephen J. Boyer[1]*, Jennifer M. Burke*[1]*, Catherine R. Brennan*[1]*, Warren Brini*[1]*, William Collibee*[1]*, Julie A. Dixon*[1]*, Jacques Dumas*[1]*, Frederick Ehrgott*[1]*, Holia Hatoum-Mokdad*[1]*, Zhenqui Hong*[1]*, Harold C. Kluender*[1]*, Wendy Lee*[1]*, Xin Ma*[1]*, Raymond Reeves*[1]*, Robert N. Sibley*[1]*, Tiffany Turner*[1]*, Wai Wong*[1]*, Yanlin Zhang*[1]*, Cheryl Brink*[2]*, Christopher Carter*[2]*, Yong Chang*[2]*, Du-Shieng Chien*[3]*, Christian Cortes*[2]*, James Elting*[2]*, Randall M. Jones*[2]*, Mark*

McHugh[2], Adrienne Natrillo[3], Barbara Polony[2], Patrick Vincent[2], Dean Wilkie[2], Deborah Webb[3], and Guochang Zhu[2]. (1) Department of Chemistry Research, Bayer HealthCare Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516, stephen.boyer@bayerhealthcare.com, (2) Department of Cancer Research, Bayer HealthCare Pharmaceuticals Corporation, (3) Department of Research Technologies, Bayer HealthCare Pharmaceuticals Corporation

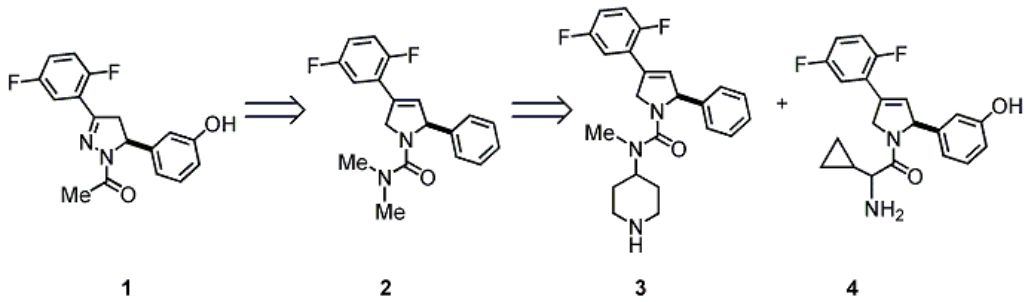
Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase VEGFR-2 are key mediators of angiogenesis. Since the growth of new blood vessels is an important step in tumor progression, inhibition of VEGFR-2 has become a major area of research for the treatment of solid tumors. We recently disclosed the furopyridazine BAY 57-9352, a potent, orally active VEGFR-2, PDGFR, and c-kit inhibitor currently in Phase I clinical trials. In this talk, we wish to report the medicinal chemistry program that culminated in the discovery of BAY 57-9352. Starting from a set of 2-carboxamidopyridyl-phthalazines, we focused on improving potency and pharmacokinetic properties. Core modifications incorporating the 2-carboxamidopyridyl moiety, including isoquinolines, furopyridazines, and thienopyridazines, were explored. Structure activity relationships of furopyridazines will be presented, leading to the identification of a compound with improved ADME properties. Additionally, the in vitro and in vivo pharmcology profiles of BAY 57-9352 will be discussed.

MEDI 11

Synthesis and characterization of 2,4-diaryl-2,5-dihydropyrrole inhibitors of the mitotic kinesin KSP: N1-Ureas and C2-phenols

Robert M. Garbaccio[1]*, Edward S. Tasber[1], Mark E. Fraley[1], George D. Hartman[1], Robert B. Lobell[2], Carolyn A. Buser[2], Weikang Tao[2], Hans E. Huber[2], Nancy E. Kohl[2], Lawrence C. Kuo[3], Youwei Yan[3], Maricel Torrent[4], Thomayant Prueksaritanont[5], and Donald Slaughter[5]. (1) Department of Medicinal Chemistry, Merck & Co., Inc, 770 Sumneytown Pike, P.O. Box 4, WP 14-1, West Point, PA 19486-0004, Fax: 215-652-6345, robert_garbaccio@yahoo.com, (2) Department of Cancer Research, Merck & Co., Inc, (3) Department of Structural Biology, Merck & Co., Inc, (4) Molecular Systems, Merck & Co., Inc, (5) Department of Drug Metabolism, Merck & Co., Inc*

KSP (HsEg5) is a mitotic kinesin that is essential for the formation of a bipolar spindle and for the proper segregation of chromosomes during mitosis. Inhibition of KSP results in collapse of the bipolar spindle assembly which leads to mitotic arrest and apoptosis. Therefore, inhibitors of KSP have potential as general antiproliferative agents useful for the treatment of cancer. In this presentation, the development of 2,4-diaryl-2,5-dihydropyrroles as novel, potent and selective inhibitors of KSP is disclosed. The evolution of this structural class from the lead dihydropyrazole (**1**) to the dihydropyrrole (**2**) will be described with emphasis on the identification of N1-ureas (**3**) and C2-phenols (**4**) that provided both potency and aqueous solubility. Two distinct synthetic routes are discussed towards these inhibitors as are relevant X-ray structures and physical properties. The ability of these compounds to inhibit tumor growth *in vivo* in mice is also presented.

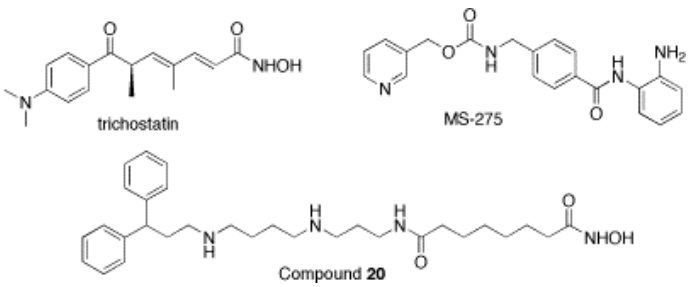


MEDI 12

Polyaminohydroxamic acid derivatives as histone deacetylase (HDAC) inhibitors

Sheeba Varghese[1]*, Anchalee Jiemjit*[2]*, Steven D. Gore*[2]*, Tiffany Baran*[1]*, Robert A. Casero*[2]*, and Patrick M. Woster*[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, 3341 Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI 48202, Fax: 313-577-2033, ak0286@wayne.edu, (2) The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University*

Acetylation and deacetylation of histones, which are carefully mediated by histone acetyl transferases (HAT) and histone deacetylases (HDAC), modulate chromatin architecture and thus regulate transcription. In some forms of human cancer, mutations lead to excessive recruitment of HDACs, and critical tumor suppressor factors such as the cyclin-dependent kinase inhibitor p21WAF1, are not expressed, resulting in the proliferation of undifferentiated tumor cells. HDAC inhibitors are a promising class of antitumor agents that induce histone hyperacetylation, reactivate suppressed genes and promote differentiation of the cells, ultimately resulting in apoptosis. Structure/activity studies have to date focused on the surface recognition and zinc-binding moieties in HDAC inhibitors such as trichostatin, but have not explored any interactions with amino acid groups adjacent to the inhibitor binding site. To this end, we have synthesized a series of alkyl substituted polyaminohydroxamic acids and have shown that they are potent HDAC inhibitors in vitro. These data have facilitated elucidation the structural features required for activity in this series. The most active analogue, compound 20, caused marked histone H3 and H4 hyperacetylation and significantly greater expression of p21 than trichostatin or MS-275 in ML-1 myelocytic leukemia cells at submicromolar concentrations. These studies suggest that polyaminohydroxamic acids represent an important new class of HDAC inhibitors.

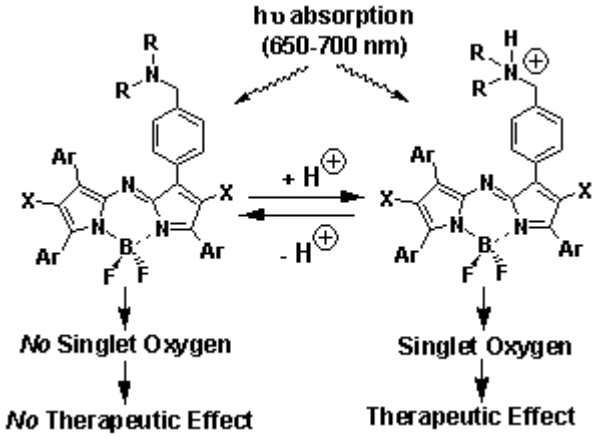


MEDI 13

Supramolecular photonic therapeutic agents: pH Responsive anti-cancer drugs

***Donal F. O'Shea**, Shane McDonnell, and Michael Hall, Centre for Synthesis and Chemical Biology, Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland, donal.f.oshea@ucd.ie*

Despite its promising results to date, a well-documented drawback of Photodynamic Therapy (PDT) is a lack of selectivity. A new approach to achieving selectivity based upon the reversible on/off switching of the therapeutic property (i.e. singlet oxygen generation) of a PDT agent in response to an endogenous analyte will be described. Control can be exerted over this process by integrating a pH responsive receptor onto the PDT agent, which makes the generation of singlet oxygen pH dependant. For example, systems can be constructed such that at a pH of 8.0 the excited state energy of the photosensitizer can be decayed by a photoinduced electron transfer (PET) mechanism, resulting in little singlet oxygen being generated, but at a pH of 6.5 the PET mechanism does not operate and singlet oxygen is produced. The principles of this reversible on/off switching mechanism could be applied in response to a variety of endogenous analytes.



MEDI 14

Design and synthesis of an array of selective androgen receptor modulators

***Ryan P. Trump**[1], Philip Turnbull[2], Jean-Baptiste E. Blanc[1], Robert W. Wiethe[1], Eugene L. Stewart[3], Matilde Caivano[4], David Gray[4], William J. Hoekstra[1], and Timothy M. Willson[1]. (1) High Throughput Chemistry, GlaxoSmithKline, 5 Moore Dr, Research Triangle Park, NC 27709, Fax: 919-315-0430, ryan.p.trump@gsk.com, (2) Department of Medicinal Chemistry, GlaxoSmithKline, (3) Computational, Analytical, and Structural Sciences, GlaxoSmithKline, (4) Screening and Compound Profiling, GlaxoSmithKline*

Selective Androgen Receptor Modulators (SARMs) have the potential to treat of conditions such as hypogonadism and androgen deficiency in aging males (ADAM). In an attempt to find new SARMs, a pharmacophore model of the androgen receptor (AR) was used to discover an initial 4-amino benzonitrile hit. An array of analogs was designed using shape comparison and fast docking computer algorithms. An efficient and parallel synthesis was developed that allowed rapid synthesis of 1,300 analogs of the initial hit. Representatives of the array

members showing high potency and efficacy in a reporter-gene cell-based functional assay will be discussed.

MEDI 15

Novel potent allosteric inhibitors of HCV NS5B polymerase

Christian Brochu[1], *René Coulombe*[1], *James R. Gillard*[1], *Eric Jolicoeur*[1], *Peter Kohlbauer*[2], *Peter Kühn*[2], *Marc-André Poupart*[1], *Sylvain Lefebvre*[1], *Ginette McKercher*[1], *George Kukolj*[1], *and Pierre L. Beaulieu*[1]. *(1) Boehringer Ingelheim (Canada) Ltd., R&D, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, Fax: 450-682-4189, (2) Boehringer Ingelheim GmbH*

An estimated 3% (~170 million) of the world's population suffers from chronic HCV infection that can cause progressive liver diseases, cirrhosis of the liver and eventually hepatocellular carcinomas. Existing therapies are sub-optimal for approximately 50% of the patient population, and the need for new specific antiviral agents is of great importance. Among the proteins encoded by the HCV genome, the NS5B enzyme, an RNA-dependent RNA polymerase, was shown to be essential for viral replication. High-throughput screening of our compound collection using a modified HCV NS5B construct allowed the identification of a specific class of benzimidazoles 5-carboxamide inhibitors. Optimization of these initial hits led to highly potent inhibitors in an in vitro assay, which were also active in a cell-based assay using subgenomic HCV RNA replication (replicons). Successful soaking of these compounds into apo NS5B crystal revealed the inhibitor's binding site on the thumb domain of NS5B and provided insight into the mechanism by which this class of compounds inhibits the polymerase activity. The optimization effort and structural information using these inhibitors will be discussed.

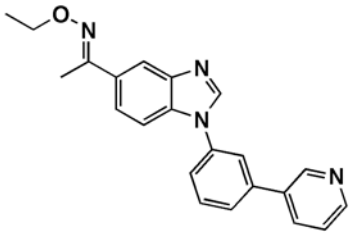
MEDI 16

Identification and *in vivo* characterization of allosteric modulators of the $GABA_A$ ion channel with functional selectivity for the $\alpha3\beta3\gamma2$ subtype

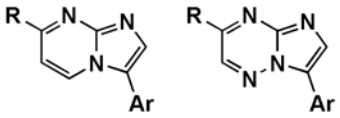
David J. Hallett[1], *John R. Atack*[2], *J. Luis Castro*[2], *Susan Cook*[2], *Robert W. Carling*[3], *Rebecca Dias*[2], *Gerard R. Dawson*[2], *Simon Goodacre*[2], *Alexander Humphries*[2], *Sarah Kelly*[2], *Rachel J. Lincoln*[2], *George R. Marshall*[2], *Ruth M. McKernan*[2], *Leslie J. Street*[3], *David S. Reynolds*[2], *Michael G. N. Russell*[3], *Alison Smith*[2], *Wayne F. A. Sheppard*[2], *Joanne L. Stanley*[2], *Spencer Tye*[2], *Keith A. Wafford*[2], *and Paul J. Whiting*[2]. *(1) Medicinal Chemistry, The Neuroscience Research Centre, Merck Sharp and Dohme, Terlings Park, CM20 2QR Harlow, United Kingdom, david_hallett@merck.com, (2) Neurosciences Research Centre, Merck, Sharp and Dohme Research Laboratories, (3) The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories*

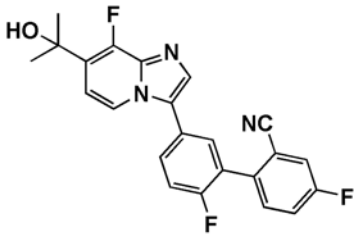
γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. One of its sites of action is the $GABA_A$ receptor, a pentameric supramolecular complex that forms a GABA-gated ion channel controlling chloride ion flux in the neuron,

thereby leading to inhibition of neuronal activity. $GABA_A$ receptor function can be allosterically modulated by benzodiazepines (BZs) and recent transgenic and pharmacological advances have provided many new insights into which $GABA_A$ receptor subtypes (i.e. α1-, α2-, α3- or α5-containing receptors) are associated with particular pharmacological features of the BZs. However, the contribution of the α2 versus the α3 receptor subunit to the anxiolytic and anti-convulsant activity of BZs remains unclear. Using the Neurosearch compound NS-2710 as a starting point, we developed several series of novel imidazo-azine $GABA_A$ receptor modulators culminating in the α3 selective ligand TP-003. This presentation will highlight key medicinal chemistry milestones together with the behavioural effects of these compounds in rodents and non-human primates.



NS-2710





TP-003

MEDI 17

Discovery of a potent, selective and orally active 5-HT6 receptor agonist, WAY-181187

Derek C. Cole[1]*, Joseph R. Stock*[1]*, William J. Lennox*[1]*, Ronald C. Bernotas*[1]*, John W. Ellingboe*[1]*, Louis Leung*[2]*, Deborah Smith*[3]*, Gouming Zhang*[3]*, Ping Li*[3]*, Lin Qian*[3]*, Lee A. Dawson*[3]*, Steve Boikess*[3]*, Sharon Rosenzweig-Lipson*[3]*, Chad E. Beyer*[3]*, and Lee E. Schechter*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, (2) Drug Safety and Metabolism, Wyeth Research, (3) Neuroscience, Wyeth Research*

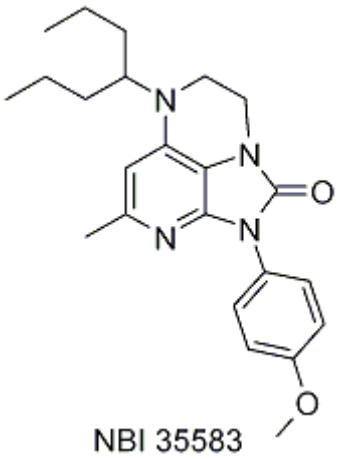
There are now approximately fifteen different human serotonin (5-HT) receptors which have been cloned, divided into seven subclasses (5-HT_{1-7}). The 5-HT_6). receptor is one of the latest identified and belongs to the G-protein coupled receptor (GPCR) superfamily and is positively coupled to adenylyl cyclase. The CNS localization of 5-HT_6 receptors and their affinity for certain CNS drugs have created intense interest in identifying selective 5-HT_6 modulators both as tools for studying the receptor and as potential therapeutic agents. To date 5-HT_6 antagonists have been identified by several companies and have advanced to clinical trials for memory and cognitive disorders. In contrast, the identification of selective 5-HT_6 receptor agonists has proven much more difficult. As part of a program to develop 5-HT_6 modulators at Wyeth, we identified a novel series of receptor agonists. This presentation will discuss the discovery and SAR of the series leading to the identification of WAY-181187 a novel and selective high affinity (Ki = 2 nM) 5-HT_6 receptor ligand which behaves as a full agonist (EC50 = 6.6 nM; Emax = 93%). The pharmokinetic profile and in vivo evaluation of this clinical candidate will be discussed.

MEDI 18

Design and synthesis of tricyclic corticotropin-releasing factor-1 (CRF1) antagonists

***John P Williams**, Department of Medicinal Chemistry, Neurocrine Biosciences, 12790 El Camino Real, San Diego, CA 92130, Fax: 858-617-7619*

Small molecule, non-peptide antagonists of the corticotropin-releasing factor (CRF) neuropeptide should prove effective in treating stress and anxiety related disorders. In an effort to identify antagonists with improved physicochemical properties, tricyclic CRF1 antagonists were designed, synthesized and tested for biological activity. The SAR as well as the in vitro and in vivo characterization of several classes of tricyclic antagonists will be discussed. The compound NBI 35583 is a representative example, which proved to be high affinity antagonist with a pKi value of 8.2 and the compound is a functional CRF1 antagonist in vitro and in vivo. In addition, after more than a decade of medicinal chemistry in the area, an analysis of what the future holds for CRF1 antagonists will be presented.



NBI 35583

MEDI 19

Design and synthesis of constrained imidazoles as CRF1R antagonists

***Xiaojun Han**, Jodi Michne, Edward Ruediger, Rita Civiello, Sokhom Pin, Kevin Burris, Lynn Balanda, Lawrence Fung, Jay Knipe, Shelly Ren, Dedong Wu, Qi Gao, Stella Huang, Tracey Fiedler, Kaitlin Browman, Robert Macci, Matthew Taber, Jie Zhang, and Gene Dubowchik, Neuroscience Chemistry, PRI, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT CT 06492, Fax: 203-677-7702, xiaojun.han@bms.com*

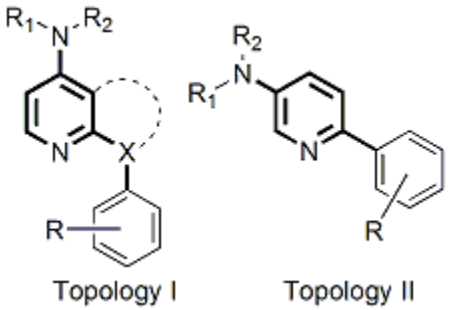
Corticotropin-releasing factor (CRF), a 41-residue neuropeptide, secreted in the hypothalamus, mediates stress responses by stimulating the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. The resulting secretion of ACTH initiates the release of adrenal glucocorticoids, which impose their pathophysiological effects through the HPA (hypothalamic-pituitary-adrenal) axis. The clinical relevance of the HPA/stress/depression hypothesis has been supported by the fact that high CRF levels have been detected in the cerebrospinal fluid in more than half of depressed patients, and that treatment with antidepressants normalize

these levels. These findings, along with the desire to target a new antidepressant mechanism that might avoid problems associated with current therapies, have inspired us to discover highly selective, small molecule CRF1R antagonists. In this Talk, we report our efforts in the design, synthesis, binding studies and behavioral efficacy of a novel series of constrained imidazoles as CRF1R antagonists.

MEDI 20

Topology II CRF–1 receptor antagonists

Raymond F Horvath[1]*, J Kehne*[2]*, D Hoffman*[2]*, R Brodbeck*[3]*, L Fung*[4]*, and Y Yamaguchi*[1]*. (1) Department of Medicinal Chemistry, Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, Fax: 203-483-7027, rhorvath@nrgn.com, (2) Department of Pharmacology, Neurogen Corporation, (3) Department of Biochemistry, Neurogen Corporation, (4) Department of Drug Metabolism, Neurogen Corporation*



Corticotropin releasing factor (CRF) is thought to play a significant role in depression and stress-related disorders. As a consequence, development of CRF-1 receptor antagonists has been an area of intense research for nearly 15 years, though relatively few compounds have advanced beyond the discovery stage. It is possible that the issues encountered are related to structure and not pharmacology of the HPA axis or of central CRF systems. Most antagonists discovered to date have evolved from Topology I where the sp^2 ring nitrogen is critical for activity, but the core may be a 5 or 6 membered heteroaromatic ring. We have discovered that the biaryl template Topology II, derived by excising an atom spacer and aligning substituents along the same regiochemical axis results in a new series of potent CRF antagonists. Our extensive efforts to de-risk analogs from Topology II have afforded a source of advanced candidates. SAR and behavior profiles of this new series will be presented.

MEDI 21

Use of molecular modeling and informatics to aid safety assessment in drug discovery projects

Scott Boyer*, Safety Assessment, AstraZeneca, Molndal 43183, Sweden, scott.boyer@astrazeneca.com*

Effective experimental evaluation of the safety of a new drug candidate as early as possible in the drug discovery process necessitates a theoretical background of both the biology and chemistry involved. Molecular modelling and informatics provide an important base upon which experimental strategies to design safer drugs can be built. This presentation will review some of the most critical areas of need in molecular modelling, including QSAR methods for hERG and mutagenesis, evaluation of metabolically unstable sites and automated warning systems

for reactive intermediate formation. Emphasis will be placed on model validation and assessment of prediction reliability. In addition, methods borrowed from the virtual screening area will be presented which aid in identifying possible off-target pharmacologies that may mediate side effects. All methods presented will focus on evaluating effects related to the chemical structure in order to give the medicinal chemist guidance on safety-related endpoints throughout the drug discovery process.

MEDI 22

QSAR models for predicting p-glycoprotein activity of antagonists for a GPCR target

Sookhee Ha[1]*, Christopher Tong*[2]*, Rebecca Perlow-Poehnelt*[1]*, Jiunn H. Lin*[3]*, J. Christopher Culberson*[1]*, Robert P. Sheridan*[1]*, and Jerome Hochman*[3]*. (1) Molecular Systems, Merck & Co, 126 E Lincoln Ave, Rahway, NJ 07065, Fax: 732-594-4224, sookhee_ha@merck.com, (2) Department of Biometrics, Merck & Co, (3) Drug Metabolism and Pharmaceutical Research, Merck Research Laboratories*

No abstract available.

MEDI 23

NOMAD: A software platform for investigating structure-activity and structure-property relationships

W. Patrick Walters*, Rieko Arimoto, Paul Charifson, Brian McClain, and Brian Goldman, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139-4242, Fax: 671-444-6688, pwalters@vrtx.com*

The quality of a predictive model is dependent on an appropriate choice of molecular descriptors and learning algorithm. In order to build a robust model, one must typically investigate a number of different methodologies. In order facilitate such comparisons, we have implemented NOMAD, a software platform for building and evaluating structure-activity relationships. NOMAD enables users to easily “mix and match” a variety of descriptors, feature selection techniques and machine learning methods. The NOMAD compute engine is coupled to a graphical user interface that allows users to investigate model quality, and easily explore relationships between chemical structure and biological activity. This presentation will provide an overview of the NOMAD architecture as well as examples of the system's use in drug discovery projects.

MEDI 24

The effects of structural changes on molecular properties: Matched molecular pair analysis

Andrew G Leach*, Computational Chemistry, AstraZeneca, Mereside, Alderley Park, Macclesfield SK10 4TG, United Kingdom, andrew.leach@astrazeneca.com*

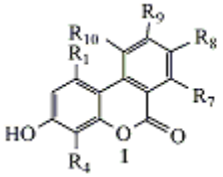
Abstract text not available.

MEDI 25

6*H*-Benzo[*c*]chromen-6-one derivatives as selective ERβ agonists

Wanying Sun[1], *Lovji D. Cama*[1], *Elizabeth Birzin*[2], *Sudha Warrier*[2], *Louis Locco*[2], *Ralph Mosley*[1], *Milton M. Hammond*[1], *and Susan P. Rohrer*[2]. *(1) Department of Medicinal Chemistry/Merck Research Laboratories, Merck Co, PO Box 2000, Rahway, NJ 07065, Fax: 732-594-9556, wanying_sun@merck.com, (2) Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Merck & Co*

A series of 6H-benzo[c]chromen-6-one (1) and 6H-benzo[c]chromene (2) derivatives were prepared as selective ERβ agonists. Bis hydroxylation at position 3 and 8 was essential for activity in a HTRF coactivator recruitment assay. Additional modifications at both phenyl rings led to compounds with ERβ<10nM potency and >100-fold selectivity over ERα. Molecular modeling studies identified a binding mode for these compounds in which the tricyclic core of the chromenone derivatives spans the length of the steroid estradiol and the lactone ring is oriented in the binding pocket to map to the “B” ring of the steroid away from helix 12.



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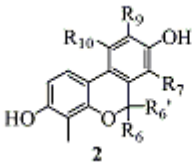

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MEDI 25

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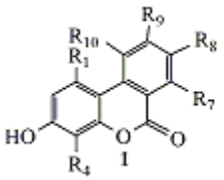
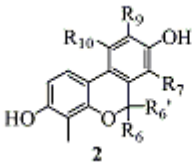


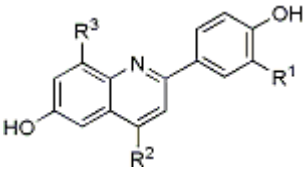


MEDI 26

4,8-Disubstituted 2-phenyl-quinolines as potent and selective estrogen receptor β ligands

An T. Vu[1]*, Stephen T. Cohn*[1]*, Eric S. Manas*[1]*, Heather A. Harris*[2]*, and Richard E. Mewshaw*[3]*. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, vua@wyeth.com, (2) Women's Health Research Institute, Wyeth Research, (3) Chemical and Screening Sciences, Wyeth Research*

The discovery of a second subtype of estrogen receptor, estrogen receptor beta (ERβ), has prompted intense research to elucidate its physiological functions and identify its potential therapeutic targets. Recently, a series of 2-phenyl-quinolines was discovered as a new class of ERβ-selective ligands. Analogues with substitution at the C4 (R^2) or C8 (R^3) position displayed substantial selectivity for ERβ. In this report, we disclose our further effort toward optimization of ERβ affinity and selectivity by introducing substituents at both the C4 and C8 positions of the 2-phenyl-quinoline framework. A number of 4,8-disubstituted 2-phenyl-quinolines exhibited low nanomolar affinity and as high as 100 fold ERβ selectivity, demonstrating the synergistic effects of the disubstitution. A select group of compounds were profiled as either full or partial ERβ agonists in a cell-based functional assay measuring the transcription of KRT19 mRNA. The uterine weight estrogenic bioassay of the most selective compounds showed no significant uterine stimulation, thus indicating no activation of ERα in this sensitive estrogen target organ. The design, synthesis and biological evaluation of the 4,8-disubstituted 2-phenyl-quinolines will be discussed.

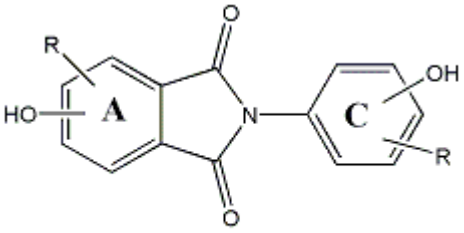


MEDI 27

4-Hydroxy-N-phenyl substituted phthalimides as selective estrogen receptor beta (ERb) ligands

John W. Ullrich[1]*, Robert Singhaus*[1]*, Raymond Unwalla*[2]*, and Heather A. Harris*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, Ullricj@Wyeth.com, (2) Structural Biology, Wyeth Research, (3) Women's Health Research Institute, Wyeth Research*

The estrogen receptor (ER) mediates a number of physiological processes via its endogenous ligand, (17β)-estradiol. The discovery of a second estrogen receptor subtype, ERβ, has generated interest in the pharmacology of this receptor and its role in estrogen signaling. ERβ selective ligands would help elucidate the receptor function but this goal has proven quite challenging since the alpha and beta isoforms differ by only two amino acids in the ligand binding domain (LBD). We will discuss the discovery of novel phthalimides (I) and the optimization of their ERβ affinity and selectivity through introduction of substituents on the A and C rings, guided by an X-ray structure of the ERβ LBD. The resulting compounds had moderate ERβ affinity but were 45-fold selective over the ERα isoform. The design, synthesis and biological evaluation of the 4-hydroxy-N-phenyl substituted phthalimides will be discussed.



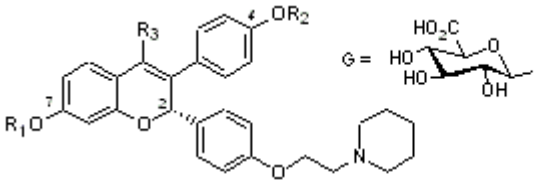
I

MEDI 28

Synthesis and deuterium-labeling of pure SERM acolbifene (EM-652.HCl, SCH 57068.HCl) glucuronides

Jean-yves Sancéau*, Denis Larouche, Brigitte Caron, Patrick Bélanger, Agnès Coquet, Alain Bélanger, Sylvain Gauthier, and Fernand Labrie, Medicinal Chemistry, Oncology and Molecular Endocrinology Research Center (CHUL) and Laval University, 2705 Boulevard Laurier, Québec, QC G1V4G2, Canada, jean-yves.sanceau@crchul.ulaval.ca*

Acolbifene (EM-652•HCl, SCH 57068•HCl), a highly potent and orally active selective estrogen receptor modulator (SERM), is currently in advanced clinical trials for treatment of estrogen-dependent breast cancer. Acolbifene-7-glucuronide (major) and acolbifene-4'-glucuronide (minor) were identified as metabolites of acolbifene in the human. The two monoglucuronides and a diglucuronide as well as the corresponding ^{2}H-labelled derivatives were synthesized for use as preclinical and clinical trial standards especially for LC-MS/MS analysis. All glucuronides were prepared by Schmidt glycosylation of monoprotected acolbifene with a glucuronyl imidate at -10°C to prevent epimerization at C-2 position. The two monoglucuronides of acolbifene were separated by semi-preparative HPLC. Incorporation of three deuteriums was achieved by alkylation of a chromanone intermediate with $C^{2}H_{3}MgI$ followed by dehydration with $C^{2}H_{3}CO_{2}{}^{2}H/{}^{2}H_{2}O$. Then, chemical resolution and salt neutralization gave [$^{2}H_{3}$]acolbifene.



$R_1 = R_2 = H$, $R_3 = CH_3$; acolbifene (EM-652·HCl, SCH 57068·HCl)

$R_1 = R_2 = H$, $R_3 = C^2H_3$; [$^2H_3$]acolbifene

$R_1 = G$, $R_2 = H$, $R_3 = CH_3$ or C^2H_3; $R_1 = H$, $R_2 = G$, $R_3 = CH_3$ or C^2H_3; monoglucuronides

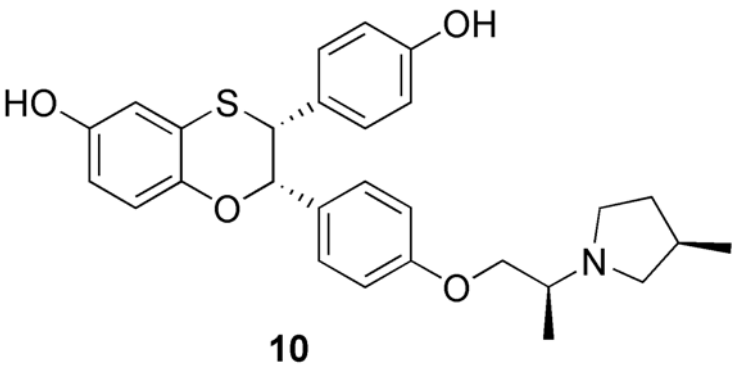
$R_1 = R_2 = G$, $R_3 = CH_3$ or C^2H_3; diglucuronides

MEDI 29

Dihydrobenzoxathiin SERAMs: Discovery of an optimized antagonist side chain and application of novel side chains to existing SERM platforms

Timothy A. Blizzard[1], *Frank DiNinno*[2], *Jerry D. Morgan II*[2], *Helen Y. Chen*[2], *Jane Y. Wu*[2], *Seongkon Kim*[2], *Wanda Chan*[2], *Elizabeth T. Birzin*[2], *Yi Tien Yang*[2], *Lee Yuh Pai*[2], *Edward C. Hayes*[2], *Carolyn A. DaSilva*[2], *Ralph T. Mosley*[1], *Paula M.D. Fitzgerald*[2], *Nandini Sharma*[2], *Susan P. Rohrer*[2], *James M. Schaeffer*[2], *and Milton L Hammond*[2]. *(1) Merck Research Laboratories, RY800-B116 P.O. Box 2000, Rahway, NJ 07065, tim_blizzard@merck.com, (2) Merck Research Laboratories, Rahway, NJ 07065*

An optimized side chain for dihydrobenzoxathiin SERAMs was discovered and attached to four dihydrobenzoxathiin platforms. The novel SERAMs (e.g. 10) show exceptional estrogen antagonist activity in uterine tissue and an MCF-7 breast cancer cell assay. Two novel side chains (A & B) which had previously been found to enhance antagonist activity in the dihydrobenzoxathiin SERM series were applied to three known SERM platforms. The novel side chains did not substantially improve the antagonist activity of the existing (non-dihydrobenzoxathiin) platforms.



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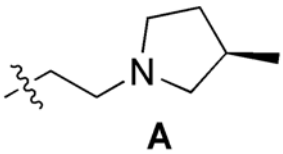

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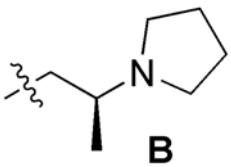

B

MEDI 30

Discovery of tissue-selective osteoanabolic SARMs

Jiabing Wang, *Carol A. McVean, David B. Whitman, and Mark E. Duggan, Department of*

Medicinal Chemistry, Merck Research Laboratories, P O Box 4, West Point, PA 19486, Fax: 215-652-7310, jiabing_wang@merck.com

The androgen receptor (AR), a member of the nuclear hormone receptor superfamily, has many pharmacologic functions, including promoting sexual differentiation and regulating anabolism. Although androgens have been shown to increase bone mineral density in postmenopausal women, they are not prescribed for this indication because they stimulate facial hair growth and other undesirable actions. We have identified a class of Selective Androgen Receptor Modulators (SARMs) that stimulate periosteal bone formation in cortical bone in ovariectomized rats with minimal effects on virilization endpoints. The SAR of this series will be disclosed along with an in vivo model for evaluating tissue- selective actions.

MEDI 31

New ligands for estrogen receptors

Jelena M. Janjic[1]*, Miranda Sarachine*[2]*, Claire Coleman*[3]*, Peter Wipf*[3]*, and Billy W. Day*[1]*. (1) Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15261, jmj47@pitt.edu, (2) Department of Pharmacology, University of Pittsburgh, (3) Department of Chemistry, University of Pittsburgh*

The two known estrogen receptors, ER-alpha and ER-beta, are the products of different genes on separate chromosomes. Of these, ER-alpha has been the most extensively studied, and its expression in breast cancer determines the ER positive phenotype. ER-beta, on the other hand, was discovered only recently and its role in breast cancer pathology remains unclear. ER-beta inhibits E2-induced proliferation of T47D breast cancer cells in addition to decreasing the expression of cell cycle related genes. Clinical studies have shown a positive correlation between ER-beta expression with disease-free survival and overall survival in breast cancer patients. Furthermore, ER-beta expression has been inversely correlated with HER2 expression. ER-beta activation with a selective ER-beta agonist could antagonize the stimulating activity of the ER-alpha in breast cancer cells, and such an ER-beta agonist could help overcome acquired resistance. Therefore, we began a search for such agents. A one-pot hydrozirconation-transmetallation-aldimine addition sequence that leads to allylic amides, homoallylic amides, and C-cyclopropylalkylamides was significantly accelerated by microwave technology and used for library preparation. The library was screened in a fluorescence polarization-based homogenous in vitro assay against ER-alpha and ER-beta. A dual color fluorescence polarization assay was designed and developed in-house to test screening hits for specific agonism, antagonism and/or coregulator binding interference.

MEDI 31

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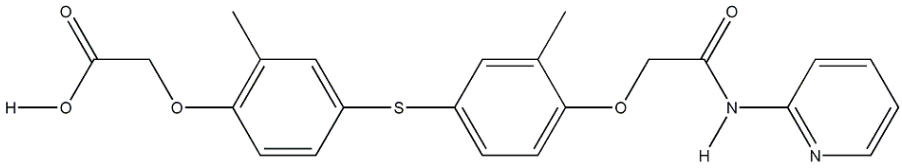
MEDI 32

Discovery of (4-phenylsulfanyl-phenoxy)-acetic acids as a novel class of PPARδ agonists

Rajiv Sharma[1]*, Jonathan Houze*[1]*, Joshua Gergely*[1]*, Michelle Akerman*[1]*, Frank Kayser*[1]*, Jean Danao*[2]*, and Jurgen Lehmann*[2]*. (1) Medicinal Chemistry, Amgen San Francisco, 1120 Veterans Blvd, S. San Francisco, CA 94080, rajivs@amgen.com, (2) Biology, Amgen San Francisco*

A recent report that a selective PPARδ agonist was able to increase HDL (among other effects) in a pre-diabetic obese rhesus monkey model of metabolic syndrome X has generated considerable interest in PPARδ as a target for therapeutic intervention. In this poster, we will describe the discovery of (4-phenylsulfanyl-phenoxy)-acetic acids as a novel class of PPARδ agonists. Starting with the HTS lead (1), SAR explorations led to the discovery of (2) which has potent cellular activity and excellent oral bioavailability. Details of the SAR trends and synthesis of analogs of (2) will be discussed.



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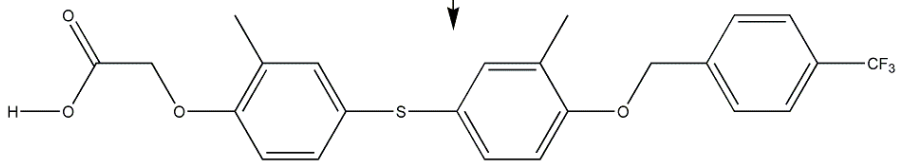


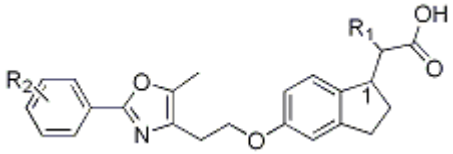
(2)

MEDI 33

Design, synthesis, and SAR of indane acetic acid derivatives: A new class of dual PPAR alpha/gamma agonists

Hai-Jun Zhang[1]*, Neil Bifulco*[1]*, Ken Boakye*[2]*, William Bullock*[1]*, Thomas Claus*[2]*, Philip Coish*[1]*, Miao Dai*[1]*, Fernado E. Dela Cruz*[2]*, David Dickson*[1]*, Ann Gore-Willse*[2]*, Dongping Fan*[1]*, Helena Hoover-Lilly*[2]*, Tindy Li*[1]*, Derek B. Lowe*[1]*, Margit MacDougall*[2]*, Gretchen Mannelly*[1]*, Mary-Katherine Monahan*[1]*, Ingo Mugge*[1]*, Stephen O'Connor*[1]*, Mareli Rodriguez*[1]*, Tatiana Shelekhin*[1]*, Laurel Sweet*[2]*, Andreas Stolle*[1]*, Ming Wang*[1]*, Yamin Wang*[1]*, Chengzhi Zhang*[1]*, Kake Zhao*[1]*, Qian Zhao*[1]*, Jian Zhu*[2]*, Manami Tsutsumi*[2]*, and Robert Schoenleber*[1]*. (1) Department of Chemistry Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, hai-jun.zhang.b@bayer.com, (2) Department of Metabolic Disorders Research, Bayer Research Center*

A novel series of antidiabetic indane acetic acid derivatives, which are potent and selective PPAR alpha/gamma dual agonists, was designed and synthesized. Through the use of fluorescence resonance energy (FRET) and cell-based assays α substituted 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazole-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acids were identified as PPAR alpha and gamma dual agonists. Structure-activity relationship studies showed that the S configuration of carbon 1 on the indane ring is essential for activity. Small alkyl substituents (R1) α to the acid, such as ethyl and methyl, are critical for balanced alpha and gamma activities. Para-substitution (R2)on the oxazole phenyl ring plays an important role in alpha activity.



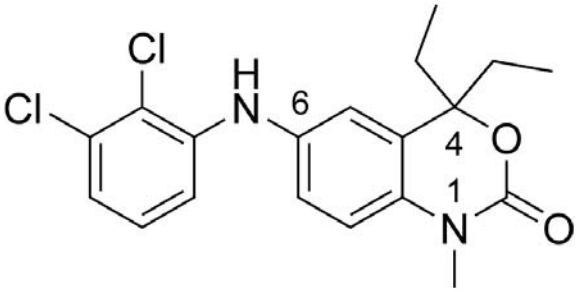
MEDI 34

6-(Arylamino)-4,4-disubstituted-1-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-ones as nonsteroidal progesterone receptor antagonists

Jeffrey C. Kern[1]*, Eugene A. Terefenko*[1]*, Andrew Fensome*[1]*, Ray J Unwalla*[1]*, Jay Wrobel*[1]*, Zhiming Zhang*[2]*, Yun Zhu*[2]*, Jeffrey Cohen*[2]*, Richard Winneker*[2]*, and Puwen Zhang*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, KernJ@wyeth.com, (2) Women's Health Research Institute, Wyeth Research*

A few series of 5- and 6-aryl substituted benzene-fused heterocycles were discovered and reported as progesterone receptor (PR) modulators over the last several years. We recently disclosed that 6-aryl benzoxazin-2-ones are PR antagonists (Zhang, et al. J. Med. Chem. 2002, 45, 4379-4382). In a continuation of this work we examined the SAR of 6-arylamino benzoxazinones and found the targets such as 1, with an extra amino linker between the

pendent 6-aryl groups and benzoxazinone core, remained as PR antagonists. A number of compounds with various substitutions at the 1- and 4-positions as well as different 6-aryl groups were prepared and tested in the T47D cell alkaline phosphatase assay. Interestingly, the SARs unveiled from these analogs were quite different from those of their parent compounds. For example, in contrast to their parent compounds, a methyl substitution at the 1-position significantly increased the potency of 6-arylamino benzoxazinones in the T47D cell alkaline phosphatase assay. A few 6-arylamino benzoxazinones (e.g. 1, IC50 = 5 nM) had low nanomolar in vitro potency and were potent PR antagonists in the T47D cell alkaline phosphatase assay. In this presentation, the synthesis and in vitro SAR of novel 6-arylamino benzoxazinones will be discussed.



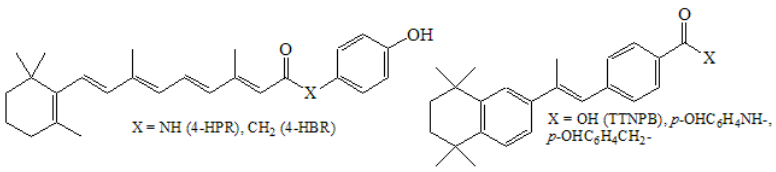
1, Alk. Phos. IC_{50} 5 nM

MEDI 35

Stable analogs of retinamides derived from TTNPB

Victoria V. Abzianidze[1], *Michael D. Collins*[2], *Nirca J. Nieves*[3], *Margaret Clagett-Dame*[4], *and Robert W. Curley Jr.*[1]. *(1) Division of Medicinal Chemistry, The Ohio State University, 500 West 12th Ave., Columbus, OH 43210, Fax: 614-292-2435, abzianidze.1@osu.edu, (2) School of Public Health, UCLA, (3) Pharmaceutical Sciences Division, University of Wisconsin-Madison, (4) Department of Biochemistry, University of Wisconsin-Madison*

Retinoids are known to play a major role in the modulation of a wide variety of cellular processes, such as proliferation, differentiation and apoptosis. They have been intensively studied for their effectiveness as cancer chemotherapeutic agents. However, their antitumor effects have been compromised with high incidence of undesirable side effects. A class of synthetic aromatic retinoid analogs, arotinoids, is found capable of exerting high biological activity but high toxicity. Recent study on the retinamide 4-HPR and its C-linked analog 4-HBR suggests that the nonhydrolyzable C-linked structure provides long term tolerability resulting in significant chemotherapeutic advantage. In this study, the synthesis of nonhydrolyzable analogs of N-(4-hydroxyphenyl)aromatic retinamide derived from arotinoid TTNPB will be presented and preliminary biological study will be discussed.

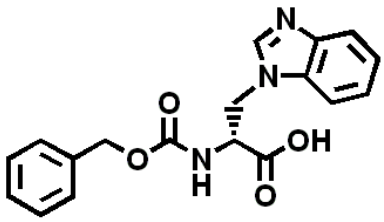


MEDI 36

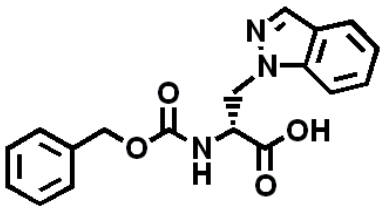
Synthesis of novel heterocyclic amino acids and their incorporation into somatostatin analogs

***Audrey Kelleman**, Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Dr, Mail Box 0343, La Jolla, CA 92093-0343, akellema@chem.ucsd.edu, Michael S. VanNieuwenhze, Department of Chemistry and Biochemistry, University of California-San Diego, and Murray Goodman, Department of Chemistry and Biochemistry, University of California San Diego*

It has been known since the 1970s that the tryptophan residue in somatostatin and related peptidic analogs is an important contributor to human somatostatin receptor binding. In our effort to gain a better understanding of the receptors and their tolerance for heterocyclic side chains other than indole, we designed amino acids 1 – 3. Here we describe the synthesis of these novel amino acids and their incorporation into c[Phe-Pro-Phe-Xxx-Lys-Thr], also known as L-363,301.



1



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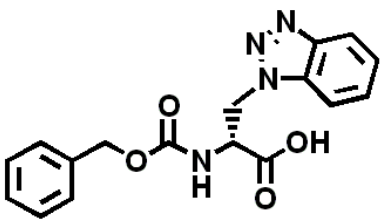

3

MEDI 37

New macrocycles as high affinity antagonists to the motilin receptor

***Eric Marsault**, Sylvie Beaubien, Kamel Benakli, Robert Déziel, Graeme Fraser, Hamid R. Hoveyda, Annick Landry, Luc G. Ouellet, Mark L. Peterson, Carl Saint-Louis, Martin Vézina, and Zhigang Wang, Tranzyme Pharma Inc, 3001, 12e Avenue Nord, Sherbrooke, QC J1H 5N4, Canada, emarsault@tranzyme.com*

The motilin receptor plays a central role in the regulation of gastric motility. Molecules that interact with this receptor are potentially useful for the treatment of functional GI disorders. We hereby disclose a new class of macrocyclic antagonists at the human motilin receptor (hMOT-R), first identified by HTS of our proprietary library. This library (Figure 1 for generic structure) is composed of macrocyclic small molecules characterized by the presence of a unique nonpeptidic tether element which closes the ring and further restricts the conformation of the resulting structure. Subsequent lead optimization, including substitution of side chain moieties and variations in the tether structure, led to the discovery of potent antagonists with low nanomolar affinity at the hMOT-R. The SAR will be presented, as well as two general approaches used to construct this new class of molecules via parallel synthesis.

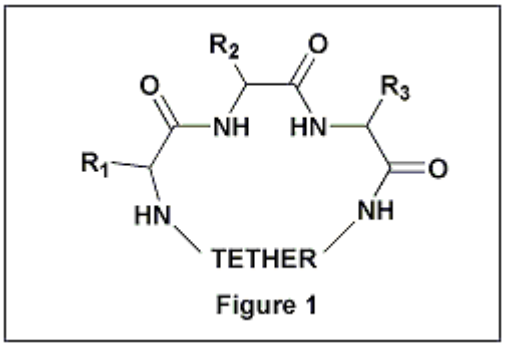

Figure 1

MEDI 37

New macrocycles as high affinity antagonists to the motilin receptor

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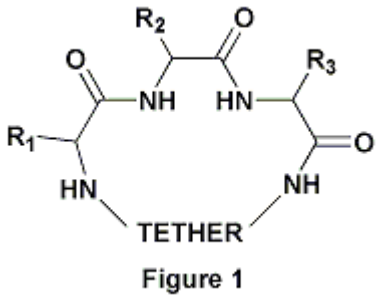


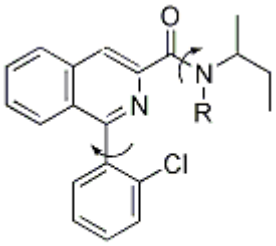
Figure 1

MEDI 38

Rotational barriers in the peripheral benzodiazepine receptor ligand, PK 11195: Determination by quantum chemistry and NMR

Victor W. Pike[1]*, Emmanuelle Briard*[1]*, Fabrice G. Siméon*[1]*, H. Umesha Shetty*[1]*, and Yong-Sok Lee*[2]*. (1) Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Rm B3 C346A, 10 Center Drive, Bethesda, MD 20892, Fax: 301 480 5112, pikev@mail.nih.gov, (2) Center for Molecular Modeling, Division of Computational Bioscience, Center for Information Technology, National Institutes of Health*

PK 11195 (**1**) is a prototypical high affinity ligand for the 'peripheral benzodiazepine receptor' (PBR). The interaction of **1** with PBR has been modelled but is still not well understood, while other ligand classes for PBR continue to be developed. The vast majority of high affinity PBR ligands are tertiary amides, while secondary amide counterparts (*e.g.* **2**) have generally low affinity. We performed quantum chemical calculations and ^{1}H- and ^{13}C-NMR experiments to gain insight into the conformer populations of **1** and **2** that are available for binding to PBR. Theory and experiment provide very similar values for *Z* to *E* amide bond rotational barriers in **1** (~17.7 kcal/mol) and **2** (~25 kcal/mol) and also identify a sizeable rotational barrier to aryl-aryl group rotation (~16.5 kcal/mol). The energetics of the *E* conformer is comparable to that of *Z* in **1** but not in **2**, and this may underpin the difference in binding affinities to PBR.



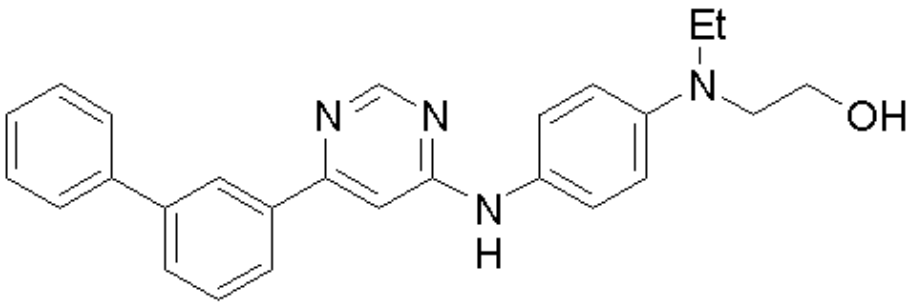
1, R = Me
2, R = H

MEDI 39

Aminopyrimidines as neuroprotective agents

Tina Morgan Ross[1]*, Robert Zivin*[2]*, Paul Burnett*[3]*, Malcolm K. Scott*[2]*, Elfrida Grant*[2]*, Douglas E. Brenneman*[4]*, and Allen B. Reitz*[4]*. (1) CNS Research, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, P.O. Box 776, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-4985, tross@prdus.jnj.com, (2) (3) Johnson & Johnson Pharmaceutical Research and Development, L.L.C, (4) Drug Discovery Division, Johnson & Johnson Pharmaceutical Research and Development, L.L.C*

Compound 1 displays neuroprotective activity in the P19 cell line. In order to improve upon solubility and other ADME properties, an analog program around 1 was undertaken employing a microdiverse organic synthesis technology for drug discovery. This involved diversity selection probes around an active drug entity, utilizing rapid synthesis microtube microtiter plate tools, automated purification techniques and evaluation of biological data for quick iteration of the SAR program. A series of 76 derivatives were prepared based upon DIVA CADD analysis. The synthesis of new targets was expedited by the convenient microtiter plate format involving the Aldrich small sample service. Aminopyrimidine 1 was tested in the middle cerebral arterial occlusion (MCAO) model, looking for potentiation of glutamate excitotoxicity.



1

MEDI 39

Aminopyrimidines as neuroprotective agents

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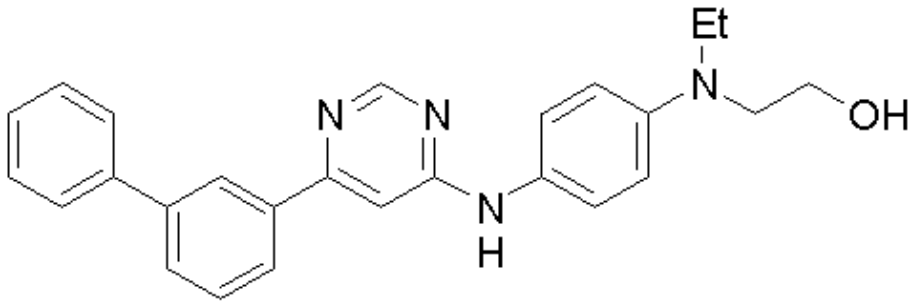


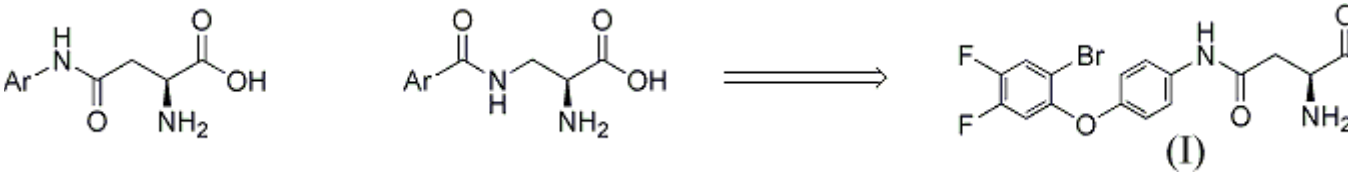
1

MEDI 40

Excitatory amino acid transporters (EAATs): II. Identification of potent and selective EAAT-2 inhibitors

Alexander Greenfield[1]*, Cristina Grosanu*[1]*, John Dunlop*[2]*, Beal McIlvain*[2]*, Tikva Carrick*[2]*, Brian Jow*[2]*, Qiang Lu*[2]*, Dianne Kowal*[2]*, Kristi Fan*[1]*, John P Williams*[3]*, and John A. Butera*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Discovery Neuroscience, Wyeth Research, (3) Department of Medicinal Chemistry, Neurocrine Biosciences*

Excitatory amino acid transporters (EAATs) play an important role in maintaining glutamate homeostasis in the mammalian central nervous system. EAAT2 subtype located in the glia is thought to be responsible for the bulk of the glutamate uptake in forebrain regions. In the course of our studies directed toward the development of selective pharmacological tools for elucidation of the functional role of EAATs, we identified a series of potent EAAT2 blockers. Herein we describe the synthesis and biological activities of aryl-ether, biaryl and fluorene aspartic acid and diaminopropionic acid analogs as potent inhibitors of EAAT2. Compound (I) represents one of the most potent and selective inhibitors of EAAT2 known.



(I)

MEDI 41

Excitatory amino acid transporters (EAATs): I. The search for selective EAAT

modulators

John A. Butera[1], *Alexander Greenfield*[1], *Cristina Grosanu*[1], *John Dunlop*[2], *H. Beal McIlvain*[2], *Tikva Carrick*[2], *Brian Jow*[2], *Qiang Lu*[2], *Dianne Kowal*[2], *and John P Williams*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4129, buteraj@wyeth.com, (2) Discovery Neuroscience, Wyeth Research, (3) Department of Medicinal Chemistry, Neurocrine Biosciences*

Elevated levels (>1 micromolar) of extracellular glutamate concentration have been associated with excitotoxic conditions due to the subsequent activation of ionotropic glutamate receptors. The mammalian transporter EAAT2 (and to a lesser extent, EAAT1) which is expressed in glial cells is thought to be primarily responsible for the high affinity sodium-dependant uptake and clearance of the bulk (>80%) of excess glutamate from the synapse. Thus, enhancement of the EAAT2 transporter should provide a more efficient clearance of glutamate and perhaps limit excitotoxic injury after ischemia. Conversely, selective inhibition of the post-synaptic neuronal human transporter EAAT3, may provide locally increased levels of glutamate in close proximity to metabotropic glutamate receptors resulting in their up-regulation. This may prove beneficial in the treatment disorders involving deficient glutamatergic function such as cognitive disorders and schizophrenia. To probe and test these hypotheses, potent EAATs-subtype selective small molecules are needed as pharmacological tools. To address this need, we chose to run two high-throughput screens in an effort to identify selective modulators of the human transporters EAAT2 and EAAT3. The assays measured effects of the compounds on the uptake of [3H]L-glutamate in several cell lines transfected with EAAT2 or EAAT3. This poster will detail the characterization, development and syntheses of several structural classes of potent and novel EAAT modulators.

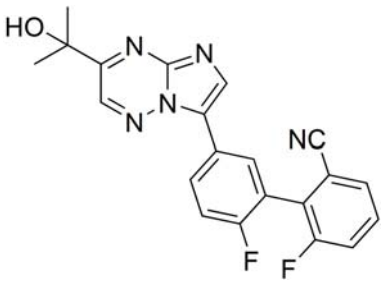
MEDI 42

Discovery and SAR of imidazo[1,2-*b*][1,2,4]triazines as $GABA_A$ $\alpha_{2/3}$ subtype selective agonists for the treatment of anxiety

Michael G. N. Russell, *Robert W. Carling, Leslie J. Street, Richard T. Lewis, Andrew Mitchinson, Andrew S. R. Jennings, Melissa Hinch, John R. Atack, Susan M. Cook, Frances Bromidge, Keith A. Wafford, George R. Marshall, David S. Reynolds, Joanna Stanley, Rachael Lincoln, Spencer Tye, Wayne Sheppard, Bindi Sohal, Andrew Pike, Maria Dominguez, and José L. Castro, The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, United Kingdom, Fax: 44-1279-440390, michael_russell@merck.com*

The $GABA_A$ receptor is a ligand-gated chloride ion channel that has a pentameric structure composed from a family of at least 16 subunits (a_{1-6}, b_{1-3}, g_{1-3}, d, e, p, and q), but comprising generally of two a, two b, and one g subunit. The benzodiazepine (BZ) binding site is an allosteric site located between the a and g subunits. $GABA_A$ receptors containing the a_1 subtype are involved in the sedative effects of BZs whereas the a_2 and/or a_3 subtypes mediate the anxiolytic effects. Therefore, BZ site agonists with selectivity for the $a_{2/3}$ subtypes may be anxiolytics with a potential for reduced side effects. We will describe the identification of a series of imidazo[1,2-*b*][1,2,4]triazines leading to the selection of a clinical candidate, a high

affinity partial agonist at the a_3 subtype and an antagonist at the a_1 subtype, with good bioavailability and long half-life. In animal models it was a non-sedating anxiolytic.



MEDI 43

Neuroprotective effects of EGIS-11229, a 2,3-benzodiazepine type AMPA antagonist

József Barkóczy[1]*, István Ling*[1]*, Gyula Simig*[1]*, Gábor Gigler*[2]*, Annamária Simó*[2]*, Angela Benedek*[2]*, Krisztina Móricz*[2]*, Márta Ágoston*[2]*, Miklós Végh*[2]*, Gábor Kapus*[2]*, Szabolcs Kertész*[2]*, György Lévay*[2]*, László Hársing*[2]*, and Gábor Szénási*[2]*. (1) Chemical Research Division, EGIS Pharmaceuticals, Keresztúri u 30-38, 1106 Budapest, Hungary, Fax: 361-265-5613, barkoczy.jozsef@egis.hu, (2) Preclinical Department, EGIS Pharmaceuticals*

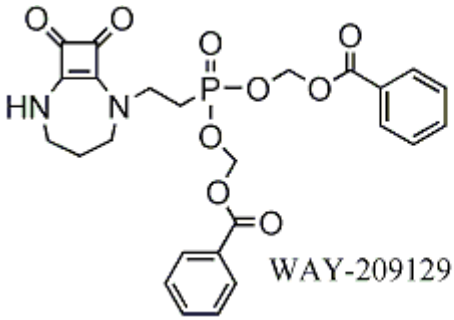
Our synthetic efforts to improve metabolic stability of 2,3-benzodiazepine type non-competitive AMPA receptor antagonists led to the derivative EGIS-11229. Introducing a methyl group ortho to the amino group on the aniline moiety enhanced efficacy, and hindered acetylation of the amino group resulting in outstanding metabolic stability and long duration of action. EGIS-11229 inhibited AMPA currents in rat telencephalon neurones (IC_{50}=1.6 μM) *in vitro*. In global ischaemia models, EGIS-11229 decreased neuronal death in the CA1 area of the hippocampus by 47 % at 20 mg/kg i.p. in gerbils, and by 58 % at 5 mg/kg i.p. in rats at 4 day after bilateral carotid occlusion. In a permanent focal cerebral ischaemia test in rats, EGIS-11229 markedly reduced cerebral infarct volume from the dose of 0.3 mg/kg i.p. In conclusion, EGIS-11229 is a highly active non-competitive AMPA antagonist that may be suitable for the treatment of ischaemic stroke and neurodegenerative disorders.

MEDI 44

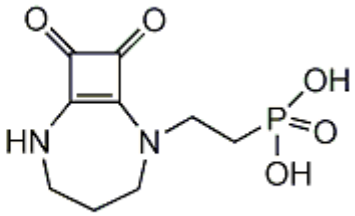
Derivatives to improve the oral bioavailability and subsequent plasma and brain levels of [2-(8,9-dioxo-2,6-diaza-bicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonic acid (EAA-090, perzinfotel), a competitive NMDA antagonist

Reinhardt B. Baudy[1]*, John A. Butera*[1]*, Jean Sze*[1]*, Hong Chen*[1]*, Uday Jain*[1]*, Matthew Hoffmann*[2]*, Michael K. May*[2]*, and Michael R. Brandt*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, baudyr@wyeth.com, (2) Drug Safety and Metabolism, Wyeth Research, (3) Neuroscience, Wyeth Research*

EAA-090 (perzinfotel) is a potent competitive NMDA antagonist displaying low oral bioavailability in rats. Derivatives were examined to improve the oral bioavailability. Several oxymethylene-spaced diesters of EAA-090 were prepared and their stability was tested in rat whole blood and rat plasma. WAY-209129 demonstrated desirable kinetics in its 2-step conversion to EAA-090 via the monoester, with the t ½ for the appearance of EAA-090 being slightly longer in rat whole blood (1.29 hr) compared to rat plasma (0.87 hr). Administration of a 10 mg/kg p.o. dose of [14C]-labeled WAY-209129 to rats resulted in significantly higher concentrations of EAA-090 in plasma (7.4-fold) and brain (5.4-fold), compared to a 30 mg/kg p.o. dose of [14C]-EAA-090 itself. These data indicate that the derivatives resulted in superior bioavailability for EAA-090.



WAY-209129



EAA-090

MEDI 45

Pharmacokinetic and pharmacodyamic effects of an oxymethylene-spaced diphenylester derivative of perzinfotel (EAA-090: [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0] non-1(7)-en-2-yl)-ethyl]phosphonic acid) in inflammatory and neuropathic pain models

Reinhardt B. Baudy[1]*, Hong Chen*[1]*, Uday Jain*[1]*, Christine Huselton*[2]*, Cheryl Mugford*[1]*, Rana Ramdass*[2]*, Hamza Kandoussi*[2]*, Michael R. Brandt*[3]*, and Jeffrey D. Kennedy*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, baudyr@wyeth.com, (2) Drug Safety and Metabolism, Wyeth Research, (3) Neuroscience, Wyeth Research*

Perzinfotel (EAA-090)is a selective, competitive NMDA receptor antagonist with high affinity for the glutamate site. Previous studies have demonstrated that perzinfotel is efficacious in a variety of inflammatory and neuropathic pain models. However, perzinfotel has low oral bioavailability. To increase the oral activity of perzinfotel, an oxymethylene-spaced diphenylester derivative (1) of perzinfotel was synthesized and evaluated in in vitro assays of stability/activity and in vivo tests of oral activity. In vitro, compound 1 was relatively stable in buffers from pH 1.0 to pH 7.4, as well as in simulated gastric fluid but demonstrated considerable conversion in pH 8.5 buffer and simulated intestinal fluid (degradation after 4 h was 78% and 57%, respectively). In rat plasma, compound 1 was rapidly converted in the first step to the intermediate (K1 >10), and then converted to parent compound perzinfotel at a moderate rate (K2=0.85). In binding assays, both compound 1 and the intermediate had low affinity for the NMDA receptor (4.2 and 17 mM, respectively) compared to perzinfotel (37 nM). Pharmacokinetic studies indicated that the systemic exposure (AUC) of perzinfotel produced by a single oral dose of 10 mg/kg compound 1 was 2.5-fold greater than that produced by a single oral dose of 30 mg/kg perzinfotel. Consistent with these results, compound 1 displayed an apparent potency and duration of action significantly greater than perzinfotel after oral

administration in pain models. These results demonstrate that an oxymethylene-spaced diphenylester derivative of perzinfotel increases the oral activity of perzinfotel while maintaining efficacy in models of inflammatory and neuropathic pain.

MEDI 46

Synthesis and discovery 3-amino piperidine and pyrolidine-based inhibitors of neurotransmitter re-uptake transporters

*Manuel Cases[1], **John J. Masters**[2], Louise Haughton[1], Gordon Campbell[1], Teresa Mann[1], Helene Rudyk[1], Magnus W. Walter[1], Graham Timms[1], Jeremy Gilmore[1], David R. Dobson[1], Craig White[1], John R. Boot[1], Jeremy D. Findlay[1], Lorna Hayhurst[1], Ann Helene Kluge[1], Sivi Mahadevan[3], Francoise J. Brunelle[3], Claude L. Delatour[3], Annie A. Lavis[3], Kenneth W. Perry[2], Frank P. Bymaster[2], Linda Thompson[2], and Susan Hemrick-Luecke[2]. (1) Eli Lilly and Company Ltd, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU206PH, United Kingdom, (2) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, jjm@lilly.com, (3) Lilly Development Centre*

Advances in the clinical treatment of neurological disorders have been accomplished by the use of drugs that inhibit neurotransmitter re-uptake transporter function. Small molecule inhibitors that are selective for the serotonin transporter (5HT) have been used for several years as effective treatments for depression. Selective inhibitors of the norepinephrine transporter (NET) are also effective in the treatment of both depression and attention deficit hyperactivity disorders (ADHD). Small molecules that display various in vitro selectivities for inhibition of neurotransmitter re-uptake transporters, including the dopamine transporter (DAT), have also been used as effective therapeutics. In this poster, we present the structure activity relationships for a select group of novel 3-amino piperidine and pyrollidine-based inhibitors of neurotransmitter re-uptake transporters. The synthetic routes, binding affinities and selectivity to the transporters (5HT, NET, DAT) in vitro will be presented. Small animal pharmacokinetic and pharmacodynamic profiles for select molecules in vivo will also be disclosed.

MEDI 47

Discovery of novel (2,4,5)-trisubstituted asymmetric pyran derivatives exhibiting selective affinity for the norepinephrine transporter: Importance of regioselectivity and stereoselectivity in binding activity, Part-I

*Shijun Zhang[1], Juan Zhen[2], Maarten Reith[2], and **Aloke K Dutta**[1]. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, Fax: 313-577-2033, adutta@wayne.edu, (2) Department of Psychiatry, New York University School of Medicine*

In our effort to design and discover novel non-tropane based molecules for developing pharmacotherapies for cocaine addiction, we recently have embarked on development of 3,6-disubstituted pyran derivatives targeting monoamine transporter systems. These pyran analogs are the bioisosteric versions of our earlier structurally constrained cis-3,6-disubstituted piperidine derivatives which exhibited potent and selective affinities towards DAT in a stereo-selective manner. Our recent work in pyran series of compounds yielded results which

indicated that the mode of interactions of these pyran molecules with the monoamine transporters may well be different from their piperidine counterparts. In general, we have noted a slight reduction of affinity in these pyran derivatives for the DAT compared to their piperidine counterparts. In this regard, we have also demonstrated that the cis-3,6-disubstituted pyran derivatives actually represent pharmacophoric structures for DAT interaction as either cis- or trans-2,4-disubstituted and trans-3,6-disubstituted compounds were much weaker at DAT. In our further effort to elaborate on the structure of 3,6-disubstituted pyran molecule, novel (2, 4, 5)-trisubstituted pyran derivatives were designed and synthesized. Efficient asymmetric syntheses were carried out to synthesize both the enantiomers and their geometric isomers. Higher potency and selectivity was observed in the (-)-isomer for monoamine transporters. Regioselectivity in binding activity was also observed in these compounds. Detailed synthesis procedure and biological characterization will be presented. Supported by DA 12449 (AKD).

MEDI 47

Discovery of novel (2,4,5)-trisubstituted asymmetric pyran derivatives exhibiting selective affinity for the norepinephrine transporter: Importance of regioselectivity and stereoselectivity in binding activity, Part-I

*Shijun Zhang[1], Juan Zhen[2], Maarten Reith[2], and **Aloke K Dutta**[1]. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, Fax: 313-577-2033, adutta@wayne.edu, (2) Department of Psychiatry, New York University School of Medicine*

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MEDI 48

Further structural exploration of novel (2,4,5)-trisubstituted asymmetric pyran derivatives: Exploration of different N-benzyl substitutions on activity for monoamine transporters, Part-II

Shijun Zhang[1]***, Fernando Fernandez***[1]*, Juan Zhen*[2]*, Maarten Reith*[2]*, and Aloke K Dutta*[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, Fax: 313-577-2033, (2) Department of Psychiatry, New York University School of Medicine*

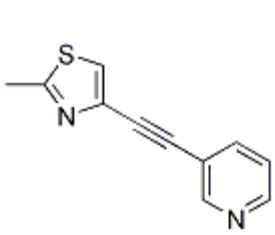
Following our preliminary results, a more elaborate structure activity relationship study was carried out with novel (2,4,5)-trisubstituted pyran template to delineate molecular determinants required for interaction with the binding domains on monoamine transporters. Different N-benzylic substitutions were introduced in order to evaluate influence of electronic and steric factors on potency and selectivity. All the designed analogues were prepared by following asymmetric synthesis pathway which was established by us. Both enantiomers were synthesized to evaluate stereo-selectivity in binding interaction. The results indicated that the presence of a hydroxyl group on pyran ring contributed towards additional interaction with both SERT and NET when the effect was more prominent with NET. This could be due to the formation of a H-bond between the hydroxyl group and the monoamine transporter. Stereochemistry of the hydroxyl group, however, was important for such interaction, as the potency of these compounds for monoamine transporter was enantioselective. Detailed description of analogues design and biological results will be described. Supported by DA 12449 (AKD).

MEDI 49

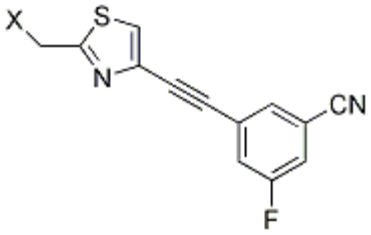
Synthesis of an easily ^{18}F-labeled and high affinity candidate radioligand for PET imaging of brain mGluR5 receptors

Fabrice G. Siméon*, Velvet M. Patterson, Frederick T. Chin, Robert B. Innis, and Victor W. Pike, Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Rm B3 C346A, 10 Center Drive, Bethesda, MD 20892, Fax: 301-480-5112, simeonf@mail.nih.gov*

MTEP (**1**) has provided a lead for some promising radioligands for imaging human brain mGluR5 receptors with positron emission tomography (PET) *in vivo*. Easily ^{18}F-labeled ligands are still however sought for this purpose. We have developed a strategy for labeling in a fluoromethyl group at the 2-position of the 1,3-thiazole ring. Target fluoro compound (**2**) was prepared in 3 steps via 4-(trimethylsilyl-ethynyl)-2-fluoromethyl-1,3-thiazole (TFT) and bromo analog (**3**) in 8 steps. **2** was found to have an IC_{50} of 26 pM. Treatment of **3** with [^{18}F]fluoride ion gave [^{18}F]**2** in high radiochemical yield under mild conditions (MeCN, 80^{0}C, 20 min) for evaluation as a PET radioligand. Labeling at the 2-position of the 1,3-thiazole ring opens up the possibility to explore multiple variations in the substitution pattern of the phenyl ring in a search for effective PET radioligands. TFT may serve as a key synthon for the generic syntheses of many such ligands.



(1)



2, X = F
3, X = Br

MEDI 50

Discovery and biological profile of a new class of metabotropic receptor 1 allosteric antagonist

Satoru Itoh, *Atsushi Satoh, Yasushi Nagatomi, Yukari Hirata, Gentaroh Suzuki, Toshifumi Kimura, Akio Satow, Mikiko Hata, Hiroshi Kawamoto, and Hisashi Ohta, Tsukuba Research Institute, Banyu Pharmaceutical Co, Ltd, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan, Fax: 81-29-877-2029*

A glutamate is one of major excitatory neurotransmitter in the central nervous system and it acts on ionotropic glutamate receptors such as NMDA and non-NMDA receptors and on G-protein coupled metabotropic glutamate receptors (mGluRs). mGluRs are considered to be drug targets to modulate glutamate transmission for treatment of various neurological and psychiatric diseases including pain, ischemic damage and anxiety. We have recently identified a series of 4-(1-Aryltriazol-4-yl)-tetrahydropyridines as a novel allosteric mGluR1 antagonist. Among the optimal compounds, the urea analog demonstrated low nanomolar antagonistic activity against human mGluR receptors expressed in CHO cells and exhibited in vivo antagonistic effect in rodents. The SAR and biological profile of this series will be presented.

MEDI 51

Design and synthesis of novel mGluR5 antagonists

Santosh S Kulkarni[1], *Barbara Nightingale*[2], *Christina M. Dersch*[2], *Richard B. Rothman*[2], *and Amy Hauck Newman*[1]. *(1) Medicinal Chemistry Section, NIDA-IRP, NIH, DHHS, 5500 Nathan Shock Drive, Baltimore, MD 21224, Fax: 410-550-6855, Skulkami@intra.nida.nih.gov, (2) Clinical Psychopharmacology Section, NIDA-IRP, NIH, DHHS*

The metabotropic glutamate receptor 5 (mGluR5) is a Group I excitatory amino acid receptor of the neurotransmitter glutamate. It is located postsynaptically in the cortex, hippocampus, caudate-putamen and nucleus accumbens. Recently, the mGluR5 has been implicated in the mediation of locomotor stimulant effects and self-administration of cocaine, using the antagonist MPEP or a mutant mGluR5 mouse model. Thus the discovery of selective and bioavailable mGluR5 antagonists has been targeted as a non-dopaminergic strategy toward the discovery of medications to treat cocaine-abuse. Our initial attempts to design novel mGluR5 antagonists were based on a preliminary ligand binding hypothesis at the transmembrane domain of the receptor protein. The systematic variation of the

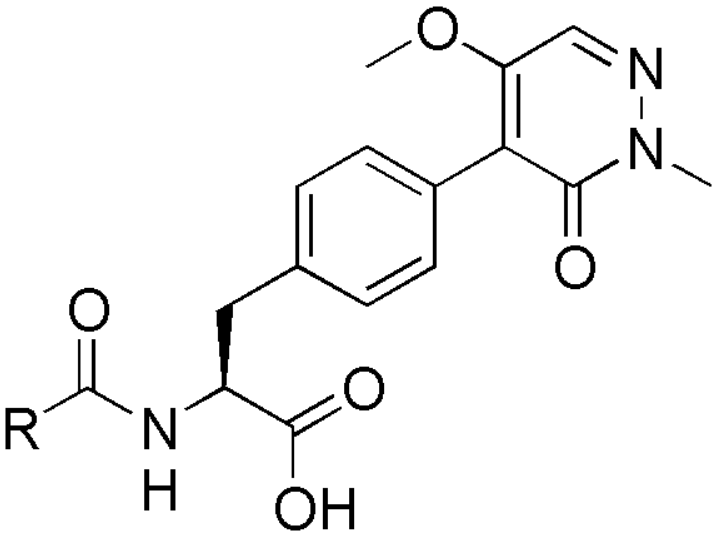
pharmacophoric groups lead to identification of a novel series of benzamide analogues. The initial lead compound demonstrated micromolar affinity at the mGluR5. However, further optimization of this compound has identified compounds with improved binding affinities and antagonist profiles, in vitro. Structure-activity relationships, molecular modeling and pharmacological evaluation of these compounds will be presented.

MEDI 52

Pyridazinone derived phenylalanine amides as alpha4 integrin antagonists

Yong Gong[1], *Joseph K. Barbay*[1], *Alexey B. Dyatkin*[1], *Tamara A. Miskowski*[2], *Edward S. Kimball*[1], *Stephen M. Prouty*[1], *M. Carolyn Fisher*[1], *Rosemary Santulli*[1], *Craig R. Schneider*[1], *Nathaniel H. Wallace*[1], *John A. Masucci*[1], *William E. Hageman*[1], *Scott Ballentine*[1], *Dennis J. Hlasta*[1], *Pamela J. Hornby*[2], *and Wei He*[2]. *(1) Drug Discovery, Johnson and Johnson Pharmaceutical R&D, L.L.C, Welsh and McKean Roads, P.O. Box 0776, Spring House, PA 19477, ygong@prdus.jnj.com, (2) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C*

Integrin receptors alpha4beta1 and alpha4beta7 play an essential role in cell adhesion and cell trafficking via their interactions with vascular cell adhesion molecule 1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Inhibition of such interactions might provide new treatments for inflammatory and autoimmune diseases. A series of pyridazinone-functionalized phenylalanine amides has been prepared and evaluated for inhibition of cellular adhesion mediated by the alpha4beta1/VCAM-1 and alpha4beta7/MAdCAM-1 interactions. Potent dual antagonists of alpha4beta1 and alpha4beta7 were generated. The pharmacokinetic properties of selected compounds have been determined in rats. The use of ester prodrugs can lead to improved oral bioavailability. Data from in vivo leukocytosis studies will also be presented.

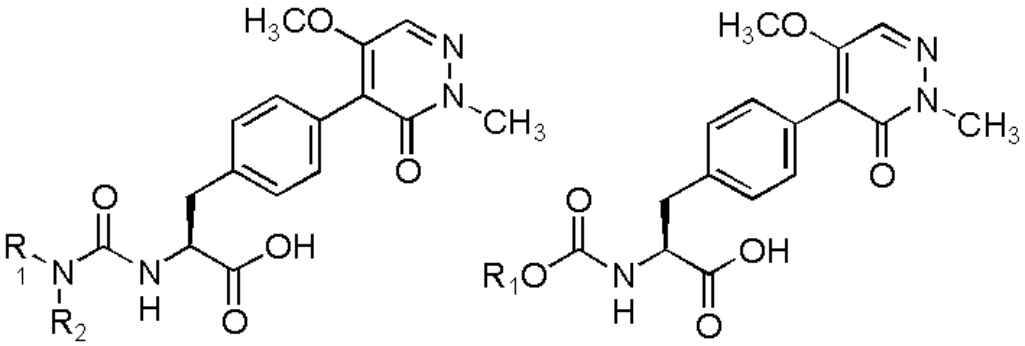


MEDI 53

N-Ureido and N-carbamido pyridazinone-functionalized phenylalanines as alpha4beta7 integrin antagonists

Joseph K. Barbay[1], *Yong Gong*[1], *Alexey B. Dyatkin*[1], *Tamara A. Miskowski*[2], *Edward S. Kimball*[1], *Stephen M. Prouty*[1], *M. Carolyn Fisher*[1], *Rosemary Santulli*[1], *Craig R. Schneider*[1], *Nathaniel H. Wallace*[1], *William E. Hageman*[1], *John A. Masucci*[1], *Scott Ballentine*[1], *Dennis J. Hlasta*[1], *Pamela J. Hornby*[2], *and Wei He*[3]. *(1) Drug Discovery, Johnson and Johnson Pharmaceutical R&D, L.L.C, Welsh and McKean Roads, P.O. Box 0776, Spring House, PA 19477, Fax: 215-628-3297, kbarbay@prdus.jnj.com, (2) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, (3) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C*

The alpha4 integrin family consists of the heterodimeric transmembrane proteins alpha4beta1 and alpha4beta7, which are expressed on the surface of leukocytes. Through interaction with endothelial cell surface proteins (e.g. VCAM-1 and MAdCAM-1), these integrins are involved in the recruitment of leukocytes to sites of inflammation; antagonists of alpha4 integrins have therapeutic potential as anti-inflammatory agents. The synthesis and biological activity of a series of pyridazinone-modified phenylalanine analogs based on urea and carbamate scaffolds will be described. These antagonists display selective inhibition of alpha4beta7/MAdCAM-1 versus alpha4beta1/VCAM-1 mediated cellular adhesion. Pharmacokinetic properties of selected antagonists, dosed as carboxylic acids or as ester pro-drugs, have been determined. A member of the series demonstrated activity upon oral administration (60 mg/kg, bid) in the dextran sodium sulfate colitis model in mice.



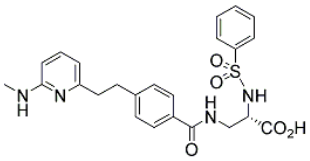
MEDI 54

Synthesis and biological studies of an integrin alpha-v-beta,5 guided therapeutic

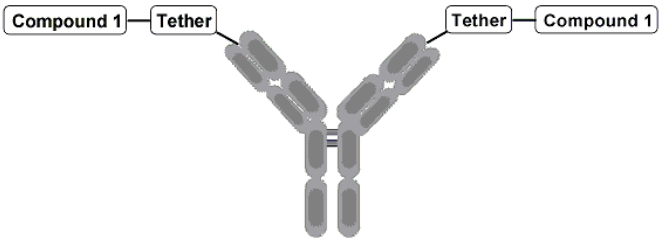
Amir P. Tamiz[1], *David C. Griffith*[1], *Teresa Aja*[1], *Lingna Li*[1], *Fang Liao*[1], *Krishnan Subbiah*[1], *Michael Whiney*[1], *Miriah Leclerc*[1], *Curt Bradshaw*[1], *Rodney Lappe*[1], *Sanjib Das*[2], *Subhash C. Sinha*[2], *and Carlos F. Barbas III*[2]. *(1) Chemistry, CovX Research LLC, 9381 Judicial Drive Suite 200, San Diego, CA 92121, Fax: 858-964-2090, (2) The Scripps Research Institute*

Synthesis and biological studies of an aVb3,5 integrin Guided Therapeutic are described. The Guided Therapeutic was prepared by covalently attaching a chemically modified aVb3,5 specific small molecule to the two reactive binding sites of an antibody via a novel tether. We compared the receptor binding activity and the efficacy, in a tumor xenograft model, of the

small molecule antagonist (Compound 1), and the integrin Guided Therapeutic antagonist (compound 2). Compound 2 exhibited improved potency in a receptor binding assay when compared to Compound 1 (Ki = 1.0 nM and 15 nM respectively) and significantly inhibited tumor growth at 800-fold lower dose in a xenograft model using the human ovarian cancer cell line OVCAR-5.



Compound 1



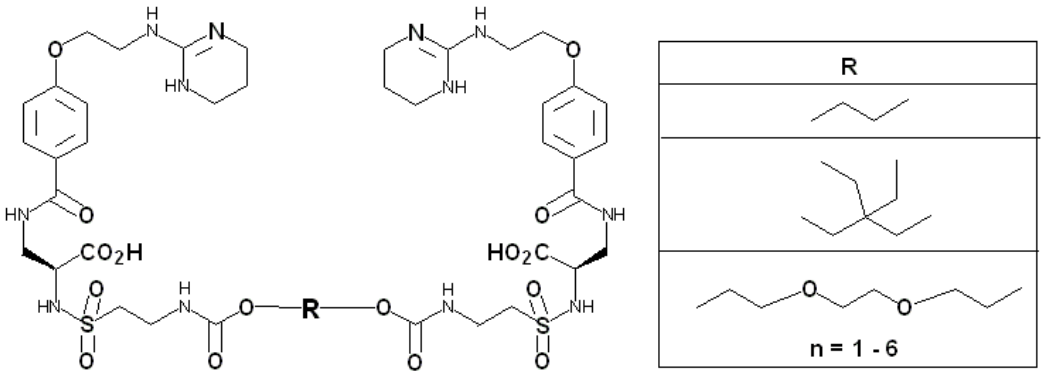
Compound 2
Guided Therapeutic

MEDI 55

Novel bivalent integrin antagonist compounds

Anand Francis[1]*, Christopher A. Burnett*[1]*, Zhimin Shen*[2]*, King C. P. Li*[1]*, and Narasimhan Danthi*[1]*. (1) Molecular Imaging Laboratory, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, Fax: 301-435-2714, ndanthi@cc.nih.gov, (2) Vaccine Research Center, National Institute of Allergy and Infectious Diseases*

The $\alpha_v\beta_3$ receptor is a heterodimeric transmembrane receptor protein that has important roles in cell-cell and cell-matrix interactions. In cancer, osteoporosis and several other diseases, $\alpha_v\beta_3$ is shown to be involved in angiogenesis and tissue restructuring. Due to the upregulation of $\alpha_v\beta_3$ in tumor angiogenesis, it is often targeted for imaging and therapy. Multivalency is an important concept that is emerging in drug discovery research. In this paper we describe the design and synthesis of several bivalent integrin $\alpha_v\beta_3$ antagonists. In the $\alpha_v\beta_3$ plate binding assay, compounds with long linkers (R) showed higher affinity compared to the compounds with shorter linkers or the monomeric compound.

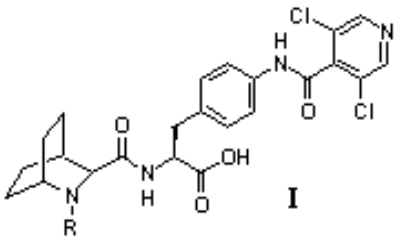


MEDI 56

Phenylalanine amide derivatives as alpha4 integrin antagonists

Tamara A. Miskowski[1], *Alexey B. Dyatkin*[2], *Yong Gong*[2], *Joseph K. Barbay*[2], *M. Carolyn Fisher*[2], *Edward S. Kimball*[2], *Rosemary Santulli*[2], *Craig R. Schneider*[2], *Nathaniel H. Wallace*[2], *Scott Ballentine*[2], *Dennis J. Hlasta*[2], *Pamela J. Hornby*[2], *and Wei He*[3]. *(1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, Welsh & McKean Roads, P.O. Box 0776, Spring House, PA 19477, tmiskows@prdus.jnj.com, (2) Drug Discovery, Johnson and Johnson Pharmaceutical R&D, L.L.C, (3) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C*

Integrin receptors α4β1 and α4β7 are key regulators of physiologic and pathologic responses in inflammation and autoimmune disease. They play an essential role in cell adhesion and cell trafficking via their interactions with vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). We recently presented a series of N-substituted [2.2.2]azabicyclo phenylalanine carboxamide derivatives (**I**). Several modifications of this series have resulted in discovery of new series of pyridazinone derivatives (**II**). These derivatives have been prepared and evaluated for inhibition of cellular adhesion mediated by the α4β1/VCAM-1 and α4β7/MAdCAM-1 interactions. Many of these compounds exhibited selectivity for α4β7/MAdCAM-1. Inhibition of this interaction may be beneficial in the treatment of inflammatory bowel diseases such as Crohn's disease. The structure activity relationships of this novel series of compounds will be presented.



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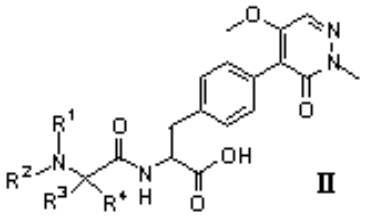

II

MEDI 56

Phenylalanine amide derivatives as alpha4 integrin antagonists

Tamara A. Miskowski[1], *Alexey B. Dyatkin*[2], *Yong Gong*[2], *Joseph K. Barbay*[2], *M. Carolyn Fisher*[2], *Edward S. Kimball*[2], *Rosemary Santulli*[2], *Craig R. Schneider*[2], *Nathaniel H. Wallace*[2], *Scott Ballentine*[2], *Dennis J. Hlasta*[2], *Pamela J. Hornby*[2], *and Wei He*[3]. *(1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, Welsh & McKean Roads, P.O. Box 0776, Spring House, PA 19477, tmiskows@prdus.jnj.com, (2) Drug Discovery, Johnson and Johnson Pharmaceutical R&D, L.L.C, (3) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C*

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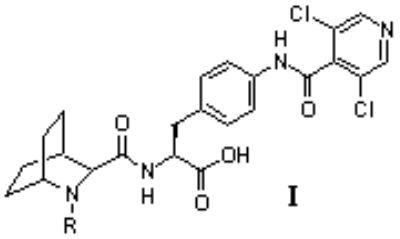

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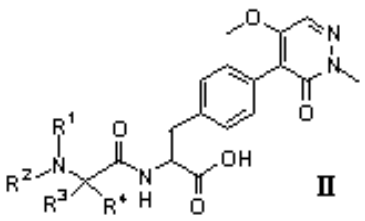


II

MEDI 57

Novel small-molecule antagonists of the chemokine receptor CXCR3

Marc-Raleigh Brescia[1]*, Andrew G. Cole*[1]*, Ilana L. Stroke*[2]*, Christopher Haskell*[3]*, Sofia Ribeiro*[3]*, Srilatha Simhadri*[2]*, Joan J. Zhang*[1]*, Zahid Hussain*[1]*, Kenneth C. Appell*[2]*, Ian Henderson*[1]*, and Maria L. Webb*[2]*. (1) Department of Chemistry, Pharmacopeia Drug Discovery, Inc, P.O. Box 5350, Princeton, NJ 08543, Fax: 609-655-4187, mbrescia@pharmacop.com, (2) Department of Biology, Pharmacopeia Drug Discovery, Inc, (3) Department of Immunology, Berlex Biosciences*

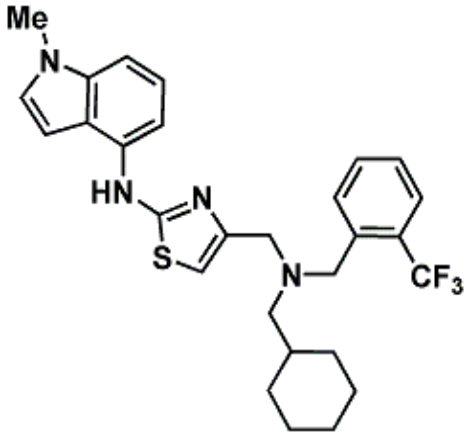
The natural chemokine ligands for the chemokine receptor CXCR3 are thought to play a key role in directing activated T-cells to sites of inflammation. Inhibition of CXCR3 function has been implicated in the treatment of a number of disorders relating to T-cell mediated function, including inflammatory bowel disease, rheumatoid arthritis and diabetes. We describe the identification of novel small-molecule antagonists of CXCR3 from a ~24,000-member ECLiPs™ library employing a cell-based, dual agonist/antagonist high-throughput screen. The SAR was subsequently investigated and resulted in functional antagonist potencies of approximately 60 nM as determined by monitoring the reduction in I-TAC (interferon-inducible T-cell α chemoattractant/CXCL11)-stimulated calcium release for a cell line over-expressing human CXCR3.

MEDI 58

Discovery and optimization of 2-aminothiazole derivatives as CCR4 antagonists

Xuemei Wang[1]*, Feng Xu*[1]*, Qingge Xu*[1]*, Hossen Mahmud*[1]*, Jonathan Houze*[2]*, Liusheng Zhu*[1]*, Michelle Akerman*[1]*, George Tonn*[1]*, Liang Tang*[1]*, Daniel J. Dairaghi*[3]*, Tassie L Collins*[1]*, and Julio C. Medina*[1]*. (1) Amgen SF, 1120 Veterans Boulevard, South San Francisco, CA 94080, (2) Medicinal Chemistry, Amgen San Francisco, (3) ChemoCentryx Inc*

CCR4 is a chemokine receptor preferentially expressed on Th2 cells and plays a major role in the infiltration of T cells into inflamed tissues. CCR4 and its ligands, TARC and MDC, are found in increased levels in patients with asthma and atopic dermatitis. Therefore, it has been suggested that CCR4 inhibitors may represent a novel approach to the treatment of these and other immune disorders mediated by Th2 cells. In this study, a series of 2-aminothiazole derivatives was optimized for increased CCR4 antagonistic activity and pharmacokinetic properties. We will report on the discovery of a series of orally bioavailable, highly potent CCR4 antagonists with improved pharmacokinetic properties.



MEDI 59

Design, synthesis and structure-activity relationship studies of novel 4,4-disubstituted piperidine based CCR5 antagonists as anti-HIV-1 agents

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HIV/AIDS continues to be a threat to global public healthcare. While current anti-HIV therapies result in a dramatic increase in life expectancy of HIV patients, new drugs are needed to further address issues such as the emergence of resistant HIV-1 strains, long-term treatment side effects and improvement in therapy compliance. With the discovery that chemokine receptors are gates for HIV-1 entry into the host cell, design and development of CCR5 chemokine receptor antagonists as anti-HIV-1 agents has been actively pursued in the pharmaceutical industry. Recent success of several small molecules in clinical trials further supports the role of CCR5-based therapies as the next generation of anti-HIV medicines.

Our laboratories have recently discovered a novel class of 4,4-disubstituted piperidine based CCR5 antagonists. Herein will be described the synthesis and structure-activity relationship studies of these derivatives, leading to highly potent antagonists with improved pharmacokinetics and acceptable secondary pharmacology profiles.

MEDI 60

Mechanistic studies of novel voltage-gated sodium channel blockers as inhibitors of prostate cancer

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The recent discovery of neuronal-type voltage-gated sodium channel (VGSC) expression in human prostate cancer (PCa) cells combined with the implicated mitogenic role of the transient cellular influx of sodium ions, led us to mechanistically investigate the potential use of VGSC-blockers as inhibitors of PCa *in vitro*. From a ligand based discovery platform, two structural classes were designed and synthesized. Compounds were evaluated by direct displacement of [^{3}H]-BTX from synaptosomes for binding and electrophysiologically assessed using $Na_V1.5$ for functional block. Assaying these VGSC-blockers across a panel of androgen-dependent and androgen-independent PCa cell lines for proliferation inhibition identified several novel inhibitors. These small molecule VGSC-blockers were further investigated for effects on viability, invasion, apoptosis, and effects on PSA secretion in a manner to elucidate the role of the VGSC in PCa growth and metastasis. The data accumulated from these studies supports the use of VGSC blockers as a strategy targeting human PCa.

MEDI 60

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MEDI 61

Chemical evolution of tricyclic antidepressants into novel monocyclic amines with potent sodium channel activity

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Investigation of tricyclic antidepressants as sodium channel blockers has recently shown increasing interest within the field of pain therapeutics. The demand for a highly effective treatment of chronic pain, without the cardiotoxicities associated with most, has led us to further pursue this area. Herein, we show our findings from a comprehensive structure activity relationship of analogues based upon amitriptyline, a known tricyclic antidepressant. Thus far our lead compound, containing a monocyclic amine structure, shows 94.6% functional block of sodium channels at 10 μM concentration, which is a three-fold increase in current block in comparison to amitriptyline. Both binding assay using [^{3}H]-BTX and electrophysiological methods were carried out to evaluate these analogues. From our SAR,we have also established that the tricyclic motif is unnecessary for activity and modification of the amine portion is detrimental to block.

MEDI 62

Disjunctive approaches towards new steroidal sodium channel blockers based on a cholic acid scaffold

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Batrachotoxin (BTX) is a neurotoxin isolated from the skin of Phyllobates terribilis or Colombian poison dart frog. BTX is a known inhibitor of the neuronal voltage-gated sodium channel (NVSC). The focus of this project involves using a disjunctive approach on BTX in an effort to identify novel synthetic small molecules that inhibit NVSC's. With this goal in mind, we embarked upon the synthesis of molecules containing the steroidal BTX core starting from commercially available cholic acid. In a direct displacement assay we found that methyl cholate displaced 43% of the tritiated BTX from site two of the NVSC at a concentration of 40 μM, and blocked 20% of sodium current in Nav 1.2 NVSC at a concentration of 30 μM. These findings led us to synthesize other cholic acid derivatives and evaluate their ability to inhibit NVSC's.

MEDI 63

Comparative molecular field analysis and synthesis of novel sodium channel blockers from a combined phenytoin-lidocaine pharmacophore

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The voltage gated sodium channel remains a rich area for the development of novel blockers. In this study we used comparative molecular field analysis (CoMFA), to generate a 3-D model based upon local anesthetics, hydantoins, and α-hydroxyphenylamides. Correlation by partial least squares (PLS) analysis of in vitro sodium channel binding activity (expressed as log IC_{50}) and the CoMFA descriptor column generated a final non-cross-validated model with R^2 = 0.926 for the training set. The CoMFA steric and electrostatic maps described a binding site predominately hydrophobic in nature. Using this model, we designed and predict the sodium channel binding activity for a series of novel sodium channel blockers that utilized overlapping structural features of phenytoin, hydroxy amides, and the local anesthetic lidocaine. Synthesis and subsequent sodium channel evaluation of compound **37** (predicted tritiated H-BTX IC_{50} = 7 μM, actual IC_{50} = 6 μM) confirmed the accuracy of our model. Finally, patch clamp electrophysiology was used to establish that these compounds are novel inhibitors of sodium channel current.

MEDI 64

Identification and characterization of small molecule modulators of KChIP/Kv4 function

Lynne P. Greenblatt[1], *Mark Bowlby[2], Pranab Chanda[2], Wade Edris[2], Joe Hinson[2], Flora Jow[2], Alan Katz[1], Girija Krishnamurthy[1], Keith Pitts[1], Kevin Ryan[2], and Howard Zhang[2]. (1) Chemical and Screening Sciences, Wyeth Research, CN-8000, Princeton, NJ 08543, Fax: 732-274-4850, greenbl1@wyeth.com, (2) Discovery Neuroscience, Wyeth Research, Princeton*

Potassium channels and their associated subunits are important contributors to electrical excitability in many cells types. In this study a yeast two-hybrid assay was used to identify inhibitors such as a diaryl-urea (Compound 1) that binds to and modulates the formation of the Kv4/KChIP complex. Compound 1 altered the apparent affinity of KChIP1 to Kv4.3-N in a Biacore® assay, but did not dissociate the two proteins in size-exclusion chromatography experiments. Kv4.2/KChIP1 current amplitude and kinetics were altered with compound exposure, supporting the hypothesis of a compound induced conformational change in the protein complex. Fluorescence spectroscopy of a unique tryptophan residue in KChIP1 was consistent with compound binding in a small hydrophobic cleft of KChIP1. Molecular modeling using the KChIP1 crystal structure indicates that compound binding may occur in the small tryptophan-containing binding pocket located on the hydrophilic side of the protein.

MEDI 65

Structure-activity relationship studies on diaminopyrimidines as growth hormone secretagogue receptor (GHS-R) antagonists

Bo Liu[1], *Gang Liu*[2], *Mei Liu*[2], *Zhili Xin*[2], *Hongyu Zhao*[3], *Michael D. Serby*[3], *Christi Kosogof*[3], *Lissa T.J. Nelson*[4], *Bruce G. Szczepankiewicz*[2], *Wiweka Kaszubska*[2], *Verlyn G. Schaefer*[3], *Douglas H. Falls*[3], *Christine A. Collins*[3], *and Hing L. Sham*[3]. *(1) Metabolic Disease Research, GPRD, Abbott Laboratories, 100 Abbott Park Road, Dept. R4MC AP10 LL14, Abbott Park, IL 60064, Fax: 847-938-1674, bo.x.liu@abbott.com, (2) Global Pharmaceutical Research and Development, Abbott Laboratories, (3) Global Pharmaceutical Research and Development, Metabolic Disease Research, Abbott Laboratories, (4) R4MC, Global Pharmaceutical R & D, Abbott Laboratories*

Ghrelin, a 28 amino acid peptide, was recently identified in rat stomach as an endogenous ligand for growth hormone secretagogue receptor (GHS-R). Besides being a potent growth hormone secretagogue and regulator of other endocrine functions, ghrelin is also implicated in the short- and long-term regulation of energy balance. A selective small molecule GHS-R antagonist can potentially lead to reduced food intake, decreased adiposity, and body weight reduction in humans.

Recently, we reported the discovery of novel isoxazole and tetralin carboxamides as GHS-R antagonists. Continuing the pursuit of additional potent and selective GHS-R antagonists, we identified from HTS a diaminopyrimidine compound as a pure, competitive GHS-R antagonist with an IC50 of 660nM in a calcium flux (FLIPR) cellular assay and 75% oral bioavailability in rat. Extensive SAR in 4-position of benzyl group revealed that certain electron withdrawing groups could provide over 40-fold improvement of potency. Further modification of the 6-position of pyrimidine yielded analogs with single-digit nanomolar potency in FLIPR assay. This poster will describe the syntheses and SAR studies of pyrimidine core and 4- and 6-substituents of pyrimidine ring.

MEDI 66

Discovery of potent, selective and orally bioavailable growth hormone secretagogue receptor (Ghs-R) antagonists

Zhili Xin[1], *Michael D. Serby*[2], *Hongyu Zhao*[2], *Mei Liu*[1], *Bo Liu*[3], *Charles W Hutchins*[1], *Kathy Sarris*[1], *Hoff Ethan*[1], *Douglas H Falls*[1], *Christine A. Collins*[4], *Chunwei Lin*[1], *Christopher A Ogiela*[4], *Michael E. Brune*[4], *Gene Bush*[1], *Brian Droz*[1], *Tom Fey*[1], *Vicki Knourek-Segel*[1], *Robin Shapiro*[4], *Peer Jacobson*[1], *David Beno*[1], *Teresa Turner*[1], *Hing L. Sham*[4], *and Gang Liu*[1]. *(1) Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, zhili.xin@abbott.com, (2) Global Pharmaceutical Research and Development, Metabolic Disease Research, Abbott Laboratories, (3) Metabolic Disease Research, GPRD, Abbott Laboratories, (4) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division*

Ghrelin is an octanoylated 28 amino acid peptide produced primarily by the stomach and

released in response to acute or chronic fasting and weight loss. Accumulating data suggests that ghrelin antagonism may result in reduction of food intake, adiposity, and body weight , thus lead to desired effects in anti-obesity therapy. A series of diaminopyrimidine-based ghrelin antagonists was originally identified from high throughput screening. The diaminopyrimidine pharmacophore has been previously reported as dihydrofolate reductase inhibitors with antimalarial and anticancer activities. Dihydrofolate reductase (DHFR) inhibition is known to cause GI toxicity and bloody diarrhea in dogs. The challenges in this series are expected to be achieving more favorable selectivity over DHFR activities. Our efforts have led to the discovery of a number of potent and DHFR selective ghrelin inhibitors with good PK profile. Structure-activity relationship (SAR) studies and in vivo efficacy in food intake and body weight reduction will be reported.

MEDI 67

Diaminopyrimidines as growth hormone secretagogue receptor antagonists

Michael D. Serby[1], *Gang Liu*[1], *Hongyu Zhao*[1], *Bruce G. Szczepankiewicz*[1], *Christi Kosogof*[1], *Wiweka Kaszubska*[2], *Douglas H. Falls*[1], *Verlyn G. Schaefer*[1], *Eugene N. Bush*[1], *Robin Shapiro*[1], *Brian A. Droz*[1], *Victoria E. Knourek-Segel*[1], *Thomas A. Fey*[1], *Michael E. Brune*[1], *David Beno*[1], *Teresa Turner*[1], *Christine A. Collins*[1], *Peer B Jacobson*[1], *and Hing L. Sham*[1]*. (1) Global Pharmaceutical Research and Development, Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, (2) Global Product Development, Serono International S.A*

Ghrelin, a uniquely octanoylated oligopeptide, has been identified as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R). Released mainly in the stomach and also in hypothalamus, ghrelin is believed to be associated with the sensation of hunger and long-term energy homeostasis. A potent and selective small molecule antagonist of GHS-R could have great potential as an anti-obesity drug. A pyrimidine-based screening hit was identified as a functional antagonist of GHS-R (IC50 = 2.1 uM in FLIPR assay). We discovered a potent antagonist with a binding IC50 of 12 nM and a FLIPR IC50 of 170 nM. Although this compound gave a poor oral PK profile, it was used as a proof-of-concept tool in vivo which led to some interesting results. Many other compounds were also discovered to have good potency in our cellular assays. Some of the synthetic chemistry, structure-activity relationships, and in vivo pharmacology will be presented.

MEDI 68

A-784168, a novel TRPV1 receptor antagonist as analgesic agent

Brian S. Brown[1], *Guo Zhu Zheng*[1], *Robert G. Schmidt*[1], *Ryan G. Keddy*[1], *John Robert Koenig*[1], *Tammie K. Jinkerson*[2], *Heath A. McDonald*[1], *Minglei Cui*[2], *Prisca Honore*[1], *Kennan C. Marsh*[3], *John F. Darbyshire*[1], *Carol S. Surowy*[1], *Robert Moreland*[2], *Michael Jarvis*[4], *Connie R. Faltynek*[1], *and* ***Chih-Hung Lee***[5]*. (1) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, (2) Global Pharmaceutical Products Division, Neuroscience Research, Abbott Laboratories, (3)*

Global Pharmaceutical Research & Development, Abbott Laboratories, (4) 4PM, Abbott Laboratory, (5) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Rd., abbott park, IL 60064, Fax: 847-938-0072, lance.lee@abbott.com

The vanilloid receptor TRPV1 is a membrane-bound, non-selective ion channel, which can be activated by a number of noxious stimuli including heat, protons, and ligand agonists such as capsaicin. Activation of TRPV1 results in cation influx, and transmission of the stimuli's nociceptive effects. Data obtained with TRPV1 antagonists and knockout mice implicate receptor involvement in the response to noxious heat and inflammatory pain, suggesting that a maybe an effective TRPV1 antagonist for pain therapeutics. A-784168 is a novel TRPV1 antagonist that shows potent, competitive inhibition of capsaicin-induced Ca influx in vitro, and potent antinociception in animal pain models. SAR and biological effects of A-784168 analogs will also be presented.

MEDI 69

Novel, potent TRPV1 receptor antagonists

*Brian S. Brown, **Ryan G. Keddy**, Guo Zhu Zheng, Robert G. Schmidt, John Robert Koenig, Prisca Honore, Michael F. Jarvis, Carol S. Surowy, Connie R. Faltynek, and Chih-Hung Lee, Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064*

The vanilloid receptor TRPV1 (VR1) is a membrane-bound, non-selective ion channel found primarily on sensory afferent neurons (A-d and C fibers), which can be activated by a number of noxious stimuli including heat, protons, and ligand agonists such as capsaicin. Optimization of a high-throughput screening hit led to the discovery of the novel TRPV1 antagonist A-784168, which shows potent, competitive inhibition of capsaicin-induced Ca2+ influx in vitro, and potent antinociception in animal pain models.

MEDI 70

SAR of a new series of indole and indazole ureas as TRPV1 antagonists

***Irene Drizin*[1], *Arthur Gomtsyan*[1], *Erol K. Bayburt*[1], *Richard J. Perner*[1], *Stanley Didomenico*[1], *John Robert Koenig*[2], *Heath McDonald*[1], *Prisca Honore*[2], *Carol T. Wismer*[1], *Kennan Marsh*[3], *Jill Wetter*[3], *Michael F. Jarvis*[2], *Connie R. Faltynek*[2], *and Chih-Hung Lee*[1]. *(1) Neuroscience Research, GPRD, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-6101, irene.drizin@abbott.com, (2) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, (3) R4EK, GPRD, Abbott Laboratories*

The capsaicin sensitive TRPV1 receptor is a member of the mammalian transient receptor potential (TRP) channel family and is highly expressed on small diameter (C-fiber) nociceptive sensory neurons. It is also expressed at lower levels in other noneuronal tissues such as skin and bladder. This receptor has been called a polymodal detector of noxious stimuli since it can be activated in several ways. Low pH, heat and naturally occurring ligands such as capsaicin

and resinoferotoxin activate TRPV1 causing burning pain sensation. TRPV1 antagonists continue to be an attractive target for the discovery of novel analgesic agents. Interest in these compounds is supported by the finding that mice lacking the TRPV1 receptor do not develop thermal hyperalgesia following acute inflammation. Herein we report a new series of indole and indazole ureas that demonstrated in vitro activity in blocking capsaicin activation of TRPV1. The most potent derivatives of this series were assessed in both inflammatory and neuropathic in vivo pain models.

MEDI 71

4-(Pyridin-2-yl)-piperazine-N-cyano-1-carboxamidine analogs as vanilloid receptor 1 antagonists

***Xiaoming Zhou**, Qun Sun, Chongwu Zhang, Kenneth J. Valenzano, Jinchen Huang, Kevin C. Brown, and Donald J. Kyle, Discovery Research, Purdue Pharma L. P, 6 Cedar Brook Drive, Cranbury, NJ 08512, Fax: 609-409-6930, xiaoming.zhou@pharma.com*

A series of 4-(pyridin-2-yl)-piperazine-N-cyano-1-carboxamidine analogs were developed vanilloid receptor 1 antagonists based on the lead compound N-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carboxamide (BCTC) and evaluated for VR1 antagonist activity in capsaicin-induced (CAP) and pH 5.5-induced (pH) FLIPR assays in a human VR1-expressing HEK293 cell line. The synthesis and structure-activity relationships of 4-(pyridin-2-yl)-piperazine-N-cyano-1-carboxamidine analogs were described.

MEDI 72

Comparative protein structure modeling of the human Angiotensin II Type 1 (AT-1) receptor: Insights into the molecular determinants of the AT-1-ligand interactions

***Akshay Patny**, Prashant V. Desai, and Mitchell A. Avery, Department of Medicinal Chemistry, University of Mississippi, 417, Faser Hall, School of Pharmacy, University, MS 38677, akshay17@olemiss.edu*

Angiotensin II Type 1 receptor (AT-1) belongs to the family of G-protein coupled receptors (GPCRs). AT-1 antagonists like losartan and telmisartan are effectively used in the treatment of hypertension. A model of the human AT-1 receptor with all connecting loops was constructed from the 2.6 Å resolution crystal structure (PDB id: 1L9H) of the bovine rhodopsin. Initial model generated by MODELLER was subjected to stepwise refinement by first docking one of the representative non-peptide AT-1 antagonist followed by several rounds of iterative molecular dynamics simulations and energy minimizations. The model was validated based on its ability to explain several site-directed mutagenesis results and known ligand-receptor interactions. For further validation, additional non-peptide AT-1 inhibitors were docked in the active site of the model. Promising correlation between the docked score and the corresponding binding affinity of the ligands clearly indicates that a reasonable model of the AT-1 receptor has been derived which can be utilized for future structure based drug design projects.

MEDI 72

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MEDI 73

N6-Ethyl-2-alkynyl adenosine derivatives as a selective human A3 adenosine receptor agonist

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Adenosine is an endogenous nucleoside which modulates many physiological processes through four G-protein-coupled receptors: A1, A2A, A2B and A3. The most recently identified A3 receptor has biological effect on central nervous system, cardiovascular system and immune system. Due to the low homology of A3 receptors between species, some highly selective rat A3 agonists such as Cl-IB-MECA is not as selective at human. It was not until 2003 that the first hA3 selective Cl-IB-MECA derivative—CP-608039 was reported. Here we report a series of N6-ethyl-2-alkyny-NECA (5'-N-ethylcarboxamidoadenosine) analogue as selective human A3 receptor agonist with higher potency than Cl-IB-MECA and comparable A3 selectivity to CP-608039.

MEDI 74

Structure-activity relationships of 2-chloro-N6-substituted-4'-thioadenosine-5'-

uronamides as human A3 adenosine receptor agonists

Lak Shin Jeong[1]*, Hyuk Woo Lee*[1]*, Zhan-Guo Gao*[2]*, Kenneth A. Jacobson*[2]*, Dae Hong Shin*[2]*, Jeong A Lee*[1]*, and Ae Yil Kim*[1]*. (1) Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, 11-1 Seodaemun-ku, Daehyun-dong, Seoul, South Korea, Fax: 82-2-3277-2851, lakjeong@mm.ewha.ac.kr, (2) Molecular Recognition Section, NIDDK, NIH*

In order to find the A3 adenosine receptor (AR) agonists with high affinity and selectivity, we have carried out structure-activity relationships at the A3 AR of novel 4'-thionucleoside analogues. The series of 2-chloro-N6-substituted-4'-thioadenosine-5'-uronamides were synthesized from the direct condensation of 2,6-dichloropurine with a 4-sulfoxide derivative, which was efficiently synthesized on a preparative scale from D-gulonic ã-lactone. From this study, 2-chloro-N6-methylthioadenosine 5'-methyluronamide was found to be the most potent and selective agonist at the human A3 AR. It was also revealed that, similar to 4'-oxoadenosine analogues, at least one hydrogen on the 5'-uronamide moiety was necessary for high affinity of binding at the human A3 AR. Furthermore, bulky substituents on the 5'-uronamide reduced binding affinity, but in some cases large 5'-uronamide substituents, such as substituted benzyl and 2-phenylethyl groups maintained moderate affinity with reduced efficacy, leading to A3 AR partial agonists or antagonists. In several cases for which the corresponding 4'-oxonucleosides have been studied, the 4'-thionucleosides showed higher binding affinity to the A3 AR. Binding affinity and selectivity toward other AR subtypes will be presented.

MEDI 75

Design, synthesis, and biological evaluation of novel adenosine A_{2A} receptor antagonists

Lisa S. Silverman[1]*, John Caldwell*[1]*, William J. Greenlee*[1]*, Eugenia Y. Kiselgof*[1]*, Julius Matasi*[1]*, Deen Tulshian*[1]*, Leyla Arik*[2]*, and Carolyn Foster*[2]*. (1) CV/CNS Department of Chemical Research, Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7164, lisa.silverman@spcorp.com, (2) CNS Department of Biological Research, Schering Plough Research Institute*

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. Four subtype adenosine receptors have been located in the brain and classified as A_1, A_{2A}, A_{2B}, and A_3. The adenosine A_{2A} receptor, abundantly expressed in striatum, is a member of the G-protein coupled receptor (GPCR) family that couples to stimulate adenylate cyclase activity. Adenosine A_{2A} receptors coexist with dopamine D_2 receptors. The stimulation of A_{2A} receptors leads to a decrease in D_2 receptor-mediated neurotransmission. Further, it has been discovered that dopamine deficiency in the brain can initiate the onset of Parkinson's disease (PD), a neurodegenerative motor disorder. Consequently, adenosine A_{2A} receptor antagonists can offer potential value as an anti-symptomatic treatment for PD. A summary of the synthesis and SAR of a novel class of A_{2A} receptor antagonists will be presented.

MEDI 75

Design, synthesis, and biological evaluation of novel adenosine A_{2A} receptor antagonists

Lisa S. Silverman[1], *John Caldwell*[1], *William J. Greenlee*[1], *Eugenia Y. Kiselgof*[1], *Julius Matasi*[1], *Deen Tulshian*[1], *Leyla Arik*[2], *and Carolyn Foster*[2]. *(1) CV/CNS Department of Chemical Research, Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7164, lisa.silverman@spcorp.com, (2) CNS Department of Biological Research, Schering Plough Research Institute*

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. Four subtype adenosine receptors have been located in the brain and classified as A_1, A_{2A}, A_{2B}, and A_3. The adenosine A_{2A} receptor, abundantly expressed in striatum, is a member of the G-protein coupled receptor (GPCR) family that couples to stimulate adenylate cyclase activity. Adenosine A_{2A} receptors coexist with dopamine D_2 receptors. The stimulation of A_{2A} receptors leads to a decrease in D_2 receptor-mediated neurotransmission. Further, it has been discovered that dopamine deficiency in the brain can initiate the onset of Parkinson's disease (PD), a neurodegenerative motor disorder. Consequently, adenosine A_{2A} receptor antagonists can offer potential value as an anti-symptomatic treatment for PD. A summary of the synthesis and SAR of a novel class of A_{2A} receptor antagonists will be presented.

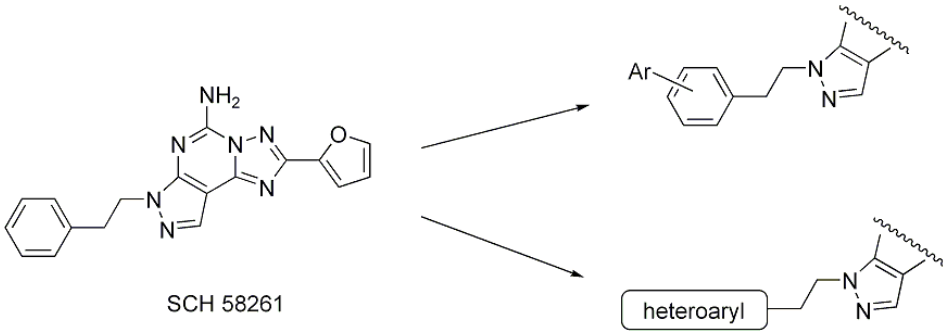
MEDI 76

Biaryl and heteroaryl derivatives of SCH 58261 as potent and selective adenosine A_{2A} receptor antagonists

Unmesh Shah[1], *Craig D. Boyle*[1], *Samuel Chackalamannil*[2], *Bernard Neustadt*[1], *Carolyn Foster*[3], *Leyla Arik*[3], *Ying Zhai*[4], *Jean E. Lachowicz*[4], *Kwokei Ng*[5], *Shiyong Wang*[5], *Angela Monopoli*[4], *and Ennio Ongini*[4]. *(1) CNS/CV Chemical Research, Schering-Plough Research Institute, K-15-2/2545, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7164, unmesh.shah@spcorp.com, (2) Chemical Research, Schering-Plough Research Institute, (3) CNS Department of Biological Research, Schering Plough Research Institute, (4) CNS Department of Biological Research, Schering-Plough Research Institute, (5) Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute*

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors classified as A_1, A_{2A}, A_{2B}, and A_3. The adenosine A_{2A} receptor, a member of the G-protein-coupled receptor family, is found in large amounts in brain striatum. Adenosine A_{2A} receptors coexist with dopamine D_2 receptors and stimulation of A_{2A} receptors causes a decrease in D_2 receptor-mediated neurotransmission. It has been discovered that dopamine deficiency in the brain leads to Parkinson's disease. Thus, adenosine A_{2A} receptor antagonists could be of value as anti-Parkinson's drugs.

SCH 58261 has previously been identified as a potent and selective A_{2A} antagonist. Our efforts focused on improving the *in vitro* and *in vivo* properties of SCH 58261. Design, synthesis, and evaluation of novel biaryl and heteroaryl analogs were carried out. The discovery of several potent and selective compounds exhibiting interesting *in vivo* properties will be discussed.

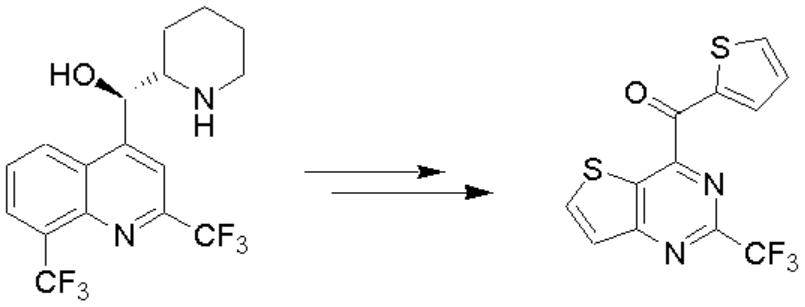


MEDI 77

(-)-Mefloquine as a starting point for the discovery of selective adenosine A_{2A} receptor antagonists

Allan M. Jordan[1]*, Karen Benwell*[1]*, Ian A. Cliffe*[1]*, Colin T. Dourish*[1]*, Paul R. Giles*[1]*, Roger J. Gillespie*[1]*, Tony R. Knight*[1]*, Joanne Lerpiniere*[1]*, A. Misra*[2]*, Simon E. Ward*[1]*, and Scott M. Weiss*[1]*. (1) Medicinal Chemistry, Vernalis (R+D) Ltd, Granta Park, Abington, Cambridge CB1 6GB, United Kingdom, Fax: 01223 895556, (2) Vernalis Research Ltd, Wokingham, RG41 5UA, United Kingdom*

The adenosine A_{2A} receptor plays an important role in regulating smooth and well-coordinated movement, in part by modulating the activity of dopamine sensitive neurons in the striatum. Blockade of the adenosine A_{2A} receptor has been shown to offer considerable promise as a novel treatment for the symptoms of Parkinson's disease. As part of our ongoing efforts to discover new treatments for this condition, we have shown that the (-)-enantiomer of the antimalarial drug mefloquine is a reasonably potent and moderately selective adenosine A_{2A} receptor antagonist (K_i 61 nM, 4-fold selective against A_1 receptors). Using this compound as a starting point, a series of iterations led to the identification of a novel non-xanthine chemical class of adenosine A_{2A} antagonists with improved potency and selectivity. For example, VER-4187 has a binding K_i of 12 nM at human adenosine A_{2A} receptors. The evolution and evaluation of this series will be described.



(-)-mefloquine VER-4187

MEDI 78

Human $P2Y_6$ receptor: Molecular modeling and structure-based drug design

Stefano Costanzi[1], *Pedro Besada*[2], *Bhalchandra V. Joshi*[2], *Savitri Maddileti*[3], *Liaman Mamedova*[2], *Dae Hong Shin*[2], *Maria J Gonzalez-Moa*[4], *Victor E. Marquez*[4], *T. Kendall Harden*[3], *and Kenneth Jacobson*[2]. *(1) Chemical Biology, NIDDK, NIH, 12A Center Drive Rm 4051 MSC 5646, Bethesda, MD 20892-5646, Fax: 301-480-4586, stefanoc@intra.niddk.nih.gov, (2) Molecular Recognition Section, NIDDK, NIH, (3) School of Medicine, Univ. of North Carolina, (4) Laboratory of Medicinal Chemistry, NCI, NIH*

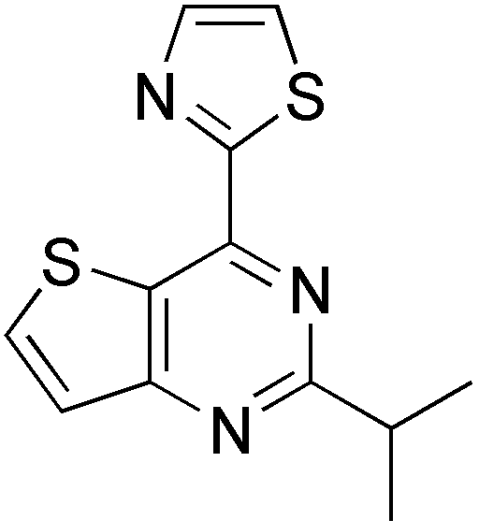
The $P2Y_6$ receptor is the only G protein-coupled receptor preferentially activated by UDP. A rhodopsin-based homology model of the human $P2Y_6$ receptor was submitted to 10 ns of MD in an explicit hydrated lipid bilayer. Subsequently, UDP was docked into the putative binding site. Ligand-receptor interactions were studied considering simultaneously the flexibility of the ligand and the receptor (induced fit). Structural analysis of bound UDP indicated a South conformation for the ribose moiety. Therefore, a UDP analogue locked in the South conformation was designed, synthesized and tested. It was ~10-fold more potent than the unlocked, ribose equivalent in activation of phospholipase C in astrocytoma cells expressing the human $P2Y_6$ receptor. Since most P2Y receptor subtypes prefer the North ribose conformation, this South nucleotide provides a lead for the development of selective and potent $P2Y_6$ ligands.

MEDI 79

Synthesis and SAR of novel thieno[3,2-d]pyrimidine derivatives as selective antagonists of the adenosine A_{2A} receptor

Allan M. Jordan[1], *Ian A. Cliffe*[1], *Claire E. Dawson*[1], *Colin T. Dourish*[1], *Paul R. Giles*[1], *Roger J. Gillespie*[1], *Tony R. Knight*[1], *Anthony Lawrence*[1], *Joanne Lerpiniere*[1], *A. Misra*[2], *Robert M. Pratt*[1], *Richard S. Todd*[1], *Rebecca Upton*[1], *and Scott M. Weiss*[1]. *(1) Medicinal Chemistry, Vernalis (R+D) Ltd, Granta Park, Abington, Cambridge CB1 6GB, United Kingdom, Fax: 01223 895556, (2) Vernalis Research Ltd, Wokingham, RG41 5UA, United Kingdom*

Adenosine receptors comprise four distinct sub-types, designated A_1, A_{2A}, A_{2B} and A_3. In the brain, adenosine A_{2A} receptors are located primarily in the striatum, playing a key role in regulating movement. There is strong evidence that adenosine A_{2A} receptor antagonists may provide a novel therapy for the treatment of Parkinson's disease with a lower risk of dyskinesias. In the preceding poster, we describe the discovery of a series of thieno[3,2-d] pyrimidine derivatives as potent, selective adenosine A_{2A} receptor antagonists. We herein describe the further development of this series, yielding considerable improvements in both potency and selectivity. For example, VER-6623 has a K_i of 1.4 nM at human adenosine A_{2A} receptors and is highly selective over human A_1, A_{2B}, and A_3 receptors (K_i 273, 821, and 508 nM respectively). Moreover, a number of these compounds are active in animal models of Parkinson's disease. The synthesis and evaluation of this series is described.



VER-6623

MEDI 80

Uncharged isocoumarin-based inhibitors of urokinase-type plasminogen activator

Justin J. Heynekamp[1]*, Lucy A. Hunsaker*[2]*, Lorraine M. Deck*[1]*, and David L. Vander Jagt*[2]*. (1) Department of Chemistry, University of New Mexico, Chemistry Department, MSC03 2060, Albuquerque, NM 87131, juster@unm.edu, (2) Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine*

Urokinase-type plasminogen activator (uPA) plays a major role in extracellular proteolytic events associated with tumor cell growth, migration and angiogenesis. Consequently, uPA is an attractive target for the development of small molecule active site inhibitors. Most of the recent drug development programs aimed at nonpeptidic inhibitors targeted at uPA have focused on arginino mimetics containing amidine or guanidine functional groups. There is a general problem of limited bioavailability of these charged inhibitors. In the present study, uPA inhibitors were designed on an isocoumarin scaffold containing uncharged substituents. 4-Chloro-3-alkoxyisocoumarins were synthesized in which the 3-alkoxy group contained a

terminal bromine; these were compared with similar inhibitors that contained a charged terminal functional group. Additional variations included functional groups attached to the seven position of the isocoumarin scaffold. N-[3-(3-Bromopropoxy)-4-chloro-1-oxo-1H-isochromen-7-yl]benzamide was identified as an uncharged lead inhibitor of uPA, Ki = 0.034 μM. Modeling studies were also performed.

MEDI 81

Synthesis of pyridoxal phosphate derivatives with antagonist activity at the $P2Y_{13}$ receptor

Yong-Chul Kim[1]*, Jung-Sun Lee*[1]*, Katrin Sak*[2]*, Frederic Marteau*[2]*, Liaman Mamedova*[3]*, Jean-Marie Boeynaems*[4]*, and Kenneth A. Jacobson*[5]*. (1) Department of Life Science, Gwangju Institute of Science and Technology, 1 Oryong-dong, Buk-gu, Gwangju 500-712, South Korea, Fax: +82-62-970-2484, yongchul@gist.ac.kr, (2) Institute of Interdisciplinary Research, Free University of Brussels, (3) Molecular Recognition Section, NIDDK, NIH, (4) Department of Clinical Pathology, Erasme Hospital, (5) Molecular Recognition Section, NIDDK, National Inst. of Health*

We have synthesized a series of derivatives of the known P2 receptor antagonist PPADS (pyridoxal-5'-phosphate-6-azo-phenyl-2,4-disulfonate) and examined their ability to inhibit functional activity of the recombinant human $P2Y_{13}$ nucleotide receptor expressed in 1321N1 human astrocytoma cells co-expressing Ga16 protein (AG32). Analogues of PPADS modified through substitution of the phenylazo ring, including halo and nitro substitution, and 5'-alkyl phosphonate analogues were synthesized and tested. A 6-benzyl-5'-methyl phosphonate analogue was prepared to examine the effect of stable replacement of the azo linkage. The highest antagonistic potency was observed for 6-(3-nitrophenylazo) derivatives of pyridoxal-5'-phosphate. The 2-chloro-5-nitro analogue (MRS 2211) and 4-chloro-3-nitro analogue (MRS 2603) inhibited ADP (100 nM)-induced inositol trisphosphate (IP3) formation with pIC_{50} values of 5.97 and 6.18, respectively, being 45- and 74-fold more potent than PPADS. The antagonism of MRS 2211 was competitive with a pA_2 value of 6.3. MRS2211 and MRS2603 inhibited PLC responses to 30 nM 2-methylthio-ADP in human $P2Y_1$ receptor-mediated 1321N1 astrocytoma cells with IC_{50} values of >10 and 0.245 μM, respectively. Both analogues were inactive (IC_{50} > 10 μM) as antagonists of human $P2Y_{12}$ receptor-mediated PLC responses in 1321N1 astrocytoma cells. Thus, MRS2211 displayed > 20-fold selectivity as antagonist of the $P2Y_{13}$ receptor in comparison to $P2Y_1$ and $P2Y_{12}$ receptors, while MRS2603 antagonized both $P2Y_1$ and $P2Y_{13}$ receptors.

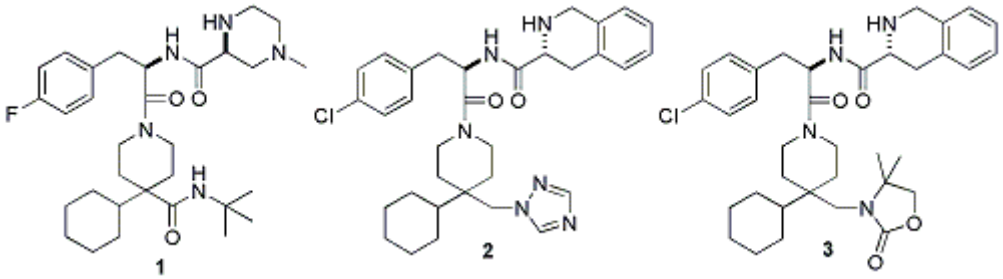
MEDI 82

Optimization of privileged structure for selective and potent melanocortin subtype-4 receptor ligands

Qingmei Hong[1]*, Raman K. Bakshi*[2]*, Rui Tang*[3]*, Rubana N. Kalyani*[4]*, Tanya MacNeil*[3]*, David*

H. Weinberg[3], Lex H. T. Van der Ploeg[2], Arther A. Patchett[4], and Ravi Nargund[3]. (1) Department of Medicinal Chemistry, Merck Resarch Laboratories, 126 E. Lincoln Avenue, P.O.Box 2000, Rahway, NJ 07065, qingmei_hong@merck.com, (2) Merck, (3) Merck Research Laboratories, (4) N/A

Over the last decade the melanocortin-4 receptor subtype has attracted considerable attention from medicinal chemists and biologists because of it's potential in the treatment of obesity and sexual dysfunction. Recent efforts at Merck resulted in the identification of small molecule agonist 1 and 2. Currents presentation will be focused on the optimization of privileged structure in small molecule 1 and 2 to the molecule 3.

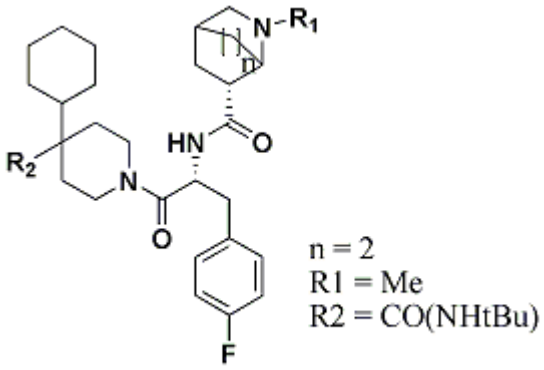


MEDI 83

SAR and pharmocology of potent and selective melanocortin subtype-4 receptor agonists with azabicyclo carboxamide moiety

***Liangqin Guo**, Zhixiong Ye, Khaled J. Barakat, Patrick G. Pollard, Brenda L. Palucki, Iyassu K. Sebhat, Raman K. Bakshi, Rui Tang, Rubana N. Kalyani, Aurawan Vongs, Charles I. Rosenblum, Tanya MacNeil, David H. Weinberg, Qianping Peng, Constantin Tamvakopoulos, Randy R. Miller, Ralph A. Stearns, Erin McGowan, William J. Martin, Airu S. Chen, Joseph M. Metzger, Howard Y. Chen, Alison M. Strack, Euan MacIntyre, Lex H. T. Van der Ploeg, Matthew J. Wyvratt, and Ravi P. Nargund, Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, RY 50G-332, Rahway, NJ 07065, Fax: (732)-594-3007, liangqin_guo@merck.com*

The melanocortin receptors are part of the family of five seven-transmembrane G-protein-coupled receptors and mediate a variety of physiological functions. The melanocortin subtype-4 receptor (MC4R) has been linked to the regulation of energy homeostasis, feeding regulation and sexual functions. Considerable research effort has been spent on identifying selective non-peptide MC4R agonists for potential treatment for obesity and sexual dysfunction. In this presentation we report the discovery of a series of isoquinuclidines containing MC4R agonists which possess potent in vitro and in vivo activities towards MC4R and show attenuated undesirable ancillary activities such as bioactivation leading to covalent binding to proteins. Compound 1 was the most interesting analog identified in this series and was studied in considerable detail. It exhibits excellent binding affinity (IC50 = 8 nM) and functional activity (EC50 = 11 nM with 81% activation). Furthermore, it is efficacious in lowering food intake in both rats and mice at 20 mpk PO. The synthesis, structure-activity-relationship studies and pharmacology of selected compounds in this series will be discussed.



1

MEDI 84

2-Aminoquinoline MCH1R antagonists: Structure-activity determinants and binding mode investigations

***Trond Ulven**, Thomas M. Frimurer, Jean-Marie Receveur, Paul Brian Little, Øystein Rist, Pia K. Nørregaard, and Thomas Högberg, 7TM Pharma A/S, Fremtidsvej 3, Horsholm DK-2970, Denmark, Fax: +45 3925 7776, tu@7tm.com*

Melanin-concentrating hormone (MCH) plays an important role in the control of food intake, and evidence suggest that the orexigenic effect of this neuropeptide is largely mediated through the G protein-coupled seven-transmembrane receptor MCH1R, which thus represents a potential target in treatment of obesity. We identified a series of 2-aminoquinoline MCH1R antagonists by in silico screening of commercial compound libraries with a 3D pharmacophore model based on a series of benzamide MCH1R antagonists. Structure-activity exploration revealed quite specific demands in the western part of the molecules and around the quinoline core, whereas a large degree of structural freedom was found in the eastern part. Results from docking of representative compounds into an MCH1R homology model led us to revise our original binding hypothesis and our pharmacophore. The new binding mode hypothesis, which includes an interaction between Asp123 in TM3 and the quinoline nitrogen, was supported by specially designed compounds.

MEDI 84

2-Aminoquinoline MCH1R antagonists: Structure-activity determinants and binding mode investigations

***Trond Ulven**, Thomas M. Frimurer, Jean-Marie Receveur, Paul Brian Little, Øystein Rist, Pia K. Nørregaard, and Thomas Högberg, 7TM Pharma A/S, Fremtidsvej 3, Horsholm DK-2970, Denmark, Fax: +45 3925 7776, tu@7tm.com*

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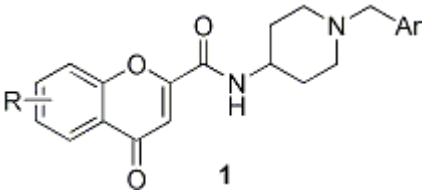
antagonists by in silico screening of commercial compound libraries with a 3D pharmacophore model based on a series of benzamide MCH1R antagonists. Structure-activity exploration revealed quite specific demands in the western part of the molecules and around the quinoline core, whereas a large degree of structural freedom was found in the eastern part. Results from docking of representative compounds into an MCH1R homology model led us to revise our original binding hypothesis and our pharmacophore. The new binding mode hypothesis, which includes an interaction between Asp123 in TM3 and the quinoline nitrogen, was supported by specially designed compounds.

MEDI 85

4-Oxo-4H-chromene-2-carboxamides as melanin concentrating hormone antagonists: Structure-activity relationship of antiobesity therapeutics

Jennifer C. Freeman[1], *John K. Lynch*[1], *Mathew M. Mulhern*[1], *Andrew S. Judd*[1], *Rajesh R. Iyengar*[1], *Gang Zhao*[1], *Sevan Brodjian*[1], *Doug Falls*[1], *Brian D. Dayton*[1], *Christopher A. Ogiela*[1], *Hanna E. Sidorowicz*[1], *Robin Shapiro*[1], *Victoria Knourek-Segel*[1], *Michael Brune*[1], *Sandra T. Leitza*[2], *Gilbert J. Diaz*[2], *Hing L. Sham*[1], *Christine A. Collins*[1], *and Philip R. Kym*[1]. *(1) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division, 100 Abbott Park Road, Abbott Park, IL 60064, Jennifer.Freeman@abbott.com, (2) Integrative Pharmacology, Abbott Laboratories, Global Pharmaceutical Research Division*

Melanin-concentrating hormone (MCH) is a cyclic 19 amino acid neuropeptide involved in regulation of food intake and energy homeostasis. Mice lacking melanin-concentrating hormone receptor 1 (MCHr1) are lean, resistant to weight-gain on a high fat diet, and demonstrate elevated metabolism rates. Therefore, antagonists of MCHr1 may represent an attractive target for obesity treatment. A series of 4-oxo-4H-chromene-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amides, 1, were prepared in order to examine the effect of substitution on 4-oxo-4H-chromene on ligand binding and antagonism of MCHr1. Antagonists were found to be high-affinity ligands for MCHr1 and potent inhibitors of MCH-mediated calcium release. The best analogs exhibited good plasma and CNS exposure upon oral dosing in diet-induced obese mice and were efficacious upon oral dosing in a chronic model of weight loss.



1

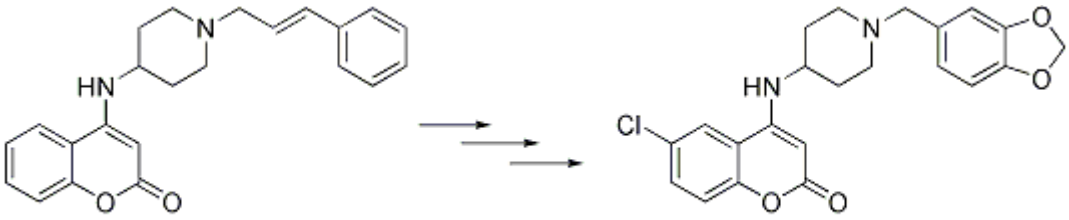
MEDI 86

Discovery, lead optimization and in vivo studies on coumarin-based small molecule MCHr-1 antagonists

Rajesh R. Iyengar[1], *Andrew J. Souers*[1], *John K. Lynch*[1], *Andrew S. Judd*[1], *Ju Gao*[1], *Jennifer C. Freeman*[1], *Mathew Mulhern*[1], *Anil Vasudevan*[2], *Dariusz Wodka*[2], *Christopher Blackburn*[3],

James Brown[3], Jennifer Lee Che[3], Courtney A. Luchaco-Cullis[3], Sujen Lai[3], Matthew J. Lamarche[3], Thomas H. Marsilje[3], Jonathan B. Roses[3], Bradley Geddes[3], Michael A. Patane[3], Dennis G. Fry[1], Brian D. Dayton[1], Sevan Brodjian[1], Doug H. Falls[1], Michael E. Brune[1], Eugene N. Bush[1], Robin Shapiro[1], Victoria E. Knourek-Segel[1], Thomas A. Fey[1], Cathleen A. McDowell[1], Thomas B. Farb[1], Glenn A. Reinhart[4], Lee C. Preusser[4], Kennan C. Marsh[5], Lisa E. Hernandez[5], James M. Schmidt[5], Hing L. Sham[1], Christine A. Collins[1], and Philip R. Kym[1]. (1) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division, 100 Abbott Park Road, Abbott Park, IL 60064-6101, Fax: 847-938-1674, rajesh.iyengar@abbott.com, (2) Medicinal Chemistry Technologies, Abbott Laboratories, Global Pharmaceutical Research Division, (3) Millennium Pharmaceuticals, (4) Integrative Pharmacology, Abbott Laboratories, Global Pharmaceutical Research Division, (5) Preclinical Safety, Abbott Laboratories, Global Pharmaceutical Research Division

Melanin Concentrating Hormone (MCH) is an orexigenic peptide that has been implicated in the hypothalamic regulation of food intake and body weight regulation. MCH-KO mice are lean and hypophagic while mice overexpressing the protein are susceptible to obesity and subsequent insulin resistance. As a result of this pharmacological validation, the discovery of MCHr-1 small molecule antagonists has been the focus of a number of pharmaceutical companies. Here, we describe the discovery and lead optimization of aminopiperidine-coumarin compounds as potent MCHr-1 antagonists. A potent, orally bioavailable small molecule MCHr-1 antagonist was identified and characterized in rodent models of obesity and in vivo toxicology, and for cardiovascular safety in an anesthetized dog model.



Screening hit A-798

MEDI 87

Identification and SAR of hERG selective Melanin-concentrating hormone receptor 1 antagonists

***Mathew M. Mulhern[1]**, Andrew Judd[1], Jennifer Freeman[1], John Lynch[1], Rajesh Iyengar[1], Andrew J. Souers[1], Ju Gao[1], Gang Zhao[1], Dariusz Wodka[1], Gilbert Diaz[2], Ruth Martin[2], Sevan Brodjian[1], Doug Falls[1], Brian Dayton[1], Hing L. Sham[1], Christine A. Collins[1], and Philip R. Kym[1]. (1) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division, 100 Abbott Park, Abbott Park, IL 60064, Fax: 847-938-1674, Mathew.Mulhern@Abbott.com, (2) Integrative Pharmacology, Abbott Laboratories, Global Pharmaceutical Research Division*

Melanin-concentrating hormone receptor 1 (MCHr1) is a 19-membered, cyclic neuropeptide expressed in the lateral hypothalamus that has been implicated in the regulation of food intake and energy expenditure. MCHr1 KO mice are hypophagic and lean with an increased

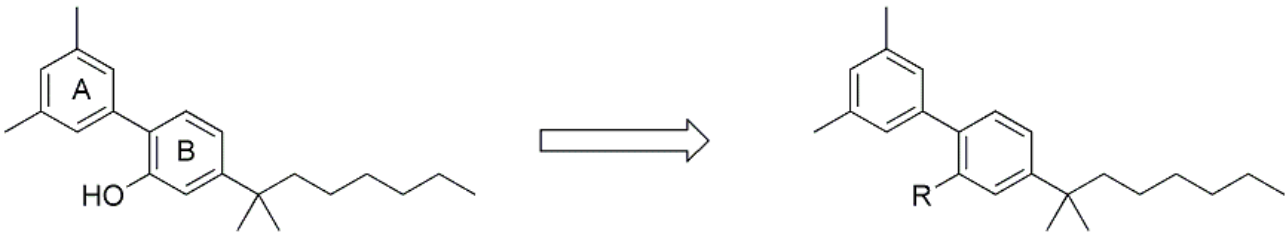
metabolism, and are less susceptible to weight gain on a high fat diet. This suggests that selective orally efficacious MCHr1 antagonists may serve as an effective treatment for obesity. Drug-induced QT prolongation via hERG (human ether-a-go-go-related gene) K+ channel blockade has been associated with the development of cardiac arrhythmias and must be considered in the development of a therapeutic index. In this poster, we present the synthesis and SAR of a chromone-based lead series focusing on optimization of hERG selectivity versus MCHr1 potency.

MEDI 88

Synthesis and structure activity relationship of biaryl cannabinoid mimetics: Phenol replacements

Q. Jean Zhou[1]*, Karin Worm*[1]*, Roland E. Dolle*[1]*, Gabriel Stabley*[2]*, and Robert N. DeHaven*[2]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, jzhou@adolor.com, (2) Department of Pharmacology, Adolor Corporation*

Biaryl phenol 1, a cannabinoid mimetic first described by researchers at Merck Frosst, exhibits potent affinity towards CB1 and CB2 receptors. Previously, we reported the synthesis and SAR around the ring A and the side chain at ring B. In order to further explore the SAR of compound 1, herein, we report the synthetic approaches towards analogs 2, replacing the phenol group by various substituents. The binding data of analogs 2 to CB1 and CB2 receptors and resulting SAR will be presented.



1

2, R = NH_2, COR',CH_2OH, ...

MEDI 89

WITHDRAWN

MEDI 89

WITHDRAWN

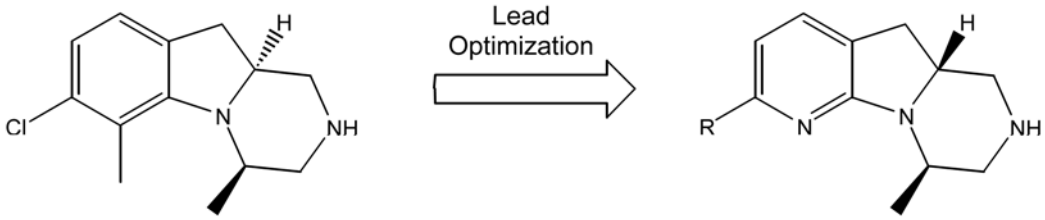
MEDI 90

Synthesis and biological evaluation of novel pyrido[3',2':4,5]pyrrolo[1,2-a]pyrazines as

potent and selective 5-HT$_{2C}$ receptor agonists

Hans G. F. Richter[1], *D. R. Adams*[2], *A. Benardeau*[1], *M. J. Bickerdike*[2], *J. M. Bentley*[3], *T. J. Blench*[2], *I. A. Cliffe*[2], *J. E. P. Davidson*[2], *C. Dourish*[2], *P. Hebeisen*[1], *G. A. Kennett*[2], *A. R. Knight*[2], *C. S. Malcolm*[2], *P. Mattei*[1], *A. Misra*[2], *J. Mizrahi*[1], *N. J. T. Monck*[2], *J-M. Plancher*[1], *S. Roever*[1], *J. R. A. Roffey*[2], *S. Taylor*[1], *and S. P. Vickers*[2]. *(1) Discovery Research, F. Hoffmann - La Roche Ltd, CH-4070 Basel, Switzerland, (2) Vernalis Research Ltd, Wokingham, RG41 5UA, United Kingdom, (3) Centre of Excellence for Drug Discovery, GlaxoSmithKline S.p.A, 37135 Verona, Italy*

In the last years substantial evidence from both human and animal studies has been accumulated suggesting a crucial role for the 5-HT2C receptor in regulating the control of food intake. Therefore, selective 5-HT2C receptor agonists offer a novel opportunity for the treatment of obesity. Selectivity especially over 5-HT2A and 5-HT2B receptors is important because activity on 5-HT2A receptors can cause psychotomimetic side effects whereas activity on 5-HT2B receptors may increase the risk of developing valvular heart disease. Based on our previous work on 1,2,3,4,10,10a-hexahydro-1H-pyrazino[1,2-a]indoles and through further lead optimization we identified 5,5a,6,7,8,9-hexahydro-pyrido[3',2':4,5]pyrrolo[1,2-a]pyrazines as a new class of potent human 5-HT2C receptor agonists with improved binding selectivity profiles and increased in vivo potency in rats after oral administration. In addition several of these analogues had low potential to induce phospholipidosis and showed reduced hERG affinity in vitro. The synthesis, structure-activity relationship (SAR) and structure-property relationship (SPR) of this class of compound will be discussed.



RO0721256

MEDI 91

Development of dual-acting benzofurans and benzomorpholines as dual thromboxane A2 receptor antagonists and prostacyclin receptor agonists

Michihiro Ohno*, Takahiro Takeda, Yoichiro Tanaka, Kei Makita, Mitsuko Miyamoto, Naohiro Yamada, and Atsushi Ohtake, Pharmaceutical Research Laboratories, Toray Industries, Inc, 1,111 Tebiro, Kamakura 248-8555, Japan, Fax: 81-467-32-4791, michihiro_ono@nts.toray.co.jp*

Prostacyclin (PGI2) is an unstable, powerful endogenous inhibitor of platelet aggregation, and thromboxane A2 (TXA2) is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction. The balance between TXA2 and PGI2 greatly affects maintenance of the homeostasis of the circulatory system. We discovered a novel series of benzofuran-7-yl-oxyacetic acid derivatives and 3,4-dihydro-2H-benzo[1,4]

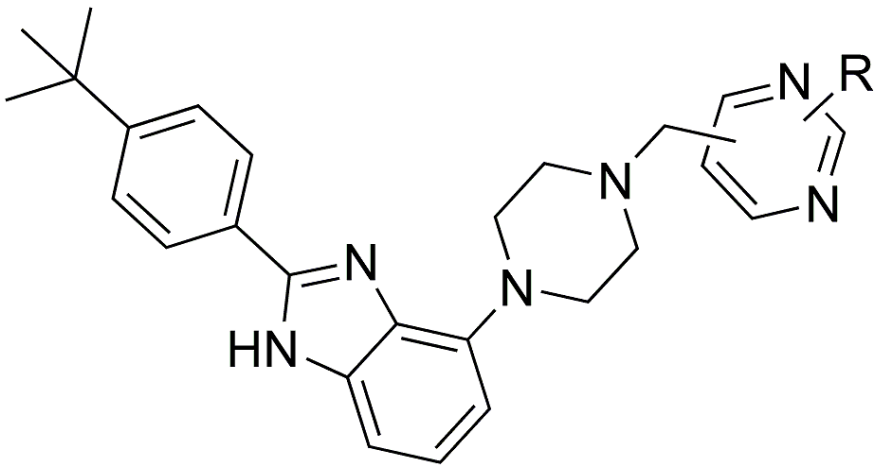
oxazin-8-yloxyacetic acid derivatives as potent dual-acting agents to block the TXA2 receptor and to activate the PGI2 receptor. We report the synthesis, structure-activity relationship (SAR) and in vitro, ex vivo and in vivo pharmacology of this series of compounds. The most promising candidate in the series with Ki = 50 nM for TXA2 receptor antagonism and Ki = 430 nM for PGI2 receptor agonism demonstrated a neuronal protective effect in a cynomolgus monkey middle cerebral artery occlusion-reperfusion model employing positron emission tomography (PET).

MEDI 92

Pyrimidine substituted 2-phenyl-4-piperazinylbenzimidazole inhibitors of Gonadotropin Releasing Hormone

John F. Mehlmann[1]*, Jeffrey C. Pelletier*[1]*, Joseph T. Lundquist IV*[1]*, Joshua E. Cottom*[2]*, Linda Shanno*[2]*, Murty V. Chengalvala*[2]*, and Irene B. Feingold*[3]*. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, (2) Women's Health and Bone, Wyeth Research, (3) Drug Safety and Metabolism, Wyeth Research*

Gonadotropin-Releasing Hormone (GnRH) antagonists are desirable as a means to control sex-hormone dependant disorders such as endometriosis, breast cancer, prostate cancer and precocious puberty in children. To date only peptide antagonists and superagonists are available via parenteral routes. Our goal is to develop small molecule antagonists for oral administration. To this end, we have found that the attachment of heterocycles to a piperazinyl substituted benzimidazole moiety leads to active compounds. Several discrete parallel libraries of 2-substituted pyrimidines incorporated within this scaffold have been prepared. Their in vitro activity on human and rat GnRH will be presented.



MEDI 93

Synthesis of 4'-carboxamido N-Boc-2',6'-dimethyl-L-phenylalanines as surrogates for DMT in opioid receptor ligands

Chaozhong Cai[1]*, Henry J. Breslin*[1]*, Tamara A. Miskowski*[2]*, Sui-Po Zhang*[2]*, Pamela Hornby*[1]*,*

and Wei He[1]. (1) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, Welsh & McKean Roads, P.O.Box 776, Spring House, PA 19477, Fax: 215-628-4985, ccai@prdus.jnj.com, (2) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C

Replacement of the phenolic OH by the bioisosteric carboxamido group in opioid peptide or nonpeptide ligands has recently gathered more interest. These carboxamido analogues of the phenolic OH have shown the potential for an improved ADME profile (e.g., increased metabolic stability and reduced O-glucuronide formation), while retaining the favorable binding affinity and bioactivity. To examine the carboxamido replacement of the phenol moiety in a well established OR synthetic amino acid, 2',6'-dimethyltyrosine (DMT), we developed an efficient method to synthesize a series of 4'-carboxamido N-Boc-2',6'-dimethyl-L-phenylalanines from DMT by palladium-catalyzed carbonylation. We subsequently prepared 4'-carboxamido-2',6'-diMe-Phe analogues possessing low nanomolar opioid binding affinities both for delta and mu receptors.

MEDI 94

Synthesis and SAR studies for 3,4-disubstituted oxyindoles as potent and selective antagonists of the EP3 receptor for PGE2

*J Singh[1], **N. Zhou**[1], G Hategan[1], W Zeller[1], L Zhao[1], P Yu[1], L Enache[1], J Zhang[1], E Onua[1], J Ramirez[2], G Palsdottir[2], G Halldorsdottir[2], T Andersson[2], and M Gurney[2]. (1) deCODE Chemistry, 2501 Davey Road, Woodridge, IL 60517, Fax: 630-783-4646, jsingh@decode.com, (2) deCODE genetics, Inc*

Development of compounds as antagonist for one of a family of highly homologous receptors continues to be a major challenge. The EP3 receptor is one of the four related GPCR receptors (EP1-EP4) that bind prostaglandin E2 (PGE2). EP3 is expressed on platelets and mediates PGE2 amplified platelet aggregation. Here we describe the synthesis, structure-activity relationships (SAR) and biological evaluation of a series of 3,4-disubstituted oxyindoles which show potent antagonistic activity against the human EP3 receptor and high selectivity versus other prostanoid receptors—other human EP receptor family members (hEP1, hEP2, hEP4) and the human FP and IP receptors.

MEDI 95

Synthesis, biological evaluation and metabolic stability of 3,4-disubstituted indoles as potent and selective EP3 receptor antagonists

*J Singh[1], N Zhou[1], G Hategan[1], **W Zeller**[1], A Polozov[1], M Goldsmith[1], M Krohn[1], H Anderson[1], R Mishra[1], J Zhang[1], E Onua[1], J Ramirez[2], G Palsdottir[2], G Halldorsdottir[2], T Andresson[2], and M Gurney[2]. (1) Medicinal Chemistry Department, deCODE Chemistry, 2501 Davey Road, Woodridge, IL 60517, Fax: 630-783-4646, jsingh@decode.com, wzeller@decode.com, (2) deCODE genetics, Inc*

The EP3 receptor is one of four related GPCR receptors (EP1-EP4) that bind prostaglandin E2

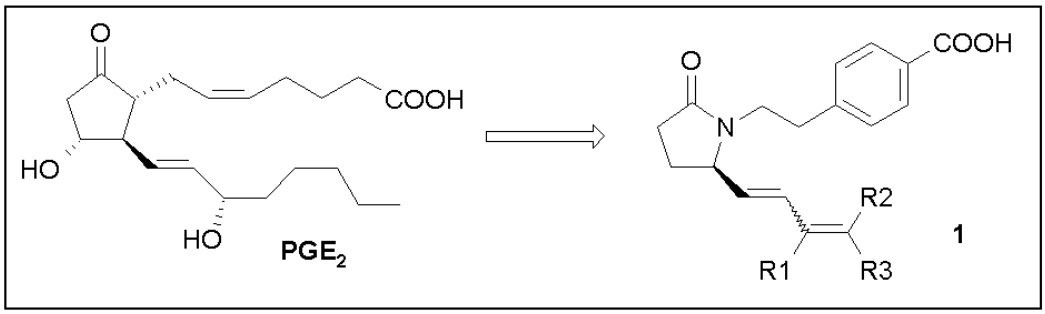
(PGE2). Population genetic studies conducted in Iceland have identified DNA variants of the gene encoding the EP3 receptor that confer a significantly increased risk for peripheral arterial occlusive disease (PAOD). deCODE's drug discovery effort led to the generation and validation of a pharmacophore model that resulted in the identification of peri-substituted heterocycles as prototypical EP3 receptor antagonists. Synthesis and SAR for a series of 3,4-disubstituted indoles which show potent antagonistic activity against the EP3 receptor and high selectivity towards the EP3 versus other members of the human prostanoid receptor family will be described. In addition, data on in-vitro ADME, pharmacokinetics following oral dosing in rodents and ex-vivo inhibition of platelet aggregation induced by PGE2 will be presented for a selected set of analogs.

MEDI 96

Discovery of novel aza-prostaglandin derivatives analogs of PGE2 as selective EP2 and EP4 receptors agonists

*Gian Luca Araldi[1], **Nadia Brugger**[1], Bagna Bao[2], David Fischer[2], Srinivasa Karra[1], Sean McKenna[2], Yufang Xiao[1], and Zhong Zhao[1]. (1) Medicinal Chemistry Group, Serono Research Institute, One Technology Place, Rockland, MA 02370, Fax: 781-681-2939, gian.araldi@serono.com, nadia.brugger@serono.com, (2) Lead Discovery Group, Serono Research Institute*

The preparation and assessment of biological activity of azaprostaglandin derivatives **1** analogues of natural PGE_2 is described. Replacement of the hydroxyl cyclopentanone ring with a chemically more stable heterocyclic ring, substitution of the unsaturated α-alkenyl chain with a metabolically more stable phenethyl chain and conversion of the ω-chain to a substituted diene led to the development of potent and selective analogs of natural PGE_2 with improved pharmacokinetic profile. Receptor selectivity tuning was obtained by the appropriate selection of the ω-chain. The discovery of a potent selective EP_2 and EP_4 receptors dual agonist is described, as well as the optimization of its synthesis. This novel analogue revealed to be particularly efficacious in various in vivo models, like bronchodilation, ulcerative colitis or ovulation induction.



MEDI 97

Structure-based design of a class of potent small molecule inhibitors of Bcl-2 and Bcl-

xL proteins

Guozhi Tang[1]*, Zaneta Nikolovska-Coleska*[1]*, Renxiao Wang*[1]*, Jie Guo*[1]*, Mei Lan Liu*[1]*, Su Qiu*[1]*, York Tomita*[2]*, and Shaomeng Wang*[1]*. (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, Fax: 734-647-9647, tanggle@med.umich.edu, (2) Georgetown University*

Overexpression of B-cell lymphocyte/leukemia-2 (Bcl-2) and its homologous Bcl-xL proteins plays an important role for the resistance of many types of human cancer to current chemotherapeutic agents and radiation therapies. Non-peptide, cell-permeable, small molecules inhibitors that bind to the BH3 binding groove in Bcl-2 and Bcl-xL proteins can effectively antagonize the anti-apoptotic activity of Bcl-2 and Bcl-xL through blocking the interaction of Bcl-2/Bcl-xL with pro-apoptotic proteins such as Bid and Bad. Design of small-molecule inhibitors of Bcl-2/Bcl-xL is currently being pursued as a highly promising therapeutic strategy for new anti-cancer drug design. Based on the three-dimensional structures of Bcl-xL, Bcl-2 and their complexes with gossypol, we have designed a new class of highly potent non-peptide, small-molecule inhibitors of Bcl-2 and Bcl-xL proteins. Our results suggest that this class of potent small-molecule inhibitors of Bcl-2/Bcl-xL may have a great therapeutic potential for the treatment of many forms of cancer. We wish to present the design, synthesis, biochemical and biological evaluation for this class of novel small-molecule inhibitors of Bcl-2 and Bcl-xL proteins.

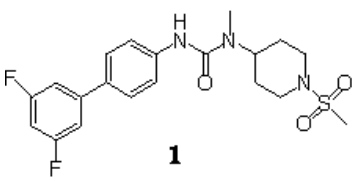
MEDI 98

Discovery of novel orally active and selective ureido-NPY Y5 antagonists

Guoqing Li*, Ying Huang, Joseph Kelly, Andrew Stamford, William Greenlee, Deborra Mullins, Mario Guzzi, Xiaoping Zhang, Joyce J. Hwa, Jun Gao, Lorraine Ghibaudi, Sam Weihaus, and K-C. Cheng, Schering-Plough Research Institute, 2015 Galloping Hill Road/ MS 2545, Kenilworth, NJ 07033, Guoqing.li@spcorp.com*

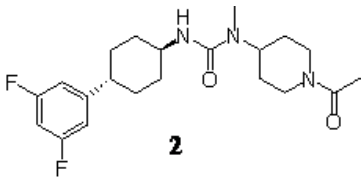
Neuropeptide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems in mammals. This peptide mediates a number of physiological functions through its various receptor subtypes. Extensive reports have suggested that the Y_5 receptor subtype plays a key role in regulation of food intake and energy expenditure. Consequently the NPY Y_5 receptor has generated tremendous interest in the pharmaceutical industry as a target of anti-obesity treatment.

Based on the first generation NYP Y5 antagonist **1**, extensive SAR studies were carried out. While keeping the good binding affinity and functional activity in the new antagonists, we focused on the optimization of PK, brain penetration ratio and other properties. The mutagenicity liability of the aminobiphenyl fragment of **1** was also addressed by a cyclohexyl replacement. This effort leads to the discovery of a novel NPY Y5 antagonist **2**. The ID_{50} of **2** in D-Trp^{34}-NPY-induced feeding assay is 2.1 mg/kg.



1

r/h Y5 Ki = 0.4 nM
rY5 Kb=0.4 nM
B/P= 1 (DIO rat)
C. Monkey IV $T_{1/2}$= 48 hr
Kinetic Solubility 25μM
D-Trp34 : >50%I @1 mpk



2

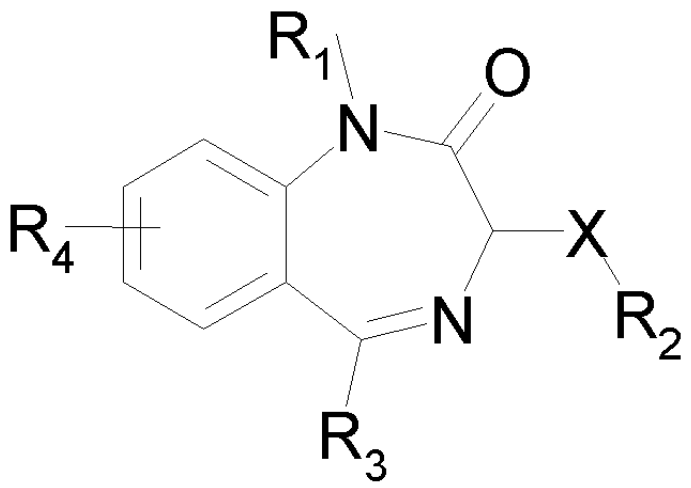
r/h Y5 Ki = 1.8 nM
rY5 Kb=2.7 nM
$AUC_{0\text{-}6h}$ =9188 hr ng/ml
C6h =1107 ng/ml
B/P= 1 (6h, DIO rat)
Kinetic Solubility >250 μM
[D-Trp^{34}]NPY : ID_{50}=2.1 mg/kg po

MEDI 99

Benzodiazepines as selective bradykinin B2 receptor antagonists

Carmen Leung[1]*, V. Santhakumar*[1]*, Mirek Tomaszewski*[1]*, Christopher Walpole*[1]*, Simon Woo*[1]*, Lynda Adam*[2]*, Joanne Butterworth*[2]*, Claude Godbout*[2]*, Kemal Payza*[2]*, and Marie Roumi*[3]*. (1) Department of Chemistry, AstraZeneca R&D Montréal, 7171 Frédérick-Banting, St. Laurent (Montréal), QC H4S 1Z9, Canada, Fax: 514-832-3232, carmen.leung@astrazeneca.com, (2) Department of Molecular Pharmacology, AstraZeneca R&D Montréal, (3) Department of Drug Metabolism and Pharmacokinetics, AstraZeneca R&D Montréal*

Bradykinin (BK) is a nonapeptide produced by the action of kallikrein enzymes or a mixture of mast cell tryptase and elastase on kininogens. Two subtypes of BK receptors, B1 and B2, which belong to the family of G-protein coupled receptors (GPCRs), are expressed in a number of types of human tissue. Activation of these receptors by BK or BK-related peptides has been implicated in a number of disease states, suggesting B1 and B2 receptors as potential targets for therapeutic intervention. In particular, animal studies indicate that the activation of B2 receptors by kinins is involved in the initiation and maintenance of inflammatory pain, hinting at the potential of B2 receptor antagonists as analgesics. The discovery of a series of benzodiazepine compounds as potent and selective B2 receptor antagonists will be presented.

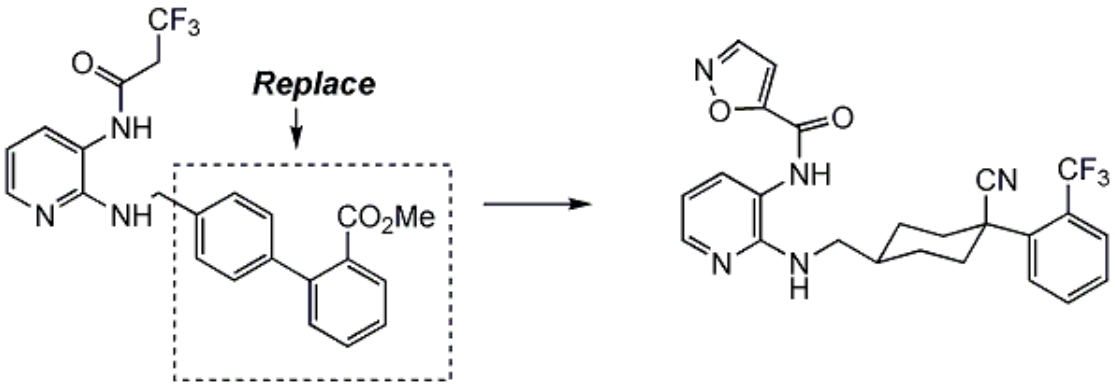


MEDI 100

Potent and selective BK-1 antagonists – 4-substituted phenyl cyclohexanes

John J. Lim[1]*, M. Kristine Markowitz*[1]*, K.L. Murphy*[1]*, S.S. O'Malley*[1]*, R. W. Ransom*[2]*, Ray S. Chang*[1]*, D.J. Pettibone*[1]*, R.M. Freidinger*[3]*, M. G. Bock*[3]*, and D.S. Su*[3]*. (1) Department of Medicinal Chemistry, Merck & Co, WP 14-3, P.O. Box 4, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-3971, john_lim@merck.com, (2) Department of Pharmacology, Merck Research Laboratories, (3) Department of Medicinal Chemistry, Merck Research Laboratories*

Bradykinin (BK) plays an important role in the pathophysiological processes accompanying pain and inflammation. Selective bradykinin B1 receptor antagonists have been shown to be anti-nociceptive in animal models and could be novel therapeutic agents for the treatment of pain and inflammation. We have explored chemical modifications in a series of a 4-substituted phenyl cyclohexanes which resulted in the discovery of an effective replacement to the biphenyl core of previously disclosed 2,3 diamino pyridines. The synthesis, SAR, and optimization of the pharmacokinetic profile of these compounds will be presented.

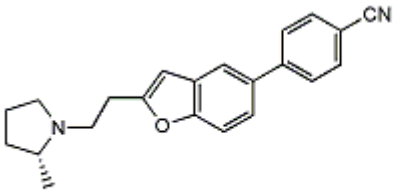


MEDI 101

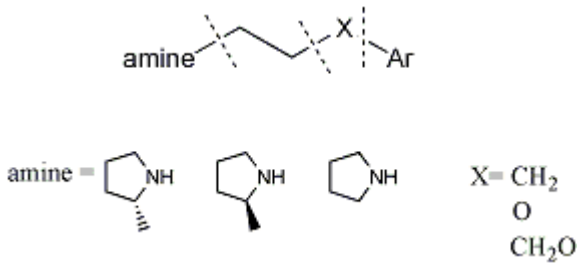
SAR of pyrrolidine containing H3 antagonists: Trends across multiple chemical series

***Diana L Nersesian**, Lawrence A Black, Thomas R Miller, Timothy A Esbenshade, Arthur A Hancock, and Marlon D Cowart, Neuroscience, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6123, diana.nersesian@abbott.com*

The histamine H3 receptor, primarily located in the CNS, is a presynaptic auto receptor that controls the release of histamine as well as other neurotransmitters implicated in a variety of central nervous system activities. A survey of amines in the benzofuran series of H3 antagonists, exemplified by ABT-239, showed that R-2-methylpyrrolidine provided the highest potency. General consensus was that R-2-methyl pyrrolidine was the preferred amine for binding to the H3 receptor; however, data verifying this binding superiority was limited. A library of varied, but simple compounds, containing an aryl-linker-amine matrix, was prepared to determine which amine increases potency at the H3 receptor. Three elements of the molecules were varied as shown below, the amine portion with pyrrolidine, R-2-methyl pyrrolidine, and S-2-methyl pyrrolidine, the flexible linker, and various aryl moieties. The SAR trends for the different series will be described.



ABT-239

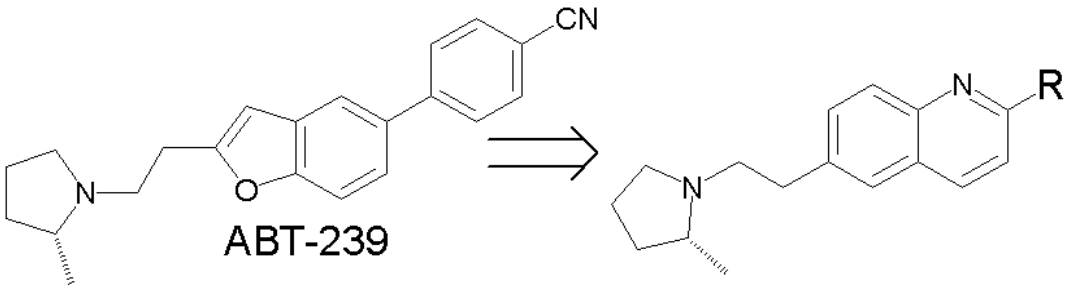


MEDI 102

Bicyclic heteroaromatic histamine H_3 antagonists: Synthesis, potency, and in vivo profiles of analogs optimized for drug-likeness

***Robert J. Altenbach**, Huaqing Liu, Timothy A. Esbenshade, Gerard B. Fox, Arthur A Hancock, and Marlon Cowart, Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, R4MN, AP9A, 100 Abbott Park Road, Abbott Park, IL 60064-6123, Fax: 847-937-9195, robert.j.altenbach@abbott.com*

The pharmacological profile of ABT-239, a benzofuran-based histamine H_3 antagonist targeted for cognitive and attention disorders with efficacy in animal models, has been recently described. To probe the SAR, the benzofuran core of ABT-239 was replaced with a variety of bicyclic heteroaromatic cores. In a series of quinolines, the Friedlander cyclization allowed for a broad variety of replacements for the 4-CN-Ph group of ABT-239. Most of the analogs were potent and selective H_3 ligands with good overall drug-like properties (e.g. CLogP, solubility, low m.w., moderate protein binding). Examples included compounds with high potency in binding (K_i(nM) = 0.26/0.93 (human/rat)) and functional (K_b = 2.95 nM (hH_3 FLIPR)) assays. Several derivatives had excellent PK (F% 30-100%; $t_{1/2}$ 1-10 hrs; brain/blood ratio 0.45-42x) and metabolic properties. Several compounds were found efficacious in two behavior models: the five-trial inhibitory avoidance acquisition model (0.3 mg/kg) and a social recognition memory model (0.01 mg/kg).

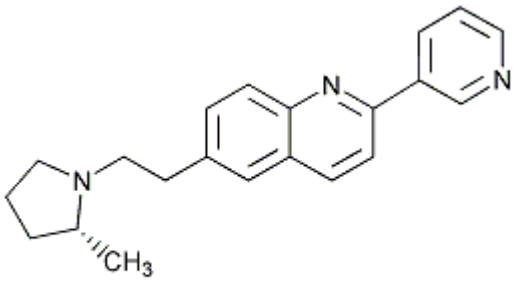


MEDI 103

Design, synthesis, and structure-activity relationship of novel non-imidazole histamine H3 antagonists

*Huaqing Liu[1], **Robert J. Altenbach**[1], Thomas R. Miller[2], Timothy A. Esbenshade[1], Arthur A Hancock[1], and Marlon Cowart[1]. (1) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, R4MN, AP9A, 100 Abbott Park Road, Abbott Park, IL 60064-6123, Fax: 847-937-9195, huaqing.liu@abbott.com, robert.j.altenbach@abbott.com, (2) Neuroscience Research, R4MN, Abbott Laboratories*

Histamine H3 receptors control the release of histamine from histaminergic neurons in the central nervous system (CNS). They can also modulate the release of other important neurotransmitters important for cognition as well. It is widely believed that H3 receptor antagonists have the potential to serve as therapeutics for memory and learning deficits, Alzheimers's disease, epilepsy, and ADHD. We have recently found a series of quinoline compounds to be highly potent H3 antagonists with binding Ki values at rat H3 receptors ranging 0.4 –10 nM and human H3 receptors ranging 0.1 –5 nM. Selected high potency compounds were profiled more extensively, and found to be selective for H3, versus H1, H2, H4, and other receptors. The synthesis of the series was quite flexible, utilizing as the key step a Friedlander condensation between an ortho-aminoaldehyde and a variety of aryl and heteroaryl acetophenones. Synthesis and in vitro properties will be described.

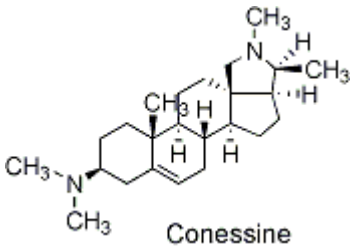


MEDI 104

Discovery of novel natural alkaloid conessine as potent histamine H3 receptor antagonist

Chen Zhao[1]*, Y. L. Bennani*[2]*, S. Gopalakrishnan*[1]*, M. Sun*[1]*, T. A. Esbenshade*[1]*, K. M. Krueger*[1]*, T. R. Miller*[1]*, D. G. Witte*[1]*, Kennan C. Marsh*[3]*, M. D. Cowart*[1]*, and A. A. Hancock*[1]*. (1) Department of Neuroscience Research, GPRD, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6123, chen.zhao@abbott.com, (2) Vertex Pharmaceuticals, (3) Neuroscience Research, GPRD, Abbott Laboratories*

A naturally occurring alkaloid, conessine, was found to interact potently with H3 receptors in a radioligand-based high-throughput screen. Confirmatory studies showed high potency at both human and rat H3 receptors (pKi = 8.27 and 7.91, respectively). The compound is also a competitive antagonist, based on results from FLIPR and GTPgS binding assays. Further in vitro tests show that conessine is selective for both human and rat H3 receptors, compared to the H1, H2 and H4 receptor subtypes. In rat, the compound efficiently penetrates the brain (brain/plasma ratio is 44.4x at 1 hour after 1 mg/kg IV dosing) and displays a long CNS half-life. Conessine is the fourth natural product found to have H3 receptor antagonist activity, but it is much more potent than the other three (verongamine, carcinine and aplysamine). In spite of high potency, due to specific consequences of its dibasic nature, conessine itself lacks acceptable overall drug-like properties. In order to explore the potential of this novel structure, two conessine derivatives were made, in which the determined potencies revealed key elements required for binding. The knowledge obtained from the interesting natural product conessine could help design more structurally novel compounds with drug-like properties.



Conessine

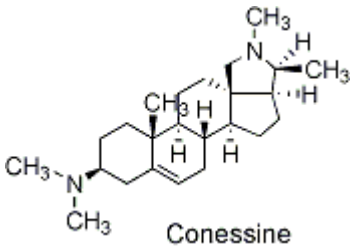
MEDI 104

Discovery of novel natural alkaloid conessine as potent histamine H3 receptor antagonist

Chen Zhao[1]*, Y. L. Bennani*[2]*, S. Gopalakrishnan*[1]*, M. Sun*[1]*, T. A. Esbenshade*[1]*, K. M. Krueger*[1]*, T. R. Miller*[1]*, D. G. Witte*[1]*, Kennan C. Marsh*[3]*, M. D. Cowart*[1]*, and A. A. Hancock*[1]*. (1) Department of Neuroscience Research, GPRD, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6123, chen.zhao@abbott.com, (2) Vertex Pharmaceuticals, (3) Neuroscience Research, GPRD, Abbott Laboratories*

A naturally occurring alkaloid, conessine, was found to interact potently with H3 receptors in a radioligand-based high-throughput screen. Confirmatory studies showed high potency at both human and rat H3 receptors (pKi = 8.27 and 7.91, respectively). The compound is also a competitive antagonist, based on results from FLIPR and GTPgS binding assays. Further in vitro tests show that conessine is selective for both human and rat H3 receptors, compared to the H1, H2 and H4 receptor subtypes. In rat, the compound efficiently penetrates the brain (brain/plasma ratio is 44.4x at 1 hour after 1 mg/kg IV dosing) and displays a long CNS half-life. Conessine is the fourth natural product found to have H3 receptor antagonist activity, but it

is much more potent than the other three (verongamine, carcinine and aplysamine). In spite of high potency, due to specific consequences of its dibasic nature, conessine itself lacks acceptable overall drug-like properties. In order to explore the potential of this novel structure, two conessine derivatives were made, in which the determined potencies revealed key elements required for binding. The knowledge obtained from the interesting natural product conessine could help design more structurally novel compounds with drug-like properties.



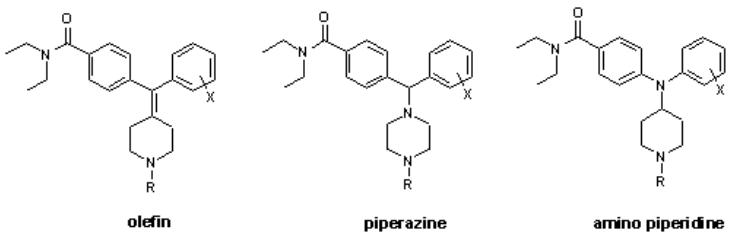
Conessine

MEDI 105

Synthesis and pharmacological evaluation of selective, potent delta opioid agonists as novel analgesics

Andrea Penwell[1]*, Andrew Griffin*[2]*, Paul Jones*[2]*, Sylvain Bernard*[2]*, Carmen Leung*[2]*, Simon Woo*[2]*, William Brown*[2]*, Christopher Walpole*[2]*, Maryse Labarre*[3]*, Martin Coupal*[3]*, Stéphane St-Onge*[3]*, Lejla Hodzic*[3]*, Dominic Salois*[3]*, and Kemal Payza*[3]*. (1) Department of Chemistry, AstraZeneca R&D Montréal, 7171 Frédérick-Banting, Ville St. Laurent, QC H4S 1Z9, Canada, Fax: 514-832-3232, Andrea.Penwell@astrazeneca.com, (2) Department of Chemistry, AstraZeneca R&D Montréal, (3) Department of Pharmacology, AstraZeneca R&D Montréal*

It is well established that three main opioid receptor subtypes exist in the central and peripheral nervous systems – mu, delta and kappa. Morphine and morphine-like compounds act at the mu opioid receptor and although potent analgesics, they are associated with unwanted side effects such as tolerance, addiction and respiratory depression. The investigation of delta agonists as novel analgesics with a reduced side effect profile will be presented. Our chemical strategy has mainly focused on developing highly selective agonists based on the olefin, piperazine and amino piperidine scaffolds shown below.



MEDI 106

Rationale and synthesis of potent dual δ/μ opioid receptor ligands for motility disorders

Henry J. Breslin*, Tamara A. Miskowski, Chaozhong Cai, Santosh V. Coutinho, Sui-Po Zhang, Pamela J. Hornby, and Wei He, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, Welsh and McKean Rds, P.O. Box 0776, Spring House, PA 19477, Fax: 215-628-4985, HBreslin@prdus.jnj.com*

Compounds that modulate opioid receptors (ORs) are well recognized as useful therapeutic agents for pain management (centrally active) and GI motility regulation (peripherally active). Recently we reported on a small set of dual δ/μ OR ligands with potential utility for GI indications (J.Med.Chem. 2004, 47, 5009-5020). Further refinement of our preliminary leads, via a structure activity relationship (SAR) exercise, has resulted in a second generation of dual δ/μ analogues that possess significantly improved activities for both the δ (up to 10 fold more potent; Ki 0.1nM) and μ (up to 180 fold more potent; Ki 0.3 nM) ORs. These related SAR results will be presented.

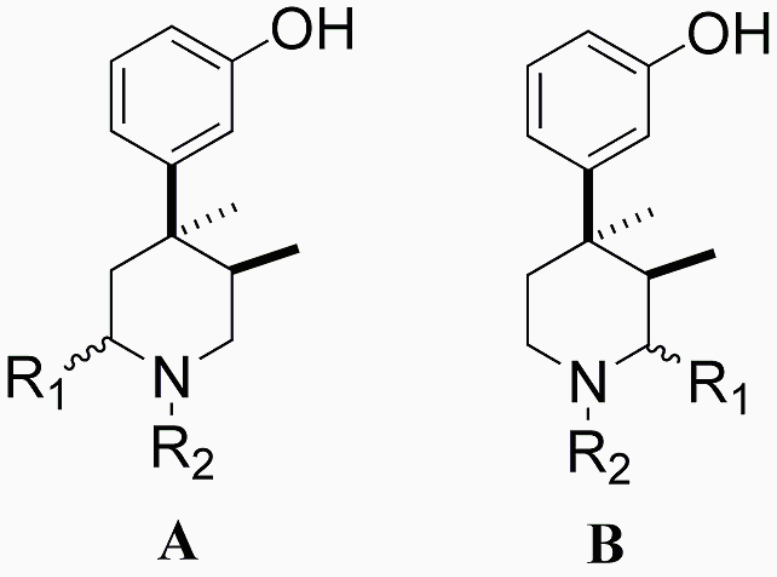
MEDI 107

Synthesis and structure activity relationship of a series of 2- and 6-substituted trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists

Allan J. Goodman*[1], Bertrand Le Bourdonnec[1], Mathieu Michaut[1], Hai Fen Ye[1], Thomas M. Graczyk[2], Serge Belanger[1], Robert N. DeHaven[2], and Roland E. Dolle[1]. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, agoodman@adolor.com, (2) Department of Pharmacology, Adolor Corporation*

The series of trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines have been widely investigated as opioid receptor antagonists. Structure activity relationships (SAR) in this series has focused largely on substitution of the piperidine nitrogen and modification of the phenolic moiety. To

investigate the effects of substitution at the 2- or 6- position of the piperidine ring on opioid receptor binding, novel analogs (A, B) were prepared. Synthesis, SAR and in vitro profile of these novel derivatives will be presented.



MEDI 107

Synthesis and structure activity relationship of a series of 2- and 6-substituted trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists

Allan J. Goodman[1], *Bertrand Le Bourdonnec*[1], *Mathieu Michaut*[1], *Hai Fen Ye*[1], *Thomas M. Graczyk*[2], *Serge Belanger*[1], *Robert N. DeHaven*[2], *and Roland E. Dolle*[1]. *(1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, agoodman@adolor.com, (2) Department of Pharmacology, Adolor Corporation*

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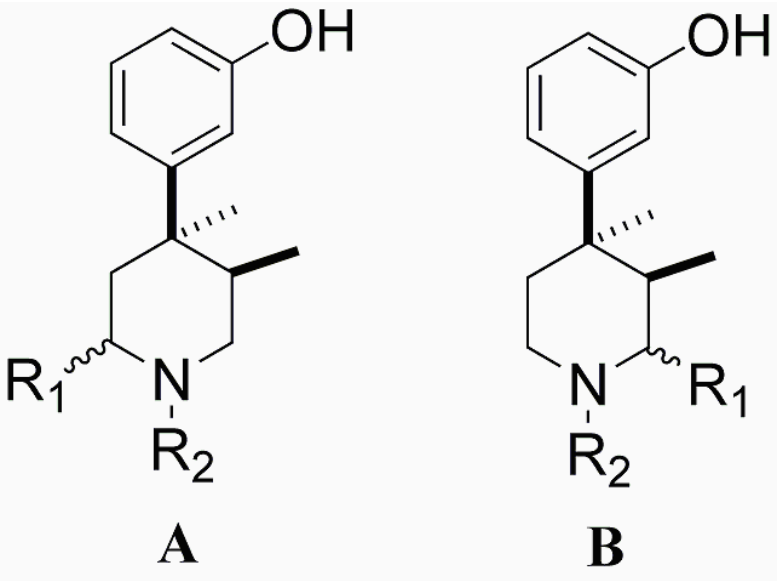


MEDI 108

Design, synthesis and biological evaluation of mu opioid selective biaryl-substitiuted 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one derivatives

Alfonzo D. Jordan[1]*, Michael J. Orsini*[2]*, Steven A. Middleton*[2]*, Peter J. Connolly*[2]*, Douglas E. Brenneman*[1]*, Kevin Pan*[1]*, and Allen B. Reitz*[1]*. (1) Drug Discovery Division, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, P.O. Box 776, Welsh and McKean Roads, Spring House, PA 19477, Fax: 215-628-4985, ajordan@prdus.jnj.com, (2) JNJPRD, Raritan, NJ*

Abstract: The 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one substructure found in spiperone has been widely used in medicinal chemistry and drug discovery over the past 40 years. We have prepared a series of N-(biarylalkyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one compounds and evaluated them at opioid (mu, delta, kappa) and Opioid Receptor Like-1 (ORL-1) receptors. We also evaluated their functional properties at the mu and ORL-1 (nociceptin) receptors. Structures may have utility in the treatment of a variety of human disorders, such as cough, chronic or neuropathic pain anxiety, and depression,. We have conducted structure activity relationship studies based upon the 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one scaffold. Substitution of the piperidine nitrogen with biarylalkyl groups of varying substitution led to a series that displayed a high degree of affinity for the mu-opioid receptor.

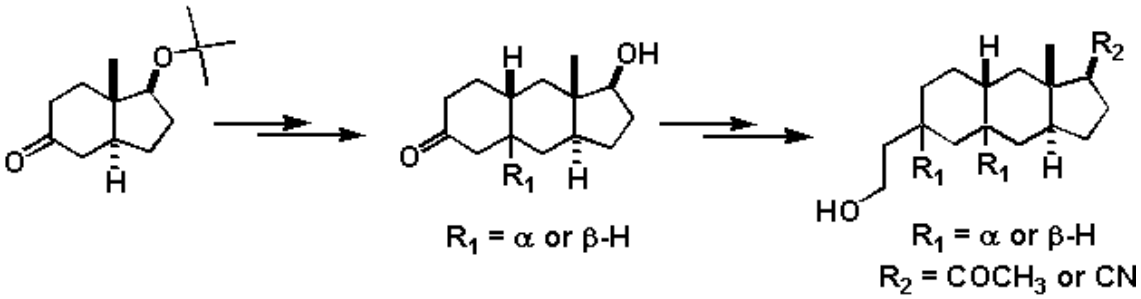
MEDI 109

Synthesis and evaluation of the benz[*f*]indene neurosteroid analogues

Jamie B Scaglione[1]*, Brad D. Manion*[2]*, Alex S. Evers*[3]*, Steven Mennerick*[4]*, Charles F. Zorumski*[4]*, and Douglas F. Covey*[5]*. (1) Chemical Biology Program, Washington University School of Medicine, 660 S. Euclid, Campus Box 8103, St. Louis, MO 63110, Fax: 314-362-7058, jlbruns@artsci.wustl.edu, (2) Department of Anesthesiology, Washington University*

School of Medicine, (3) Departments of Anesthesiology and Molecular Biology and Pharmacology, Washington University School of Medicine, (4) Departments of Psychiatry and Anatomy and Neurobiology, Washington University School of Medicine, (5) Department of Molecular Biology and Pharmacology, Washington University School of Medicine

Neuroactive steroids have anxiolytic, anticonvulsant, anesthetic, and hypnotic properties. These effects appear to be mediated by modulation of γ-aminobutyric acid type A ($GABA_A$) receptors. Structure-activity relationships have established a pharmacophore for positive modulation of the $GABA_A$ receptor that consists of a 17β-hydrogen bond acceptor and a 3α-hydrogen bond donor. While the distance between these groups and their orientation is important, it is unclear what role the steroid ring system serves other than that of a spacer. To address the importance of the hydrophobic framework we synthesized a series of benz[*f*] indenes and evaluated their effects on the following: (1) electrophysiology of *Xenopus* oocytes expressing recombinant $GABA_A$ receptors (2) displacement of [^{35}S]*tert*-butylbicyclophosphorothionate ([^{35}S]TBPS) from the $GABA_A$ receptor picrotoxin binding site and (3) anesthesia induction assay by tadpole loss of righting reflex.

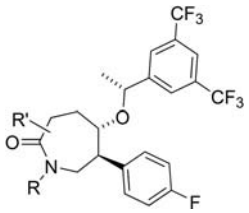


MEDI 110

NK1 Antagonists based on seven membered lactam scaffolds

Jason M Elliott[1]*, Emma J Carlson*[1]*, Gary G. Chicchi*[2]*, Olivier Dirat*[1]*, Maria Dominguez*[1]*, Ute Gerhard*[1]*, Richard Jelley*[1]*, A. Brian Jones*[1]*, Marc M Kurtz*[2]*, Kwei-lan Tsao*[2]*, and Alan Wheeldon*[1]*. (1) The Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow CM20 2QR, United Kingdom, jason_elliott@merck.com, (2) Merck Research Laboratories, Rahway, NJ 07065*

The utility of neurokinin-1 receptor (NK_1R) antagonists for the treatment of chemotherapy-induced emesis has now been established. There have been many reports of NK_1R antagonists in which the elements necessary for binding are constructed around five or six-membered cyclic cores. However, extension to larger ring sizes is rare. We have now found that the use of core scaffolds based on seven-membered rings leads to novel NK_1R antagonists combining relatively simple, compact structures with high *in vitro* hNK_1R affinity and promising *in vivo* properties.



MEDI 111

Design and synthesis of thrombin receptor antagonists

Martin Clasby[1]*, Samuel Chackalamannil*[1]*, Michael Czarniecki*[1]*, Dario Doller*[1]*, Keith Eagen*[1]*, William J. Greenlee*[1]*, Grace Kao*[1]*, Yan Lin*[1]*, Hsingan Tsai*[1]*, Yan Xia*[1]*, Jacqueline Agans-Fantuzzi*[2]*, Ho-Sam Ahn*[2]*, George Boykow*[2]*, Matthew Bryant*[2]*, Mahdu Chintala*[2]*, Carolyn Foster*[2]*, and Janice Lau*[2]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, martin.clasby@spcorp.com, (2) Biological Research, Schering-Plough Research Institute*

The Thrombin receptor (protease activated receptor-1, PAR-1) is a member of the superfamily of seven transmembrane G-protein coupled receptors. Thrombin is a multi-functional protease involved in haemostasis and wound healing. PAR-1 mediates the cellular actions of thrombin, for example, platelet aggregation, cell proliferation, and inflammatory responses. Through this mechanism thrombin is the most potent activator of platelets and this activation plays a critical role in the progression of thrombosis. Because of this a PAR-1 antagonist ought to have significant therapeutic utility in treating disorders such as thrombosis and atherosclerosis without interfering with thrombin's role in the coagulation cascade. This is predicted to lead to significant safety benefits with regard to bleeding liabilities over current antithrombotic therapies (e.g. thrombin and factor Xa inhibitors). The design, synthesis and activity of a novel series of thrombin receptor antagonists based upon metabolism of our first generation development candidate will be described.

MEDI 112

Rational design and synthesis of bicyclic proline analogs as potential cyclophilin A inhibitors

Lynn M. Betts *and Nicolas Moitessier, Department of Chemistry, McGill University, 801 Sherbrooke St. West, Room 206, Montreal, QC H3A 2K6, Canada, lynn.betts@mail.mcgill.ca*

We will present a series of functionalized bicyclic cores that have been designed as potential inhibitors of Cyclophilin A. These scaffolds were “rationally designed” using two integrated strategies: predictive power provided by in-house computational approaches combined with efficient synthetic planning. Virtual techniques provide valuable information regarding the shape and functionality of potentially active compounds while synthetically, cost, feasibility and scalability are limiting considerations.

MEDI 112

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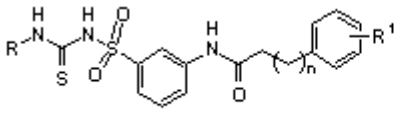
We will present a series of functionalized bicyclic cores that have been designed as potential inhibitors of Cyclophilin A. These scaffolds were “rationally designed” using two integrated strategies: predictive power provided by in-house computational approaches combined with efficient synthetic planning. Virtual techniques provide valuable information regarding the shape and functionality of potentially active compounds while synthetically, cost, feasibility and scalability are limiting considerations.

MEDI 113

Design and synthesis of arylsulfonyl thioureas as novel potent cyclophilin ligands

Larisa E. Serdyuk*, Douglas E. Wilkinson, Sean K. Hamilton, Sergei A. Belyakov, Ling Wei, Bert E. Thomas IV, Gregory S. Hamilton, Edmond Massuda, Marigo Stathis, Mike Fuller, Camilo J. Rojas, Joseph P. Steiner, Shirley Huang, George Liu, and Yong-Qian Wu, Guilford Pharmaceuticals Inc, 6611 Tributary Street, Baltimore, MD 21224, serdyukl@guilfordpharm.com*

Cyclophilin A (CyPA) is a member of peptidylprolyl isomerase (PPIases or rotamase) cyclophilin's family, which binds cyclosporin A (CsA) and plays critical roles in a variety of biological processes. High levels of CyPA in the brain promise therapeutic utility for cyclophilin ligands in treating CNS disorders, thus suggesting cyclophilin as a new target for neurological drug design. Previously we reported the results of lead identification through “virtual screening” and the synthesis of our first series of non-peptidic cyclophilin ligands (J. Med. Chem. 2003, 46, 1112-1115). Here we describe design, synthesis and SAR of arylsulfonyl thioureas (structure 1), as a new series of potent cyclophilin ligands along with their biological activity.



1

R = Aryl, Alkyl

R^1 = H, F, CN, OMe, CF_3, etc.

n = 1 - 4

MEDI 114

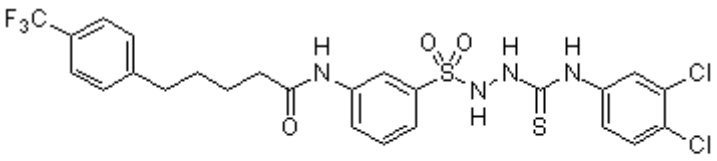
Design and synthesis of arylsulfonylthiosemicarbazides as potent, nonpeptidic cyclophilin inhibitors

Yong-Qian Wu, ***Douglas E. Wilkinson****, Gregory S. Hamilton, Joseph Steiner, Sean Hamilton, Bert E. Thomas IV, Edmond Massuda, Mike Fuller, Marigo Stathis, and Sergei A. Belyakov, Guilford Pharmaceuticals Inc, 6611 Tributary St., Baltimore, MD 21224,*

wuy@guilfordpharm.com, wilkinsond@guilfordpharm.com

The therapeutic potential of nonimmunosuppressive cyclophilin inhibitors is indicated both pathologically by cyclophilin's role in HIV infectivity and neurologically by the high expression of cyclophilins within the nervous system coupled with strong evidence for their role in neuroprotection provided by various studies involving cyclosporin A and its nonimmunosuppressive analogs. In our efforts to exploit this potential, we've uncovered several new classes of potent, nonpeptidic cyclophilin inhibitors.

As previously reported, initial virtual screening for nonpeptidic inhibitors of the peptidylprolyl isomerase activity of cyclophilin lead to the discovery of our first series of relatively simple, moderately active compounds. Computer model driven SAR around this first series of compounds produced a more potent second generation of thiosemicabazide-based compounds which was further optimized to generate a novel class of sulfonylthiosemicarbazide-based inhibitors exhibiting low to sub-micromolar activity for the rotamase inhibition of cyclophilin. Synthetic strategies, SAR results and details of the biological characterizations are presented.



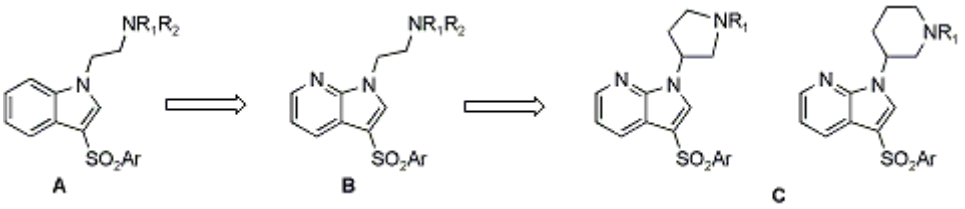
GPI 18940 200 nM IC_{50}

MEDI 115

Novel 1-(azacyclyl)-3-arylsulfonyl-1H-pyrrolo[2,3-b]pyridines as 5-HT6 agonists and antagonists

Hassan Elokdah[1]*, Albert J. Robichaud*[2]*, David Z. Li*[3]*, Geraldine R. McFarlane*[3]*, Ronald C. Bernotas*[3]*, Gregory J. Tawa*[3]*, Guo Ming Zhang*[4]*, Deborah L. Smith*[4]*, and Lee E. Schechter*[4]*. (1) Chemical & Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, elokdah@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Chemical and Screening Sciences, Wyeth Research, (4) Neuroscience, Wyeth Research*

1-Aminoethyl-3-arylsulfonyl-1H-indoles A are 5-HT6 receptor ligands with modest activity in a functional 5-HT6 assay. Introduction of an additional nitrogen in the phenyl ring of the indole provides 1-aminoethyl-3-arylsulfonyl-1H-pyrrolo[2,3-c]pyridines B with both enhanced 5-HT6 affinity and functional activity, many acting as 5-HT6 agonists. We sought to constrain the basic side chain as part of a ring to make 1-(azacyclyl)-3-arylsulfonyl-1H-pyrrolo[2,3-b] pyridines C incorporating a piperidinyl or pyrrolidinyl ring system. We will describe the challenging synthesis of these compounds as well as their 5-HT6 binding and in vitro functional activity.

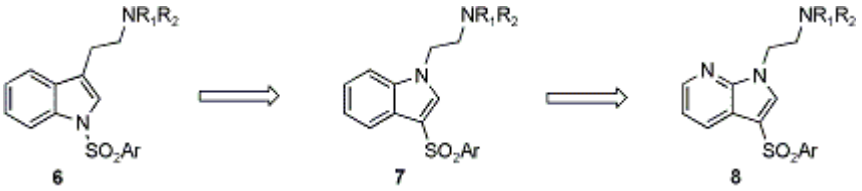


MEDI 116

Novel 1-(2-aminoethyl)-3-arylsulfonyl-1H-pyrrolo[2,3-b]pyridines as 5-HT$_6$ agonists and antagonists

Ronald C. Bernotas[1], *Steven Lenicek*[2], *Schuyler A. Antane*[2], *Guo Ming Zhang*[3], *Deborah L. Smith*[3], *Joseph Coupet*[3], *and Lee E. Schechter*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, bernotr@wyeth.com, (2) Chemical & Screening Sciences, Wyeth Research, (3) Neuroscience, Wyeth Research*

1-Arylsulfonyl-tryptamines **6** are 5-HT$_6$ receptor ligands. Recently, we have shown 1-(2-aminoethyl)-3-arylsulfonyl-1H-indoles **7**, in which the relative locations of the arylsulfonyl and basic side chain on the indole core are “flipped” relative to each other, are also good 5-HT$_6$ ligands. Introduction of an additional nitrogen in the indole ring provides 1-(2-aminoethyl)-3-arylsulfonyl-1H-pyrrolo[2,3-b]pyridines **8**. Many of these compounds proved to be high affinity 5-HT$_6$ ligands (K_i @ h-5-HT$_6$ < 10 nM). Depending on substitution, full agonists or full antagonists in a 5-HT$_6$ functional (cyclase) assay were identified.



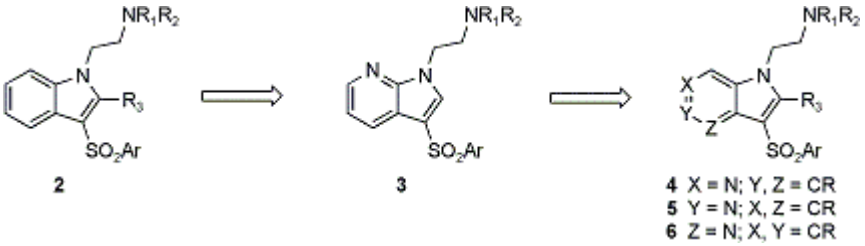
MEDI 117

1-(2-Aminoethyl)-3-(arylsulfonyl)-1H-pyrrolopyridines as novel 5-HT$_6$ receptor ligands

Ronald C. Bernotas[1], *Schuyler A. Antane*[2], *Steven Lenicek*[2], *Simon N. Haydar*[2], *Albert J. Robichaud*[3], *Guo Ming Zhang*[4], *Deborah L. Smith*[4], *Joseph Coupet*[4], *and Lee E. Schechter*[4]. *(1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, bernotr@wyeth.com, (2) Chemical & Screening Sciences, Wyeth Research, (3) Chemical and Screening Sciences, Wyeth Research, Princeton, (4) Neuroscience, Wyeth Research*

We have demonstrated that many 1-(2-aminoethyl)-3-arylsulfonyl-1H-indoles **2** are 5-HT$_6$ ligands. Introduction of an additional nitrogen in the indole ring provided 1-(2-aminoethyl)-3-

arylsulfonyl-1H-pyrrolo[2,3-b]pyridines **3**, which proved to have generally higher 5-HT_6 affinity compared to **2**. Appropriate substitution on **3** led to full agonists or full antagonists in a 5-HT_6 functional (cyclase) assay. We report here the synthesis of the three regioisomeric pyrrolopyridines (**4**, **5**, and **6**) by several routes and describe their 5-HT_6 binding and functional activity.

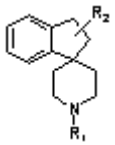


MEDI 118

Spirocyclic indanes as ligands for the NOP (ORL-1) receptor

R. Richard Goehring*, Xiaoming Zhou, Jin-Cheng Huang, Lisa J. Barnett, Qun Sun, Sam F. Victory, Kenneth J. Valenzano, Wendy S. Miller, Shen Shan, and Donald J. Kyle, Discovery Research, Purdue Pharma, L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, richard.goehring@pharma.com*

As part of a program to identify novel ligands for the NOP (formerly ORL-1) receptor, high throughput screening identified the spirocyclic indane/piperidine ring system as a useful scaffold. Synthetic exploration has lead to a series of potent and selective NOP antagonists which were shown to bind competitively with the native ligand to a common binding site at the NOP receptor. The SAR in this series, atypical for NOP ligands, will be presented.



MEDI 119

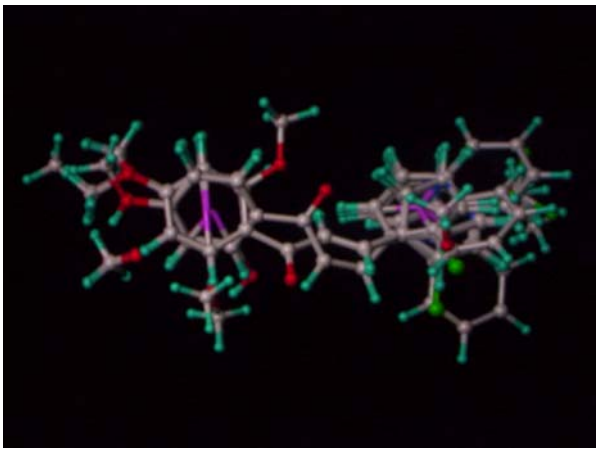
Development of predictive CoMFA and CoMSIA models for alkoxylated and hydroxylated chalcones as anti-malarial agents

Devendra Puntambekar*, Mange Ram Yadav, and Rajani Giridhar, Department of Medicinal chemistry, The M.S University of Baroda, Pharmacy department, Faculty of Tech & Engg, Kalabhavan, P O Box -51, Baroda, Baroda 390001, India, devendra_res@yahoo.co.uk*

Abstract:

Comparative molecular field analysis (CoMFA) and Comparative molecular similarity indices (CoMSIA) was performed on a series of alkoxylated and hydroxylated chalcones as

antimalarial agents. The ligand molecular superimposition on template structure was performed by atom/shape based RMS fit methods. The removal of outliers from the initial set of 69 compounds improved the predictivity of the models. The statistically significant model was established from 52 compounds, which were validated by evaluation of test set of 14 compounds. The atom and shape based alignment yielded best predictive CoMFA model (r2cv = 0.674, r2ncv = 0.957, r2pred = 0.670, F value = 83.040, r2bs = 0.992 with six components) while CoMSIA model yielded (r2cv = 0.610, r2ncv = 0.913, r2pred = 0.726, F value = 50.115, r2bs = 0.947 with seven components). The contour maps obtained from 3D-QSAR studies were appraised for the activity trends of the molecules. The results indicate that steric, electrostatic, hydrophobic and hydrogen bond donor substituents play significant role in the antimalarial activity of these compounds.



MEDI 120

A novel one-pot synthesis of thalidomide and its derivatives under microwave irradiation

***Ellis Benjamin**, Chemistry, Morgan State University, 1700 E. Cold Spring Lane, Baltimore, MD 21251, Fax: 4443-8858286, yhijji@morgan.edu, and Yousef Hijji, Chemistry Departemnt, Morgan State University*

The cyclic imide moiety is commonly found in many anti-HIV, and anti-cancer pharmaceuticals, such as thalidomide. Several rapid high-yield microwave techniques for the synthesis of unsubstituted, N-methoxy imides and thalidomide derivatives are presented here. Two novel microwave techniques for the synthesis of unsubstituted cyclic imides was established using cyclic anhydrides, ammonium chloride, with DMAP (catalytic) (69 – 90 %) yield, and cyclic anhydrides with ammonium acetate (59 – 100 %) yield. A second synthetic technique using cyclic anhydrides with methoxylamine hydrochloride provided the imides in (61 – 99 %) yield. We have created a two-step one-pot microwave synthesis of thalidomide and its derivatives using DMAP, NH4Cl, multiple anhydrides, and Glutamic acid in a conventional microwave resulting in (32 - 53 %) yield.

MEDI 120

A novel one-pot synthesis of thalidomide and its derivatives under microwave

irradiation

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MEDI 121

Synthesis of radiolabeled 5-(aminomethyl)-2l-aminopyrrolo[2,3-d]pyrimidine-4(3H)-one (preQ1) and 2-amino-5-[(1S, 2R, 3S)-2, 3-dihydroxycyclopent-4-enylamino-methyl] pyrrolo[2, 3-d]pyrimidine-4(3H)-one (queuine)

***Sureyya Olgen** and George A. Garcia, Department of Medicinal Chemistry, University of Michigan, 428 Church St., Ann Arbor, MI 48109-1065, solgen@umich.edu*

Radiolabelled 5-(aminomethyl)-2*l*-aminopyrrolo[2,3-d]pyrimidine-4(3H)-one ($preQ_1$) and 2-amino-5-[(1S, 2R, 3S)-2, 3-dihydroxycyclopent-4-enylamino-methyl]pyrrolo[2, 3-d]pyrimidine-4 (3H)-one (queuine) have been synthesized to study the recognition of tRNA by tRNA-guanine transglycosylase (TGT). $PreQ_1$ was synthesized via the reduction of the oxime (Figure 1), prepared from reduction of 5-(cyano)-2*l*-aminopyrrolo[2,3-d]pyrimidine-4(3H)-one to the aldehyde and subsequent treatment of the aldehyde with hydroxylamine hydrochloride. A convenient method for the synthesis of Q base was the amine exchange reaction between pyrrolopyrimidine and cyclopentylamine which was previously reported by Akimoto *et al*. (J. Chem. Soc. Perkin Trans. I, (1988), 1637-44 (Figure 2). Enzymological characterization of these TGT substrates will also be reported.

Figure 1

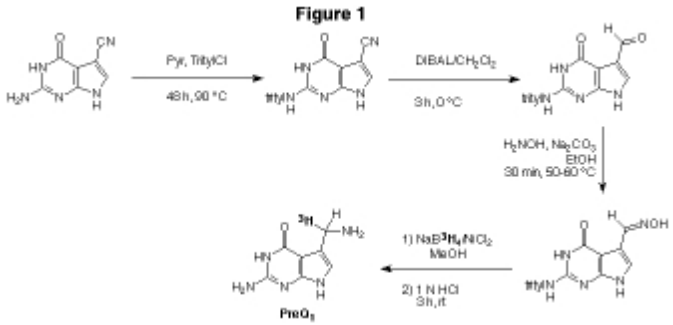
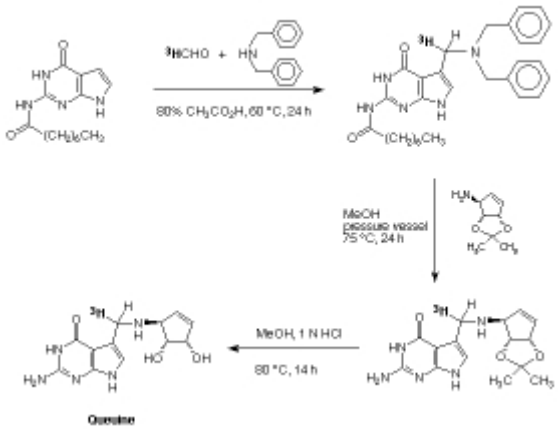


Figure 2



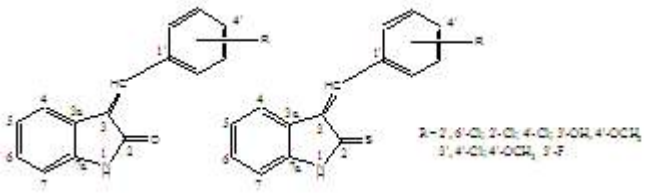
MEDI 122

Design and synthesis of novel indole deivatives as anti-angiogenic agents

Sureyya Olgen[1]*, Dogu Nebioglu*[1]*, and Eiichi Akaho*[2]*. (1) Pharmaceutical Chemistry, University of Ankara, Faculty of Pharmacy, Tandogan, Ankara 06100, Turkey, solgen@umich.edu, (2) Faculty of Pharmaceutical Sciences & High Technology Research Institute, Kobe Gakuin University*

Angiogenic theory presents an exiting opportunity for the development of novel small molecule anticancer agents that are noncytotoxic and lack drug resistance. Protein Tyrosine Kinase (PTK) functions has been associated with wide variety of human diseases including; cancers, pulmonary fibrosis, liver cirrhosis, kidney sclerosis, various inflammatory diseases including psoriasis and rheumatoid arthritis. The potential design and synthesize 3-substituted indoline derivatives for various PTK subtypes can support to treat a wide variety of human diseases. In our project we focus on synthesis and docking studies of 3-(substituted-benzylidene)-1, 3-dihydro indolin derivatives (Figure 1). These compounds were designed in order to provide answers to the following questions; 1-What are the electronic and steric effects of the substitutions in the phenyl ring at the C-3 position of 3-substituted indolin derivatives on the inhibitory potency? 2-What are the differences between the 3-(substituted)indolin-2-ones, 3 (substituted)indolin-2-thiones derivatives on the activity? Many compounds are known which inhibit by competitive binding to the tyrosine site. However, most of these inhibitors have low potency and moderate selectivity. It can conclude that much work is still required to decipher the appropriate targets and course of therapy for small molecule anticancer agents. Consequently, to find novel active indole derivatives can be promising agents to treat cancer and other diseases which were mentioned above.

Figure 1



MEDI 123

Lipophilicity coefficients of new potential PET dopamine D_2 and D_3 receptor ligands (*E*)-4, 3, 2-[^{11}C]methoxy-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-cinnamoylamides and (*E*)-4, 3, 2-[^{18}F]fluoro-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-cinnamoylamides

*Mingzhang Gao, **Ji-Quan Wang**, and Qi-Huang Zheng, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, Room L3-202, Indianapolis, IN 46202, Fax: 317-278-9711, migao@iupui.edu, jiqwang@iupui.edu*

(*E*)-4, 3, 2-[^{11}C]Methoxy-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-cinnamoylamides (**1a-c**) and (*E*)-4, 3, 2-[^{18}F]fluoro-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-cinnamoylamides (**1d-f**) have been synthesized as new potential brain D_2 and D_3 receptor radioligands for biomedical imaging technique positron emission tomography (PET) to study various neurological and psychiatric disorders. The ability of PET brain imaging agents to penetrate the blood-brain barrier (BBB) could be due, at least in part, to their lipophilicity. As part of our efforts to explore novel PET brain radioligands, we measured lipophilicity coefficients (log P) of **1a-f** by C-18 HPLC method. The lipophilicity range of analogs may serve as one important parameter to guide selection of new candidates. These log P values will be compared, and correlations between lipophilicity and in vivo PET imaging properties of selected analogs will be made.

MEDI 124

Synthesis of carbon-11 and fluorine-18 labeled 2-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline analogues as new potential PET AMPA receptor ligands

*Mingzhang Gao, **Ji-Quan Wang**, and Qi-Huang Zheng, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, Room L3-202, Indianapolis, IN 46202, Fax: 317-278-9711, migao@iupui.edu, jiqwang@iupui.edu*

The AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid) receptor antagonists may be useful as potential neuroprotective agents in the treatment of neurological diseases such as epilepsy, ischemia, Parkinson's disease, and multiple sclerosis. In vivo biomedical imaging technique positron emission tomography (PET) coupled with appropriate receptor radioligands has become a clinically valuable and accepted diagnostic tool to image brain diseases. Carbon-11 and fluorine-18 labeled 2-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline analogues were synthesized for evaluation as new potential PET imaging agents for brain AMPA receptor. The carbon-11 tracers 2-acetyl-1-aryl-6-[^{11}C]

methoxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines were prepared by *O*-[^{11}C]methylation of hydroxy-precursor 2-acetyl-1-aryl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines using [^{11}C]methyl triflate and isolated by solid-phase extraction (SPE) purification procedure. The fluorine-18 tracer 2-acetyl-6,7-dimethoxy-1-(4'-[^{18}F]fluorophenyl)-1,2,3,4-tetrahydroisoquinoline was prepared by [^{18}F]fluorination of the nitro-precursor 2-acetyl-6,7-dimethoxy-1-(4'-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline with K^{18}F/Kryptofix 2.2.2 through nucleophilic substitution and purification with the HPLC method.

MEDI 125

Development of [11C]MPT as a potential agonist PET tracer for 5-HT1A receptor imaging

*Vattoly J Majo[1], Ramin V. Parsey[1], Hadassah Tamir[1], Matthew Millak[1], Shu-Chi Hsiung[1], Jaya Prabhakaran[1], Norman R. Simpson[2], Julie Arcement[1], Ronald L. Van Heertum[2], J. John Mann[3], and **J. S. Dileep Kumar**[4]. (1) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, (2) Department of Radiology, Columbia University, (3) Department of Psychiatry, Radiology & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, (4) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, dk2038@columbia.edu*

Molecular imaging of 5-HT1AR has important implications for understanding the pathophysiology and therapeutic interventions of neuropsychiatric and neurodegerative disorders. The most successful radioligands studied so far for 5-HT1AR are based on antagonist ligands, which bind with equal affinity to both G-protein-coupled high affinity (HA) state and uncoupled low affinity (LA) state of 5-HT1AR. Agonist ligands, however, bind preferentially to the HA state of the receptor to provide a more meaningful functional measure of 5-HT1AR. Herein we report [11C-O-methyl]-2-{4-[4-(7-methoxynaphthalen-1-yl)piperazin-1-yl]-butyl}-4-methyl-2H-[1,2,4]triazine-3,5-dione ([11C]MPT) as a potential 5-HT1AR agonist PET tracer. MPT is a selective 5-HT1AR ligand with Ki = 1.3 nM. cAMP and GTP?S assays confirmed that MPT is an agonist with EC50 value lower than that of serotonin. Labeling experiments using desmethyl-MPT with [11C]CH3OTf in the presence of NaOH at room temperature in acetone provided [11C]MPT in 25% radiochemical yield (EOB). PET images obtained in anesthetized baboon show that [11C]MPT penetrates BBB and accumulates in 5-HT1AR specific regions. The radioactive uptake was selectively blocked with WAY100635 and 8-OH-DPAT further demonstrating the specificity of [11C]MPT to 5-HT1AR. The volumes of distribution (VT) of [11C]MPT in baboon correlate well with [11C]WAY100635 VT in baboons. The details of synthesis, pharmacology and in vivo PET evaluation of [11C]MPT will be presented.

MEDI 126

Synthesis and in vivo evaluation of [11C]MPM as a 5-HT2A receptor PET ligand

***Jaya Prabhakaran**[1], Ramin V. Parsey[1], Vattoly J Majo[1], Norman R. Simpson[2], Julie*

Arcement[1], Ronald L. Van Heertum[2], J. John Mann[3], and J. S. Dileep Kumar[1]. (1) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, jaya@neuron.cpmc.columbia.edu, (2) Department of Radiology, Columbia University, (3) Department of Psychiatry, Radiology & Division of Neuroscience, Columbia University & New York State Psychiatric Institute

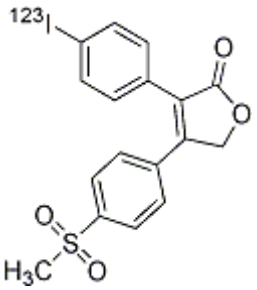
Serotonergic 5-HT2A receptors are of considerable interest to study the complex pathophysiology of schizophrenia and depression and also been proposed as putative targets for antipsychotic drugs. The utility of the radiotracers that have been developed so far for in vivo imaging of 5-HT2AR are limited due to their high nonspecific binding, inadequate pharmacological selectivity or longer equilibrium time for the ligand to reach target and reference region. In the present work, we report the radiosynthesis of [11C-O-methyl] (2R, 4R)-4-hydroxy-2-[2-[2-[2-(3-methoxy)phenyl]ethyl]phenoxy]ethyl-1-methyl pyrrolidine ([11C])MPM. MPM is a selective and high affinity (Ki = 1.6 nM) 5HT2A ligand, which has been studied for its inhibition of platelet aggregation induced by 5-HT2A receptors. We are interested to study the efficacy of [11C]MPM as a potential imaging agent for 5HT2A receptors in brain to study its implications in schizophrenia and depression. MPM and desmethylMPM were prepared from 3-hydroxymethylphenol in good yield. The total time required for the synthesis of [11C]MPM is 30 minutes from EOB using [11C]MeOTf in the presence of NaOH in acetone. The radiochemical yield obtained was 20% (EOB) and 99% chemical and radiochemical purities along with a specific activity >1000 Ci/mmol at the time of imaging studies. PET studies in anesthetized baboon showed a high uptake and widespread distribution of radioactivity in brain. Details of synthesis and in vivo evaluation of [11C]MPM will be presented.

MEDI 127

Synthesis of an iodine-123 labeled rofecoxib analogue: A potential SPECT agent

*George W. Kabalka[1], **Arjun R. Mereddy**[2], Brandy Belue[1], and Hildegard Schuller[3]. (1) Departments of Chemistry and Radiology, The University of Tennessee, Buehler Hall, Knoxville, TN 37996-1600, Fax: 865-974-2997, kabalka@utk.edu, (2) Departments of Chemistry & Radiology, University of Tennessee, Knoxville, TN 37996, amereddy@utk.edu, (3) Department of Pathology, Veterinary Teaching Hospital, University of Tennessee College of Veterinary Medicine*

In vitro studies with cell lines derived from adenocarcinomas of the lungs, pancreas, colon, stomach, breast and prostate, as well as experiments in relevant animal studies and epidemiological studies in humans, have provided evidence that cyclooxygenase inhibitors (both COX-1 and COX-2) can significantly reduce the risk for development of this cancer family. Cyclooxygenase inhibitors are thus being evaluated in cancer prevention and treatment trials. Recent reports have revealed that the chronic use of COX-2 inhibitors may increase the rate of cardiovascular morbidity. Monitoring patients undergoing chronic treatment with COX-2 inhibitors prior to and during therapy could become important in the future. Nuclear medicine imaging utilizing SPECT or PET could help in this regard. We have developed a rapid and convenient method (Nucl Med Biol 2004, 31, 935-938) for preparing an iodine-123 labeled rofecoxib analogue.

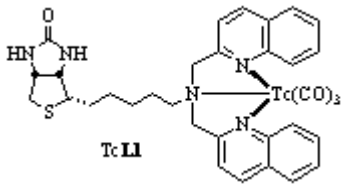


MEDI 128

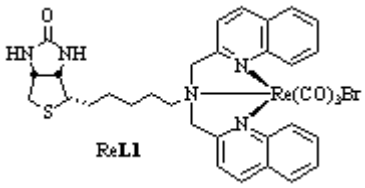
Biotin derivatives for radiotherapeutics and fluorescent in vivo models

Shelly James[1]*, Kevin Maresca*[2]*, John Valliant*[3]*, John W. Babich*[2]*, Laurie Doering*[4]*, and Jon A. Zubieta*[5]*. (1) Department of Chemistry, Syracuse University, East Syracuse, NY 13057, shjames@syr.edu, (2) Molecular Insight Pharmaceuticals, (3) Department of Chemistry, McMaster's University, (4) Department of Pathology and Molecular Medicine, McMaster's University, (5) Department of Chemsitry, Syracuse University*

The extensive contemporary interest in the coordination chemistry of the group 7 congeners technetium and rhenium reflects their significant role in the design of new radiopharmaceuticals for imaging and therapy, respectively. When appended to a biologically active molecule, a targeted approach to drug design can be achieved utilizing technetium and rhenium radionuclides. Biotin, a member of the B-complex group of vitamins, binds to the glycoprotein avidin with the strongest known binding between a ligand and a protein, resulting in numerous biochemical applications. Compounds **TcL1** and **ReL1** were readily synthesized, and the fluorescence properties of **ReL1** explored. The fluorescence lifetime of **ReL1** is sufficiently long enough to enable time-gating techniques to be used during in vitro imaging studies. The corresponding ^{99m}Tc analogue was also prepared and found to be stable. This study demonstrates that fluorescent and radioactive biotin-derived probes may be prepared to allow in vitro and in vivo imaging studies.



TcL1



ReL1

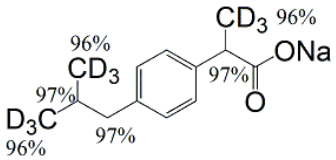
MEDI 129

Efficient deuterium labeling method of biologically active compounds

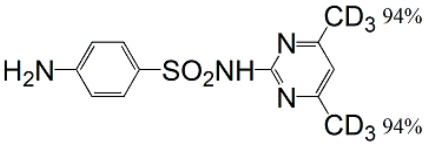
Hiroyoshi Esaki*, Fumiyo Aoki, Tomohiro Maegawa, Hironao Sajiki, and Kosaku Hirota, Department of Medicinal Chemistry, Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502-8585, Japan, Fax: +81-58-237-5979, yakuhin@gifu-pu.ac.jp*

There is an increasing demand for the synthesis of deuterium-labeled compounds used in

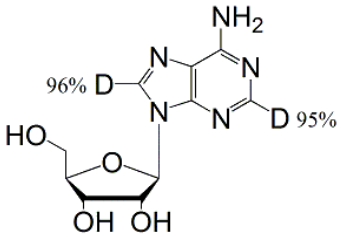
studies a better understanding of the drug metabolism and of higher-order structure of biomolecules, and so on. While the various procedures toward deuterium-labeled compounds have been reported, post-synthetic deuterium exchange reaction of the unlabelled compounds by a catalytic method is prominent for its applicability. We have shown that hydrogen atoms on benzylic carbons are effectively exchange into deuterium atoms using Pd/C in the presence of a catalytic amount of hydrogen gas in D_2O at room temperature. Furthermore, the application of heat could promote the catalyst activity of the Pd/C-H_2-D_2O system and lead to a H-D exchange reaction even on non-activated carbons. Multi-deuterated products using a wide range of unlabelled starting materials including biologically active compounds such as pharmaceuticals and nucleosides can be easily prepared by application of these systems.



Ibuprofene Na



Sulfamethazine



Adenosine

MEDI 130

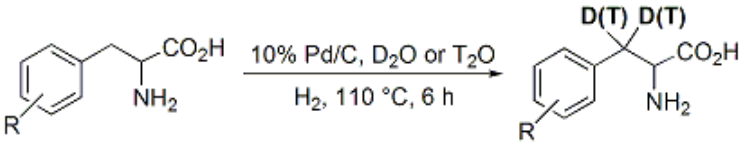
Facile and efficient isotope labeling method for phenylalanine derivatives catalyzed by Pd/C

Tomohiro Maegawa[1], *Akira Akashi*[1], *Hiroyoshi Esaki*[1], *Fumiyo Aoki*[1], *Hironao Sajiki*[1], *Kosaku Hirota*[1], *Kenjiro Tatematsu*[2], *and Yukio Mori*[2]. *(1) Department of Medicinal Chemistry, Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502-8585, Japan, Fax: +81-58-237-5979, maegawa@gifu-pu.ac.jp, (2) Laboratory of Radiochemistry, Gifu Pharmaceutical University*

Amino acids labeled with deuterium or tritium are applied to wide range of studies such as metabolism, structural analysis and dynamics of peptides and proteins. Although a number of methods for the preparation of deuterium-labeled amino acids are reported, appropriately labeled amino acids are still extremely expensive and rarely commercially available.

Recently, we found that efficient and regioselective deuterium incorporation into the benzylic position of L-phenylalanine derivatives was achieved by thermal control using heterogeneous Pd/C-H_2-D_2O system. And also, further deuterium incorporation at the a-position was observed at higher temperature.

We also developed simple and facile tritium labeling methods of phenylalanine derivatives. Tritium labeled compounds are used for a tracer to detect a trace amount of wide range of compounds. Our Pd/C-H_2-T_2O system is also applicable to a tritium incorporation method to phenylalanine derivatives and the simple and easy workup procedure can provide a safe and environmentally benign tritium labeling method without chromatographic purification.



MEDI 131

New effective tool for selecting optimal catalytic technology for chemical transformations

Johannes G. Donkervoort *and James A. Schwindeman, Engelhard Corporation, Strijkviertel 67, De Meern 3454 PK, Netherlands, Fax: 31-30-6669340, hans.donkervoort@engelhard.com*

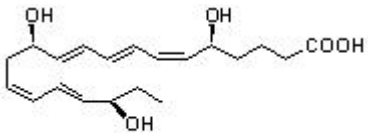
In this presentation a new and efficient web-based tool will be presented that allows the user to select the optimum catalytic tool for organic transformations. A novel and unique attribute of this tool is that it allows the selection of the catalyst for the selective hydrogenation of one functional group over another functional group also present in the same molecule.

MEDI 132

Scale up synthesis of resolvin E1 and its bioaction

Tomomichi Chonan[1], *Makoto Arita*[2], *Kiyoshi Takayama*[1], *and Charles N. Serhan*[2]. *(1) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403, Yoshino-cho, Kita-ku, Saitama-shi 331-9530, Japan, (2) Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Harvard Medical School*

ResolvinE1 (RvE1 **1**), a new oxygenated product of eicosapentaenoic acid (EPA), was identified as an endogenous ligand involved in resolution of inflammation. RvE1 and its receptor signaling might provide a new therapeutic strategy for chronic inflammatory diseases. The stereochemical assignment of RvE1 was established by physical matching study as 5S,12R,18R-trihydroxy eicosa-6*Z*,8*E*,10*E*,14*Z*,16*E* -pentaenoic acid, and its receptor was identified (J Exp Med. 2005;201(5):713-22). Since RvE1 is produced small quantities in vivo, we have developed methods for the scale up synthesis of RvE1 in order to explore biological and pharmacological investigation and achieved it in high purity. Its structure was elucidated by spectroscopic methods. The biological property of RvE1 was confirmed in mouse zymosan A-induced peritonitis. A summary of these results will be presented.



1

MEDI 133

Investigation of method evaluating the activities of SOD-like antioxidants using the whole synthesis-typed ROS sensor

Makoto Yuasa, *Kenichi Oyaizu, Aritomo Yamaguchi, Seiko Ohseki, Tomohiro Kobayashi, Yuujiro Toyoda, Satoshi Tsutsui, and Masahiro Nanba, Department of Pure & Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan, Fax: +81-4-7123-9890, yuasa@rs.noda.tus.ac.jp*

The whole synthesis-typed reactive oxygen species (ROS) sensor, which is modified with electropolymerized iron porphyrin derivative, is designed and prepared. The activities of superoxide dismutase (SOD)-like antioxidants are electrochemically measured with this ROS sensor. The activity of SOD as an antioxidant determined from this method corresponds to that from conventional method using cytochrome c. The result of vitamin c is obtained in a similar manner as above. This method is used as an extremely valuable tool in an evaluation of the activities of antioxidants.

MEDI 134

WITHDRAWN

MEDI 134

WITHDRAWN

MEDI 135

Evaporative light scattering and polymeric SPE: A combined approach for compound repository analysis and clean up

Aubrey J Mendonca[1], *Paul A Boguszewski*[2], *A F Coffey*[2], *John W Davies*[2], *A A MacDonald*[1], *and F P Warner*[2]. *(1) Amherst Fields Research Park, Polymer Laboratories Inc, 160 Old Farm Road, Amherst, MA 01002, Fax: 413 253 2476, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd*

There has been recent interest in the storage and handling of compounds in large medicinal chemistry repository collections, in particular the problems associated with the stability of compounds stored in DMSO. Herein, Polymer Laboratories will describe the use of an evaporative light scattering (ELS) technique, which can be used to determine degradation of a sample stored in DMSO. During the ELS analysis the DMSO solvent peak is deleted, allowing an unambiguous interpretation. If a compound collection requires re-purification, Polymer Laboratories has also developed complimentary SPE materials which will remove salt forming acids (formic, acetic and trifluoroacetic) from the samples, post preparative HPLC, in a fast and effective manner.

MEDI 136

Solid phase extraction of metals: Facile removal of active metal species prior to compound screening

Aubrey J Mendonca[1], *Paul A Boguszewski*[2], *Andrew F Coffey*[2], *John W Davies*[2], *Alasdair A MacDonald*[1], *and Frank P Warner*[2]. *(1) Amherst Fields Research Park, Polymer Laboratories Inc, 160 Old Farm Road, Amherst, MA 01002, Fax: 413 253 2476, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd*

The diversity and reliability of organometallic reactions has increased greatly over the last few decades, and it is commonplace to see such reactions in high throughput and process chemistry environments. The removal of active metal species containing Palladium, Tin, Platinum and Ruthenium from organic reactions and samples is, therefore, essential to provide clean and safe compounds for screening. There are several products on the market that are effective in scavenging metal species, but they require long residency time in the reactions in order to reduce the metal concentrations to an acceptable level of <5 ppm. Polymer Laboratories has developed a highly effective thiol containing polymeric SPE media, which can reduce the concentration of certain metal species to less than 1ppm after just one pass through the SPE device under gravity. Examples illustrating the clean up of Palladium, Ruthenium and Tin catalytic reactions will be shown.

MEDI 137

One-step scaffold hopping with novel synthetic strategies

László Ürge[1]*, Ákos Papp*[1]*, Richard Jones*[2]*, Norbert Varga*[2]*, and Ferenc Darvas*[1]*. (1) ComGenex Inc, 7. Zahony u, Budapest H-1031, Hungary, laszlo.urge@comgenex.hu, (2) Thales Nanotechnology Inc*

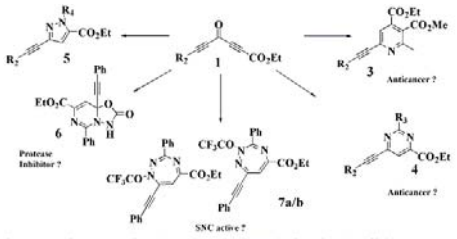
Scaffold hopping is a frequently used strategy during the hit-to-lead process. Several software applications are available to generate de novo structures from primary hits based on 3D pharmacophore models, shape similarity or 2D bioanalogous transformations. One of the critical issues is to execute ‘wet' chemistry based on the proposed virtual transformations. Frequently the transformations introduce more flexibility into the molecules simply via saturation of side-chains or ring-systems. We report a novel continuous flow catalytic hydrogenation system, which could solve this problem in one-step. In combination with the EMIL (Example Mediated Innovation for Lead Evolution) software, which creates bioanalogous expansion of the chemical space, we can design and perform direct hydrogenation experiments, which selectively lead to fully or partially saturated novel scaffolds. The presentation will focus on the integration of microfluidics chemistry with the Lead Multiplier software into a medicinal chemistry platform, applicable for one-step scaffold hopping demonstrated with various examples.

MEDI 138

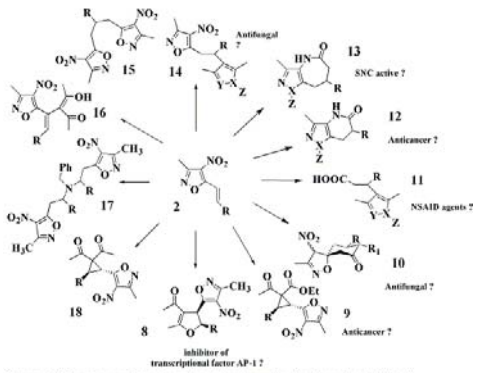
Diversity oriented synthesis(DOS) using poly-functional scaffolds

Eleanor F. Duffy*, Department of Pharmaceutical and Medicinal Chemistry, Centre for Synthesis and Chemical Biology, Royal College of Surgeons in Ireland, 123, St. Stepthen's Green, Dublin 2, Dublin, Ireland, Fax: 00 353 1 4022168, eduffy@rcsi.ie, and Mauro F. A. Adamo, Department of Pharmaceutical and Medicinal Chemistry, Centre for Synthesis and Chemical Biology*

Our approach towards the generation of chemical diversity involved the use of building blocks which contain a number of chemically distinct functionalities, which could be selectively reacted. We hypothesised that a molecule in which n distinct functionalities are present, which could be reacted through a number y of selective transformations, allows development of chemical diversity in a number (nxy) of directions. To test this hypothesis, we have designed the poly-functional scaffolds 1 and 2 (Scheme 1). We were delighted to find that several classes of templates were accessible from 1 and 2 (5, 6 and 7 member rings; mono-cyclic and bi-cyclic structures). With the exception of compounds 12 and 13, the synthesis summarised in schemes 1 and 2 were achieved through one-pot procedures. Compounds 2 are stable solid products, which could be prepared in one step from commercially available materials.



Scheme 1: Summary of results collected using poly-functional scaffolds 1



Scheme 2: Summary of results collected using poly-functional scaffolds 2

MEDI 139

WITHDRAWN

MEDI 140

Crystallization of pharmaceuticals on self-assembled monolayers on gold

Kasim Biyikli, *Branko Zugic, Garrett P. Ebersole, Joshua B. Allor, and John C. MacDonald, Department of Chemistry & Biochemistry, Worcester Polytechnic Institute, 100 Institute Rd., Worcester, MA 01609-2280, Fax: 508 831-5933, biyiklik@wpi.edu*

We are investigating whether nucleation and growth of crystals of pharmaceuticals can be induced and controlled using self-assembled monolayers (SAMs) on bulk surfaces and in microfluidic channels. Our strategy is to crystallize drugs such as barbital and acetaminophen from solutions in contact with SAMs functionalized with a variety of different organic functional groups. We have crystallized these compounds from solutions on SAMs functionalized with a variety of polar and nonpolar organic groups. Growth of polymorphs was achieved by slow evaporation of solvent at RT (thermodynamic conditions) and by rapid cooling of hot solutions to RT (kinetic conditions). Temperature was controlled using a heating/cooling stage built in our laboratory. We have carried out similar crystallization experiments in microfluidic devices to screen for polymorphs using simultaneous high throughput crystallization on a range of surfaces. The results of these experiments and the influence of chemically modified surfaces in controlling polymorphism will be discussed.

MEDI 141

Nucleation and growth of polymorphs of pharmaceuticals on bulk substrates and in microfluidic channels with chemically modified surfaces

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We are investigating whether nucleation and growth of polymorphs of pharmaceuticals such as barbital can be controlled on surfaces using self-assembled monolayers (SAMs). We have crystallized these compounds from solutions placed on SAMs functionalized with a variety of polar and nonpolar organic groups. Growth of polymorphs has been achieved by slow evaporation of solvent at RT (thermodynamic conditions) and by rapid cooling of hot solutions to RT (kinetic conditions). Temperature was controlled using a heating/cooling stage built in our laboratory. We have carried out similar crystallization experiments in microfluidic devices to screen for polymorphs using simultaneous high throughput crystallization on a range of surfaces. These devices consist of PDMS (polydimethylsiloxane) that has been patterned with microchannels and then bonded to gold or glass substrates. The results of these experiments and the influence of chemically modified surfaces in controlling polymorphism will be discussed.

MEDI 142

Natural products analysis by new continuous polarity/volume gradient TLC

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Methanol extracts of herbal supplements were analyzed by a new TLC method—continuous polarity/volume gradient TLC. The extracts were loaded on a silica gel TLC plate that was sandwiched in-between a front and a back plates with the absorbent layer facing the front plate and developed by a binary solvent mixture wherein one solvent is more polar and volatile than the other. The front plate has numerous holes for restricted evaporation of solvent. The concentration of more polar/volatile solvent in the TLC plate gradually decreases due to evaporation as the solvent mixture migrates, resulting in a continuous gradient of decreasing polarity and flow rate in the direction from sample origin to solvent front. Comparing to the conventional TLC, the new method provides much narrower bands, clearer boundary, higher sensitivity, and superior resolution than the conventional TLC, but is as simple as the conventional method.

MEDI 143

Structural characterization and molecular investigation of a serendipitously discovered bioactive macromolecule, lignin sulfate

Arjun Raghuraman[1]*, Jay N. Thakkar*[1]*, Gunnar Thor Gunnarsson*[1]*, Michael Hindle*[2]*, and Umesh R. Desai*[3]*. (1) Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, 410 N. 12th Street, Richmond, VA 23298-0540, Fax: 8038287625,*

arjunbass@yahoo.com, (2) Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University, (3) Department of Medicinal Chemistry, Virginia Commonwealth University

The herpes simplex virus (HSV) utilizes cell-surface glycosaminoglycan, heparan sulfate, to gain entry into cells and cause infection. In a search for synthetic mimics of heparan sulfate to prevent HSV infection, we discovered potent inhibitory activity arising from sulfation of monomeric flavonoid. Yet, detailed screening indicated that the sulfated flavonoid was completely inactive and the potent inhibitory activity arose from a polymeric substance present in the parent flavonoid. The active principle was identified through a battery of biophysical and chemical analyses as sulfated form of lignin, a 3-dimensional network polymer composed of substituted phenylpropanoid monomers. Mass spectral analysis of parent lignin and its sulfated derivative indicates the presence of p-hydroxycinnamyl monomers interconnected through uncondensed beta-O-4– and condensed beta-5–type linkages. High-performance size exclusion chromatrography shows a wide molecular weight distribution from 1.5 kDa to 60 kDa suggesting significant polydispersity. PAGE analysis indicates a highly networked polymer that differs significantly from linear charged polymers with respect to electrophoretic mobility. Molecular modeling of a beta-O-4– and a beta-5–linked lignin sulfate dimer suggests high probability of mimicking common heparan sulfate sequences, thus supporting the biological activity results. Structurally, the macromolecule lignin sulfate presents a multitude of hydrophobic, hydrogen bonding and anionic domains capable of interacting with biomolecules. Thus, lignin sulfate represents a number of interesting structures with potential medicinal benefits.

MEDI 144

The role of planar chromatography in column purification

***Jack Liu**, Biotage, Discovery Chemistry Group US, 1725 Discovery Drive, Charlottesville, VA 22911, Fax: 434-979-4743, JLiu@biotage.com*

Planar chromatography or thin layer chromatography (TLC) is commonly used as a simple but efficient tool for pre-purification, preliminary separation and monitoring of organic synthesis. This paper addresses the use of planar chromatography to optimize column purification of organic compounds. In this study, isocratic or gradient elution is used for column separation of different type of organic compounds. The interdependence between retardation factors (Rf) of TLC and column retention volume (CV) of both isocratic and gradient elution are analyzed. The results show that Rf and CV have a nonlinear relationship. This phenomenon translates into more difficult separation of weakly retarded solutes of complex sample when column elution is used under similar conditions. Gradient elution offers more flexibility when the depth of gradient is properly adjusted based on the retardation factor to achieve better separation. It is hoped that the approach can be used for more efficient column purification.

MEDI 145

The application of evaporative light scattering detection to high throughput HPLC methods

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The large numbers of compounds generated by combinatorial chemistry has presented new challenges in the HPLC laboratory. The emphasis of the analysis in this field of research is to minimize sample analysis time, thus dramatically increasing sample throughput. Typically, methods employed to achieve this goal use short columns, rapid gradients and high eluent flow rates. These requirements place great demands on the HPLC detection method, particularly with respect to compound sensitivity and detector baseline stability. A key function of this type of approach is the ability to detect the presence of all compounds from the synthesis, and to determine the structure of all components detected. Evaporative light scattering detection (ELSD) is universal, and will detect compounds irrespective of their optical properties. This poster describes the benefits of the PL-ELS 2100 evaporative light scattering detector for high-throughout screening at ambient temperature, and its transparency to DMSO and operation with LC-MS.

MEDI 146

A protocol to accomplish "Homo-Robinson" annulation: Application to the guanacastepene problem

***Heedong Yun**, Department of Chemistry, Columbia University, Havemeyer Hall, MC 3135, 3000 Broadway, New York, NY 10027, hy2013@columbia.edu, and Samuel J. Danishefsky, Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research*

Guanacastepene A is the parent member of a family of diterpene natural products. Initial interest arose from it antibacterial activity. The novel structure and possibility of other biological activity have stimulated continuing interest in the compound. A formal synthesis of guanacastepene A will be reported using the concept of "Homo-Robinson" annulation. Other examples of this methodology will be described.

MEDI 147

Plusbacin A3: Efforts towards the solution phase synthesis

***Aaron Wohlrab**, Department of Chemistry, University of California, 9500 Gilman Drive, La Jolla, CA 92093, awohlrab@ucsd.edu, Ryan Lamer, Department of Chemistry, Univeristy of California San Diego, and Michael S. VanNieuwenhze, Department of Chemistry and Biochemistry, University of California, San Diego*

Plusbacin A3 is a naturally occurring cyclic depsipeptide antibiotic isolated from Pseudomonas sp. with promising in vitro and in vivo activity against vancomycin and methicillin resistant gram positive bacteria. An understanding of its conformational characteristics coupled with the structure/activity based relationships of its analogs will prove insightful for the development of new antibiotics. Current efforts are directed towards the total synthesis of Plusbacin A3, its analogs, a variety of model systems to study the efficiency as well as site selectivity of macrocyclization, and 2DNMR studies to determine its solution structure.

MEDI 148

Synthetic studies toward Nogalamycin

Ryan B. Lamer[1]*, Luis R. Rivera*[2]*, Tristan Beaudette*[1]*, Michelle Tetalman*[1]*, and Michael S. VanNieuwenhze*[1]*. (1) Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Dr, Mail Code 0358, La Jolla, CA 92093-0358, Fax: 858-822-0386, rlamer@ucsd.edu, (2) Department of Chemistry, University of Puerto Rico*

Nogalamycin is an anthracycline antitumor antibiotic isolated from Streptomyces nogalator. Although highly active, toxicity data precludes its use as an anti-cancer agent. Research is underway to design an efficient, flexible route to the Nogalamycin core structure that will allow for simple access to natural and synthetic analogues.

MEDI 149

Synthesis of enone analogues of the natural product curcumin

Waylon M. Weber[1]*, Lucy A. Hunsaker*[2]*, Lorraine M. Deck*[1]*, and David L. Vander Jagt*[2]*. (1) Department of Chemistry, University of New Mexico, MSC03 2060, Albuquerque, NM 87123, waylonw@unm.edu, (2) Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine*

The natural product curcumin, present in the spice turmeric, has long been used in Asia as a medicinal for the treatment of a wide range of disorders. Numerous studies of the mechanism of curcumin have focused on its anti-inflammatory properties and on its anti-angiogenesis activity. More recently, curcumin was reported to inhibit aggregation of the Alzheimer peptide Aβ. Curcumin is known to have anti-oxidant activity. We reported recently that analogs of curcumin can retain or even have enhanced biological activity compared to curcumin and that the biological activity does not correlate with anti-oxidant activity, suggesting that curcumin and analogs have specific biological targets. Curcumin is a polyphenolic dienone. Here we describe the synthesis of three classes of enone analogs of curcumin.

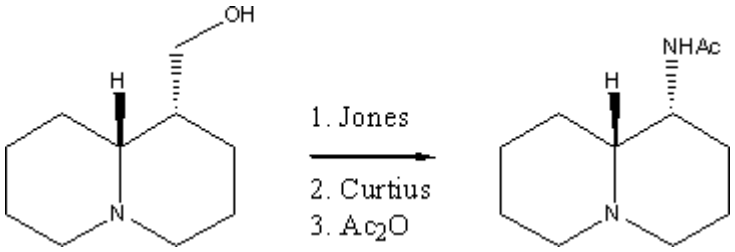
MEDI 150

Synthesis and stereochemistry of epiquinamide

Richard W. Fitch *and Gordon D. Sturgeon, Department of Chemistry, Indiana State University, 600 Chestnut Street, Science Building, Room S35E, Terre Haute, IN 47809, Fax: 812-237-2232, rfitch@carbon.indstate.edu*

Epiquinamide has been prepared in straightforward fashion by semisynthesis from (-)-lupinine. The key to this transformation is a modified Curtius rearrangement of lupinoic acid. Comparison of the stereochemistry to our prior racemic epi-epiquinamide and the natural product will be discussed. Also presented will be preliminary structure-activity relationships of some N^1-acyl analogs and the stereochemical dependence of activity for three of the four

possible diastereomers.

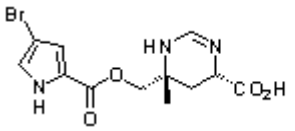


MEDI 151

A concise total synthesis of bromopyrrole alkaloid Manzacidin A

***Hongfeng Chen**, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, LLC, 1000 Route 202, Raritan, NJ 08869, Fax: 908-526-6469, hchen13@prdus.jnj.com, James C. Lanter, Drug Discovery, Johnson&Johnson Pharmaceutical R&D, Xuqing Zhang, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L. L. C, and Zhihua Sui, Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development*

The manzacidins are a unique subclass of the bromopyrrole alkaloid marine natural products identified by their incorporation of an unusual tetrahydropyrimidine moiety. Although preliminary testing identified a range of intriguing biological activity including α-adrenoceptor blockage, antagonism of serotonergic receptor, and activation of actomyosin ATPase, further evaluation has been hampered by a lack of available material. Utilizing recently developed methodology for the asymmetric construction of 1,3-diamines we now report a concise total synthesis of Manzacidin A that is amenable to the production of reasonable quantities of this material and its derivatives.



Manzacidin A

MEDI 152

A total synthesis of (-)-treprostinil using stereoselective Pauson Khand reaction

***Kuanquiang Gao**, Department of Chemistry, University of Illinois, 845 W Taylor Street, 4500SES, Chicago, IL 60607, Fax: 312-996-0431, kgao2@uic.edu, Robert M. Moriarty, Department of Chemistry, University of Illinois at Chicago, and Jeffrey R. Deschamps, Naval Research Laboratory*

The total synthesis of (-)-Treprostinil was accomplished from common intermediate used to prepare enantiomer (+)-Treprostinil. The synthesis features using stereoselective intramolecular Pauson Khand reaction as a key step to build tricycle core and Mitsunobu inversion of the side-chain hydroxyl group. The absolute configuration of (-)-Treprostinil was

confirmed by an X-ray structure of the L-valine amide derivative.

MEDI 153

Synthesis of Sansalvamide A derivates

Joseph D. Brown[1]*, Ahmet Kekec*[2]*, and Shelli McAlpine*[2]*. (1) Department of Chemistry, San Diego State University, 5500 Campanile Dr, San Diego, CA 92182-1030, Fax: 619 594-5580, jdbrown1998@hotmail.com, (2) Department of Chemistry and Biochemistry, San Diego State University*

Sansalvamide is a depsipeptide that belongs to a class of biologically active molecules exhibiting anticancer activity. Because little is known about the mechanism of action of Sansalvamide A, the structure-activity relationship between the active compounds and its biological target may provide information for the development of a new class of anticancer agents. We are synthesizing peptide and depsipeptide derivatives of Sansalvamide A using both L and D amino acid. These compounds have been submitted for biological assays with a collaborator allowing us to compare the structure activity relationship of these derivatives to those of the natural product.

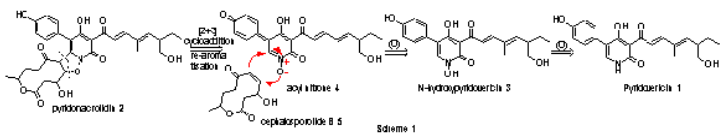
MEDI 154

Studies towards the biomimetic synthesis of pyridomacrolidin

Nageswara R Irlapati*, Jack E Baldwin, and Robert M Adlington, Department of chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, United Kingdom, nageswararao.irlapati@chem.ox.ac.uk*

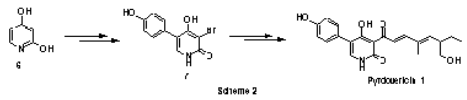
Studies towards the biomimetic synthesis of pyridomacrolidin.

Pyridovericin **1** and pyridomacrolidin **2** are novel secondary metabolites isolated from the entomopathogenic fungus, *Beauveria bassiana* in 1996 by Nakagawa *et al*. Biologically, these compounds have been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100mg/ml making them potential therapeutic leads against a variety of proliferative and inflammatory diseases. Hence, the existence of these two compounds in the same fungus and their structural similarity prompted us to design a biomimetic route from pyridovericin **1** to pyridomacrolidin **2** (Scheme 1).

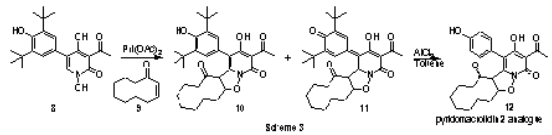


Scheme 1

To investigate this proposal, we completed the total synthesis of pyridovericin **1**. Our synthesis involved the use of powerful Suzuki coupling to produce the bromide **7**, which after transmetallation, subsequent alkylation followed by oxidation and deprotection gave compound **1** (Scheme 2).



We also investigated an unusual oxidative cyclisation by carrying out a model study demonstrating the possible biomimetic route to pyridomacrolidin **2** (Scheme 3). Regio- and stereospecific [3+2] cycloaddition of an *in situ* generated unusual di-*t*-butylated acyl nitrone with *Z*-2-cyclodecenone and subsequent aromatisation was the key step in our proposed biomimetic synthesis. Finally a pyridomacrolidin analogue was prepared *via* Friedel-Crafts di-de-*t*-butylation.

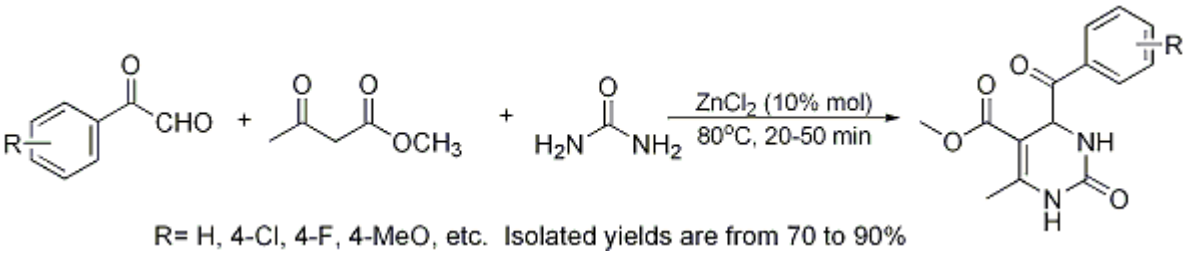


MEDI 155

Solvent-free synthesis of novel dihydropyrimidinones scaffolds

***Qiang Yu**, Fengping Wei, **Liangfu Huang**, Zhiqiang Fang, and Wuping Ma, Synchem, Inc, 1700 Mount Prospect Rd, Des Plaines, IL 60018, qyu@synchem.com, lhuang@synchem.com*

Many dihydropyrimidinones possess interesting pharmacological activities. Previously, we have investigated the application of arylglyoxals as substrates in the Biginelli multi-component reactions (MCRs). The extra ketone group which is inherited from the arylglyoxal, provides a potential site for further transformation. Herein we report a highly efficient and environment friendly solvent-free process by employing ZnCl2 as a catalyst. This remarkable procedure was performed under solvent-free at 80°C within 20 to 50 minutes. This result led to a low cost, easier isolation, high yield, and scaleable reaction. A focus library has been constructed by applying the above condition.



MEDI 156

Recent progress on the synthesis and chemical-biological properties of nucleoside boranophosphate analogues

***Ping Li**, Mikhail I. Dobrikov, Hongyan Liu, Charlotta K. Wennefors, and Barbara R. Shaw, Department of Chemistry, Duke University, Box 90346, Durham, NC 27708*

Substitution of one of the non-bridging oxygen atoms with a borane (BH_3) group in normal phosphates results in boranophosphates. They are efficient and near perfect mimics of natural nucleic acids in permitting reading and writing of genetic information with high yield and accuracy. Boranophosphates have recently attracted considerable attention in antiviral and anticancer drug design because of their unique biochemical properties and the potential to act as nucleotide prodrugs. This presentation focuses on the recent progress on the synthesis and chemical-biological properties of nucleoside boranophosphate analogues.

MEDI 157

Synthesis of ribo- and deoxyribonucleoside α-*P*-borano- and α-*P*-thiodiphosphates by a phosphoramidite approach

Zhihong Xu *and Barbara Ramsay Shaw, Department of Chemistry, Duke University, Durham, NC 27708*

Dideoxynucleoside (ddN) based inhibitors of reverse transcriptase are the first drugs used in the chemotherapy of AIDS. Mechanistic studies show that a ddN must be activateded in a series of phosphorylation reactions to the corresponding 5'-triphosphate (ddNTP), which is incorporated as a chain truncator into the viral DNA strand. A major problem of currently used nucleoside analogs is their inefficient activation by the phosphorylating enzymes (kinases), resulting in a lower than therapeutically desired concentration of the active ddNTP analog in infected cells. In order to overcome toxicity and drug resistance limitations in clinical trials, new nucleotide analogs are being studied, which include the replacement of one non-bridging oxygen atom by a sulfur or borane group in the α-*P* position of various nucleotides. Recent studies reported that the *Rp* isomer of α-*P*-borane- and *Sp* isomer of α-*P*-sulfur-substituted dideoxynucleoside diphosphates (ddNDPs) show enhanced catalytic efficiency for NDP kinase in fluorescence presteady-state experiments [B. Schneider et al., *Nucleos. Nucleot. & Nucl. Acids*, 2001, 297]. The α-*P*-borano-ddNTPs are better chain terminators for drug resistant viral reverse transcriptases (RTs) than parent ddNTPs [M.I. Dobrikov et al., *Nucleos. Nucleot. & Nucl. Acids*, 2003, 1651]. As part of our nucleoside prodrug analogs research, the chemical syntheses of α-*P*-boranodiphosphates of ribo- and deoxyribonucleoside have been initiated. Here we report an efficient synthesis of ribo- and deoxyribonucleoside α-*P*-borano- and thiodiphosphates through our newly developed phosphoramidite approach. The reactions were monitored by ^{31}P-NMR, and the final products were separated by anion exchange chromatography and reverse phase HPLC. The α-*P*-diastereomers were identified by spectroscopic methods.

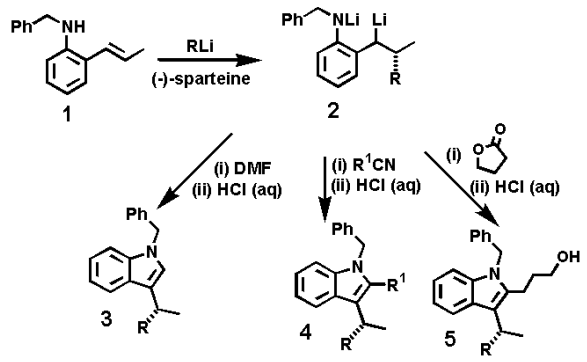
MEDI 158

Enantioselective carbolithiation cascade reaction for indole synthesis

Anne-Marie L. Hogan *and Donal F. O'Shea, Centre for Synthesis and Chemical Biology, Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland, donal.f.oshea@ucd.ie*

The key biochemical roles played by the indole ring system in nature ensure that it maintains

an intense interest from medicinal and synthetic chemists. This privileged scaffold is a common motif for drug targets, and as such the development of new synthetic methods is of considerable value. Specifically indoles with a chiral centre adjacent to the indole ring at the C-3 position, based on indolobutyric acid, are known COX-2 inhibitors. Our current synthetic strategy is to exploit a (-)-spartiene controlled enantioselective carbolithiation of 2-propenyl-phenylamines (1) to provide the chiral intermediate lithiated species (2). Depending on choice of electrophile, a diverse set of functionalised indoles such as the disubstituted (3) or tri-substituted (4) or (5) can be prepared in high selectivity (80-90% ee) all from a common intermediate. The scope of the cascade reaction will be outlined in terms of reaction conditions, alkyllithiums, electrophiles and tolerance of substrate substituents.



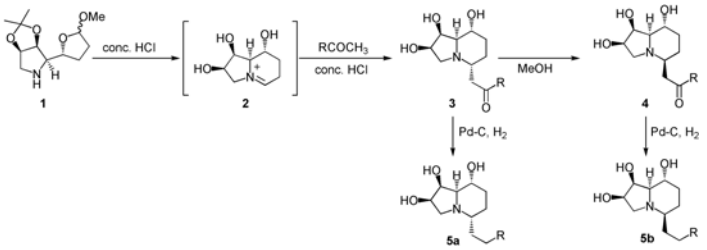
MEDI 159

Synthesis of new GMII inhibitors, diversity-oriented 5-substituted swainsonine analogues, via stereoselective Mannich reaction

Shinichi Nakayama[1]*, Hideko Nagasawa*[1]*, Tomoya Fujita*[1]*, Toshihiro Hashimoto*[2]*, Yoshinori Asakawa*[2]*, Yoshihiro Uto*[1]*, Hitoshi Hori*[1]*, and Douglas A. Kuntz*[3]*. (1) Department of biological science & technology, The university of tokushima, Minamijosanjima-cho 2-1, Tokushima 770-8506, Japan, Fax: +81-88-656-9164, kinnikun21@ybb.ne.jp, (2) Faculty of parmacentical science, Tokushima Bunri University, (3) Department of Medical Biophysics, University of Toronto*

A potent Golgi α-mannosidase (GMII) inhibitor, (-)-swainsonine, exhibits pleiotropic effects such as anticancer activities including metastasis and immunomodulatory effects. To develop more potent immunomodulatory anticancer agents and gain insight on the molecular bases of these activities, we synthesized 5-substituted swainsonine analogues stereoselectivity using our developed diversity-oriented modification reaction (ref.1). We have developed amine acetal **1** as a versatile intermediate for the preparation of 5α- (**3**) and 5β-acyl swainsonine analogues (**4**). They were synthesized by stereoselective Mannich reaction of an *in situ* generated (-)-swainsonine iminium ion intermediate **2** followed by their epimerization reaction. Their carbonyl groups were reduced by Pd-catalyzed hydrogenation to afford 5α- (**5a**) and 5β-alkyl analogues (**5b**). Some of these new 5α-substituted swainsonine analogues possessing aromatic group showed more potent α-mannosidase inhibitory activities than swainsonine itself. To gain

insight on the molecular bases of these activities, we also analyzed the crystal structures of *Dorosophila* GMII in complex with some of these swainsonine analogues.



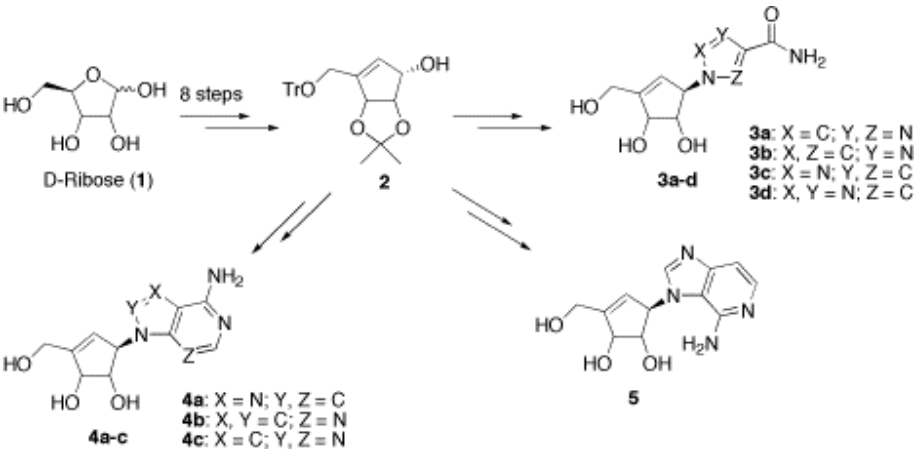
Ref.1: Fujita, T.; Nagasawa, H.: Uto, Y.; Hashimoto, T.; Asakawa. Y.; Hori, H. *Org. Lett*, **2004**, 6, 827-830.

MEDI 160

Development of efficient synthetic methods for chiral cyclopentenol derivatives using ring-closing metathesis (RCM) reaction and synthesis of unnatural neplanocin A (NPA) analogues

Jong-Hyun Cho *and Chung K. Chu, Department of Pharmaceutical and Biomedical Sciences, The University of Georgia, College of pharmacy, Athens, GA 30602, Fax: 706-542-5381, jcho@rx.uga.edu*

An efficient and convenient methodology for the synthesis of a cyclopentenol derivative **2** as a chiral building block for neplanocin A (NPA) and its analogues has been developed. The selective protection of allylic hydroxyl group and ring-closing metathesis (RCM) reaction with the 2nd-generation Grubbs catalyst were employed as key steps. This significantly improved protocol was applied to obtain **2** in 10 g scale with 52 % overall yield (8 steps) from D-ribose. The intermediate was successfully applied to synthesize several unnatural carbocyclic nucleosides (**3a-d**) as well as deaza NAP analogues (**4a-c** and **5**) in high yields.



MEDI 161

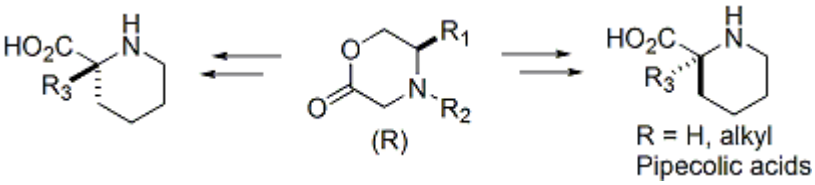
WITHDRAWN

MEDI 162

Enantioselective synthesis of 2-substituted pipecolic acids and its application

Duen-ren Hou[1]*, Shin-Yi Hung*[1]*, and Chung-Cheng Hu*[2]*. (1) Department of Chemistry, National Central University, 300 Jung-Da Rd., Jung-Li City 320, Taiwan, Fax: 886-3-4227664, drhou@cc.ncu.edu.tw, (2) Department of Applied Chemistry, National University of Kaohsiung*

Pipecolic acids is a nonproteinogenic amino acid present in natural products with useful pharmacological properties, such as the immunosuppressant FK 506 and the antifungal antibiotic demethoxyrapamycin. Herein we present an effective and selective method to prepare both enantiomers of pipecolic acid and its 2-alkyl derivatives. Synthetic progress toward NMDA receptor will be reported.

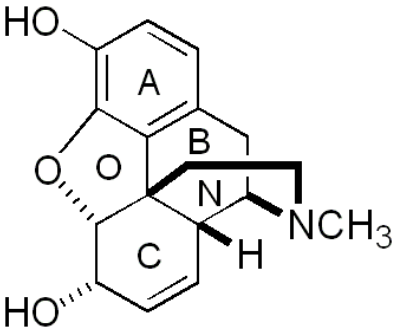


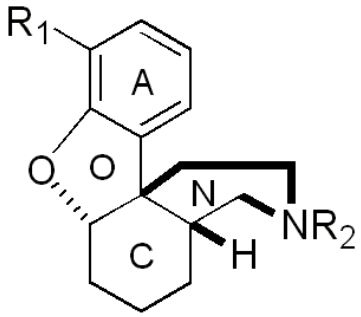
MEDI 163

Synthesis and opioid binding affinity of (-)-octahydro-1H-benzofuro[3,2-e]isoquinolines

Ling-Wei Hsin[1]*, Li-Te Chang*[1]*, C. M. Dersch*[2]*, and R. B. Rothman*[2]*. (1) Institute of Pharmaceutical Sciences, National Taiwan University, No. 1, Jen-Ai Road, Section 1, Room 1336, Taipei 10018, Taiwan, Fax: 886-2-2351-2086, lwh@ntumc.org, (2) Clinical Psychopharmacology Section, IRP, NIDA, NIH*

Octahydro-1H-benzofuro[3,2-e]isoquinolines, which possess the ACNO partial structure of morphine, displayed potent oral analgesic and narcotic-antagonism activity. However, due to significant σ-receptor binding affinity and inefficiency in their synthesis ACNO derivatives have not been developed for clinical use. We noticed that these ACNO compounds were synthesized and pharmacologically investigated in racemic forms. Based on the structure-activity relationship of morphine and related compounds, the undesired σ-receptor activity may come from the (+)-isomers. Thus, we have developed an asymmetric synthetic methodology for preparation of (-)-ACNO derivatives of morphine. The three chiral centers in ACNO skeleton were constructed via a reaction sequence of asymmetric transfer hydrogenation, Heck reaction, and catalytical hydrogenation. The opioid receptor binding affinities of a novel series of N-substituted (-)-octahydro-1H-benzofuro[3,2-e]isoquinolines were determined.





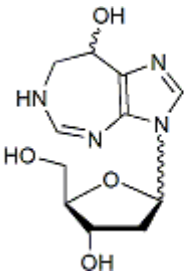
morphine

MEDI 164

Preparation and identification of pentostain isomers

***Liping Gao**, Wuyi Wang, and Meizheng Liu, Chempacific Corperation, 6200 Freeport Center, Baltimore, MD 21224, Fax: 410-633-5808, lgao@chempacific.com*

As an efficiency drug for hairy cell leukemia (HCL), pentostatin is exceedingly tight-binding inhibitor, showing Ki = 2.5 x 10-12 M, against human erythrocytic adenosine deaminase. From either fermentation or synthetic sources, pentostatin contains somehow chemical isomers as significant impurities, which have to be identified and characterized during cGMP production. In this presentation, we will report preparation and identification of these isomers as followings.



Pentostatin: 8R-beta
Isomer I: 8S-beta
Isomer II: 8R-alpha
Isomer III: 8S-alpha

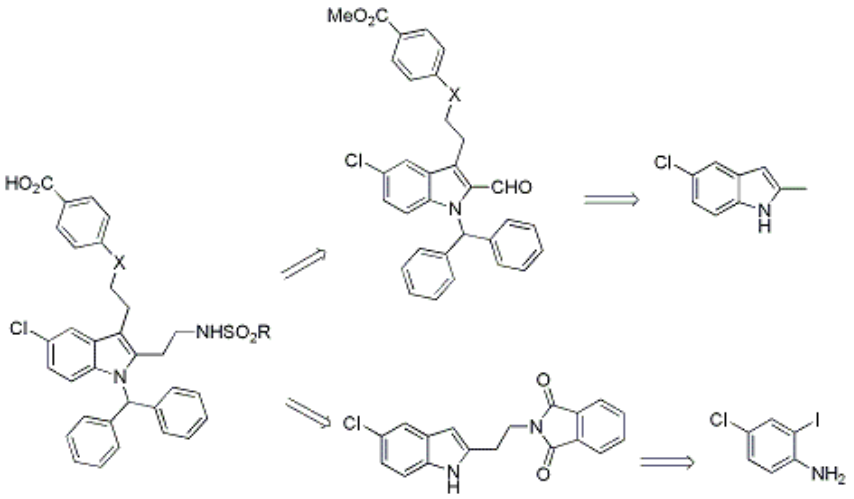
MEDI 165

Indole inhibitors of cPLA2α: Synthetic routes

***Richard Vargas**[1], Katherine L. Lee[1], Mark Behnke[1], Lihren Chen[1], Wei Li[1], Paresh M. Thakker[1], Weiheng Wang[1], Fuk-Wah Sum[2], Alexander Oliphant[2], Kun Wu[2], Vishnu Hegde[3], Marina Shen[4], and John C McKew[1]. (1) Department of Chemical and Screening Sciences, Wyeth Research, 200 Cambridgepark Drive, Cambridge, MA 02140, rvargas@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Organix Incorporated, (4) Department of Inflammation Biochemistry, Wyeth Research*

During the course of our medicinal chemistry effort to study the structure-activity relationship of our indole inhibitors of cytosolic phospholipase A_2a (cPLA$_2$a), our medicinal chemistry team

employed several strategies to synthesize substituted indoles. An initial route utilized commercially available 5-chloro-2-methylindole as the starting material. This material was elaborated in a linear fashion to final compounds. Once the C2 linker was optimized, we designed more convergent routes to advanced intermediates. This poster will describe different synthetic routes to cPLA$_2$a inhibitors and the advantages and disadvantages of each route.



MEDI 166

Carbocyclic N-3 isonucleosides as SAHase inhibitors for antiviral chemotherapeutics

*Brian A. Bakke, **Sylvester L. Mosley**, Joshua M. Sadler, Narsesh K. Sunkara, and Katherine L. Seley, Department of Chemistry and Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-2608, bbakke@umbc.edu, smosley1@umbc.edu*

Inhibition of biologically significant enzymes critical to nucleotide metabolism and viral replication is a well-established chemotherapeutic approach to the treatment of many diseases. Transcriptional 5'-capping of viral mRNA has been implicated as an “elongation checkpoint” critical to the replication cycle of many viruses. This capping process is accomplished by various methyltransferases, therefore disruption of methylation becomes an attractive target for therapy. This can be accomplished in several ways; in particular, by direct inhibition of methyltransferases (MeTase) and/or indirect inhibition of S-adenosyl-L-homocysteine hydrolase (SAHase), both established cellular targets for antiviral, antiparasitic and anticancer agents. Modified nucleosides, in particular carbocyclic nucleosides, have exhibited potent inhibitory activity against both SAHase and MeTase. Inspection of the recent literature has revealed a close correlation between SAHase inhibition and potent biological activity against negative stranded (-)-RNA viruses (i.e. Arenaviridae, Paramyxoviridae, Rhabdoviridae), double stranded (±)-RNA viruses (Reoviridae), poxviridae, as well as HIV-1, thus supporting the importance of SAHase as a viable chemotherapeutic target. Herein we report the design, synthesis and preliminary biological activity of a new class of structurally novel carbocyclic nucleosides.

MEDI 167

Seldi proteinchip array analysis of hepatitis B virus infection and hepatocellular carcinoma

***Rui Zhu**, Department of Surgery, The University of Hong Kong, Pokfulam Road, Hong Kong, Hong Kong, Fax: 852-28171006, zhurui@hkusua.hku.hk, Qing-Yu He, Department of Chemistry, The University of Hong Kong, and Jen-Fu Chiu, Institute of Molecular Biology, The University of Hong Kong*

Background: Currently, the only serological marker, α-fetoprotein, used for monitoring the progress of Hepatitis B virus (HBV) infection into Hepatocellular Carcinoma (HCC) did not provide satisfactory sensitivity and specificity. We employed ProteinChip SELDI-ToF technology to search for differentially expressed protein patterns that may be used clinically for predicting HCC incident, directing treatment and judging prognosis.

Methods: Proteomes in sera from 4 groups of subjects, including 20 HBV in immune tolerance phase (Low NIS score), 20 HBV in immune clearance phase (High NIS score), 20 HCC and 15 normal control, were profiled by five types of ProteinChip Arrays (IMAC3-Cu, WCX2, SAX2, H50 and NP20) and analyzed by SELDI-ToF mass spectrometry. Resulting data were subjected to statistical calculation and cluster analysis.

Results: In total, 35 serum proteomic features were found significantly and consistently different in expression among the four groups of samples. Two protein peaks with molecular weights at 5806Da and 2793Da respectively showed most substantial changes with an increased-expression order from normal control $\rightarrow$ L-NIS $\rightarrow$ H-NIS $\rightarrow$ HCC.

Conclusion: The selected proteomic features can be combined to form a pattern or index formula for potential use in predicting HCC, directing treatment and judging prognosis.

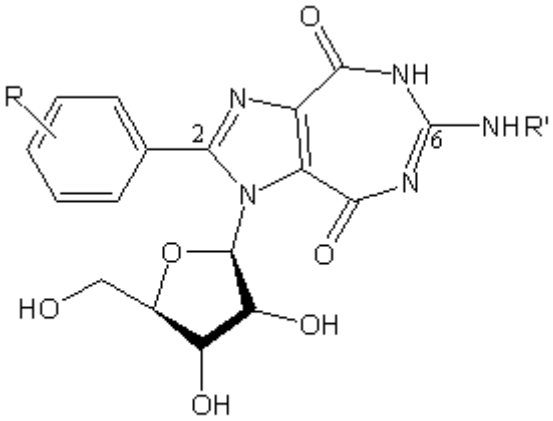
MEDI 168

Synthesis and in vitro anti-HCV screening of a series of ring-expanded ("fat") nucleosides containing the imidazo[4,5-e][1,3]diazepine-4,8-dione ring system

***Peng Zhang** and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, zhpeng1@umbc.edu*

Hepatitis C virus (HCV) is one of the major illnesses in the United States, with more than 5 million people infected, resulting in approximately 10,000 annual mortalities. HCV is also one of the predominant co-infections in HIV patients, and is the frequent cause of the end-stage liver disease resulting in death. There is no anti-HCV vaccine yet available, and the current treatment options as well as their clinical benefits are far limited, including a combination therapy with interferon-a and a non-selective and toxic drug ribavirin. Prompted by the promising in vitro anti-HCV activity of some ring-expanded nucleobases and nucleosides recently synthesized in this laboratory, we set out to explore further systematic structure-activity relationship studies, and report here the results of such studies on a series of ring-expanded ("fat") nucleoside analogues containing the imidazo[4,5-e][1,3] diazepine-4,8-dione

ring system and a variety of substituents at the 2- and 6-positions of the heterocyclic ring.



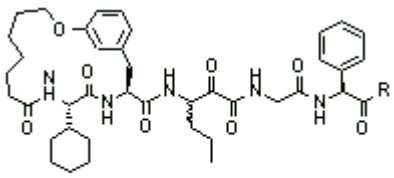
R= *m*- or *p*-OMe or Halogens; R' = Alkyl or Aralkyl

MEDI 169

m-Tyrosine- and tic-based macrocyclic inhibitors of Hepatitis C Virus (HCV) NS3 protease: Synthesis and biological activity

***Kevin X Chen**, F. George Njoroge, John Pichardo, Andrew Prongay, Nancy Butkiewicz, Nanhua Yao, Vincent Madison, and Viyyoor Girijavallabhan, Schering-Plough Research Institute, 2015 Galloping Hill Rd, K-15-3545, Kenilworth, NJ 07033, Fax: 908-740-7152, kevin.chen@spcorp.com*

The inhibition of HCV NS3 serine protease has been a focus of intensive research in recent years. One of our approaches has been to explore hydrophobic interactions between a P2-P4 macrocycle and Ala156 of the protease. The synthesis of á-ketoamide macrocyclic HCV inhibitor of structure type 1 will be reported. Starting with either m-tyrosine methyl ester or 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(S)-3-carboxylic acid (Tic) methyl ester, two amide bond formations with Boc-Chg-OH and 6-hydroxyheptanoic acid gave a phenol-alcohol, the precursor to the macrocycle. The key step in the synthesis, macrocyclization, was achieved through a Mitsunobu reaction. Macrocyclic acid was coupled to the right hand tripeptide (Nva-CH(OH)-Gly-Phg-R) to afford the á-hydroxyamide which, upon Dess-Martin periodinane oxidation, furnished the desired m-tyrosine-based macrocyclic HCV inhibitor 1. The biological activity (Ki*) of these inhibitors against HCV NS3 protease will be discussed.



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MEDI 170

Hepatitis C virus NS3 serine protease inhibitors: Discovery of potent P2' moiety

Ashok Arasappan[1], *F. G. Njoroge*[2], *T-Y. Chan*[2], *F. Bennett*[1], *S. L. Bogen*[1], *K. Chen*[1], *H. Gu*[1], *L. Hong*[2], *E. Jao*[1], *Y-T. Liu*[2], *R. G. Lovey*[1], *T. Parekh*[1], *R. E. Pike*[2], *P. Pinto*[1], *B. Santhanam*[2], *Srikanth Venkatraman*[3], *H. Vaccaro*[2], *H. Wang*[2], *X. Yang*[1], *Z. Zhu*[2], *N. Patel*[1], *J. McCormick*[1], *Brian McKittrick*[1], *A. K. Saksena*[2], *V. Girijavallabhan*[1], *J. Pichardo*[1], *N. Butkiewicz*[1], *R. Ingram*[1], *B. Malcolm*[1], *A. Prongay*[1], *N. Yao*[1], *B. Marten*[1], *V. Madison*[1], *S. Kemp*[4], *O. Levy*[4], *M. Lim-Wilby*[4], *S. Tamura*[4], *and A. K. Ganguly*[2]. *(1) Schering Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033, Fax: 908-740-7152, ashok.arasappan@spcorp.com, (2) Chemical Research, Schering-Plough Research Institute, (3) Infectious Diseases and Tumor Biology, Schering Plough Research Institute, (4) Dendreon Corporation*

Hepatitis C virus (HCV) is the etiologic agent of non-A, non-B hepatitis leading to liver cirrhosis, heptacellular carcinoma and liver failure in humans. Since identification of the hepatitis C virus, the most prominently studied HCV target is the NS3 serine protease contained within the N-terminal region of the NS3 protein. This chymotrypsin-like serine protease is implicated in the viral replication and hence is an attractive target for HCV antiviral therapeutics. Hexapeptide derivatives (P6-P1') containing alpha-ketoamide electrophilic trap have been reported by our group and others to be potent inhibitors of HCV NS3 serine protease. Limited work has been undertaken in the P' region to enhance the binding affinity. This poster will describe the SAR studies of the P' region which resulted in the discovery of a new P2' moiety with enhanced HCV NS3 serine protease inhibitory activity.

MEDI 171

Novel 2-oxoimidazolidine-4-carboxylic acid derivatives as hepatitis C virus NS3 serine protease inhibitors

Ashok Arasappan, *F. George Njoroge, Tejal N. Parekh, John Pichardo, Nancy Butkiewicz, Andrew Prongay, Nanhua Yao, and Viyyoor Girijavallabhan, Schering Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033, Fax: 908-740-7152, ashok.arasappan@spcorp.com*

An estimated 3% of the human population worldwide is infected by Hepatitis C virus (HCV) which leads to liver cirrhosis, heptacellular carcinoma and liver failure. Since the existing therapies are far from ideal, there is an urgent need for new and more effective treatment protocol for HCV infections. A promising area of research for the development of anti-HCV agents is inhibition of the NS3 serine protease, since it is implicated in the viral replication. Most of the HCV NS3 serine protease inhibitors reported thus far are peptide-like molecules derived from the cleavage site sequences. Based on the P2 moiety, these reported inhibitors could be classified as leucine or proline based analogs. Replacement of naturally occurring proline residue with a non-natural proline surrogate may impart beneficial biological and pharmacological properties to the peptide inhibitors. This poster will describe the incorporation of 2-oxoimidazolidine-4-carboxylic acid derivative, as a novel P2 scaffold in the design and synthesis of potent HCV NS3 serine protease inhibitors.

MEDI 172

P2 Diamino acid derivatives as hepatitis C virus NS3 serine protease inhibitors

***Ashok Arasappan**, F. George Njoroge, Haining Gu, Tejal N. Parekh, John Pichardo, Nancy Butkiewicz, Andrew Prongay, Nanhua Yao, and Viyyoor Girijavallabhan, Schering Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033, Fax: 908-740-7152, ashok.arasappan@spcorp.com*

Hepatitis C virus (HCV), the causative agent of chronic liver disease, affects an estimated 170 million humans worldwide. Currently, the FDA approved treatment regimens for this infection are alpha-interferon monotherapy and alpha-interferon-ribavirin combination therapy. While recent approval of pegylated version of alpha-interferon, PEG-INTRON and PEGASYS, have improved the therapeutic effectiveness, it is still far from ideal. Inhibitors of HCV NS3 serine protease offer considerable promise as effective antiviral therapeutics, since proof of concept has already been established. This poster will describe the incorporation of 1,n (n=2-5)diamino acid derivatives as novel P2 surrogate in the design and synthesis of potent HCV NS3 serine protease inhibitors.

MEDI 173

Application of phenylphosphate mimetics to the design and synthesis of olefin metathesis-derived Grb2 SH2 domain-binding macrocycles

***Terrence R Burke Jr.**[1], Sang Uk Kang[1], Won Jun Choi[1], Zhen-Dan Shi[1], Rajeshri Karki[1], Jason Phan[2], Karen M. Worthy[3], Lakshman Bindu[3], Marc C. Nicklaus[1], David S. Waugh[2], and Robert J. Fisher[3]. (1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, Fax: 301-846-6033, tbuke@helix.nih.gov, (2) Macromolecular Crystallography Laboratory, CCR, NCI, NIH, (3) Protein Chemistry Laboratory, SAIC-Frederick*

The phenylphosphate moiety plays a key role in the recognition and binding of phosphotyrosyl (pTyr)-containing peptides to SH2 domains. However, the hydrolytic lability and (-2) charge of the phosphoryl group limit its use in whole cell systems. A family of olefin metathesis-derived macrocycles has recently been reported, some of which bind to Grb2 SH2 domain protein with diffusion-limited association rates. However, to date these macrocycles have only been reported bearing di-acidic phenylphosphate mimetics. In the current work this macrocyclic platform was used to examine a variety of phenylphosphate mimetics, including both phosphorus and non-phosphorus-containing analogues. The design, synthesis and evaluation of these peptidomimetics in a Grb2 SH2 domain-binding system will be covered.

MEDI 174

Design and synthesis of depeptidized P2-P4 biaryl macrocyclic inhibitors of hepatitis-C NS3-4A protease

***Srikanth Venkatraman**[1], F. George Njoroge[1], Viyyoor Girijavallabhan[1], V. Madison[2], N. Yao[2], Andrew Prongay[3], Nancy Butkiewicz[4], and John Pichardo[4]. (1) Medicinal Chemistry, Schering Plough Research Institute, 2015, Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7152, Srikanth.Venkatraman@spcorp.com, (2) Structural Chemistry, Schering-Plough*

Research Institute, (3) Structural Chemistry, Schering Plough Research Institute, (4) Virology, Schering Plough Research Institute

An estimated 3% of world population is infected with HCV making it one of the major public health concerns. HCV infection is the primary cause for liver disease leading to liver cirrhosis and hepatocellular carcinoma. NS3 is a serine protease which when bound to NS-4A cofactor facilitates development of mature virons by catalyzing the cleavage of a single polyprotien to form functional and structural proteins of HCV. The central role NS3 protease plays in the viral replication cycle makes identification of inhibitors of this enzyme attractive for development of drugs to treat HCV infections. X-ray structure of the protein reveals that it has a very shallow binding pocket at the catalytic site, a feature which makes the development of inhibitors a daunting task. In this poster we disclose a preorganized, depeptidized macrocyclic inhibitors spanning from P4-P2' using structure based drug design and X-ray information from our lead inhibitors. X-ray structure of the inhibitor bound to the active site of the enzyme was solved and will also be extensively discussed

MEDI 175

Discovery of SCH6: A new ketoamide inhibitor of the HCV NS3 serine protease

Stephane Bogen[1]*, A. Arasappan*[1]*, F. Bennett*[1]*, T-Y. Chan*[1]*, K. Chen*[1]*, S. Hendrata*[1]*, L. Hong*[1]*, H. Huang*[1]*, E. Jao*[1]*, Y-T. Liu*[1]*, R. Lovey*[1]*, J. McCormick*[1]*, T. Parekh*[1]*, R. E. Pike*[1]*, P. Pinto*[1]*, S. Ruan*[1]*, B. Santhanam*[1]*, S. Venkatraman*[1]*, H. Vaccaro*[1]*, B. Vibulbhan*[1]*, H. Wang*[1]*, Z. Zhu*[1]*, B. McKittrick*[1]*, F. G. Njoroge*[1]*, A. K. Saksena*[1]*, V. Girijavallabhan*[1]*, B. Baroudy*[2]*, N. Butkiewicz*[2]*, A. Hart*[2]*, R. Liu*[2]*, B. Malcolm*[2]*, J. Pichardo*[2]*, D. Standring*[2]*, A. Prongay*[3]*, N. Yao*[3]*, V. Madison*[3]*, S. Kemp*[4]*, O. Levy*[4]*, M. Lim-Wilby*[4]*, S. Tamura*[4]*, and A. K. Ganguly*[1]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033, stephane.bogen@spcorp.com, (2) Virology, Schering-Plough Research Institute, (3) Structural Chemistry, Schering-Plough Research Institute, (4) Dendreon Corporation*

Hepatitis C virus (HCV) infects 170 million people worldwide. Untreated HCV infections can progress to liver cirrhosis and hepatocellular carcinoma. Current treatment options can have many undesired side effects and treatment success cannot be achieved in everyone. Because of its vital role in viral replication, HCV NS3 serine protease has been actively pursued as a viral protein target by several research groups. From structure–based design approach, we identified SCH6 as a potent ketoamide inhibitor of the HCV NS3 serine protease. In addition to excellent enzyme potency (Ki*= 1.5 nM), SCH6 was also a potent inhibitor of HCV subgenomic RNA replication in vitro with IC50 and IC90 of 40 nM and 100 nM respectively. Presentation will detail the optimization of the side chains in the P and P' regions and the modification of the P2 proline moiety that lead to the discovery of SCH6.

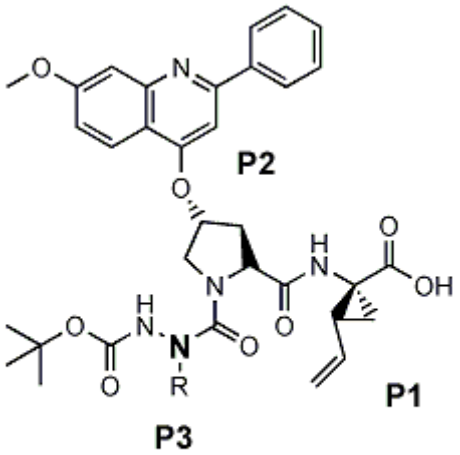
MEDI 176

Synthesis and structure-activity relationship of P3-aza-peptidomimetic analogs as potential HCV NS3-4A protease inhibitors

Peggy P. Huang[1]*, John T. Randolph*[1]*, Charles A. Flentge*[1]*, Larry L. Klein*[1]*, Kevin Kurtz*[1]*, Alex*

Konstantinidis[1], Warren M. Kati[1], Xiaolin Zhang[1], Vincent S. Stoll[2], and Dale J. Kempf[1]. (1) Global Pharmaceutical Research and Development, Abbott Laboratories, Infectious Disease Research, 200 Abbott Park Road, Abbott Park, IL 60064-3537, peggy.huang@abbott.com, (2) Global Pharmaceutical Research & Development, Abbott Laboratories

A novel series of P3-aza-peptidomimetic analogs (**I**) were prepared and evaluated as inhibitors of HCV NS3-4A protease. Activities for these compounds were poor in comparison to parent tripeptides bearing a BOC-(L)-Leu P3 group. Detailed NMR studies on two aza analogs indicated the formation of a stable β-turn conformation that prevented the proper conformation for protease inhibition. Further analogs of **I** that lack the β-turn stabilizing intramolecular H-bond were designed and prepared. Synthesis, SAR, NMR data related to the P3-aza-peptidomimetics and an x-ray crystal structure of an inhibitor/enzyme complex will be presented.



I

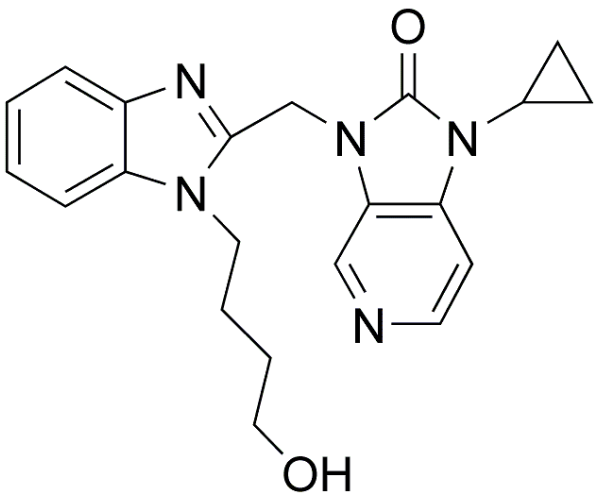
MEDI 177

Discovery of BMS-433771, a respiratory syncytial virus fusion inhibitor

Ny Sin[1]*, Kuo-Long Yu[2], Keith Combrink[2], Brian Venables[1], Xiangdong Alan Wang[2], Hatice Belgin Gulgeze[2], Rita L. Civiello[2], Kathleen F. Kadow[3], Christopher Cianci[3], Junius Clark[3], Eugene Genovese[3], Stacey Voss[3], Lucinda Lamb[3], Ivette Medina[3], Zheng Yang[4], Lisa Zadjura[5], Stella Huang[1], Dedong Wu[1], Qi Gao[1], Mark Krystal[3], and Nicholas A. Meanwell[1]. (1) Department of Chemistry, Bristol Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, Fax: 203 677 7702, Ny.Sin@bms.com, (2) Department of Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, (3) Department of Virology, Bristol-Myers Squibb Pharmaceutical Research Institute, (4) Department of Metabolism and Pharmacokinetics, Bristol Myers Squibb Pharmaceutical Research Institute, (5) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute*

Respiratory syncytial virus (RSV) is a significant cause of morbidity in children, with almost all children infected before the age of 2 years. Complications from RSV infection are especially

problematic among infants born prematurely or with underlying cardiopulmonary diseases. Elderly adults also represent a vulnerable group for RSV-related disease, especially those with weak or compromised immune systems. The humanized monoclonal antibody palivizumab (Synagis™), administered as a series of intramuscular injections, is used as a prophylactic in at-risk infant populations, whilst therapy is limited to aerosol administration of ribavirin. BMS-4337771 has been developed as an orally active inhibitor of RSV infection with potential for development as a prophylactic or therapeutic agent. The structure-activity relationships leading to the discovery of BMS-433771 as an inhibitor of RSV fusion will be described.



BMS-433771

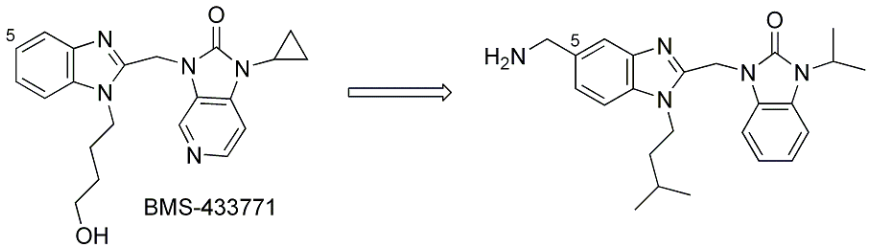
MEDI 178

Inhibitors of respiratory syncytial virus fusion: Optimization of the C-5 subsituent

Xiangdong Alan Wang[1]*, Kuo-Long Yu*[1]*, Kathleen F. Kadow*[2]*, Christopher Cianci*[2]*, Julia Roach*[2]*, Mark Krystal*[2]*, David R. Langley*[3]*, and Nicholas A. Meanwell*[1]*. (1) Department of Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research ParkWay, Wallingford, CT 06492, Fax: 203-677-7072, xiangdong.wang@bms.com, (2) Department of Virology, Bristol-Myers Squibb Pharmaceutical Research Institute, (3) Computer-Assisted Drug Design, Bristol-Myers Squibb Co*

Respiratory syncytial virus (RSV) is responsible for lower respiratory tract infections in young children and the elderly, representing a significant and probably underestimated disease burden. Ribavirin is the only approved therapeutic agent for the treatment of RSV, but efficacy is poor and use is problematic and associated with several side effects. BMS-433771 is a potent and selective inhibitor of RSV that interferes with virus-host cell fusion and meets criteria for clinical evaluation. Photoaffinity labeling experiments and resistance mapping have led to a model in which BMS-433771 binds to a cavity in the N-terminal heptad repeat of the fusion peptide, interfering with the assembly of the 6-helix bundle essential for successful virus entry. In order to extend SAR and probe aspects of the model, substitution of the benzimidazole ring at C-5 with basic functionality was pursued in an effort to examine the potential of establishing an interaction between the inhibitor and Asp200 in the proposed binding pocket. Amongst the compounds synthesized, the 5-aminomethyl analogue

demonstrated enhanced potency in a viral replication assay and retained excellent inhibitory activity toward a virus that had developed resistance to BMS-433771, suggesting additional productive interactions between inhibitor and target.



MEDI 179

Isatin oximes as inhibitors of respiratory syncytial virus fusion

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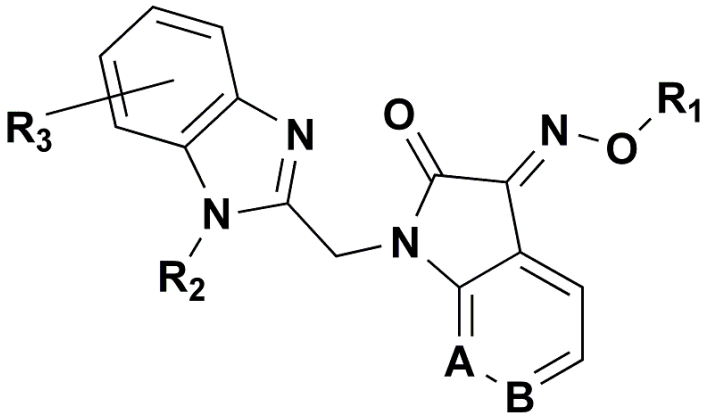
Respiratory syncytial virus (RSV) is a major cause of seasonal respiratory tract infections worldwide. RSV has been implicated as the primary cause of infant pneumonia, which results in nearly 100,000 hospitalizations per annum. By age two, all individuals will have contracted RSV, with reinfection common. Approximately 17,000 deaths per year in the US are attributed to RSV infection. Among the more high risk groups are premature births, immunocompromised individuals, and the elderly. In addition, it has been hypothesized that RSV may be responsible for acute ear infections which do not respond to antibiotic treatment, and may also play a role in the development of childhood asthma. This presentation will describe a series of novel, potent RSV fusion inhibitors, with specific emphasis on the synthesis, structure-activity relationships and MAP properties of compounds with an isatin oxime motif. Development of this series ultimately yielded molecules with acceptable HLM stability, CACO permeability and in vivo efficacy.



MEDI 180

Discovery of TAK-242, a novel inhibitor of TLR4-mediated cytokine production as an anti-sepsis agent

Takashi Ichikawa*, Masami Yamada, Masayuki Ii, Toru Yamano, Norikazu Tamura, Katsumi Itoh, and Tomoyuki Kitazaki, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan, Fax: +81-6-6300-6306, Ichikawa_Takashi@takeda.co.jp*

Sepsis is the chief cause of mortality in intensive care units. Inflammatory cytokines play an important role in the pathogenesis of sepsis, therefore a drug that inhibits multiple cytokines is expected to show clinical efficacy. Through screening of an in-house chemical library, a cyclohexene derivative bearing sulfamoyl and ester moieties was identified as an inhibitor of cytokine production from lipopolysaccharide (LPS)-stimulated macrophages. Subsequent optimization of the lead compound led to the discovery of TAK-242. TAK-242 inhibited the production of inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and nitric oxide (NO), which are induced through LPS/Toll-like receptor 4 (TLR4) signal pathway. TAK-242 showed significant in vivo efficacy in a mouse endotoxin shock model with an ED_{50} of 0.3 mg/kg. TAK-242 was selected as a clinical candidate and represents a promising new class of anti-sepsis drugs. The synthesis, structure-activity relationships and biological properties of TAK-242 will be presented.

MEDI 181

New and improved 5,10-dihydrobenzo[b][1,8]napthyridine-N-oxides as the next generation NNRTI's with better activity profiles against clinically relevant HIV-1 mutants

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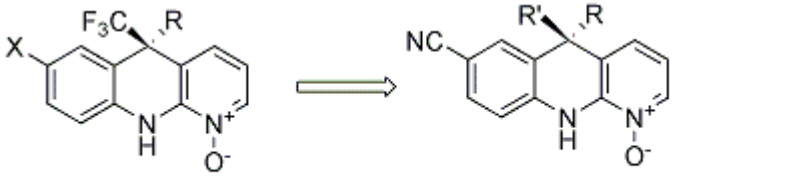
3993, anurag.srivastava@bms.com, (2) Johnson & Johnson Pharmaceutical Research & Development, L.L.C, (3) DuPont Pharmaceuticals Company, (4) Message Pharmaceuticals, (5) Discovery Chemistry Department, Bristol-Myers Squibb Co

The 5,10-Dihydrobenzo[b][1,8]napthyridine-N-oxides were prepared as part of an effort to discover next generation NNRTIs with superior resistance profiles to existing agents while maintaining ease of administration (once-daily dosing). These new tricyclic compounds demonstrated improved activities against a panel of clinically relevant single and double mutants of the HIV-1. Efforts to improve the PK profiles of these agents were directed at attenuating the physical properties of the compounds without sacrificing anti-viral activity. A number of more polar substituents were explored at C5 and C7. The synthesis and the properties of the resulting analogs are discussed in this presentation. Incorporating a cyano functionality at C7 resulted in molecules that had comparable anti-viral potency with significantly better PK properties. The new compounds were designed for use as durable components of HIV combination therapies and as constituents of salvage therapy for antiretroviral-experienced patients failing their current regimens. However, potential toxicology liabilities have prevented further development of these compounds.



X = F, Cl

R' = Alkyl and halo-alkyl groups.

MEDI 182

Linear-response study on the binding affinity of non-nucleoside RT inhibitors with HIV-1 reverse transcriptase

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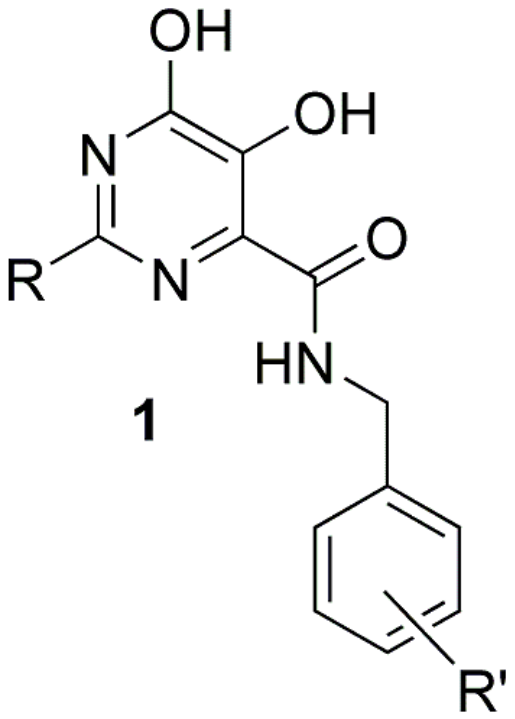
Non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors (NNRTI) bind with RT at a mainly hydrophobic pocket that is separate from the polymerase active site in RT. Several NNRTIs have been approved for clinical use, but they often induce drug-resistant mutation, providing the rationale for the development of new compounds. In order to facilitate the lead optimization of NNRTI, a computational study has been carried out on a series of 2,3-dihydrothiasolo[2,3-a] isoindol-5(9bH)-ones using the Linear-Response method (LRM) with the Liaison software of Schrodinger, Inc. The LRM method correlates the estimated binding energy with the van der Waals and electrostatic interactions between the inhibitor and protein as well as the energy required to create the cavity in the binding pocket. Using the hybrid Monte Carlo method, the correlation between predicted and experimental binding energy was good for compounds that are closely related, i.e. with only small structural modifications such as having one or two nitrogen atoms in the benzene motif, the location of the nitrogen, and presence of a methyl group. When more diverse compounds were included, the relationship leveled off, which points to a limitation in the practical use of LRM calculations in real-world drug development.

MEDI 183

Discovery and synthesis of HIV integrase inhibitors: Dihydroxypyrimidine-4-carboxamides as novel potent and selective agents

Paola Pace[1], *M. Emilia Di Francesco*[1], *Odalys Gonzalez Paz*[2], *Daria Hazuda*[3], *Ralph Laufer*[2], *Emanuela Nizi*[4], *Alessia Petrocchi*[1], *Michael Rowley*[1], *W.A. Schleif*[3], *Kara A. Stillmock*[3], *Marc V. Witmer*[3], *and Vincenzo Summa*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories - IRBM, Via Pontina Km 30,600, 00040 Pomezia (Rome), Italy, Fax: 390691093654, paola_pace@merck.com, (2) Department of Pharmacology, IRBM - Merck Research Laboratories Rome, (3) Department of Antiviral Research, Merck Research Laboratories, (4) Department of Medicinal Chemistry, IRBM - Merck Research Laboratories Rome*

N-benzyl-[5,6]-dihydroxypyrimidine-4-carboxamides 1 were discovered as a class of agents which exhibits potent inhibition of HIV-Integrase catalyzed strand transfer processes. In the current study, structural modifications on these molecules were made in order to examine effects on HIV-Integrase inhibitory potencies. It was found that a variety of groups can be introduced on the 2 position of the pyrimidine core with maintenance of good strand transfer inhibitory potency and significantly increased inhibition of the spread of HIV-1 in cell culture. Structure-activity relationship studies revealed that the insertion of basic amines to various positions in these compounds had significant effects on biological activity and pharmacokinetic profile. Details of the synthesis and properties of these inhibitors will be presented.



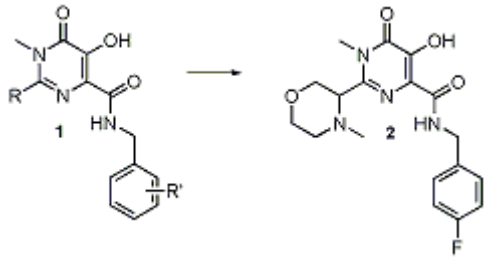
1

MEDI 184

Discovery and synthesis of HIV integrase inhibitors: Development of potent bioavailable N-methyl pyrimidones

Cristina Gardelli[1], *Emanuela Nizi*[1], *Marco Poma*[1], *Benedetta Crescenzi*[1], *Ester Muraglia*[1], *Paola Pace*[1], *Rita Scarpelli*[1], *Vincenzo Summa*[1], *Michael Rowley*[1], *Odalys Gonzalez Paz*[2], *Ralph Laufer*[2], *William A. Schleif*[3], *Kara A. Stillmock*[4], *Marc Witmer*[4], *and Daria Hazuda*[4]. *(1) Department of Medicinal Chemistry, IRBM - Merck Research Laboratories Rome, Via Pontina Km 30.600, 00040 Pomezia (Rome), Italy, Fax: 0039-06-91093654, cristina_gardelli@merck.com, (2) Department of Pharmacology, IRBM - Merck Research Laboratories Rome, (3) Vaccine and Biologics Research, Merck Research Laboratories West Point, (4) Department of Biological Chemistry, Merck Research Laboratories, West Point*

The Human Immunodeficiency Virus (HIV) encodes three enzymes essential for viral replication: a retroviral reverse transcriptase, a protease and an integrase. The latter is responsible for the integration of the viral genome into the human genome and thus represents an attractive target for chemotherapeutic intervention in the treatment of AIDS. A successful drug candidate based on inhibition of HIV Integrase has yet to emerge despite a number of laboratories working on this problem. Benzyl-dihydroxypyrimidine-carboxamides were discovered in our laboratories as a novel and metabolically stable class of agents which exhibits potent inhibition of HIV Integrase strand transfer functionality. Further efforts led to the identification of very potent compounds based on the structurally related N-Me pyrimidone scaffold 1. The work reported here describes the optimization of potency and pharmacokinetic properties of this class of compounds. The identification, the synthesis and the pharmacological characterization of N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(4-methylmorpholin-3-yl)-6-oxo-1,6-dihydropyrimidine-4-carboxamide 2 will be addressed as well.



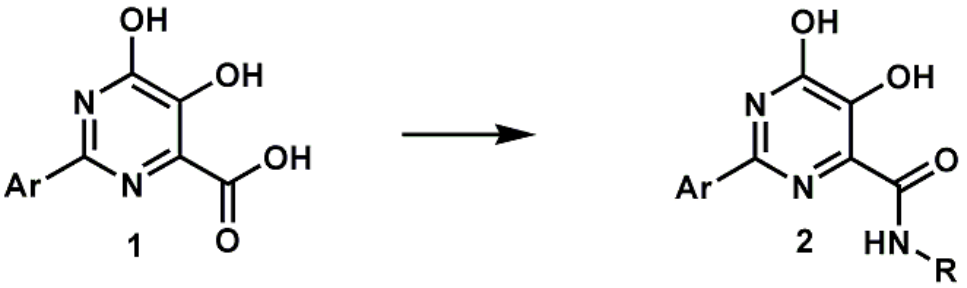
MEDI 185

From dihydroxypyrimidine carboxylic acids to carboxamide HIV integrase inhibitors

Alessia Petrocchi[1], *Paola Pace*[1], *Daria Hazuda*[2], *William A. Schleif*[2], *Kara A. Stillmock*[2], *Marc V. Witmer*[2], *Victor G. Matassa*[3], *and Vincenzo Summa*[4]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories - IRBM, Via Pontina Km 30,600, 00040 Pomezia (Rome), Italy, Fax: 390691093654, alessia_petrocchi@merck.com, (2) Department of Antiviral Research, Merck Research Laboratories, (3) (4) Department of Medicinal Chemistry, IRBM - Merck Research Laboratories Rome*

HIV integrase is a rational target for treating HIV infection and preventing AIDS. Diketoacids (DKAs) are potent HIV integrase and HCV NS5b polymerase inhibitors and can be considered as active site anchors because of their interaction with the Mg2+ ions present in the catalytic

core of the enzymes. We recently described a new class of HCV NS5b polymerase inhibitors, the dihydroxypyrimidine carboxylic acids 1, designed as a hybrid between a DKA and a meconic acid derivative, which have a similar mechanism of action. The dihydroxypyrimidine carboxylic acids inhibited HCV NS5b but not HIV integrase, different from DKAs. However, when the carboxylic acid moiety was converted to the corresponding carboxamide 2, a selective inhibition of the strand transfer reaction catalyzed by HIV integrase was observed in the nanomolar range. SAR around the carboxamide moiety was developed generating low nanomolar inhibitors with significantly improved drug-like properties with respect to the original lead. This compound class has potential for future development towards anti-HIV agents.



MEDI 186

HIV-1 integrase inhibitory peptides: Cyclization, dimerization, tetramerization and peptide inhibitory potency

Krzysztof Krajewski[1]*, Christophe Marchand*[2]*, Yves Pommier*[2]*, and Peter P. Roller*[1]*. (1) Laboratory of Medicinal Chemistry, National Cancer Institute, NIH, Boyles Str. Bldg. 376/219, Frederick, MD 21702, Fax: 301-846-6033, krajewsk@helix.nih.gov, (2) Laboratory of Molecular Pharmacology, National Cancer Institute, NIH*

HIV-1 integrase is essential for the HIV replication cycle, furthermore it is a key enzyme for the ability of the HIV virus to infect non-dividing cells. Integrase is an attractive target because it has no counterpart in mammalian cells, therefore selective integrase inhibitors should not produce any side effects. During the last few years we have carried out detailed structure-activity studies of several peptide sequences with integrase inhibitory activity. In particular we are interested in the inhibitory potency of covalent dimers, tetramers or cyclic analogs of these sequences. The peptides were linked at the C-ends, N-ends and through side chains "in the middle" of peptide sequences, using various linkers and methodologies (e.g. formation of thioether bond, amide bond or click chemistry). We observed that dimerization and tetramerization always substantially increased the peptide inhibitory potency (up to 100 times).

MEDI 187

Versatile synthesis of 2, 5A-Tat antisense chimeras for anti-HIV/AIDS

Longhu Zhou[1]*, Edgar R. Civitello*[1]*, Nidhi Gupta*[1]*, Ross Molinaro*[2]*, Robert H. Silverman*[3]*, and Paul F. Torrence*[1]*. (1) Department of Chemistry & Biochemistry, Northern Arizona University, P O Box 5698, Flagstff, AZ 86011-5698, Fax: 928-523-8111, longhu.zhou@nau.edu, (2)*

Department of Chemistry, Cleveland State University, (3) Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic Foundation

Antisense oligonucleotides have been used as a therapeutic tool to inhibit expression of a variety of genes in cell culture or in live animals, with the expected application of this technology to human diseases. The Tat peptide (RKKRRQRRR) (residues 49-57), which is a part of the 101 amino acids Tat protein, can bind in vitro to the HIV-1 TAR RNA with affinity comparable to the Tat protein. The critical role played by the Tat regulatory protein in HIV replication has made it an attractive target for therapeutic interference in HIV/AIDS. In the 2-5A arm of interferon action, the 2-5A molecule provides an unambiguous signal to initiate RNA decay through the activation of the latent 2-5A dependent RNase L, which degrades viral mRNA, resulting in an inhibition of protein synthesis. In order to target 2-5A activated RNase L to HIV RNA, we have covalently linked a modified Tat peptide and 2-5A tetramer by a 1,3-dipolar cycloaddition reaction of 2-5A azide congener with a modifed tat –alkyne peptide. This construction should also endow the resulting bioconjugate with cell-penetrating properties. RNase L assay shows that this novel 2,5A-antisense chimera can activate RNase L.

MEDI 188

Sophorolipids: Microbial glycolipids with anti-HIV and sperm-immobilizing activities

Vishal Shah[1]*, Gustavo F. Doncel*[2]*, Abul Azim*[3]*, Theodoros Seyoum*[2]*, Kristin Eaton*[2]*, Irina Zalenskaya*[2]*, Rena Hagver*[1]*, and Richard Gross*[1]*. (1) NSF-I/UCRC Center for Biocatalysis and Bioprocessing of Macromolecules, Polytechnic University, Six Metrotech Center, Brooklyn, NY 11201, Fax: 7182603075, vishand@hotmail.com, (2) CONRAD laboratory, Eastern Virginia Medical School, (3) Othmer Department of Chemical and Biological Sciences and Engineering, NSF I/UCR Center for Biocatalysis and Bioprocessing of Macromolecules, Polytechnic University*

The increased incidence of HIV/AIDS disease in women aged 15-49 years has idenfied the urgent need for a female controlled, efficacious and safe vaginal topical microbicide. To meet this challenge, sophorolipid produced by Candida bombicola and its structural analogues have been studied in this report for its spermicidal, anti-HIV and cytotoxic activities. Sophorolipid di-acetate ethyl ester derivative is the most potent spermicidal and virucidal agent of the series of SLs studied. Its virucidal activity against HIV and sperm-immobilizing activity against human semen are similar to those of N-9. However, it also induced enough vaginal cell toxicity to raise concerns about its applicability for long-term microbicidal contraception. Structure – activity relationship have been established for creating new analogs with lesser cytotoxicity and higher activity.

MEDI 189

HIV protease inhibitors with potential for once-daily dosing and reduced side effects

David A. DeGoey[1]*, William J. Flosi*[1]*, David J. Grampovnik*[1]*, Charles A. Flentge*[1]*, Larry L. Klein*[1]*, Clinton M. Yeung*[1]*, Tatyana Dekhtyar*[1]*, Lynn Colletti*[1]*, Jeffrey F. Waring*[1]*, Rita Ciurlionis*[1]*, Kennan C. Marsh*[2]*, James M. Schmidt*[1]*, Sue J. Swanson*[1]*, Vincent Stoll*[1]*,*

Mulugeta Mamo[1], Hongmei Mo[1], Warren M. Kati[1], Akhteruzzaman Molla[1], and Dale J. Kempf[1]. (1) Global Pharmaceutical Research and Development, Abbott Laboratories, Department R4CR, Building AP52, 200 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-938-2756, david.degoey@abbott.com, (2) Preclinical Safety, Abbott Laboratories, Global Pharmaceutical Research Division

A series of peptidomimetic HIV protease inhibitors was designed and synthesized. Optimization of the core regiochemistry, stereochemistry, and P3 substituent led to selection of compounds, A-792611 and A-790742, for preclinical studies. The compounds displayed low nanomolar cell culture potency against wild type HIV in the presence of human serum, low rates of metabolism in human liver microsomes, and high oral bioavailability. The combination of high potency and metabolic stability was used to predict human pharmacokinetics compatible with once-daily dosing, using a low dose of ritonavir as a pharmacokinetic booster. These compounds demonstrated low potential for lipid elevations in a microarray analysis model for the hyperlipidemia observed with some PIs, including lopinavir-ritonavir. In addition, they exhibited only marginal bilirubin elevations in an in vivo model for the hyperbilirubinemia observed with atazanavir and indinavir. Antiviral activity against PI resistant strains of HIV was evaluated.

MEDI 190

Understanding the monophosphorylation efficiency of nucleosides by deoxycytidine kinase (dCK) and their mechanism of anti-HIV activity by molecular modeling

***Vikas Yadav**, Yunho Jin, and Chung K. Chu, Department of Pharmaceutical and Biomedical Sciences, The University of Georgia, College of Pharmacy, Athens, GA 30602, Fax: 706-542-5381, yadavv@rx.uga.edu*

Nucleoside and nucleotide analogs are prodrugs that must be metabolized to their triphosphate form (TP), intracellularly to exert their activity. The nuclear kinases, deoxycytidine Kinase (dCK) and thymidine kinase 1 (TK1) provide precursors for nuclear DNA synthesis. TK1 has been shown to be strictly enantioselective and phosphorylates only Thymidine. But, dCK has broader substrate specificity and it phosphorylates several of the pharmacologically important antiviral and anticancer deoxynuclosides. In our lab over the past 20+ years we have designed several classes of novel nucleosides and tested them for activity in several antiviral and anticancer screens. Two of these L-nucleosides deserve a mention here, L-FMAU and L-OddC, both showed relatively high activity with dCK. The former has broad antiviral activities and is now in final stages of clinical testing, and L-OddC is the first L-nucleoside that shows good promise as an anti-tumor agent. This biological data has prompted us to do a comprehensive modeling study on dCK and understand the binding mode and phosphorylation efficiency of various classes of nucleosides. And couple this kinase phosphorylation data with the simultaneous modeling study of these classes of compounds at the HIV-RT level to understand the molecular basis of activity of active compounds and inactivity of inactive compounds. In this study, six classes of nucleosides covering 36 nucleosides and their nucleotide analogs were studied and both D- and L-form in each class has been chosen to understand the binding mode of these compounds with respect to dCK and HIV-RT. Good qualitative correlation has been obtained after comparing the final energies and binding modes of the these classes of nucleosides (Supported by NIH AI32351 & AI25899).

MEDI 190

Understanding the monophosphorylation efficiency of nucleosides by deoxycytidine kinase (dCK) and their mechanism of anti-HIV activity by molecular modeling

Vikas Yadav, *Yunho Jin, and Chung K. Chu, Department of Pharmaceutical and Biomedical Sciences, The University of Georgia, College of Pharmacy, Athens, GA 30602, Fax: 706-542-5381, yadavv@rx.uga.edu*

Nucleoside and nucleotide analogs are prodrugs that must be metabolized to their triphosphate form (TP), intracellularly to exert their activity. The nuclear kinases, deoxycytidine Kinase (dCK) and thymidine kinase 1 (TK1) provide precursors for nuclear DNA synthesis. TK1 has been shown to be strictly enantioselective and phosphorylates only Thymidine. But, dCK has broader substrate specificity and it phosphorylates several of the pharmacologically important antiviral and anticancer deoxynuclosides. In our lab over the past 20+ years we have designed several classes of novel nucleosides and tested them for activity in several antiviral and anticancer screens. Two of these L-nucleosides deserve a mention here, L-FMAU and L-OddC, both showed relatively high activity with dCK. The former has broad antiviral activities and is now in final stages of clinical testing, and L-OddC is the first L-nucleoside that shows good promise as an anti-tumor agent. This biological data has prompted us to do a comprehensive modeling study on dCK and understand the binding mode and phosphorylation efficiency of various classes of nucleosides. And couple this kinase phosphorylation data with the simultaneous modeling study of these classes of compounds at the HIV-RT level to understand the molecular basis of activity of active compounds and inactivity of inactive compounds. In this study, six classes of nucleosides covering 36 nucleosides and their nucleotide analogs were studied and both D- and L-form in each class has been chosen to understand the binding mode of these compounds with respect to dCK and HIV-RT. Good qualitative correlation has been obtained after comparing the final energies and binding modes of the these classes of nucleosides (Supported by NIH AI32351 & AI25899).

MEDI 191

Reductive cleavage of 1,2,4,5-tetraoxane antimalarials

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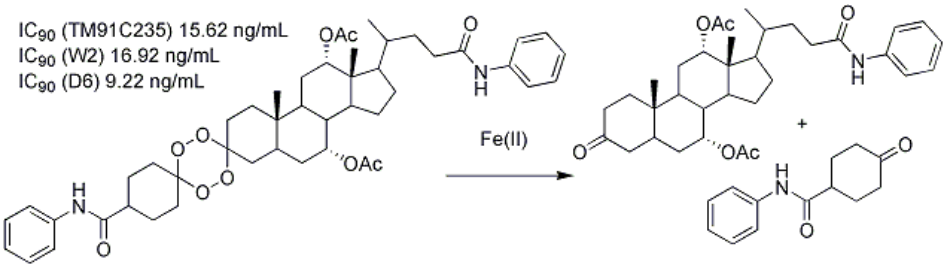
It is currently believed that that peroxide antimalarials selectively kill the Plasmodium falciparum parasite by heme or "free" iron generated carbon-centered radicals. However, it has also been reported that red blood cell (RBC) membranes are also susceptible to fatal lipid peroxidation in the presence of ART/FP-Fe(II). Unfortunately, no experimental evidence has yet been disclosed to support the formation of alkoxy radicals as possible chain initiators. Accordingly, we investigated the reaction of 1,2,4,5-tetraoxanes with FeCl2 (or cat. FP-Fe (III)/Cys) in acetonitrile and were able to recover the parent ketones as the products. The tetraoxane compounds were chosen because they demonstrate potent antimalarial activity yet

display very low toxicity. When 1,2,4,5-tetraoxanes were combined with Fe(II) in the presence of the O- and C-scavengers DMPO and DEPMPO, we discovered that only RO· adducts were detected by EPR. When hexamethyl Dewar benzene was added, a rearrangement occurred to form hexamethylbenzene suggesting an oxoferryl by-product intermediate. This data suggests that tetraoxanes exert their antimalarial activity through alkoxyl radicals generated in RBC or in the parasite. The possible reaction patways will be discussed.

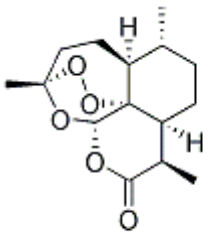


MEDI 192

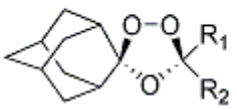
Comparison between antimalarial spiroadmantyl 1,2,4-trioxane and 1,2,4-trioxolane pairs: Important balance between chemical reactivity and steric enviroment of the peroxide bond

Xiaofang Wang[1]*, Yuxiang Dong*[1]*, Sergio Wittlin*[2]*, and Jonathan L. Vennerstrom*[1]*. (1) College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198-6025, Fax: 402-559-9543, xiaofangwang@unmc.edu, (2) Swiss Tropical Institute*

Although the 1,2,4-trioxane moiety in artemisinin is an important pharmacophore, its presence is insufficient for high antimalarial activity as most synthetic 1,2,4-trioxanes are much less active than artemisinin. The recent discovery of antimalarial 1,2,4-trioxolanes 1 prompted us to design and evaluate the structurally related 1,2,4-trioxanes 2. Using iron (II) model reactions, possible activation pathways were investigated. Results from these experiments suggest that both the chemical reactivity and steric enviroment of the peroxide bond are important factors for antimalarial activity. Details of these studies will be presented.



artemisinin



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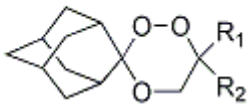


2

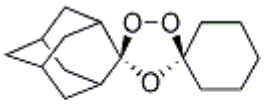
R_1	H	CH_3	-$(CH_2)_5$-	
R_2	Ph	Ph		

MEDI 193

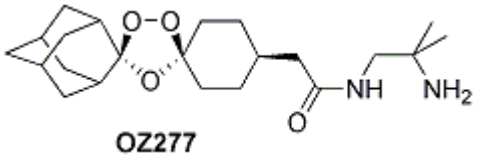
Strategies for the optimization of antimalarial 1,2,4-trioxolanes: From hydrophobic prototype OZ03 to drug candidate OZ277

Yuxiang Dong *and Jonathan L. Vennerstrom, College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198-6025, Fax: 402-559-9543, ydong@unmc.edu*

Since most synthetic peroxide antimalarials have very low water solubilities, introduction of polar functional groups is required to achieve the physicochemical properties associated with good ADME profiles. Generally, incorporation of a carboxylic acid substantially decreases in vitro antimalarial activity whereas adding other polar groups reduces in vivo antimalarial activity. This poses a significant challenge in identification of drug development candidates. In the optimization of antimalarial 1,2,4-trioxolanes, several strategies evolved that included keeping the symmetry of the target, controlling diastereoselectivity of the ozonolysis reaction, and using common scaffolds for derivatization. Details of these approaches will be presented.



OZ03



OZ277

MEDI 194

Identification of novel antileishmanial compounds through *in silico* pharmacophore development and database searching

Dawn A. Delfín[1]*, Apurba K. Bhattacharjee*[2]*, and Karl A. Werbovetz*[1]*. (1) College of Pharmacy, Division of Medicinal Chemistry, The Ohio State University, Parks Hall Room 331, 500 West 12th Avenue, Columbus, OH 43210, Fax: 614-688-8556, delfin.1@osu.edu, (2) Experimental Therapeutics, Molecular Modeling, Walter Reed Army Institute of Research*

Several dinitroaniline sulfonamides display activity against *Leishmania* parasites. A 3D pharmacophore was generated describing this activity using the computer program CATALYST. This pharmacophore, containing an aliphatic hydrophobic group, an aromatic hydrophobic group, an aromatic functionality and a hydrogen-bond acceptor, was used to search compound databases. From the Maybridge Organics database, several compounds matched the pharmacophore, and nineteen of the most promising compounds were tested for activity. Two compounds were highly active (IC_{50} values under 5 μM) and another five compounds were moderately active (IC_{50} values between 20 and 40 μM). Unlike the dinitroaniline sulfonamides, the active compounds did not show antimitotic or antitubulin activity. However, electron microscopy has shown that the kinetoplast (single parasite mitochondrion) became dilated when treated with the most active compound. Further studies to characterize the specific mechanisms of action of the most potent compounds are ongoing in our lab.

MEDI 195

Structural variants of PA-824 as potential antitubercular agents

Liang Zhang[1]*, Ujjini Manjunatha*[1]*, Michael B. Goodwin*[1]*, Thomas Keller*[2]*, Cynthia S. Dowd*[1]*,*

and Clifton E. Barry III[1]. (1) TB Research Section, NIAID, NIH, 12441 Parklawn Drive, Rockville, MD 20852, lzhang@niaid.nih.gov, (2) Novartis Institute for Tropical Diseases

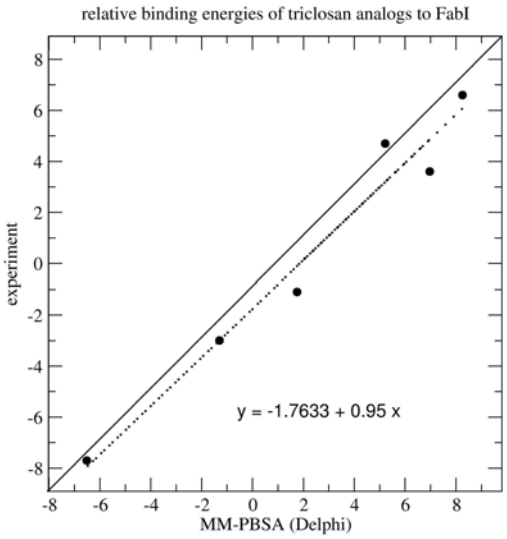
Tuberculosis is an ancient disease caused by the microorganism Mycobacterium tuberculosis that remains a major public health threat. New drugs with different modes of action are needed to shorten the duration of treatment and to fight drug-resistant strains of MTB, including multiply drug-resistant strains. PA-824, a nitroimidazooxazine derivative, is a good lead compound because it has a good MIC (0.4-0.8 ìM) against MTB H37Rv, is effective against non-replicating mycobacteria like its parent nitroimidazole metronidazole, and has demonstrated in vitro activity against multi-drug-resistant strains of MTB. One of the major problems with PA-824, however, is its insolubility in water. Structural modifications of PA-824 including subsitutents on the imidazole ring, the aromatic side-chain, and the ether linkage were synthesized to increase the potency and aqueous solubility. Chimeric molecules containing structural features present in both metronidazole and PA-824 were synthesized to begin to develop an SAR for the aerobic activity of the nitroimidazooxazines. The syntheses and antitubercular assay results will be described.

MEDI 196

Investigation of ecFabI's interaction with substrate and inhibitors, and predicting binding affinities of inhibitors using computational structural biology tools

Salma Banu Rafi[1]*, Polina Novichenok*[2]*, Kolappan Subramaniapillai*[3]*, Caroline Kisker*[4]*, Carlos Simmerling*[2]*, and Peter Tonge*[5]*. (1) Center for Structural Biology, Stony Brook University, Stony Brook, NY 11794, Fax: 631-632-1555, (2) Department of Chemistry, SUNY Stony Brook, (3) Dept of Pharmacology, Center for Structural Biology, (4) Department of Pharmacology, SUNY Stony Brook, (5) Department of Chemistry, State University of New York at Stony Brook*

Mycobacterium tuberculosis's resistance to isoniazid is on the rise. Isoniazid's proposed target is InhA, an enoyl reductase enzyme in fatty acid synthesis–II pathway. Triclosan, a common antibacterial, binds very tightly to FabI, an homolog of InhA in E.coli (FabI Ki = 7 pM and InhA Ki = 0.2µM). We use FabI as a model system to understand enzyme-substrate and enzyme-inhibitor interactions using computational structural biology tools. Triclosan has been proposed to mimic the bound substrate in the active site. GB-LD simulations on the modeled FabI-Substrate system throw light into the understanding of the entry and interaction mechanism of the substrate. This understanding helps in building a rationale for drug design. Also, 95% correlation between the experimental relative binding energies of triclosan and its analogs to FabI and those obtained using computational MM-PBSA approach, validates this method's use in predicting the relative binding energies of inhibitors to InhA before their synthesis.



MEDI 197

N-thiolated 2-oxazolidinones: A new and novel class of synthetic antibacterial agents for methicillin-resistant *Staphylococcus aureus* (MRSA)

Rajesh Kumar Mishra[1], *Kevin D Revell*[1], *Cristina Coates*[1], *Edward Turos*[1], *Sonja Dickey*[2], *and Daniel V. Lim*[2]*. (1) Department of Chemistry, University of South Florida, SCA 400, 4202 East Fowler Ave, Tampa, FL 33620, rkmannu@yahoo.com, (2) Department of Biology, University of South Florida*

Infections caused by bacteria such as methicillin resistant Staphylococcus aureus (MRSA) have become extremely difficult to treat with conventional antibiotics, leading to a sharp rise in clinical complications and deaths. The need for new anti-baterial agents and protocols for treating bacterial infections is serious. This presentation describes the anti-bacterial properties of N-thiolated 2-oxazolidinones, a new & novel family of anti-MRSA agents.

MEDI 198

Antibiotic-conjugated polyacrylate nanoparticles: New opportunities for development of anti-MRSA agents

Yang Helen Wang[1], *Edward Turos*[1], *Kerriann Robyn Greenhalgh*[1], *Suresh Kumar Reddy Guntireddygari*[1], *Sonja Dickey*[2], *and Daniel V. Lim*[2]*. (1) Department of Chemistry, University of South Florida, 4202 E. Fowler Ave SCA 400, Tampa, FL 33620, (2) Department of Biology, University of South Florida*

The synthesis and characterization of emulsified polymeric nanoparticle antibacterials for drug delivery of water-insoluble antibiotics will be discussed. We have devised a simple chemical process for the synthesis of antibiotic-conjugated polyacrylate nanospheres, which measure 40-100 nanometers in diameter, and have examined some of their properties in both aqueous and nonaqueous media. Our current investigations are directed towards applying these

nanoparticles to a number of biomedical and materials-related research areas.

MEDI 199

Synthesis and antimicrobial properties of novel S-nitroso β-lactams

***Maya Kostova**, Chemistry Department, American University, 4400 Massachusetts Ave NW, Washington, DC 20016, Fax: 202.885.1752, Balbina Plotkin, Department of Microbiology, Midwest University, and Monika Konaklieva, Department of Chemistry, American University*

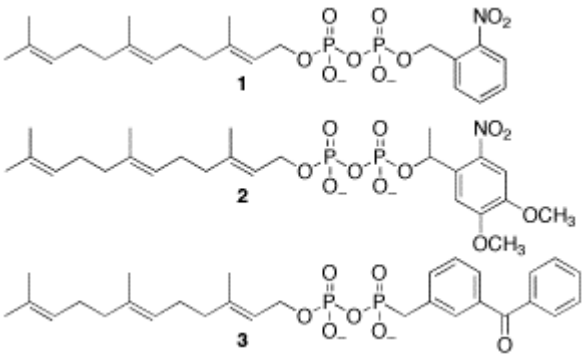
The effectiveness of antibiotics is in sharp decline due to the emergence of drug-resistant microorganisms. Currently, clinically relevant beta-lactamase inhibitors exist only against class A serine type beta-lactamases. Increasingly, bacteria are exhibiting resistance to beta-lactam antibiotics through production of beta-lactamases other than class A. We have designed monocyclic beta-lactam nitric oxide donors as inhibitors of both serine- and metallo-beta-lactamases which also have intrinsic antimicrobial activity. Findings from in vitro testing of intrinsic antimicrobial activity will be presented.

MEDI 200

Photoactive analogues of farnesyl diphosphate for studying protein prenylation

*Juhua Xu, Olivier Henry, and **Mark D. Distefano**, Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, MN 55455, Fax: 612-626-7541, diste001@umn.edu*

Protein farnesyl transferase (PFTase) catalyzes the attachment of farnesyl diphosphate (FPP) to proteins that contain a CAAX-box sequence at their C-termini. Since a large number of farnesylated proteins are involved in signal transduction pathways, there is considerable interest in understanding the critical determinants for substrate recognition and in understanding the biological function of protein prenylation. Here we report on the synthesis and preliminary studies with two types of FPP analogues. Compounds **1** and **2** are caged forms of FPP that are incorporated by PFTase at a rate approximately 100-fold less than that for FPP and liberate FPP upon photolysis. Compound **3** contains a photoactive benzophenone moiety and is designed to serve as a photoaffinity labeling reagent. Unlike previous compounds designed to study the isoprenoid binding pocket, this design allows the phosphate binding site and adjacent peptide binding site to be probed.

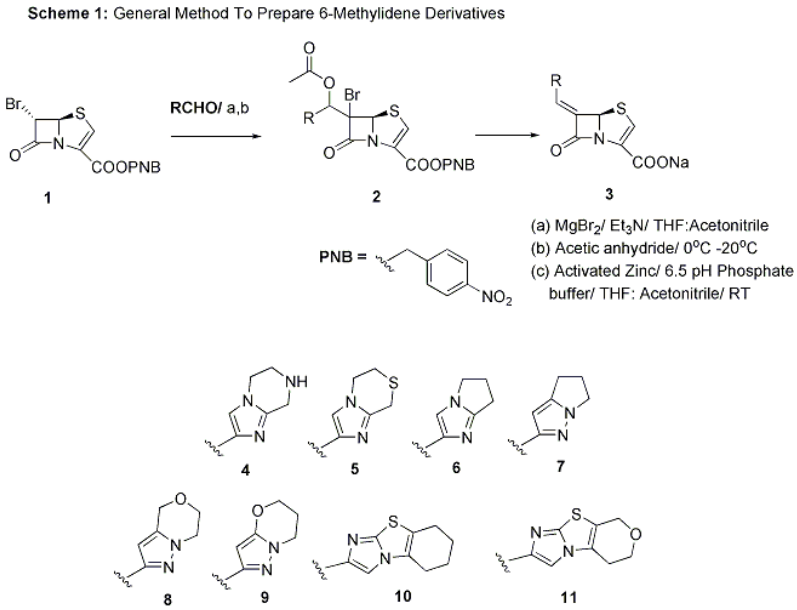


MEDI 201

Synthesis of novel bicyclic and tricyclic aldehydes for the preparation of 6-methylidene penem derivatives: A novel class of broad spectrum beta-lactamase inhibitors

Osvaldo dos Santos[1]*, Tarek S. Mansour*[1]*, Aranapakam Venkatesan*[1]*, Fuk-Wah Sum*[1]*, Yansong Gu*[1]*, Lijing Chen*[1]*, Zhong Li*[1]*, Frank Lin*[1]*, Gulnaz Khafizoa*[1]*, Takao Abe*[2]*, Hideki Ushirogochi*[2]*, Itsuk Yamamura*[2]*, and Toshio Kumagai*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, santoso@wyeth.com, (2) Wyeth KK, Saitama, Japan*

It is a well-known fact in organic chemistry that aldehydes are key synthons for a variety of organic transformations. In an ongoing effort to synthesize novel 6-methylidene penem derivatives **3,** we required several bicyclic and tricyclic aldehydes for the condensation reaction with the bromopenem intermediate **1**. Towards this end, several novel aldehydes **4-11** have been synthesized and will be presented.



MEDI 202

Combinatorial library synthesis and biological evaluation of sets of novel ß-lactamase inhibitors

Qin Sun *and Mario, H. Geysen, Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904*

Antibiotic resistance in rencent years has become a serious problem. The major reason for drug resistance is beta-Lactamase which hydrolyze the antibiotic drugs. Now all the clinical inhibitors are only active towards class A beta-lactamases, and no marketed inhibitors for class B, C, and D. Furthermore, those marketed class A inhibitors have also been found to be

inactivated by mutation of their targeted enzymes. So, new alternatives for class A inhibitors and novel active compounds for class B, C and D lactamases are in urgent demands. We have designed and synthesized several new sets of libraries for finding potent drug candidates as novel lactamase inhibitors. The libraries include cysteinyl peptide, thiol and thioester inhibitors for class B enzyme, and also some promising wide-spectrum inhibitors which taget both class A and class B or class C beta-lactamase enzymes.

MEDI 203

Penicillin bound nanoparticles: A promising new way to save old antibiotics

Suresh Kumar Reddy Guntireddygari[1], *Praveen Ramaraju*[1], *Edward Turos*[1], *Sonja Dickey*[2], *and Daniel V. Lim*[2]*. (1) Department of Chemistry, University of South Florida, 4202 E. Fowler Ave SCA 400, Tampa, FL 33620, gskreddy@yahoo.com, (2) Department of Biology, University of South Florida*

Beta-lactam antibiotics are currently mainstays of clinical treatment for bacterial infections, a position which is secure for the foreseeable future. However, their effectiveness has been compromised by the ability of drug-resistant bacteria to produce beta-lactamases, enzymes which hydrolyze the beta-lactam moiety in these antibiotics to render them inactive. We describe an approach using penicillin-bound nanoparticles to rejuvenate the activity of these important, life-saving antibiotics to make them effective again against drug-resistant bacteria.

MEDI 204

Reviving the clinical efficacy of kanamycin-B: Design and synthesis of novel kanamycin analogs and studies of their antibacterial activity against aminoglycoside resistant bacteria

Ravi Rai*, Department of Chemistry, Utah State University, 0300 Old Main Hill, mail Box #60, Logan, UT 84322-0300, Fax: 435-797-3390, rav@cc.usu.edu, and Cheng-Wei Tom Chang, Department of Chemistry and Biochemistry, Utah State University*

Amioglycoside antibiotics bearing the central aminocyclitol moiety have long been in vogue because of their potent bactericidal activity towards both gram positive and gram negative bacteria. However, of late a number of staphylococci and enterococci have shown an alarming rate of resistance to aminoglycoisde antibiotics.

The history of Kanamycin dates back to 1957 when it was first isolated, but the same compound was rendered clinically obsolete thanks, to the aminoglycoside modifying enzymes which these bacteria harbor. We have been trying to revive the clinical utility of this drug by introducing modification on the neamine moiety. Four Novel Kanamycin-B analogs with activity against aminoglycoside modifying enzymes have been synthesized. We would like to present the design, synthesis,and antibacterial activity of these compounds.

MEDI 205

Design and synthesis of novel aminoglycosides and their antibacterial studies against aminoglycoside resistant bacteria

***Ravi Rai**, Department of Chemistry, Utah State University, 0300 Old Main Hill, mail Box #60, Logan, UT 84322-0300, Fax: 435-797-3390, rav@cc.usu.edu, and Cheng-Wei Tom Chang, Department of Chemistry and Biochemistry, Utah State University*

Aminoglycoside antibiotics have long been used as bactericidal drugs. Unlike many antibiotics that are active only against gram positive bacteria, aminoglycosides have broad spectrum activity against both gram positive and negative bacteria. Their history dates back to 1943 when the first aminoglycoside Streptomcin was isolated, unfortunately their clinical usage has often been limited due to the widespread prevalence of aminoglycoside modifying enzymes and their high cytotoxicity. Kanamycin a potent drug was rendered clinically obsolete thanks to these modifying enzymes. This seminar will focus on the types and modes of action of these modifying enzymes, the various strategies to overcome this problem and our work in the synthesis of 3' – 4' Dideoxy pyranmycin and kanamycin compounds in an attempt to revive the activity of these aminoglycosides against the resistant bacteria.

MEDI 206

Isolation, characterization, and enhanced antibacterial activity of components from *Lomatium californicum*

*Shen-Chieh Chou, Molly C. Everngam, and **John J. Beck**, Department of Chemistry, Sweet Briar College, Sweet Briar, VA 24595, schou@sbc.edu, jbeck@sbc.edu*

The isolation, characterization, and bioactivity testing of five compounds from the ethyl acetate and hexanes layers from *Lomatium californicum* is described. The methanolic extract of the seeds and roots of *L. californicum* was subjected to liquid/liquid partitioning, vacuum liquid chromatography, and separation by reverse phase HPLC. Five compounds were successfully isolated and characterized by 1D and 2D NMR experimentation. The bioactivity of the known compounds falcarindiol, coniferyl ferulate, ferulic acid, and (Z)-ligustilide were confirmed against *Bacillus subtilis* and *Staphylococcus aureus*. Moreover, these compounds exhibited antibacterial enhancement when combined with the antibiotics penicillin and ampicillin. The compound senkyunolide was also isolated but in too small of quantity for similar testing.

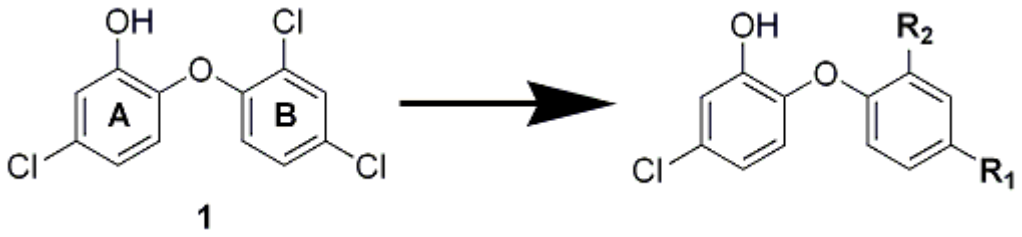
MEDI 207

Synthesis, biological activity, and X-ray crystal structural analysis of diaryl ether inhibitors of malarial enoyl acyl carrier protein reductase: 2'- and 4'-Substituted triclosan derivatives

***Joel S. Freundlich**[1], John W. Anderson[1], Dimitri Sarantakis[1], Hong-Ming Shieh[1], Edinson Lucumi[2], Mack Kuo[2], Min Yu[3], Luchezar Karagyozov[3], Guy A. Schiehser[1], David P. Jacobus[1], William R. Jacobs Jr.[4], David A. Fidock[3], and James C. Sacchettini[2]. (1) Department of Medicinal Chemistry, Jacobus Pharmaceutical Company, P.O. Box 5290, 37 Cleveland Lane, Princeton, NJ 08540, Fax: 609-799-1176, j_freundlich@jacobuspharm.com, (2) Department of*

Biochemistry and Biophysics, Texas A&M University, (3) Department of Microbiology and Immunology, Albert Einstein College of Medicine, (4) Department of Microbiology and Immunology and Howard Hughes Medical Institute, Albert Einstein College of Medicine

The global significance of developing novel anti-malarials cannot be understated. We have undertaken a program focused on optimizing the activity of inhibitors of P. falciparum enoyl acyl carrier protein reductase (PfENR). The B-ring of triclosan (1) was modified at the 2' and 4'-positions. Analysis of the X-ray crystal structure of 1 bound to the PfENR:co-factor complex suggested derivatization of the 4'-position with hydrogen-bonding groups would facilitate interaction with additional active site residues. A methylamino group off the 2'-position would allow for favorable interactions with the co-factor in addition to the enzyme. The conversion of R1 to groups with hydrogen bond donors and/or acceptors afforded less hydrophobic compounds that did not improve significantly upon the potency of 1. Alkylated methylamino derivatives at R2 achieved EC50 values <100 ng/mL, affording a >20-fold gain in potency against the parasite. These findings may provide the foundation for the further optimization of triclosan-based therapeutics.



1

MEDI 208

Designing water soluble dendritic amphiphiles for microbiocidal applications

Andre, A. Williams[1]*, Eko, W. Sugandhi*[1]*, Richard, V. Macri*[1]*, Richard, D. Gandour*[1]*, and Joseph, O. Falkinham*[2]*. (1) Department of Chemistry, Virginia Tech, Davidson Hall, Blacksburg, VA 24061, anwilli1@vt.edu, (2) Department of Biology, VA Tech*

We are designing new amphiphiles to be used as topical vaginal microbicides that provide protection against sexually transmitted pathogens. These new agents must be safe, effective, acceptable, and affordable. The ideal agent would be selective for pathogens and non-irritating; i.e., it would not damage mucosal tissue. We are synthesizing a new series of amphiphiles to explore the ‘cut-off' effect—biological activity within a homologous series of amphiphiles increases with chain length up a specific chain length; after which, it decreases with longer chain lengths. Decreased amphiphile concentration at the site of action is one reason given for the ‘cut-off' effect. We hypothesize that it is the monomer that displays antimicrobial activity not aggregates (e.g., micelles). Consequently, amphiphiles which have low values of the critical micelle concentration (CMC) should display lower antimicrobial activity. To test this hypothesis, we are synthesizing ultra-long chain amphiphiles that have good solubility and high CMCs. Multi-headed ionic amphiphiles have higher solubilities than single-headed amphiphiles in aqueous solutions. By synthesizing ultra-long chain amphiphiles with multiply head groups, we hope to explore the limits of the ‘cut-off' effect. Specifically, my current research involves the synthesis of a homologous series of ultra-long chain, tri-headed anionic amphiphiles. The multiply charged, dendritic head-group structure and the ultra-long

chains of these amphiphiles will impart properties different from those of typical amphiphiles. We believe that a dendritic structure will reduce the absorption of an amphiphile into a cell. The highly branched structure of the head group resembles the dendritic structure of glycolipids that are anchored on the outside of cells. Branching and the triple charge should retard diffusion across membranes. Given the success of ultra-long chain amphiphiles as antimicrobials, there might be a preference for absorption of these amphiphiles on pathogens as opposed to epithelial cells resulting in the reduced irritancy.

MEDI 209

Design, development and synthesis of curcumin bioconjugates and their antibacterial and antifungal activity

Satyendra Mishra[1]*, Upma Narain*[2]*, Roli Mishra*[3]*, and Krishna Misra*[3]*. (1) Department of Chemistry, Allahabad University, University Road, Allahabad 211002, India, kkmisra@yahoo.com, (2) Chemsitry Department, University of Allahabad, (3) Chemistry Department, University of Allahabad*

In this paper different curcumin bioconjugates viz. 4,4′-di-O-glycinoyl-curcumin, 4,4′-di-O-d-alaninoyl-curcumin, 4,4′-di-O-(glycinoyl-di-N-piperoyl)-curcumin, 4,4′-di-O-piperoyl curcumin, curcumin-4,4′-di-O-β-d-glucopyranoside, 4,4′-di-O-acetyl-curcumin along with piperoyl glycine, have been synthesised and characterized. All the covalent bonds used are biodegradable. This makes these derivatives as potent prodrugs, which can get hydrolysed at the target sites. These bioconjugates were tested in vitro against different bacteria and fungi. The 4,4′-di-O-(glycinoyl-di-N-piperoyl)-curcumin and 4,4′-di-O-acetyl-curcumin are more effective than Cefepime, an antibacterial drug available in market, at the same concentration. The 4,4′-di-O-(glycinoyl-di-N-piperoyl)-curcumin and 4,4′-di-O-piperoyl curcumin had antifungal activity in vitro almost comparable with fluconazole, the most popular antifungal drug. The enhanced activity of these bioconjugates vis-à-vis the parent molecule that is curcumin may be due to improved cellular uptake or reduced metabolism of these bioconjugates resulting in building up of enough concentration inside the infected cells. It opens a new era for exploring suitably designed curcumin bioconjugates as potential antibacterial/antifungal drugs.

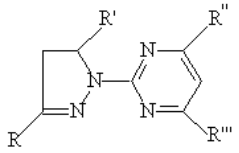
MEDI 210

Synthesis and evaluation of a series of novel pyrazoline-pyrimidine compounds for antimicrobial activity

Mariam S. Degani*, Ranjeet Bairwa, and Vasudha Chandra, Pharmacy and Fine Chemicals, UICT, Mumbai University, Nathalal Parikh Marg, Matunga, Mumbai-400019, India, Fax: 9122-2414-5614, msdegani@udct.org*

Pyrazoline-pyrimidine derivatives constitute an interesting class of organic compounds having diverse pharmacological applications including anti-microbial activity. Hence several NCE's (new chemical entities) have been synthesized having the general structure as shown below and have been tested for anti-microbial activity against several fungal and bacterial species including Mycobacteria. Some compounds have shown promising results and their QSAR has been carried out using 3D-QSAR techniques.

R, R', R''= aliphatic / aromatic substituents R'''= OH/ aliphatic / aromatic substituents



MEDI 211

Bis-indoloquinolines: New antiinfective agents with low cytotoxicity

Seth Y. Ablordeppey*, College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, Fax: (850) 599-3934, seth.ablordeppey@famu.edu, Xue Y. Zhu, Basic Pharmaceutical Sciences, Florida A&M University, Melissa Jacob, Research Institute of Pharmaceutical Sciences, University of Mississippi, Shabana I. Khan, National Center for Natural Products Research, The University of Mississippi, and Larry A. Walker, National Center for Natural Products Research, School of Pharmacy, University of Mississippi*

New anti-infective agents are in demand primarily because of their role in the treatment of AIDS-related opportunistic infections and other infectious microorganisms previously unknown to cause serious diseases. In addition, development of resistance to agents currently on the market has been rampant. The main objective of this study was to design, synthesize and evaluate antiinfective properties of agents related to the natural product cryptolepine. Previous studies in our laboratories have demonstrated that N-5 substitution is essential and modifications at specific positions on the tetracyclic ring have resulted in analogs highly potent against several opportunistic infectious microorganisms. However, limited toxicity studies have shown that some of the more potent agents are fairly toxic. Our search for new agents has now resulted in the identification of novel bis-quindolines with high potencies and much less toxic profiles. The design, synthesis and antiinfective activities of some representative agents will be presented.

This work is supported in part by grants from the NIH, Division of Research Resources, RCMI # G12 RR 03020, MBRS program, Grant # GM 08111 and a Title III award to SYA.

MEDI 211

Bis-indoloquinolines: New antiinfective agents with low cytotoxicity

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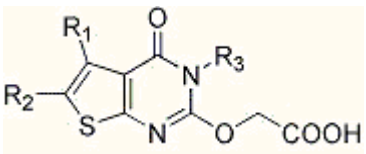
MEDI 212

Design and synthesis of novel thieno[2,3-*d*]pyrimidine derivatives as potential anti-bacterial agents

***D. Ashok**[1], Satish Goud Puppali[2], and Mallikarjun Goud Puppali[1]. (1) Dept. of Chemistry, Postgraduate College of Science, Saifabad, Osmania University, Hyderabad 500004, India, ashok_d59@yahoo.co.uk, (2) Department of Medicinal Chemistry, University of Mississippi*

Bacterial infections have emerged as public health threats, and it is important to develop an effective and rapid approach to counter the drug resistance of bacteria. As part of ongoing efforts to synthesize new anti-bacterial agents with improved activity, we have synthesized and evaluated a number of novel thieno[2,3-*d*]pyrimidine derivatives by changing alkyl and aryl groups on thiophene moiety and different substituted phenyl groups on 3rd position (i.e on Nitrogen). Many of these compounds are potential activity against *Escherichia coli* and *Staphylococcus aureus*. The synthesis and anti-bacterial activity of these compounds will be presented.



R_1, R_2 = H, Me, Et, Ph
R_3 = substituted benzenes

MEDI 212

Design and synthesis of novel thieno[2,3-*d*]pyrimidine derivatives as potential anti-bacterial agents

D. Ashok[1]*, Satish Goud Puppali*[2]*, and Mallikarjun Goud Puppali*[1]*. (1) Dept. of Chemistry, Postgraduate College of Science, Saifabad, Osmania University, Hyderabad 500004, India, ashok_d59@yahoo.co.uk, (2) Department of Medicinal Chemistry, University of Mississippi*

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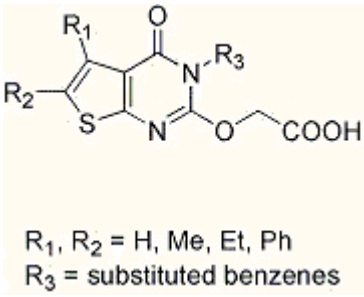


MEDI 213

New scaffold for polyvalent designs of antimicrobial peptides

Zhigang Liu*, Heather Deshazer, and Chunhui Zhou, Department of Chemistry, New York University, Department of Chemistry,Mailbox 16, 31 Washington Place,Room 1001, New York, NY 10003, Fax: 212-995-4475, zl264@nyu.edu*

Antimicrobial peptides have been proposed as prospective antibiotics agents because their effect is rapid, broad spectrum and indifferent to resistance to standard antibiotics. Among promising approaches for therapeutic application, polyvalent or multivalent designs of antimicrobial peptide offer the potential to enhance the efficacy of existing antimicrobial monomeric peptide. As an extension of this strategy, we have explored designs of antibiotics that seek to enhance the activity of known small antimicrobial peptides by grafting them on inexpensive polymer scaffolds. Antimicrobial activity is tested towards both Gram-negative bacteria E.coli and Gram-positive bacteria B.subtilis. Hemolytic activity tests are also carried out for this new design.

MEDI 214

Targeting the rhl quorum sensing cascade in Pseudomonas aeruginosa: C4 library of autoinducer analogs

***Geetanjali J Jog**, Chemistry, University at Buffalo, State University of New York, Buffalo, NY 14260, gjjog@buffalo.edu, and Hiro-aki Suga, Department of Chemistry, University at Buffalo, The State University of New York*

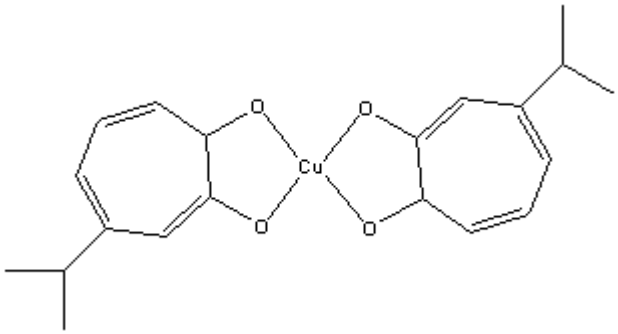
Pseudomonas aeruginosa is an opportunistic pathogen, which is commonly associated with infections in cystic fibrosis patients and nosocomial infections associated with burn- wounds and blood stream infections. Quorum sensing (QS) was identified as the regulator of the virulence factor production by this bacterium. Inhibiting quorum sensing offers an alternative form of treatment due to growing number of incidences of antibiotic resistance. In this study, we discuss the design, synthesis, and screening of analogs, targeting the rhl cascade. Our study has lead to the identification of antagonists whose features would be discussed in detail. Combination of these derivatives with those inhibiting the las circuit would significantly shut down the virulence factor production by these bacteria.

MEDI 215

Biologically active bis-(hinokitiolato)copper(II) complexes

***G.M. Arvanitis**[1], M.E. Berardini[1], C. A. Heyer[1], S.Y. Kim[1], and D.M. Ho[2]. (1) Department of Chemistry, The College of New Jersey, 2000 Pennington Rd, Ewing, NJ 08628, Fax: 609-637-5157, (2) Department of Chemistry, Princeton University*

Metal complexes of tropolone derivatives have attracted the interest of researchers in such diverse areas as materials science and medicinal chemistry. For example, bis-(hinokitiolato) copper(II) [hinokitiol = 3-isopropyl-7-oxocyclohepta-1,3,5-trienol] is an extensively polymorphic complex with reported antibacterial, antiviral, and antifungal properties. While its mechanism of activity is unknown, along with what form or forms are responsible for biochemical interactions, our structural studies suggest that the ability of this compound to hydrogen bond is a prevalent feature and may provide insight into its interaction with biological molecules. We will discuss the synthesis and characterization of this complex and several derivatives using various spectroscopic techniques and TGA.



MEDI 216

Chalcogenoxanthylium photosensitizers for use in photodynamic therapy (PDT) and photodynamic purging of blood-borne viral and bacterial pathogens

David J Donnelly[1]*, Michael R. Detty*[2]*, Scott L Gibson*[3]*, Russell Hilf*[3]*, Stephen J Wagner*[4]*, and Andrey Skripchenko*[4]*. (1) Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, NY 14260, ddonnelly@gmail.com, (2) Department of Chemistry, State University of New York at Buffalo, (3) Department of Biochemistry and Biophysics, University of Rochester School of Medicine and Dentistry, (4) American Red Cross Holland laboratory for the Biomedical Sciences, American Red Cross*

Rhodamine 123, is a highly fluorescent compound used as a mitochondrial stain in living cells. Early attempts to use rhodamine 123 as a photosensitizer were unsuccessful, due to low generation of reactive oxygen species that are associated with rhodamine derivatives. We have synthesized a series of chalcogenorhodamine dyes, where the oxygen heteroatom of rhodamine 123, has been replaced with a sulfur, selenium, or tellurium atom. These new chalcogenorhodamine photosensitizers have a much larger quantum yield for the generation of singlet oxygen and have shown considerable promise in photodynamic therapy (PDT), photoinactivation of P-glycoprotein (Pgp), and photoinactivation of viral and bacterial blood-borne pathogens. Synthetic routes have been developed that allow for systematic changes at the top of these chalcogenorhodamines. These new analogues have provided information regarding the structural components that are necessary for the optimization of biological and light harvesting properties of these heavy-atom rhodamine photosensitizers.

MEDI 217

The development of photoactivated caged biocides

Robert G. Brinson*, Sarah L Leonard, and Paul B. Jones, Department of Chemistry, Wake Forest University, 1834 Wake Forest Road, Winston-Salem, NC 27109, brinrg1@wfu.edu*

The photochemistry and microbial activity of 1-allyloxy-9,10-anthraquinones is described. When irradiated with ultraviolet or visible light under both aerobic and anaerobic conditions, these caged biocides release a bioactive aldehyde. Bioactive aldehydes generated include trans-4-hydroxy-2-nonenal (4-HNE) and acrolein. 4-HNE was produced in up to 100% yield and isolated in 91 % yield. Microbial assays with these compounds using both a modified Kirby-Bauer Assay and a turbidimetric assay show moderate bio-activity. The synthesis, photochemistry, and biological activity of these systems will be presented.

MEDI 218

Polymer nanostructures in drug delivery: Treatment and prevention of burn wound infections

Kerriann Robyn Greenhalgh[1]*, Edward Turos*[1]*, Yang Helen Wang*[1]*, G. Suresh Kumar Reddy*[1]*, and Sonja Dickey*[2]*. (1) Department of Chemistry, University of South Florida, 4202 E. Fowler Ave SCA 400, Tampa, FL 33620, (2) Department of Biology, University of South Florida*

Nanotechnology and polymer science is being utilized in this research to form a drug delivery system that can be applied to various types of drugs and other biomolecules. This system provides a way to deliver water-insoluble drugs to the body in a water-based system, and also accelerates delivery by safe-guarding the drug from outside threats until it reaches its target. Antibiotics can also be chemically modified to permit polymerization, and numerous drugs can be incorporated into the polymer to produce a broad spectrum of activity. The goal of this work is to develop a topical treatment for burn wound infections that would have a two-fold application: 1.To deliver the drug deep into the infected area, and 2. To form a protective polymeric film over the exposed area that would prevent further infection. The polymeric nanoparticles can offer enhancements to the antibiotics' activity and also to the wound healing process itself.

MEDI 219

Studying the interactions of toxic metals with protein tyrosine kinases

Yousef Ahmadibeni[1]*, Keykavous Parang*[1]*, Millie White*[1]*, and Gongqin Sun*[2]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, University of Rhode Island, Kingston, RI 02881, Fax: 401-874-5048, yahmadibeni@mail.uri.edu, (2) Department of Cell and Molecular Biology, University of Rhode Island*

A number of tyrosine kinases are activated in the presence of toxic metals. The structural effects of binding of metals, such as arsenite, cadmium, lead, cobalt, and nickel, to tyrosine kinases were examined by CD analysis. From all peptide sequences in different domains of c-Src containing one cysteine residue, only CPESLHDLMC in the CT lobe exhibited significant conformational changes. Two cysteine residues with a preserved 10-amino acid insert are also present in the C-terminal of Fyn, C-abl, Lck, Csk, and EGFR. Synthesized peptides containing these two cysteine residues and the whole c-Src and Csk proteins exhibited significant conformational changes in the presence of the metals. ^{113}Cd NMR and ^{33}S NMR studies of the peptide CPESLHDLMC confirmed the binding between the free sulfhydryl groups of the cysteine residues and cadmium. These results suggest that the cysteine residues in the C-terminal of tyrosine kinases are part of a common metal-binding domain. .

MEDI 220

Studies on the relationship between the structural and electronic parameters of some imido- substituted 2-chloro-1,4-naphthoquinones and their biological activities

Serenella Linares[1]*, Vernon R. Morris*[2]*, and Oladapo Bakare*[2]*. (1) Atmospheric Sciences, Howard University, 1310 Euclid Street NW, Washington, DC 20009, brisamarina@hotmail.com, (2) Department of Chemistry, Howard University*

Biological studies on 2-acetamido-3-chloro-1,4-naphthoquinone revealed anti-platelet, anti-inflammatory and anti-allergic activities. Similarly, 2-chloro-3-diacetylamino-1,4-

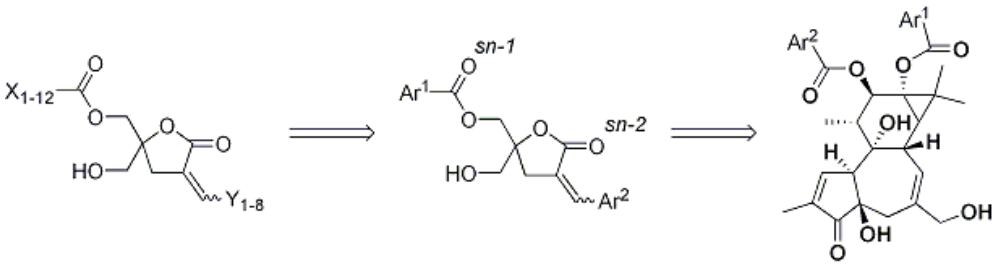
naphthoquinone and some of its analogs including open chain and cyclic analogs have been found to possess inhibitory activities against the mitogen-activated protein kinase kinase 1 (MEK 1) and some other kinases. These compounds have potential for the development of novel anticancer agents, especially as the Ras/mitogen-activated protein kinase (MapK) signaling cascade is implicated in about 30% of all human cancer. We have used Hartree-Fock (HF/6-31G*) and density functional (B3LYP) calculations to compute structural and electronic parameters for several imido-substituted naphthoquinones. We have attempted to correlate those parameters, which can be computed accurately using these quantum chemical techniques to the kinase and/or cytotoxic activities of these molecules. An understanding of this would assist us in identifying parameters necessary in designing novel analogs with improved potency.

MEDI 221

Design of C1 domain-containing isozyme-specific ligands guided by the bioassay of diacylglycerol lactone libraries

Dehui Duan[1]*, Christopher C. Lai*[1]*, James A. Kelley*[1]*, Nancy Lewin*[2]*, Peter M Blumberg*[2]*, and Victor E. Marquez*[1]*. (1) Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, 376 Boyles St., Frederick, MD 21702, Fax: 301-846-6033, dhduan1129@yahoo.com, (2) Laboratory of Cellular Carcinogenesis & Tumor Promotion, Center for Cancer Research, NCI, NIH, Bethesda, MD 20892*

Using a binding affinity-based bioassay of a small molecule library we discovered a RasGRP-specific diacylglycerol lactone (DAG-lactone) with a *p*-dimethylaminophenyl group (Ar^1) as the *sn*-1 side chain and a *p*-nitrophenyl group (Ar^2) as the *sn*-2 chain. Swapping the two chains produced little change in affinity consistent with the dual binding mode of DAG-lactones involving either *sn*-1 or *sn*-2 carbonyls, which allows the side chains to occupy the same site. Because phorbol esters bind to the same receptor in one orientation, we investigated these two polar chains as 12,13-esters of phorbol with the idea of identifying a single active isomer. Furthermore, since the DAG-lactones were 20- fold less potent than PMA in the translocation of RasGRP3 to cellular organelles, we expected the active phorbol isomer to have the specificity of the DAG-lactone and the potency of the phorbol esters. The synthesis and biological activity of these compounds will be presented.



DAG-lactone library Lead compound Phorbol ester

MEDI 222

Validation and drug targeting of aurora kinase for the treatment of pancreatic cancer

Steven L. Warner[1]*, Sridevi Bashyam*[1]*, Hariprasad Vankayalapati*[2]*, David J. Bearss*[2]*, Haiyong Han*[3]*, Daniel D. Von Hoff*[3]*, and Laurence H. Hurley*[1]*. (1) College of Pharmacy, University of Arizona, 1703 E. Mabel, PO Box 210207, Tucson, AZ 85721, warner@pharmacy.arizona.edu, (2) Montigen Pharmaceuticals, (3) Arizona Cancer Center, University of Arizona*

The Aurora kinases are serine/threonine kinases that regulate key mitotic events and are reported to be attractive targets for anti-cancer drug development. Using antisense oligonucleotides, we have shown that perturbations of Aurora A or Aurora B function lead to biological consequences in pancreatic cancer cell lines that may be useful in treatment of pancreatic cancer. Therefore, we undertook a structure-based approach that used three-dimensional models of Aurora kinase together with molecular docking simulations of novel chemical entities of low molecular weight. On the basis of these computational studies, a new generation of inhibitors derived from quinazoline and pyrimidine-based tricyclic scaffolds was designed by conjugating two or more small active fragments to form potent inhibitors of the Aurora kinases. From this series, a lead compound emerged, 4-(6,7-Dimethoxy-9H-1,3,9-triaza-fluoren-4-yl)-piperazine-1-carbothioic acid [4-(pyrimidin-2-ylsulfamoyl)-phenyl]-amide. This compound showed an IC50 of 120 nM against Aurora A and exhibited good selectivity toward Aurora compared to a panel of other kinases. In cell-based assays, the compound produced results consistent with Aurora inhibition, including G2/M cell cycle arrest and reduction in phospho-Histone H3 levels. However, these results were only observed at high µM concentrations, suggesting that further lead optimization would be required to identify a preclinical candidate for further development. Our progress toward the identification of a compound with improved enzymatic and cellular activity will be presented.

MEDI 223

Approaches to the synthesis of Lomaiviticin A

Evan S. Krygowski*, John D. Freed, Kerry Benenato, and Matthew D. Shair, Department of Chemistry & Chemical Biology, Harvard University, 12 Oxford St., Cambridge, MA 02138, krygowsk@fas.harvard.edu*

Three different synthesis plans for the natural product lomaiviticin A are discussed. The first utilizes a transannular 2+2 cycloaddition in order to set the stereochemistry of lomaiviticin A's central dimeric bond. The second attempts to set the stereochemistry through sequential Diels-Alder reactions. The third approach is based on a late stage reductive opening of an epoxyketone, followed by an oxidative homocoupling of the resulting enolate.

MEDI 224

Synthesis and structure-activity relationship studies of complex peptidyl nucleoside antibiotics

Christina S. Stauffer *and Apurba Datta, Department of Medicinal Chemistry, University of Kansas, 4062 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, KS 66045, Fax: 785-864-5326, staufcs@ku.edu*

Opportunistic fungal infections are responsible for a significant portion of systemic infections in

the immunosuppressed. With a rapidly growing population of such individuals, systemic mycotic infections are becoming a major cause of suffering and death. Limited options and various clinical liabilities associated with currently used antifungal agents attests to the need for more effective therapy. In this context, microbial derived complex peptidyl nucleoside antibiotics represent a new and promising class of antifungal agents of potent biomedical significance. As part of a program on the synthesis and structure-activity relationship studies of the antifungal peptidyl nucleosides, we have initiated a hitherto unreported study, investigating the role of the carbohydrate ring size on the biological activity of the nikkomycins. (Figure 1) A stereoselective synthesis of novel pyranosyl analogs of nikkomycin has thus been achieved and the details of the studies will be presented. Furthermore, in continuing studies, progress towards the total synthesis of a second peptidyl nucleoside antibiotic, amipurimycin, will also be discussed.

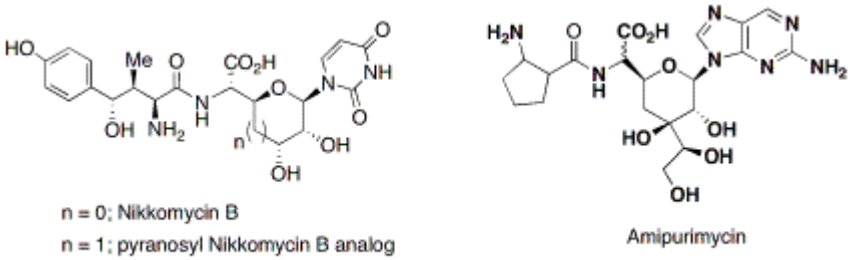


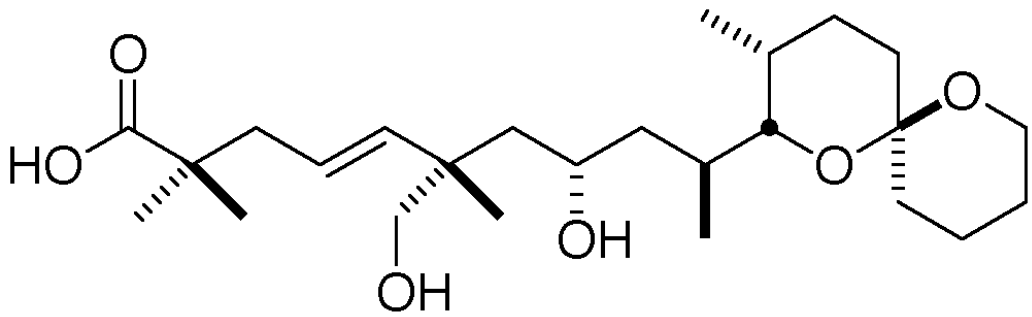
Figure 1. Complex peptidyl nucleoside antibiotics

MEDI 225

AEI:Structure-based design of okadaic acid-derived protein phosphatase inhibitors

David A. Colby *and A. Richard Chamberlin, Department of Chemistry, University of California, Irvine, Irvine, CA 92697, dcolby@uci.edu*

Okadaic acid is a powerful biological tool for studying the events associated with the inhibition of two key types of protein phosphatases, PP1 and PP2A. Using structure-based design, we have developed a series of simplified okadaic acid analogues to serve as a scaffold for probing the selectivity of PP1 and PP2A inhibition. Having selective lead compounds will form the basis of establishing the role of PP1 and PP2A inhibition as a new medicinal target.



okadaic acid analogue

MEDI 226

Developing methods to incorporate protein flexibility into drug design: HIV-1 protease as a test system

Kristin L. Meagher *and Heather A. Carlson, Department of Medicinal Chemistry, The University of Michigan, 428 Church Street, Ann Arbor, MI 48109, kmeagher@umich.edu*

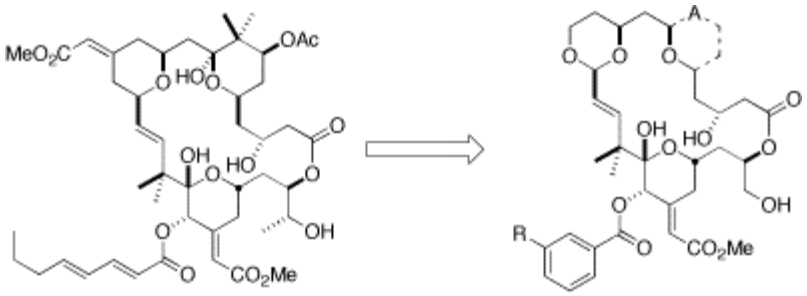
Traditionally, structure-based drug design (SBDD) is based on a single X-ray structure of a protein target complexed with a known ligand. However, using a single protein conformation provides little information on protein dynamics or the conformational changes of both ligand and protein upon binding. Therefore new techniques are needed to push the frontiers of SBDD by incorporating ensembles of protein conformations to more accurately simulate the inherent motion of the system and the potential induced fit between ligand and protein. Our method creates receptor-based pharmacophore models based on multiple protein structures (MPS), an ensemble of conformations to represent protein flexibility. To elaborate the generality of this method, we have applied it to unbound structures of HIV-1 protease (HIV-1p). Using molecular dynamics (MD) simulations to generate the MPS, we have developed pharmacophore models of the semi-open, un-complexed HIV-1p. Our models succeed in discriminating known ligands from drug-like non-inhibitors in a system that is highly dependent on protein flexibility. We have examined the influence of using MPS from independent MD simulations based on three different apo crystal structures and have also incorporated a scoring function to enable ranking and scoring of potential ligands.

MEDI 227

Function oriented synthesis: The design, synthesis, and biological evaluation of a structurally and functionally unique class of therapeutic leads for cancer treatment

Jeremy L. Baryza *and Paul A. Wender, Department of Chemistry, Stanford University, Rothway, Stanford, CA 94305, jbaryza@stanford.edu*

Bryostatin 1 is a marine natural product, currently in Phase II clinical trials, with a unique and potent spectrum of therapeutic activities including restoration of apoptosis, reversal of multidrug resistance, synergy with anticancer drugs like taxol, and immunomodulation. It has also been shown recently to be effective in an animal model of Alzheimer's disease. The low natural abundance of bryostatin 1, combined with its structural complexity has limited the available supply of material, effectively prohibiting widespread therapeutic use of the compound as well as studies to better understand its mode of action. Using a pharmacophore-guided approach, simplified analogs of bryostatin have been designed and prepared in a practical fashion. The synthesis and performance of these analogs in a novel translocation assay will be described. The compounds are as potent as the natural product but exhibit remarkable and tunable selectivity for individual PKC isozyme translocation.



MEDI 228

The role of the medicinal chemist in drug discovery: Controlling the controllables

***Don Middleton**, Department of Discovery Chemistry (IPC 424), Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom, Fax: +44-1304-651987, don.s.middleton@pfizer.com*

The presentation will describe the analysis, medicinal chemistry design and execution of a successful Discovery programme, focusing on the key issues encountered and how they were overcome.

MEDI 229

Dimerization of DJ-1 as a potential therapeutic strategy in the treatment of Parkinson's disease

***Jean-Christophe Rochet**[1], John D. Hulleman[1], Kellie L. Taylor[1], and Soumya S. Ray[2]. (1) Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, Fax: 765-494-6790, rochet@pharmacy.purdue.edu, (2) Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School*

Parkinson's disease (PD) results from a loss of dopamine neurons in the *substantia nigra*. Neuropathological evidence suggests that oxidative stress plays an important role in nigral cell death. Mutations in the gene encoding the antioxidant protein DJ-1 have been identified in some patients with early-onset PD, suggesting that DJ-1 normally protects dopamine neurons from oxidative insults. Structural data imply that the neuroprotective function of DJ-1 depends on the ability of the protein to form a homodimer, and at least one of the Parkinson's mutants has a dimerization defect. We hypothesize that the stabilization of dimeric, mutant DJ-1 may lead to an increase in antioxidant activity. Using an *in silico* screening approach, we have begun to search for small molecules that bind to the subunit interface of dimeric DJ-1. These compounds will be tested for their ability to stabilize dimeric DJ-1 in test-tube and cell-culture models. The validation of DJ-1 as a therapeutic target would be an important step towards developing new drugs in the treatment of PD.

MEDI 230

Developing inhibitors of α-synuclein oligomerization

***Michael S. Lebowitz**, Quincy K. Tran, Yong Luo, and Hossein A. Ghanbari, Panacea Pharmaceuticals, Inc, 207 Perry Parkway, Suite 2, Gaithersburg, MD 20877, Fax: 240-465-0450, msl@panaceapharma.com*

α-Synuclein oligomerization has been implicated as a key molecular pathology underlying the etiology of Parkinson's disease. As such, we are focused on the identification and characterization of novel inhibitors of the α-synuclein oligomerization process as potential therapeutic modalities for disease treatment. Towards this end we have applied phage display technology to identify peptides capable of binding to key regions of the α-synuclein protein and further screened these peptides to determine their function vis-à-vis inhibition of the oligomerization process *in vitro*. Peptides were further assessed for efficacy in a cell-based model of Parkinson's disease where they inhibited both inclusion body formation and promoted cellular survival. Peptides could be further modified by the addition of a protein transduction domain to promote and enhance intracellular their delivery. These peptides now serve as the basis for potential peptide-based or peptidomimetic therapeutics and as a springboard for the identification of small molecule drugs.

MEDI 231

Novel regulation of glutamate transporter gene activation and expression by beta lactam antibiotics

***Jeffrey D. Rothstein**, Dept of Neurology, Johns Hopkins University, 600 n. wolfe st, meyer 6-109, Baltimore, MD 21287, Fax: 410-955-0672, jrothste@jhmi.edu*

Inactivation of synaptic glutamate is principally handled by the GLT1/EAAT2 glutamate transporter. In spite of its critical importance in normal and abnormal synaptic activity, no practical pharmaceutical can positively modulate this protein. Using a blinded screen of 1040 FDA approved drugs and nutritionals, we discovered that multiple beta-lactam antibiotics are potent stimulators of GLT1/EAAT2. Selected drugs increase GLT1 protein levels in vitro by up to 10 fold. Furthermore, this action appears to be mediated thru activation of the genetic promoter for GLT1/EAAT2. More than 15 beta lactam antibiotics increased EAAT2 gene activation 2-5 fold. Beta lactams are potent antibiotics that act to inhibit bacterial synthetic pathways. They typically have no CNS side effects. When delivered to normal rats or mice, the beta lactam ceftriaxone increased brain and spinal cord protein GLT1 protein expression and functional activity of GLT1 /EAAT2 at least three fold. The drug had no effect on expression of constitutive proteins such as actin, or other glutamate transporters GLAST, EAAC1 or EAAT4. Glutamate transporters are important in normally preventing glutamate neurotoxicity. Ceftriaxone was neuroprotective in vitro when used in paradigms of ischemic injury and motor neuron degeneration, both based in part on glutamate toxicity. When used in an animal model of the fatal disease amyotrophic lateral sclerosis (ALS),delivering drug at disease onset (90 days of age)delayed loss of strength and increased mouse survival (n=20). Thus these studies provide a new class of potential neurotherapeutics that act to modulate the expression of glutamate neurotransmitter transporters via gene activation. Screening cell lines have now been used to expand the understanding and identification of small molecules that act to activate the GLT1 gene.

MEDI 232

Proteomic analysis of oxidatively modified brain proteins in Alzheimer's disease and models thereof: Insights into potential mechanisms of neurodegeneration

***D. Allan Butterfield**, Department of Chemistry, Center of Membrane Sciences, and Sanders-Brown Center on Aging, University of Kentucky, 121 Chemistry-Physics Building, Lexington, KY 40506, dabcns@uky.edu*

We previously demonstrated that extensive oxidative stress, including protein oxidation, is present in Alzheimer's disease (AD) brain in those brain regions rich in amyloid beta-peptide [Aß(1-42)], and we discovered the free radical oxidative stress associated with Aß(1-42). To identify those proteins that are oxidatively modified in AD brain, we used proteomics. Each of the proteomics-identified oxidized proteins is consistent with plausible mechanisms of neurodegeneration in AD brain and each protein is consistent with the pathology, biochemistry, or clinical symptoms of this dementing disorder. Injection of Aß(1-42) into rat brain or human Aß(1-42) expression in C.elegans recapitulates in vivo several of the oxidatively modified proteins in AD brain, as do in vitro studies employing Aß(1-42) in neuronal cultures and synaptosomes. Our proteomics results couple the oxidative stress to potential mechanisms of neurodegeneration in AD brain that may involve Aß(1-42). Support: NIH.

MEDI 233

Therapeutic approaches to Alzheimer's disease

***Mark A. Findeis**, Satori Pharmaceuticals Incorporated, 222 Berkeley Street, Suite 1040, Boston, MA 02116, Fax: 617-482-3337, mark.findeis@satoripharma.com*

Alzheimer's disease (AD) is the most common neurodegenerative disease, afflicting ~4.5 million Americans. Current therapies are considered palliative, slowing the apparent progression of the disease by months. Deposition of amyloid beta peptide 1-42 (Aβ42, "long A-beta") is an early and ubiquitous feature of AD. Aβ42 is less soluble and more toxic than the primary form of Aβ, the two residue shorter form Aβ40. Genetic mutations in the precursor protein of Aβ, and the enzymes that process it to produce Aβ, that are associated with early-onset AD increase Aβ42 levels. Lowering Aβ42 selectively is expected to slow the growth of amyloid deposits, retard transformation of diffuse amyloid plaques to the compact dense senile amyloid plaques associated with disease, and inhibit the formation of toxic oligomers of Aβ associated with acute toxicity to neurons. In this talk we will discuss efforts to identify a novel natural product with selective Aβ42 lowering activity.

MEDI 234

Acylguanidines as small molecule BACE1 inhibitors

***Derek C. Cole**[1], Ann Aulabaugh[2], Rajiv Chopra[1], Jeffrey S. Condon[1], Rebecca Cowling[3], John W. Ellingboe[1], Kristi Yi Fan[1], William F. Fobare[1], Boyd L. Harrison[1], Baihua Hu[1], Yun*

Hu[4], Lee D. Jennings[1], Guixian Jin[1], Laura Lin[1], Mei-Chu Lo[1], Peter A. Lohse[5], Frank E. Lovering[1], Michael S. Malamas[1], Eric S. Manas[1], William J. Moore[5], Mary-Margaret O'Donnell[5], Aram Oganesian[6], William, R. Solvible[1], Mark L. Stahl[1], Joseph R. Stock[1], James Strand[1], Steven Sukits[1], Mohani N. Sukhdeo[1], Kristine Svenson[1], M. James Turner[4], Erik Wagner[4], Junjun Wu[1], Ping Zhou[1], and Jonanthan Bard[4]. (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, (2) Chemical and Screening Sciences, Wyeth Research, (3) Chemical and Screening Sciences, Wyeth Research, Pearl River, (4) Department of Neuroscience, Wyeth Research, (5) ArQule, Inc, (6) Drug Safety & Metabolism, Wyeth Research

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that is the leading cause of dementia. Although the cause of AD is still unclear, evidence suggests that amyloid β-peptide, the predominant constituent of amyloid fibrils, aggregates, resulting in oligomerization, neuronal loss of function and plaque deposition. This amyloid hypothesis suggests that agents which decrease levels of Aβ should have therapeutic benefit in AD. Aβ is produced from membrane-bound β-amyloid precursor protein (APP) by sequential proteolytic cleavage by β-secretase (BACE1) and γ-secretase. Thus BACE1 is an attractive therapeutic target for the design of inhibitors of Aβ production. In this presentation, we will discuss the identification of a weak (micromolar) high-throughput screening (HTS) hit, which uses an acylguanidine moiety to form key interactions in the catalytic active site of BACE1 and displaces the flap region, relative to peptidomimetic co-structures, placing substituents in the S1 and S2' sites. Lead optimization involving structure-based combinatorial libraries led to molecules with improved interactions with these and the S1' pockets and extension from the S1 into the S3 pocket, resulting in low nanomolar potencies.

MEDI 235

Structure-activity relationships and scaffold modifications in selective androgen receptor modulators (SARMs)

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The Nuclear Hormone Receptor (NHR) superfamily of intracellular ligand-dependent transcription factors has historically been a rich source of highly druggable targets, and compounds which selectively modulate gene-transcription through activation of these receptors have the potential to provide more favorable clinical profiles than those of the native hormones. In this regard, clinical use of the endogenous agonists of the Androgen Receptor

(AR), testosterone and dihydrotestosterone, as well as related steroidal agents have demonstrated excellent anabolic efficacy in limited clinical trials. However, their use has been limited due to drawbacks associated with both the route of administration and concerns due to the side-effects and toxicity of these steroidal agonists. In order to circumvent these liabilities, several groups have been actively engaged in the discovery and development of Selective Androgen Receptor Modulators (SARMs). The most advanced of these compounds has entered clinical trials for treatment of a variety of disorders, including muscle wasting from HIV, cancer chemotherapy, chronic renal failure, male hypogonadism, benign prostatic hyperplasia, functional decline in the aging male, and osteoporosis and sexual dysfunction in both men and women. SARMs as a class hold significant potential for achieving the beneficial anabolic and cognitive enhancing effects of classical pure agonist compounds without the associated side-effects, by virtue of multiple mechanisms mediating gene- and tissue-selective action. Further exploration of structure-activity-relationships (SAR) within our previously described novel series of SARMs have resulted in a the discovery of a number of diverse scaffolds conferring potent and tissue selective agonist activity both in vitro and in vivo. Subtle changes in ligand structure were found to induce profound pharmacological differences when studied in whole-cells and in rodents. SAR from these series and an examination of selectivity mechanisms will be described.

MEDI 236

Structure-based design of selective nuclear hormone receptor ligands

Ronald L. Magolda[1]*, Andrew Fensome*[1]*, Doug Harnish*[2]*, H A Harris*[3]*, J C Keith*[2]*, Michael S. Malamas*[1]*, Eric Manas*[1]*, Richard E. Mewshaw*[1]*, Andrea Olland*[1]*, William S Somers*[1]*, Robert J. Steffan*[1]*, Eugene J. Trybulski*[1]*, Ray J Unwalla*[1]*, R C Winneker*[3]*, Jay Wrobel*[1]*, Z B Xu*[1]*, Puwen Zhang*[1]*, and Z Zhang*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, magoldr@wyeth.com, (2) Cardiovascular/Metabolic Diseases, Wyeth Research, (3) Women's Health Research Institute, Wyeth Research*

The advent of chemical genomics presents several challenges to modern medicinal chemistry. Critical to this approach is the identification of highly selective ligands to biological targets. The nuclear hormone receptor family is a rich source of targets with a defined ligand-binding domain suitable for drug intervention. Using a structure-based design approach (x-ray crystallography, modeling), we have designed and prepared several selective ligands for a number of nuclear hormone receptor. We have used these unique non-steroidal, ligands as tools to further define the pharmacological properties of these receptors. This presentation will focus on our experience with three nuclear hormone receptor targets [estrogen receptor α and β and the progesterone receptor] and their pharmacological properties.

MEDI 237

Identification of a non-steroidal LXR modulator through structure-based array design

Jon L. Collins[1]*, Nino Campobasso*[2]*, Justin Caravella*[2]*, Esther Y. Chao*[2]*, Bryan Laffitte*[2]*, Jason Nichols*[2]*, Derek Parks*[2]*, Eugene Stewart*[2]*, Ping Wang*[2]*, Robert Wiethe*[2]*, Shawn*

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The Liver X Receptor (LXR) α and LXR β are ligand-activated transcription factors of the nuclear receptor superfamily that bind to oxysterols and regulate the expression of target genes involved in cholesterol metabolism and transport, inflammation, and gluconeogenesis. The effects on gene expression are manifested in vivo as first generation LXR agonists GW3965 and T1317 show beneficial effects in multiple animal models for atherosclerosis and diabetes. The LXRs have also been shown to induce the expression of genes that control fatty acid and triglyceride metabolism. As a result, accumulation of triglycerides in the liver as well as an adverse lipid profile is observed following chronic treatment of rodents with GW3965 or T1317. LXR modulators that separate the beneficial effects from the triglyceride liability will be required for progression to the clinic. Our efforts directed towards the identification of LXR modulators with improved therapeutic indices will be described in this presentation.

MEDI 238

Selective glucocortiocoid receptor modulators

***Thomas S. Scanlan**, Department of Pharmaceutical Chemistry, University of California-San Francisco, 600 16th Street, San Francisco, CA 94143-2280, Fax: 415-502-7220, scanlan@cgl.ucsf.edu*

Corticosteroids are very effective for treating most inflammation-related disorders. However, because corticosteroids have a variety of undesired side effects, chronic corticosteroid use presents serious safety concerns. We have recently designed, synthesized, and characterized in vitro a series of non-steroid compounds that may serve as prototypes of a safer corticosteroid therapeutic. The series is based on an arylpyrazole-decalin core structure that shows exceptionally good binding affinity for the glucocorticoid receptor. In cell-based ligand activation studies, many of the compounds in the series show good potency, and some display the property of dissociating transactivation from transrepression—a feature that is believed to be important for elimination of corticosteroid associated side effects. Moreover, a number of the compounds show promising activity in in vitro studies designed to model corticosteroid side effects. The medicinal chemistry and pharmacology of these compounds will be presented.

MEDI 239

Design of a novel series of [2.2.1]-oxobicyclo based androgen receptor antagonists with an unique pharmacological profile

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Abstract text not available.

MEDI 240

Designer PPAR-gamma inverse agonist improves insulin sensitization in obese mice

William J. Hoekstra[1]*, Ryan P. Trump*[1]*, Millard H. Lambert*[2]*, Richard G. Buckholz*[3]*, Marie A. Iannone*[4]*, W. Wallace Harrington*[5]*, Robert T. Nolte*[2]*, Jeffrey E. Cobb*[5]*, Timothy M. Willson*[1]*, and Andrew N. Billin*[3]*. (1) High Throughput Chemistry, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, william.j.hoekstra@gsk.com, (2) Computational Chemistry, GlaxoSmithKline, (3) High Throughput Biology, GlaxoSmithKline, (4) GEPB, GlaxoSmithKline, (5) MV CEDD, GlaxoSmithKline*

The PPARg-activating carboxylic acid farglitazar is a potent insulin sensitizing agent. Although the precise mechanism by which farglitazar and the thiazolidinediones (TZDs) exert their antidiabetic effects is unknown, a strong candidate tissue for their direct action is PPARg-enriched adipose tissue. Both pro- and anti-adipogenic PPARg ligands promote glucose and lipid control in animal models of diabetes. We have examined adipocyte marker gene induction by representatives of a synthetic array of 160 farglitazar-related amides that were designed to occupy PPARg activation function-2 (AF2) domain's co-activator binding cleft. Herein, we disclose the mature adipocyte and macrophage gene expression profiles and noteworthy insulin sensitizing effect of the co-activator repelling PPARg inverse agonist GSK5737.

MEDI 241

The design and synthesis of BACE inhibitors: The importance of conformation for optimizing potency

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Inhibition of the aspartyl protease BACE (B-APP cleaving enzyme) is of considerable interest as a therapeutic target for the treatment of Alzheimer's disease. BACE catalyzes the first step, reported to be the rate-limiting step, in a two-step process for the cleavage of amyloid precursor protein (APP) that results in the formation of AB40/42 peptides. The accumulation of these peptides in the CNS is directly involved in the cause of Alzheimer's disease according to the amyloid hypothesis. We will present NMR and crystal structure data from three classes of inhibitors of BACE, including a macrolide, illustrating the importance of conformation of the inhibitors for optimum activity. Examples of more than one binding mode for different classes of inhibitors will be illustrated with crystal structures between BACE and inhibitors. In addition, NMR studies will be presented that show the solution conformation of inhibitors vs. the bound conformation to the enzyme that rationalize the potent enzyme inhibition observed.

MEDI 242

Structure-based design and synthesis of aspartyl protease inhibitors

***Arun K Ghosh**, Department of Chemistry, University of Illinois at Chicago, 845 West taylor Street, Chicago, IL 60607, Fax: 312-996-1547*

Aspartyl proteases continue to be major targets for AIDS and Alzheimer's diseases (AD). As part of our continuing efforts, we have designed and synthesized a number of conformationally constrained potent and selective nonpeptidal HIV protease inhibitors for AIDS and peptidomimetic inhibitors of memapsin 2 (b-secretase) for AD. In this presentation, structure-based design, synthesis and biological properties of a structurally new class of protease inhibitors will be discussed.

MEDI 243

Discovery of MK-0431, a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes

***Ann E. Weber**, Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Mailcode RY121-105, Rahway, NJ 07065*

Dipeptidyl peptidase IV (DPP-IV), a proline selective serine dipeptidase, is responsible for the N-terminal inactivation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), incretin hormones which evoke glucose stimulated insulin secretion following ingestion of a meal. In addition, GLP-1 inhibits glucagon release, slows gastric emptying, reduces appetite, and appears to regulate the growth and differentiation of the insulin producing β cells in pancreatic islets. In animal models and human studies, DPP-IV inhibitors have been shown to increase circulating levels of GLP-1, resulting in improved glucose tolerance. Thus, DPP-IV inhibitors represent a potential new therapy for the treatment of type 2 diabetes. SAR studies on two novel screening hits led to the discovery of a hybrid series of β-amino 4-phenylbutanoyl piperazine DPP-IV inhibitiors. These derivatives have excellent selectivity over the related proline peptidases DPP8 and DPP9, inhibition of which is associated with profound toxicity in preclinical species; however, they proved to have low oral bioavailability, due in part to extensive metabolism on the piperazine ring. In an effort to stabilize this ring, a series of bicyclic derivatives were prepared, culminating in the identification of a potent and selective triazolopiperazine series. Unlike their monocyclic counterparts, these analogs typically showed excellent pharmacokinetic properties. One of these, MK 0431, is currently in clinical development.

MEDI 244

Expect the unexpected: Serendipity in rational drug design

***Daniel H. Rich**, School of Pharmacy & Department of Chemistry, University of Wisconsin-Madison, 7109 Rennebohm Hall, 777 Highland Ave, Madison, WI 53705, dhrich@wisc.edu*

Medicinal chemists know that drug development rarely follows a simple linear pathway. Often compounds display unanticipated biological activities and these discoveries often provide the key information that leads to successful drug design. No where is this more evident than in the field of medicinal chemistry devoted to design and synthesis of protease inhibitors, a field now entering its fourth decade.

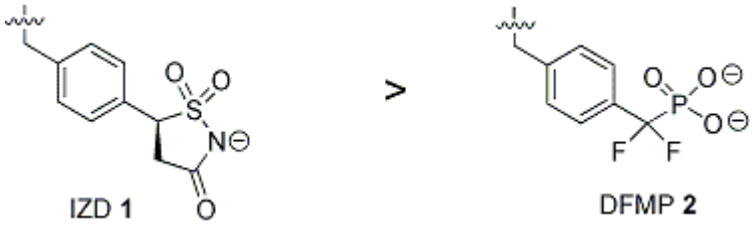
When I began my independent research career in 1970, few people thought inhibition of proteases was important to drug discovery, which was not surprising since few proteases were know to be involved in disease and no one had any good ideas about how to selectively inhibit the enzymes. This lecture will trace the evolution of the field, focusing on discoveries made in my laboratory over the past 35 years. Many serendipitous results were obtained that illustrate how systematic study of enzyme-inhibitor interactions has helped elucidate the fundamental structural biology behind enzyme catalytic mechanism and host-ligand interactions. Analysis of both the successes and failures to develop clinically useful drugs suggests strategies that might lead to more efficient future drug discovery.

MEDI 245

Structure-based design and discovery of PTP1B inhibitors incorporating novel isothiazolidinone (IZD) heterocyclic phosphotyrosine mimetics

Andrew P. Combs[1]*, Eddy W. Yue*[1]*, Michael Bower*[1]*, Paul J. Ala*[2]*, Brian Wayland*[1]*, Brent Douty*[1]*, Amy Takvorian*[1]*, Padmaja Polam*[1]*, Zelda Wasserman*[1]*, Wenyu Zhu*[1]*, Matthew Crawley*[1]*, James Pruitt*[1]*, Richard Sparks*[1]*, Brian Glass*[1]*, Dilip Modi*[1]*, Erin McLaughlin*[1]*, Lori Bolstrom*[1]*, Karl Blom*[1]*, Laurine Galya*[1]*, Mei Li*[1]*, Milton Hillman*[2]*, Lucie Gonneville*[2]*, Min Wei*[2]*, Brian G. Reid*[2]*, Mary Becker-Pasha*[2]*, Ronald Klabe*[2]*, Reid Huber*[2]*, Yanlong Li*[2]*, Gregory Hollis*[2]*, Timothy C. Burn*[2]*, Richard Wynn*[2]*, Phillip Liu*[2]*, and Brian Metcalf*[1]*. (1) Discovery Chemistry, Incyte Corporation, Experimental Station, E336/132A, 141 & Henry Clay Rd, Wilmington, DE 19880, Fax: 302-425-2708, acombs@incyte.com, (2) Discovery Biology, Incyte Corporation*

Structure-based drug design led to the discovery of novel isothiazolidinone (IZD) heterocyclic phosphotyrosine (pTyr) mimetics that when incorporated in peptide and non-peptidic scaffolds are potent (<10 nM), competitive and reversible inhibitors of protein tyrosine phosphates 1B, PTP1B. The co-crystal structures of PTP1B in complex with several analogs have been solved in high resolution, revealing that the IZD heterocycle 1 interacts extensively with the phosphate binding loop in precisely the binding mode initially designed in silico. Compounds containing the IZD heterocyclic mimetic 1 were shown to be 10-fold more potent inhibitors of PTP1B than analogous DFMP 2 providing strong evidence that the IZD is the most potent pTyr mimetic reported to date. Non-peptide inhibitors of phosphatases incorporating these novel diffusely ionizable IZD heterocyclic pTyr mimetics have provided new opportunities for the discovery novel inhibitors of phosphatases, such as PTP1B.



MEDI 246

Prodrugs of d-amphetamine with improved safety properties

Travis C. Mickle[1], *Sanjib Bera*[1], *Sven Guenther*[1], *Wendy Hirschelman*[1], *Suma Krishnan*[2], *Christopher Lauderback*[1], *Scott Moncreif*[1], *Jeff Gill*[1], *Darren Jones*[1], *Doug Linn*[1], *Andrea Martin*[1], *Christal Miller*[1], *and Diana Portlock*[1]. *(1) New River Pharmaceuticals, 1861 Pratt Drive, Suite 1090, Blacksburg, VA 24060, Fax: 540-953-3407, tmickle@nrpharma.com, (2) Vice President, Product Development, New River Pharmaceuticals*

Single amino acid, dipeptide and tripeptide prodrugs of d-amphetamine were synthesized and screened in rats for oral and intranasal bioavailability. The results were compared to the properties of d-amphetamine in an effort to identify prodrugs with physiochemical characteristics less prone to substance abuse than the parent drug. In addition, these new compounds were tested in a number of hydrolytic assays to verify that no one could obtain the drug through chemical or in vitro means. Through these assays, Lys-d-Amp was identified as having the potential to be less abusable than d-amphetamine alone. Currently, Lys-d-Amp is being studied in several human clinical trials.

MEDI 247

Novel small-molecule antimicrotubule agent, with a novel mechanism of action: Triazolopyrimidine TTI-237 for the treatment of cancer

Semiramis Ayral-Kaloustian[1], *Nan Zhang*[1], *Thai Nguyen*[1], *Richard Hernandez*[2], *Carolyn M. Discafani*[2], *Judy Lucas*[2], *Carl F. Beyer*[2], *and James J. Gibbons*[2]. *(1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, ayralk@wyeth.com, (2) Discovery Oncology, Wyeth Research*

Antimicrotubule agents are effective in the treatment of lung, breast, ovarian, and other cancers. These drugs disrupt the dynamic equilibrium of tubulin polymerization, thereby inducing mitotic arrest. Two classes of antimicrotubule drugs are commonly used: the taxanes (e.g. paclitaxel) accelerate tubulin polymerization by stabilizing assembled microtubules and obstructing depolymerization, and the Vinca alkaloids(e.g. vincristine) bind to the tubulin heterodimer, block the formation of normal microtubules, and lead to the depolymerization of existent microtubules. While these drugs are effective in inhibiting the progression of certain tumors, their cytotoxic effects on normal tissues, and side effects resulting from either the compounds themselves (mostly natural products), and/or the vehicle required for administration, are limiting factors. In addition, inherent resistance to antimicrotubule agents is encountered in many tumors, and initially sensitive tumors may acquire resistance after multiple cycles of therapy. Thus, many patients are treated with these toxic agents without receiving an anticancer benefit. There is an unmet need for identifying novel antimicrotubule drugs that overcome inherent or acquired resistance and exhibit improved pharmacokinetic properties. Our series of antimitotic agents, acting via stabilization (e.g. MAC-321) or destabilization (e.g. HTI-286) of tubulin, will be summarized. However, this presentation will mainly highlight the novel tubulin inhibitor, TTI-237, a small synthetic molecule with a novel mechanism of action. TTI-237 acts by binding at the Vinca site, yet it enhances the polymerization of tubulin as is observed with taxanes. The compound works against a variety of tumors, including those resistant to paclitaxel and vincristine. Furthermore, TTI-237 is stable and water-soluble; can be administered i.v. or p.o. in saline, without the side effects associated

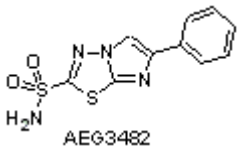
with formulation; and can be synthesized in bulk quantities efficiently. Synthesis of TTI-237 analogs, structure-activity relationships, and in vivo activity will be described. The compound is currently in Phase I clinical trials.

MEDI 248

AEG3482, a novel inhibitor of c-Jun, and inducer of HSP70 in the treatment of neuropathy

James B. Jaquith[1]*, Alain Laurent*[1]*, Patrick Bureau*[1]*, David Fenwick*[1]*, Scott Jarvis*[1]*, Alain Boudreault*[2]*, Andrew Manning*[2]*, Sharon Lin*[2]*, Andrea Romeo*[2]*, Stephen Morris*[3]*, Guillaume Levesque*[3]*, Kimberly Hewitt*[4]*, Danielle Boulais*[4]*, Catherine Cowen*[4]*, Sandra Larouche*[4]*, Joanie Lussier*[4]*, Peter Winocour*[4]*, Jon Durkin*[1]*, and John W. Gillard*[1]*. (1) Department of Chemistry, Aegera Therapeutics Inc, 810 chemin du Golf, Verdun (Montreal), QC H3E 1A8, Canada, Fax: 514-288-9280, james.jaquith@aegera.com, (2) Department of Biochemistry, Aegera Therapeutics Inc, (3) Department of Molecular Biology, Aegera Therapeutics Inc, (4) Department of Pharmacology, Aegera Therapeutics Inc*

The treatment of peripheral neuropathies induced by diabetes and chemotherapy represent an unmet need in neurology and cancer treatment. Many common chemotherapeutic agents such as the taxanes, epothilone derivatives, the vinca alkaloids, proteasome inhibitors and the platins, induce dose limiting peripheral neuropathies. AEG3482 was identified as a broad spectrum neuroprotective agent, preventing apoptosis of primary SCG neurons induced by NGF withdrawal or treatment with the chemotherapeutic agents Taxol, cisplatin or vincristine. A family of AEG3482 derivatives were prepared and evaluated in in vitro and in vivo models of peripheral neuropathy, leading to AEG33783, a development candidate for chemotherapeutic neuropathy. Mechanistic studies suggest that this family of compounds inhibit Jun kinase activity and cell death via the induction of HPS70 through an HSP90 mediated event.



AEG3482

MEDI 249

Discovery of BMS-562247, a potent and orally bioavailable coagulation factor Xa inhibitor

Donald J. P. Pinto*, Michael J. Orwat, John M. Fevig, Mimi L. Quan, Robert A. Galemmo, Stephanie Koch, Renhua Li, Charles Clark, Joseph Cacciola, Brian L. Wells, Spencer Drummond, Karen A. Rossi, Richard S. Alexander, Joseph M. Luettgen, Pancras C. Wong, Kan He, Baomin Xin, Scott J. Grossman, Robert M. Knabb, Martin L. Ogletree, Ruth R. Wexler, and Patrick Y. S. Lam, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3550, Donald.Pinto@bms.com*

Warfarin (Coumadin)® remains the current drug of choice for oral anticoagulant therapy. It is a

highly potent anticoagulant with a narrow therapeutic index, and requires careful patient monitoring. As a result, there is an unmet medical need to discover safer oral anticoagulants. Recently we described our efforts leading to the identification of razaxaban (BMS-561389), a potent factor Xa inhibitor with good efficacy and minimal bleeding. Continuing our structure-based drug-design approach, we would like to describe our efforts at further optimization of our pyrazole based inhibitors. The presentation will focus on the discovery of BMS-562247, a potent (pM), efficacious and orally bioavailable factor Xa inhibitor.

MEDI 250

Identification of DG-041, a potent and selective, prostanoid EP3 receptor antagonist, as a novel anti-platelet agent

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deCODE has identified variations in the gene encoding EP3 that confer significantly increased risk for the most severe forms of peripheral arterial occlusive disease (PAOD). The disease is estimated to effect 12-20 percent of Americans age 65 years of age or older (perhaps 8 to 12 million persons in total). During this presentation, highlights of our medicinal chemistry approach which incorporates in-vitro ADMET tools to identify barriers earlier during lead generation and SAR generation phase will be described. The evolution of this medicinal chemistry directed program led to the identification of DG-041 as a potent, selective, orally bioavailable small molecule development candidate for the prostanoid EP3 receptor. Highlights of the SAR and pre-clinical characteristics describing DG-041 as a novel anti-platelet agent will be presented.

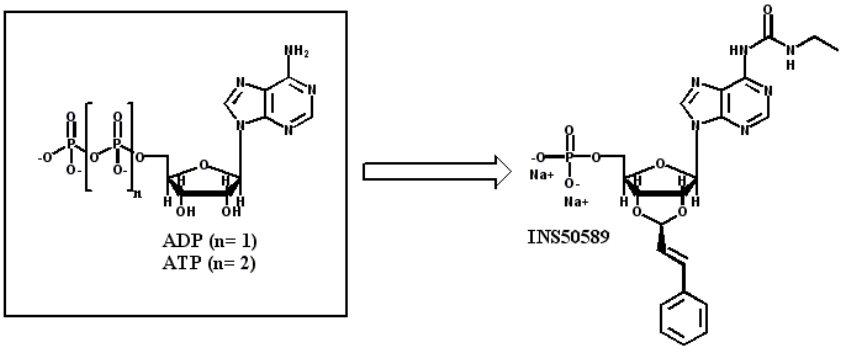
MEDI 251

INS50589, a potent, selective, and reversible inhibitor of P2Y12 mediated platelet aggregation

James G. Douglass[1], *Roshni I. Patel*[2], *Matthew C. Cowlen*[3], *Benjamin R. Yerxa*[4], *Sammy R. Shaver*[1], *Christopher S. Crean*[3], *Ward M. Peterson*[4], *Paul S. Watson*[1], *Krystof Bednarski*[1], *Robert Plourde Jr.*[1], *Sanjoy Mahanty*[2], *and José L. Boyer*[2]. *(1) Department of Chemistry, Inspire Pharmaceuticals, Inc, 4222 Emperor Blvd. Suite 200, Durham, NC 27703, jdouglass@inspirepharm.com, (2) Department of Molecular Pharmacology, Inspire Pharmaceuticals, Inc, (3) Department of Preclinical Studies, Inspire Pharmaceuticals, Inc, (4) Discovery Department, Inspire Pharmaceuticals, Inc*

ADP induces platelet aggregation via the simultaneous activation of two G-protein coupled

receptors ($P2Y_1$ and $P2Y_{12}$). Antagonism of the action of ADP at either receptor leads to inhibition of platelet aggregation, making them attractive targets for the development of medicines to treat thrombotic diseases. ATP serves as a modestly potent $P2Y_{12}$ antagonist in vivo, but undergoes rapid metabolism to other nucleotides. We studied the structure activity relationships (SAR) of modified mono and dinucleotides at $P2Y_{12}$, and identified lipophilic modifications to the ribose and base moieties that imparted potent, selective, and reversible antagonist properties at this receptor. This work led to the discovery of INS50589, having an IC_{50} of 13 nM in a washed platelet assay. INS50589 has been nominated as a clinical candidate and is currently in Phase I. The synthetic rationale leading to this molecule and the outcome of *in vitro* and *in vivo* studies will be presented.



MEDI 252

Discovery of SCH 503034, a selective, potent HCV NS3 protease inhibitor with oral bioavailability: Potential therapeutic agent for treating hepatitis C viral infection

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Hepatitis C Virus (HCV) infection is the major cause of chronic liver disease worldwide, leading to cirrhosis and hepatocellular carcinoma which affects more than 170 million people worldwide. Currently the only therapeutic regimens are subcutaneous interferon-alpha or PEG-interferon-alpha alone or in combination with oral ribavirin. Although combination therapy is reasonably successful with the majority of genotypes, its efficacy against the predominant genotype (genotype 1) affecting North America, Europe and Japan is moderate at best, with

only about 40% of the patients showing sustained virological response. In this presentation, we will disclose discovery of SCH 503034, a novel, potent, selective, orally bioavailable NS3 protease inhibitor that has been advanced to clinical trials in human beings for the treatment of hepatitis C viral infections. It is a ketoamide that reversibly binds the NS3 protease active site serine. X-ray structure of SCH 503034 complexed to the NS3 protease will be presented

MEDI 253

Lead optimization of hepatitis C viral polymerase inhibitors: An acyl pyrrolidine development candidate

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The current gold standard treatment for hepatitis C viral disease – a combination of pegylated alpha interferon and oral ribavirin – is lengthy, causes many adverse effects, and has only a moderate sustained response rate, particularly against genotype 1. There is a clear clinical need for direct acting antiviral agents. The viral NS5B polymerase is an attractive tractable target. Here we describe the evolution of the acyl pyrrolidine di-carboxylic template originating from a high throughput screening exercise against the polymerase enzyme. X-ray crystallography has revealed a novel binding mode. We have successfully exploited structure-based design to optimise potency, and will describe SAR leading to submicromolar IC50 values in the HCV replicon. The further design of molecules combining cellular potency with good pharmacokinetic profiles was a significant challenge in this series. Our approach to deliver a compound with suitable properties for further development will be presented.

MEDI 254

Design, synthesis and pharmacological evaluation of potent, selective, non-prostanoid prostaglandin F2a receptor (FP) antagonists

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Preterm delivery remains a major challenge in modern obstetrics and a serious problem in terms of perinatal mortality, disability and cost to society. Pharmacological intervention aimed at arresting preterm labor, so-called tocolytic therapy, has failed to improve neonate outcome, underlining the need to develop new therapeutic approaches. Prostaglandins play a major role in regulation of uterine activity and in molecular mechanisms of human labor and parturition. Inhibitors of prostaglandin synthesis at the level of cyclooxygenase (indomethacin, celecoxib)

have shown some tocolytic effect, but are not devoid of fetal or maternal side effects and their un-licensed use in the clinic has been raising concerns about safety. Prostaglandin F2a (PGF2a), the endogenous agonist of the FP receptor subtype, mediates contractility in uterine tissues. We report the discovery of the first non-prostanoid small molecule antagonists of the FP receptor displaying a high degree of selectivity towards all known prostaglandin receptor subtypes, as well as oral efficacy in several animal models of preterm labour.

MEDI 255

Development and application of amyloid imaging agents

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Non-invasive imaging agents capable of assessing amyloid content in vivo in the brains of Alzheimer's disease (AD) and mild cognitive impaired (MCI) subjects will be of critical importance to test the amyloid cascade hypothesis of AD, as diagnostic agents for AD, and as surrogate markers to assess the efficacy of anti-amyloid therapeutics currently under development and in clinical trials. We have determined that neutral analogues of the well known amyloid dye thioflavin-T possess many of the properties required of radiotracers to image amyloid in vivo. Imaging studies using one of these agents, carbon-11-labeled 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound B or PIB), are currently underway. Its evaluation as an agent to test the amyloid cascade hypothesis, as a diagnostic agent for AD, and as a surrogate marker to assess the efficacy of anti-amyloid therapeutics is on-going.

MEDI 256

PET in neuroscience drug discovery and development

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Imaging is a key area of ‘translational research' that provides a unique bridge from the laboratory to the clinic in many therapeutic areas. Imaging is especially important in neuroscience drug discovery and development since quantitative biomarkers as surrogate efficacy measures are often lacking and clinical trial endpoints can be confounded by high placebo response and take a long time to collect. Neuroimaging can be used pre-clinically to select candidate drug molecules during drug discovery and clinically to facilitate proof of concept testing and optimization of resources through prioritization of decision making during the development of new therapeutics. Conceptually, neuroimaging in drug discovery and development can be divided into four categories that are clearly inter-related. 1) Neuroreceptor mapping to examine the involvement of specific neurotransmitter systems in CNS diseases, drug occupancy characteristics and perhaps examine mechanisms of action; 2) Structural and spectroscopic imaging to examine morphological changes and their consequences; 3) Metabolic mapping to provide evidence of central activity and “CNS fingerprinting” the

neuroanatomy of drug effects; 4) Functional mapping to examine disease drug interactions. Positron Emission Tomography (PET) and Magnetic Resonance (MR) currently dominate the methodologies that are used for neuroimaging. Each technique, whilst powerful in its own right, has optimal value for understanding the pathophysiological characteristics of CNS diseases, their diagnosis and potential treatment outcomes when combined together due to the complimentary nature of the information provided. Neuroimaging is now central to research and drug development in the neurosciences and has begun to allow detection of the pharmacological and physiological consequences of drug action within the living brain.

MEDI 257

Imaging biomarkers: A multiplicity of targets

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In vivo radiotracer imaging offers a unique method for measuring drug action in the intact animal or living human subject. The possibilities of developing biomarkers is great, but tailoring radiotracers to specific drug actions is often necessary. Three examples of potential biomarkers will be discussed. To evaluate neuroprotective drugs aimed at the dopaminergic neuron loss in Parkinson's disease, the vesicular monoamine transporter binding radioligand [11C]dihydrotetrabenazine was developed. For symptomatic therapy of Alzheimer's disease, new cholinesterase inhibitors continue to be of interest, and can be evaluated using radiotracers that serve as enzyme substrates such as [11C]N-methylpiperidinyl propionate and [11C]N-methylpiperidinyl butyrate. Finally, receptor radioligands such as [11C]N-methyl-3-pyrrolidinyl benzilate, a muscarinic cholinergic receptor antagonist, can be used to monitor direct agonist or antagonist drug binding. Thus, biomarkers can be developed to mark many different biochemical processes, including but not limited to transporters, enzymes and receptors.

MEDI 258

Recent experiences with PET in neuroscience drug discovery and development

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This presentation will address our initial experiences involving positron-emitting radiolabeled compounds in two different neuroscience programs, namely, F-18 labeled Maxipost and its corresponding prodrug which were being developed for post-stroke neuroprotection and C-11 labeled BMS 505130 which was being developed for the treatment of sexual dysfunction. C-11 labeled BMS-505130 was prepared in a 1 step reaction from 11CH3I and the corresponding

secondary amine. MicroPET studies in rodents and PET studies in baboons were conducted to evaluate whole body distribution and regional brain uptake. F-18 labeled Maxipost was prepared by the use of microwave and chiral HPLC to obtain the desired F-18 labeled enantiomer. Subsequent rodent biodistribution were in excellent agreement with those conducted on the racemic radiolabeled material. Synthesis of the corresponding methyl phosphonate prodrug was achieved via 3 step additional steps and reverse phase HPLC.

MEDI 259

Use of PET to select patient cohorts for experimental therapy/personalized medicine

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There are many factors that can lead to a poor response of an individual patient to cancer therapy. Some reasons for poor response are hypoxia, low abundance of therapeutic targets (e.g. estrogen receptors) and acquired multidrug resistance (MDR/P-gp). These can be detected by PET imaging with appropriate radiopharmaceuticals: [^{18}F]-fluoromisonidazole, [^{18}F]-16α-fluoroestradiol and [^{11}C]-verapamil, respectively. PET provides quantitative and regional information about these characteristics of tumors in individual patients and the imaging can be repeated several times during the course of treatment to assess the evolving disease. In addition, PET can be used to image the response of a tumor to therapy. Uncontrolled tumor growth results from dysregulation of proliferation and of programmed cell death, apoptosis. Thymidine and thymidine analogs can be used to image cellular proliferation and [^{18}F]-fluoroannexin, a ligand for phosphatidyl serine exposed on the outer cell membrane, can be used to image cell death. Thus, these two imaging agents are complementary in providing a useful measure of response to cancer therapy in the individual patient. PET imaging provides an important tool for selecting patients with specific mechanisms of resistance to cancer therapy so that new drugs can be used with maximum effectiveness. It also provides an important biomarker for response to experimental therapy, an important step toward personalized medicine.

MEDI 260

Professor Murray Goodman: A pioneer in peptide science

***Fred R Naider**, Department of Chemistry, College of Staten Island, City University of New York Graduate Center and Macromolecular Assemblies Institute, 2800 Victory Blvd, Staten Island, NY 10314, Fax: 718-982-3910, naider@mail.csi.cuny.edu*

Professor Murray Goodman was a leading peptide scientist during a career that spanned more than fifty years. Early work from his laboratory made seminal contributions to understanding helix formation in polypeptides and racemization during peptide coupling reactions. Murray was noted for the breadth of his interests and his research branched out to include peptides as materials, peptides as sweeteners, peptides as drug carriers and peptidomimetics as potential

therapeutics. He was active until his sudden passing, and until that time continued to contribute new reagents, new spectroscopic approaches and novel peptides to his chosen field. Murray was a passionate advocate of peptide chemistry and was a leader of his discipline serving as President of the American Peptide Society and training ~85 doctoral students and over 200 postdoctorates. He was a sought after counselor and a patient advisor to many generations of peptide scientists. This talk will review his research, his leadership role in peptide science and his relationships with other scientists during his distinguished career.

MEDI 261

To a wonderful scholar, scientist and friend: New directions in drug delivery and in vivo imaging at Stanford

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This lecture is dedicated to the memory of Murray Goodman. It will disclose recent work on new tools for in vitro and in vivo imaging based on our work on transporters that enable or enhance the uptake of molecules into cells and tissue that either do not get in or do so only poorly. These studies utilize transfected cells and transgenic animals to quantify in real time the uptake of peptide transporter-probe conjugates into cells. The design, synthesis, and function of these new tools will be presented.

MEDI 262

The two aspects of the protein folding problem

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There are two aspects of the theoretical approach to the protein folding problem. The first is to compute the thermodynamically stable native structure, and the second is to compute the folding pathways from the unfolded to the folded native form. The evolution of physics-based computational methodology from an all-atom representation of the polypeptide chain to a united-residue representation of the chain will be discussed. Blind tests in successive CASP exercises demonstrate increasing prediction success, in computing protein structure, from one CASP test to another. As for folding pathways, two different methods are used: (1) a stochastic difference equation procedure, and (2) Lagrangian dynamics with the united-residue force field. The results of all the computations, and the methods leading to them will be discussed.

MEDI 263

Neoceptor approach to unraveling microscopic interactions between G protein-coupled receptors and their agonists

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An integrated approach to the study of drug-receptor interactions has been applied to adenosine receptors (ARs) and P2Y nucleotide receptors, all of which are G protein-coupled receptors (GPCRs). This approach is based on probing the receptor structure through site-directed mutagenesis and molecular modeling and the rational design of novel synthetic agonist and antagonist ligands. In this manner, receptor subtype selectivity has been increased, and agonists have been converted into partial agonists and antagonists. Current agonist therapy has been limited by side effects due to the wide distribution of a given GPCR. A new approach to engineering of GPCRs, termed neoceptors, has been explored, in which synthetic small molecule agonists (neoligands) are specifically tailored to activate only receptors in which the putative binding sites have been modified. This orthogonal approach to receptor activation, intended for eventual gene therapy, has been demonstrated for A_3 and A_{2A} ARs.

MEDI 264

Cyclic peptides as beta-turn mimics and benzofused enediynes

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We have prepared a library of constrained eight-membered ring lactams based upon 7-amino-8-oxo-1,2,3,6,7-pentahydroazocine-2-carboxylic acid. Conformational analysis of the 2S,7S and 2R,7S stereoisomers revealed that the 2R,7S isomer is a Type VIa beta-turn. The Type VIa beta-turn is relatively rare, typically bearing the cis amide bond found in proline-containing sequences. In addition, we have incorporated the benzofused enediyne group into 10- and 12-membered ring cyclic amino acids and explored their relative reactivity toward the Bergman reaction. N-Substituted 10-membered ring substrates gave the expected cyclization products under thermal conditions. Although the 12-membered ring amino acid benzofused enediyne was inert to the Bergman cyclization, it was found to be a Type II beta-turn in the solid state by analysis of the X-ray structure. Additionally, the 12-membered ring amino acid underwent a stereo- and regiospecific photoreduction involving a radical intermediate which was able to promote the specific nicking and cleavage of bovine serum albumin.

MEDI 265

Parathyroid hormone, ligand-receptor interactions

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PTH mediates its calciotropic activities via PTH1 receptor (PTH1R), a G protein-coupled receptor found in target tissues such as bone and kidney. In vivo, while continuous administration of PTH results in excessive bone resorption, intermittent daily administration of low doses of PTH results in significant bone anabolic effects. Design, synthesis and

conformational analysis of PTH(1-34) analogs substituted by beta3-amino acids and alpha,alpha-disubstituted amino acids helped to define the structural nature of the mid-region of this molecule. Extensive photoaffinity crosslinking studies combined with molecular modeling of the PTH-PTH1R system enabled direct mapping of the bimolecular interface leading to an experimentally-based model of the ligand-receptor complex. The non-structured mid-region PTH(1-34) is characterized by enhanced flexibility and was assigned an important functional role in the ligand-receptor interactions. This region anchors the ligand to the juxtamembrane portion of the N-terminal extracellular domain of the PTH1R thus redirecting the N-terminal activation domain of PTH towards the extracellular surface of the heptahelical bundle allowing it to traverses the external surface of the receptor between the tops of the trans-membrane helices 1 and 2 into a position that leads to receptor activation. This integrated approach, which was applied successfully to the PTH--PTH1R system, is currently used to develop small, C-terminal truncated PTH(1-34) peptides and peptidomimetics and may lead to the development of safer, more selective and non-parenterally administered PTH-like bone anabolic drugs.

MEDI 266

Farnesyl transferase inhibitors: From peptides to a clinical compound

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A family of GTP-binding proteins (p21ras) encoded by ras genes are known to play a major role in controlling cell growth and differentiation. Mutated ras genes have been found in 15% of all human carcinomas with a much higher occurrence in pancreatic adenocarcinomas (90%) and human colon tumors (50%). Ras proteins must be membrane-associated to function and post-translational modification is critical for this localization. A conserved tetrapeptide CA1A2X sequence at the C-terminus of p21ras triggers a series of post-translational processing events including the farnesylation of Cys186 by the enzyme farnesyl transferase. Inhibition of S-farnesylation of p21ras may block the growth of ras-mediated tumors. Starting from a CAAX tetrapeptide lead, SAR development led to the identification of farnesyl transferase inhibitor BMS-214662 as a clinical candidate. Unlike known farnesyl transferase inhibitors that are cytostatic, BMS-214662 induces apoptosis and leads to curative efficacy in in vivo animal models containing human tumor xenografts. Development of BMS-214662 as well as the status of farnesyl transferase inhibitors in the clinic will be discussed.

MEDI 267

Mechanism-based approaches toward the design of cysteine protease inhibitors

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Cysteine proteases are characterized by a cysteine and histidine residue in their active sites. During peptide substrate cleavage, the active site thiol nucleophile adds to the carbonyl group

of the scissile peptide bond to give a tetrahedral intermediate which then collapses to an acyl enzyme which reacts with water to give the hydrolysis products. Although all cysteine proteases share many features in common, there are distinct differences between the various clans and families of cysteine proteases. Barrett and Rawlins have classified cysteine proteases based on their sequences into clans and families. The major group of cysteine proteases belong to clan CA and includes papain, cathepsins, and calpains, among others. Clan CD is composed of caspases, legumains, separase, gingipain, and clostripain. Reversible mechanism-based cysteine proteases are usually designed to react with the cysteine thiol to give stable adducts which resemble the tetrahedral intermediate formed in substrate hydrolysis. Examples of reversible inhibitors would be peptidyl aldehydes and peptidyl alpha-ketoamides. One peptidyl ketoamide, AK295, is a potent inhibitor of calpains and can be used for the treatment of various neurodegenerative diseases. Mechanism-based irreversible inhibitors are generally designed to react with the active site thiol nucleophile. Epoxysuccinyl peptide derivatives such as E64 are very potent inhibitors of clan CA cysteine proteases, but don't inhibit clan CD enzymes effectively. Likewise, peptidyl vinyl sulfones and allyl sulfones appear to be more reactive with clan CA enzymes. In contrast, newly designed azapeptide epoxides and Michael acceptors react effectively with clan CD cysteine proteases and not effectively with clan CA enzymes. Many of these inhibitors have great potential for the treatment of a variety of diseases.

MEDI 268

Inhibitors of parasitic cysteine proteases: Homology modeling, de novo design and virtual screening

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Trypanosomiasis, leishmaniasis, and malaria are major parasitic diseases in developing countries. The existing chemotherapy of these diseases suffers from lack of safe and effective drugs and/or the presence of widespread drug resistance. Cysteine proteases are exciting novel targets for antiparasitic drug design. Homology based models of several parasitic cysteine proteases, including falcipain-2 and falcipain-3 from Plasmodium falciparum, vivapain-2 and vivapain-3 from Plasmodium vivax and cysteine protease from Leishmania donovani, were developed. The models have been used for de novo design of novel peptidomimetic inhibitors. To this point, two compounds have exhibited nanomolar IC50 values. In addition, diverse novel non-peptide drug-like inhibitors of parasitic cysteine proteases have been identified based on virtual screening of commercially available databases. The databases were pre-filtered to select drug-like molecules and docked against the homology models of the cysteine proteases. So far, more than 40 inhibitors have been identified using this approach.

MEDI 269

Design and synthesis of medium-sized ring scaffolds as ICE inhibitors for treatment of inflammatory disease

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The cytokine Interleukin-1 ß has been shown to play an important role in a variety of disease processes, including inflammation, septic shock, wound healing, and arthritis. Recently, the IL-1 receptor antagonist Kineret ® has been approved for use in the treatment of rheumatoid arthritis (RA); support that modulation of cytokine activity will provide meaningful clinical benefit. IL-1 ß is produced as a pro-form 31kDa precursor (pro-IL-1 ß), which is cleaved to the active 17.5 kDa cytokine, by the enzyme ICE (Interleukin-1 ß Converting Enzyme, Caspase-1). The enzyme is a member of the caspase (Cysteine Aspartate Specific protease) family of cysteine proteases, and as such requires Asp116-Ala117 recognition from the substrate for activation and cleavage to the mature cytokine. Using these established recognition elements, we have designed and synthesized a variety of seven and eight membered ring bicyclic and monocyclic peptidomimetic scaffolds which possess nanomolar inhibitory potency for ICE and are highly selective (>1000x) over other caspases. The design, synthesis and biological activity of these compounds will be discussed.

MEDI 270

Pyrimidoindolones as potent non-peptidic inhibitors of caspase-3

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Activation of caspases, especially the effector caspase-3, has been implicated as part of the signal transduction pathway leading to deregulation of cellular homeostasis and apoptosis. As part of a program to develop novel small molecule inhibitors of caspase-3 for the treatment of ischemic stroke, a series of 3,4-dihydropyrimido(1,2-a)indol-10(2H)-ones (pyrimidoindolones)

was identified as having potent, reversible caspase-3 inhibitory properties. This presentation will discuss the synthesis, SAR, biological properties and mechanistic studies of this novel class of non-peptidic inhibitors.

MEDI 271

Design, synthesis and pharmacology of potent azepanone-based inhibitors of the cysteine protease cathepsin K

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The recent sequencing of the human genome has revealed the presence of 12 cysteine proteases of the papain superfamily. Several of these enzymes have been implicated as causative agents in disease progression. Cathepsin K, a cysteine protease of the papain superfamily, is predominantly expressed within osteoclasts and has been shown to be the principle enzyme responsible for the degradation of the organic component of bone. Several mutations of the human gene expressing cathepsin K have been identified. These mutations result in the expression of truncated, inactive cathepsin K and are the cause of the disease known as pycnodysostosis. Additionally, mice deficient of cathepsin K display a distinct osteopetrotic phenotype. These observations suggest that the inhibition of cathepsin K may be a viable therapeutic approach for the prevention and treatment of osteoporosis. This presentation will describe the design and pharmacology of azepanone-based inhibitors of cathepsin K.

MEDI 272

Melanotropin ligands for the hMC4Rs: Multiple biological activities! One receptor? The challenge!

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Since its discovery and cloning a decade ago, the human melanocortin 4 receptor (hMC4R) has elicited a great deal of interest since this receptor and its natural ligands (alpha-MSH, agouti, delta-MSH, agouti related protein, etc.) are critical players in many biological activities including feeding behavior, sexual behavior, obesity, anorexia, heart and kidney function, and a variety of other important biological activities. Furthermore, these hormonal and neuromodulatory activities require special considerations for ligand design. With these considerations in mind, we have been designing novel peptide and peptide mimetic templates to obtain potent, selective, and bioavailable ligands that can be used as tools, drug leads, and drug candidates in the contexts in which the ligands and receptors exist. In the process, novel conformational and topographical considerations, template design, and mechanisms were considered and evaluated, and new structural tools have been created. Supported by grants from the U.S. Public Health Service, NIH.

MEDI 273

Design of melanocortin receptor agonists by conformational restriction approach

***Xinrong Tian**, Adrian G. Switzer, Rajesh K. Mishra, Timothy Field, Steve A. Derose, Eric Hu, Denny Denton, Nick Kim, Adam W. Mazur, Frank H. Ebetino, John A. Wos, Doreen Crossdoersen, Beth B. Pinney, Julie A. Farmer, Russell L. Sheldon, Martin E. Dowty, Cindy M. Obringer, and Annyodile Colson, Procter & Gamble Pharmaceuticals, 8700 Mason-Montgomery Rd, Mason, OH 45040, Fax: 513-622-1195*

We have explored various approaches for designing peptidomimetics as melanocortin agonists on the basis of linear tetrapeptide leads derived from His-D-Phe-Arg-Trp. One of our strategies involves investigating locally constrained analogs with reduced peptidyl characteristics by introducing conformational restriction between two adjacent amino acid residues of tetrapeptide leads using a cyclic scaffold. We have demonstrated that incorporating conformational restriction between Arg and Trp residues is an optimum constraining mode that led to the discovery of several series of potent melancortin agonists featuring proline, pyrrolidine, and keto-piperazine as core structures. The stereochemistry on the cyclic scaffolds has been found to have a significant impact on potency and selectivity for MC1 and MC4 receptors. To improve cellular permeability, we have also explored replacement of the highly basic guanidine moiety present in potent keto-piperazine based agonists with less basic or neutral groups. The design, synthesis, and structural activity relationships (SAR) of proline, pyrrolidine, and keto-piperazine based melanocortin agonists will be discussed.

MEDI 274

Quinazolinone guanidines as MC4R agonists: SAR of unusual pharmacokinetic properties

***Jason D Speake**, Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709-3398, jason.d.speake@gsk.com*

As part of a collaboration with Chiron aimed at identifying MC4R agonists for the treatment of obesity, several potent piperazine substituted guanidines were identified. Among these GSK045 was shown to produce a significant suppression of overnight feeding. It was noted, however, that these molecules had an unusually long tissue residence time, which did not appear to reach saturation. Indeed, the tissue t1/2's appeared to increase upon chronic dosing. SAR exploration of this phenomenon revealed a correlation between the basicity of the piperazine and tissue t1/2. Several potent non-accumulating molecules were identified and tested for their effects on food intake.

MEDI 275

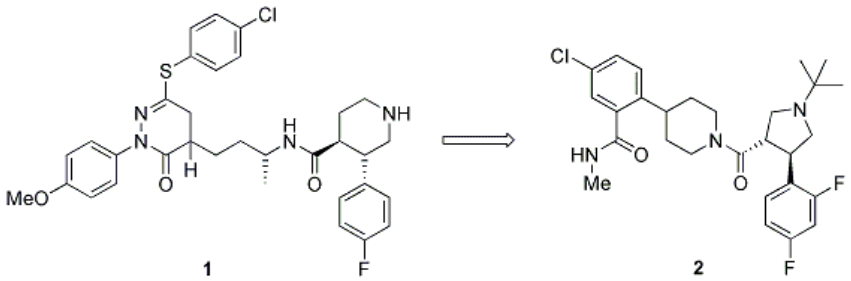
Design and syntheses of human Melanocortin subtype-4 receptor (hMC4R) agonists: Discovery of the tert-butylpyrrolidine archetype

***Feroze Ujjainwalla**, Department Of Medicinal Chemistry, Merck & Co., Inc, 126 E. Lincoln*

Avenue, RY121-120, Rahway, NJ 07065-0900, Fax: 732-594-2210, f_ujjainwalla@merck.com

The association between the melanocortin subtype-4 receptor (MC4R) pathway and the modulation of feeding has been established in a number of genetic and pharmacological studies, involving both animals and humans. These studies in part, have provided the impetus in drug discovery to identify novel, small molecule agonists of the hMC4R for the potential treatment of human obesity and erectile dysfunction. In recent reports from this laboratory, we described the discovery of a structurally unique pyridazinone derived class of subtype selective (*vs* hMC3R and hMC5R) hMC4R agonists, exemplified by compound **1**.

This presentation will describe the design and asymmetric synthesis of a new class of non-peptidyl, MC4R agonists **2**, derived from **1**. Specifically, it will detail the SAR strategy that guided the identification of **2**, with particular emphasis on potency, melanocortin receptor subtype selectivity and oral pharmacokinetics.



MEDI 276

Design, synthesis and characterization of potent and selective melanocortin-4 receptor antagonists

***Chen Chen**, Medicinal Chemistry, Neurocrine Biosciences, 12790 El Camino Real, San Diego, CA 92130, Fax: 858-617-7967, cchen@neurocrine.com*

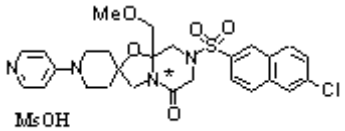
Recent studies have demonstrated that melanocortin-4 receptor (MC4R) antagonists can prevent weight loss in tumor-bearing mice, which implicates clinical usage for the treatment of cachexia. In our efforts to develop potent and selective MC4R antagonists, we designed piperazinebenzylamines bearing a 2,4-dichlorophenylalanine, by utilizing information derived from structure-activity relationships of small molecule and peptide MC4R agonists, in combination with mutagenesis of the MC4 receptor and its ligands, and computational modeling. Representative compounds were characterized in vitro in both competitive binding assay and cAMP assay, and demonstrated potent functional antagonism. One of the compounds was further studied in vivo. Thus, compound 12i, which penetrated to the brain, was demonstrated efficacy in the LLC (Lewis lung carcinoma) tumor-bearing mice by reversing food-intake reduction and protecting from loss of body weight and lean mass. Our results showed that a potent and selective MC4R antagonist would have a potential benefit in treatment of cachexia.

MEDI 277

Synthesis and pharmacological evaluation of a novel orally active factor Xa inhibitor

***Hidemitsu Nishida**, Munetaka Ohkouchi, Takafumi Mukaihira, Fumihiko Saitoh, Yuka Nakamura, Yutaka Miyazaki, Tsutomu Satoh, Masashi Mizuno, Tomoyuki Kamino, Yoshitaka Hosaka, Mikihiko Shinozaki, Tamami Oono, Hiroyuki Muramatsu, Ikuya Shiromizu, Tomokazu Matsusue, Masatsugu Kamiya, Makoto Miyauchi, Tooru Yokoyama, Chihaya Kakinuma, Takuo Ogihara, Kazutoshi Yanagibashi, and Yasuo Isomura, Research Center, Mochida Pharmaceutical Co., Ltd, 722,Jimba-Aza-Uenohara, Gotemba,Shizuoka 412-8524, Japan, Fax: +81-550-89-0945, hnishida@mochida.co.jp*

At the 228th ACS meeting, we reported a potent direct factor Xa inhibitor:M55532 with spiro [5H-oxazolo[3,2-a]pyrazine-2(3H),4'-piperidine]-5-one structure containing no strong basic group such as guanidino- and/or amidino groups. M65644 derived from M55532 is not only an optimal non-basic compound with good oral bioavailability and half-life in dog, but also exhibits improved unbound fraction in human plasma and excellent potency of in vitro APTT (CT2) in humans(0.37μM,). The significant inhibitory effect on thrombus formation in the rat A-V shunt model was observed at 10mg/kg p.o. without any prolongation of bleeding time in the rat tail cut model . The compound is at an early research stage, but we believe that it has potential to be a possible promising agent for prevention and treatment of thromboembolic disorders.



M55532

MEDI 277

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***Hidemitsu Nishida**, Munetaka Ohkouchi, Takafumi Mukaihira, Fumihiko Saitoh, Yuka Nakamura, Yutaka Miyazaki, Tsutomu Satoh, Masashi Mizuno, Tomoyuki Kamino, Yoshitaka Hosaka, Mikihiko Shinozaki, Tamami Oono, Hiroyuki Muramatsu, Ikuya Shiromizu, Tomokazu Matsusue, Masatsugu Kamiya, Makoto Miyauchi, Tooru Yokoyama, Chihaya Kakinuma, Takuo Ogihara, Kazutoshi Yanagibashi, and Yasuo Isomura, Research Center, Mochida Pharmaceutical Co., Ltd, 722,Jimba-Aza-Uenohara, Gotemba,Shizuoka 412-8524, Japan, Fax: +81-550-89-0945, hnishida@mochida.co.jp*

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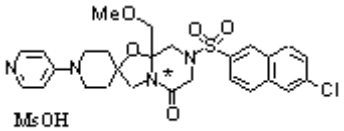


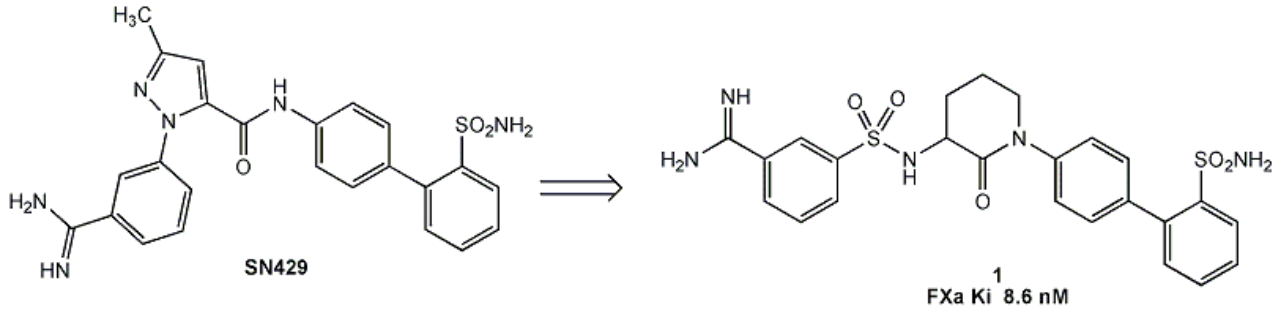
M55532

MEDI 278

Synthesis and SAR of 1-aryl-3-arylsulfonyl-2-piperidinone derived inhibitors of coagulation factor Xa

***Joanne M. Smallheer**, Shuaige Wang, Mia L. Laws, Joseph M. Luettgen, Robert M. Knabb, Ruth R. Wexler, Patrick Y. Lam, and Mimi L. Quan, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3450, joanne.smallheer@bms.com*

As part of our effort to identify novel inhibitors of coagulation factor Xa, the 1-[(3-amidino) phenyl]pyrazole carboxamide moiety of SN429 was replaced with 3-[(3-amidinophenyl) sulfonylamino]piperidone. This led to the identification of a structurally diverse chemotype that was explored as a potential backup for our pyrazole fXa clinical candidates. Optimization of the P1 sulfonamide substituent to remove the benzamidine yielded examples with neutral or less basic aryl and heteroaryl sulfonamide P1 groups that maintained good potency vs. fXa. Introduction of substitution at the sulfonamide nitrogen provided further improvements in potency as did incorporation of alternate P4 groups.



SN429

1
FXa Ki 8.6 nM

MEDI 279

Preparation of highly potent inhibitors of coagulation factor Xa containing pyrazole-fused bicyclic core structures

***John M. Fevig**, Joseph Cacciola, Joseph Buriak Jr., Yun-Long Li, Donald J. Pinto, Michael Orwat, Robert A. Galemmo, Brian Wells, Richard S. Alexander, Karen A. Rossi, Robert M. Knabb, Joseph M. Luettgen, Pancras C. Wong, Stephen Bai, Ruth R. Wexler, and Patrick Y. S. Lam, Bristol-Myers Squibb Pharmaceutical Research Institute, NJ, Fax: 609-818-3450, john.fevig@bms.com*

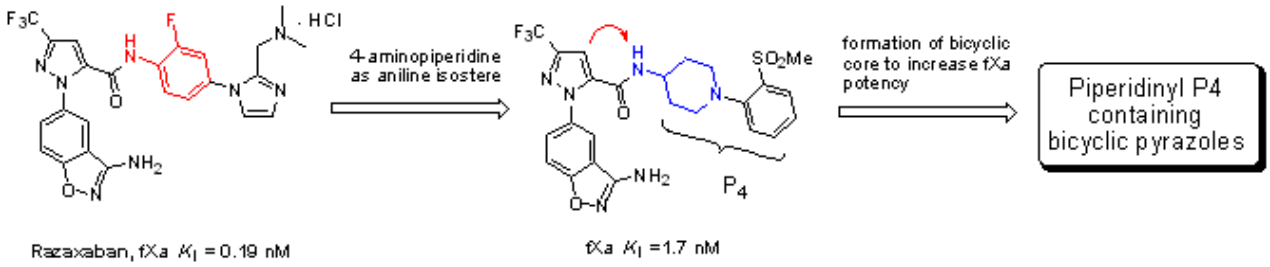
The serine protease factor Xa is a critical enzyme in the blood coagulation cascade. It acts at the convergence point of the intrinsic and extrinsic coagulation pathways and is responsible for the proteolytic cleavage of prothrombin to generate thrombin, which subsequently plays a crucial role in the formation of a fibrin clot. The selective inhibition of factor Xa has emerged as an attractive strategy for the discovery of novel antithrombotic agents. Recently, we described our efforts leading to the identification of Razaxaban (BMS-561389) as a potent pyrazole factor Xa inhibitor with good oral efficacy and minimal bleeding. Modifications of the pyrazole core have provided additional novel, highly potent factor Xa inhibitors. Here, we will describe the synthesis and biological activity of factor Xa inhibitors containing several pyrazole-fused bicyclic cores together with various P1 and P4 residues. Many of these compounds are potent, orally bioavailable and efficacious inhibitors of coagulation factor Xa.

MEDI 280

Pyrazole-based factor Xa inhibitors: Synthesis and SAR of analogs containing piperidinyl P4 residues

Jennifer X. Qiao, *Xuhong Cheng, Joanne M. Smallheer, Donald J. P. Pinto, Robert A. Galemmo, Spencer Drummond, Daniel L. Cheney, Kan He, Joseph M. Luettgen, Robert M. Knabb, Ruth R. Wexler, and Patrick Y.S. Lam, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-6810, jennifer.qiao@bms.com*

Thromboembolic diseases remain the leading cause of death in developed countries. Conventional antithrombotic therapies using either heparin or warfarin have several limitations, including excessive bleeding, due to their targeting multiple factors within the coagulation cascade. Several approaches have been pursued to discover safer and efficacious oral anticoagulants. One such approach is to inhibit thrombin generation by targeting the inhibition of coagulation factor Xa (fXa). Recently, we disclosed Razaxaban, a pyrazole-based fXa inhibitor with good potency and efficacy in humans. Using structural-based approaches, we have extended the monocyclic pyrazole SAR to include potent bicyclic pyrazole fXa inhibitors. In this presentation, we will describe the synthesis and SAR of monocyclic and bicyclic pyrazoles containing a variety of substituted piperidinyl moieties which occupy the aryl binding S4 pocket of fXa.



MEDI 281

Discovery of 1-[3-Aminobenzisoxazol-5'-yl]-3-trifluoromethyl-6-[2'-(3-(R)-hydroxy-N-pyrrolidinyl)methyl-[1,1']-biphen-4-yl]-1,4,5,6-tetrahydropyrazolo-[3,4-c]-pyridin-7-one

(BMS-740808), a potent, efficacious and orally bioavailable inhibitor of blood coagulation factor Xa

***Michael J. Orwat**, John M. Fevig, Mimi L. Quan, Robert A. Galemmo, Eugene Amparo, Richard S. Alexander, Karen A. Rossi, Angela M. Smallwood, Pancras C. Wong, Joseph M. Luettgen, Robert M. Knabb, Steven A. Bai, Kan He, Ruth R. Wexler, Patrick Y.S. Lam, and Donald J. P. Pinto, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08542, Michael.Orwat@bms.com*

Thrombotic diseases have remained the leading cause of death in developed countries. There is an unmet medical need to discover safer oral anticoagulants, due to the shortcomings of the only available oral anticoagulant Coumadin.® The common approach used by many investigators is to target the inhibition of thrombin or factor Xa in the coagulation cascade. Recently we described our efforts leading to the identification of Razaxaban (BMS-561389), a potent factor Xa inhibitor with good efficacy and minimal bleeding. This presentation will focus on scaffold and P4 optimizations of our pyrazole inhibitors which contain the novel aminobenzisoxazole P1 of Razaxaban. These efforts culminated with the identification of BMS-740808, a highly potent (30pM), efficacious and orally bioavailable inhibitor of factor Xa.

MEDI 281

Discovery of 1-[3-Aminobenzisoxazol-5'-yl]-3-trifluoromethyl-6-[2'-(3-(R)-hydroxy-N-pyrrolidinyl)methyl-[1,1']-biphen-4-yl]-1,4,5,6-tetrahydropyrazolo-[3,4-c]-pyridin-7-one (BMS-740808), a potent, efficacious and orally bioavailable inhibitor of blood coagulation factor Xa

***Michael J. Orwat**, John M. Fevig, Mimi L. Quan, Robert A. Galemmo, Eugene Amparo, Richard S. Alexander, Karen A. Rossi, Angela M. Smallwood, Pancras C. Wong, Joseph M. Luettgen, Robert M. Knabb, Steven A. Bai, Kan He, Ruth R. Wexler, Patrick Y.S. Lam, and Donald J. P. Pinto, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08542, Michael.Orwat@bms.com*

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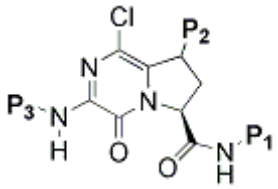
MEDI 282

Bicyclic pyrazinones as TF-FVIIa inhibitors

***Wen Jiang**[1], Aaron Schmitt[1], Jeff Bozarth[2], Alan Rendina[2], Anzhi Wei[3], Xiao Wen[3], Pancras Wong[2], Ruth Wexler[1], Scott Priestley[1], and Xiaojun Zhang[1]. (1) Discovery Chemistry,*

Pharmaceutical Research Institute, Bristol-Myers Squibb Company, P.O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3550, wen.jiang@bms.com, (2) Thrombosis Biology, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, (3) Macromolecular Structure, Pharmaceutical Research Institute, Bristol-Myers Squibb Company

The TF-FVIIa complex is an important therapeutic target for the treatment of thrombotic disease. Bicyclic pyrazinone peptidomimetics were designed to inhibit the TF-FVIIa complex. Chemistry was developed to access the S1, S2 and S3 pockets. SAR at P1, P2 and P3 lead to a potent benzamidine inhibitor with FVIIa Ki < 10nM.

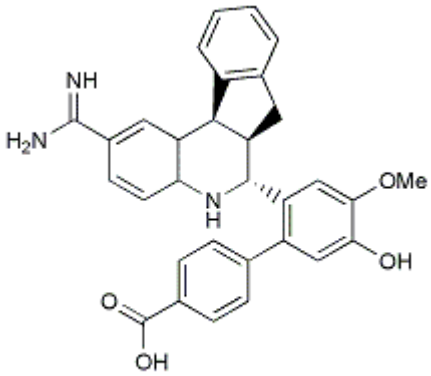


MEDI 283

A selective FVIIa inhibitor with efficacy in an arterial thrombosis model

Indawati De Lucca[1]*, Jinglan Zhou*[1]*, Eddine Saiah*[1]*, Anzhi Wei*[2]*, Xiao Wen*[2]*, Earl Crain*[3]*, Carol Watson*[3]*, Pancras Wong*[3]*, Ruth Wexler*[1]*, and Scott Priestley*[1]*. (1) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-6006, indawati.delucca@bms.com, (2) Macromolecular Structure, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, (3) Thrombosis Biology, Pharmaceutical Research Institute, Bristol-Myers Squibb Company*

Optimization of a tetrahydroquinoline screening lead resulted in the discovery of BMS-593214, a potent and selective inhibitor of coagulation factor VIIa. A crystal structure of BMS-593214 bound to FVIIa revealed key interactions in the S1 and S2 binding pockets. A gram scale synthesis of BMS-593214 was developed to enable in vivo studies. The antithrombotic and antihemostatic effects of BMS-593214 were tested in a rabbit electric current arterial thrombosis model and a rabbit cuticle bleeding time model, and the compound showed robust antithrombotic efficacy without significant prolongation of bleeding time.



BMS-593214

MEDI 284

Antithrombin activation with designed small organic activators: The design of a bicyclic–unicyclic isoquinoline based activator

Chandravel Krishnasamy[1]*, Gunnar Thor Gunnarsson*[1]*, and Umesh R. Desai*[2]*. (1) Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, 410 North 12th Street, Richmond, VA 23220, krishnasamyc@vcu.edu, (2) Department of Medicinal Chemistry, Virginia Commonwealth University*

Antithrombin, a serine proteinase inhibitor, is a major regulator of the blood coagulation cascade. It performs this function efficiently in the presence of heparin by inhibiting procoagulant proteinases, especially thrombin, factor Xa and factor IXa. Our previous work has shown that non-sugar, small, sulfated molecules can bind and activate antithrombin. Our present work focuses on the design and synthesis of a new non-sugar bicyclic-unicylic antithrombin activator based on isoquinoline skeleton that binds antithrombin with an affinity nearly 10-fold higher than our previous designs. Further, the new designed activator accelerates factor Xa inhibition ~40-fold at pH 6.0, I 0.05, 25°C suggesting enhanced activation. Molecular modeling studies indicate that the isoquinoline-based activator binds antithrombin in the pentasaccharide binding site in preference to the extended heparin binding site, a prediction supported by spectroscopic study with fluorescently-labeled antithrombin. The designed bicyclic-unicyclic isoquinoline based activator represents a second-generation antithrombin activator with better activity profile.

MEDI 285

Structure-activity relationship (SAR) of pentapeptides and hexapeptides derived from [D-Phe-Pro-D-Arg-P1'-CONH2] tetrapeptides inhibitors for thrombin

Cristina C. Clement*, Chemistry Department, Lehman College and Biochemistry Ph.D. Program, City University of New York, 365 Fifth Avenue, New York City, NY 10016-4309, Fax: 212-817-1503, cclement_us@yahoo.com, and Manfred Philipp, Department of Chemistry, Lehman College, CUNY*

Our previous studies determined a strictly correlation between the structures of the natural or non-natural amino-cid type at P1'- position in the sequence space [D-Phe-Pro-D-Arg-P1'-CONH2] and their in vitro inhibitory activity against thrombin. These new SAR investigations for thrombin inhibition expand the tetrapeptide sequence space by (P2') and (P3') amino-acids and SAR for these two positions is presented. Peptides D-Phe-Pro-D-Arg-Gly-Asp-CONH2 and D-Phe-Pro-D-Arg-Gly-Asn-CONH2 are showing inhibition for thrombin with Ki's of 130 uM and 112 uM while peptides extended with one more amino acid such as D-Phe-Pro-D-Arg-Gly-Asp-Ala-CONH2 and D-Phe-Pro-D-Arg-Gly-Asp-Lys-CONH2 are less efficient in inhibiting thrombin having Ki's of 705 uM and 643 uM, respectively. Other variations at P3' positioning the pentapeptide sequence space D-Phe-Pro-D-Arg-Gly-Asp-P3'-CONH2 such as L-Met and Gly are less effective in inhibiting thrombin (Ki's of 993.4 uM and 1.73 mM respectively). Overall the pentapeptides were stronger inhibitors than the hexapeptides but less efficient than the tetrapeptides with a couple of exceptions, such as the pentapeptides with the sequence space D-Phe-Pro-L-Arg-D-Pro-P2'-CONH2 which have Ki's of 500-800 nM or low uM. All

peptides showed competitive or mixed inhibition with respect to thrombin. These SAR studies reveal the efficacy of using D-amino acids at specific positions in defined sequence spaces for improving the inhibitory activity and selectivity toward thrombin.

MEDI 286

Potent, selective and orally bioavailable matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis

Yonghan Hu[1]*, Martin J. DiGrandi*[2]*, Xuemei Du*[2]*, Manus Ipek*[1]*, Leif M. Laakso*[2]*, Jianchang Li*[1]*, Wei Li*[1]*, Thomas S. Rush*[1]*, Jean Schmid*[2]*, Jerauld S. Skotnicki*[2]*, Steve Tam*[1]*, Jennifer R. Thomason*[1]*, Jason S. Xiang*[1]*, Qin Wang*[3]*, and Jeremy I. Levin*[2]*. (1) Department of Chemical and Screening Sciences, Wyeth Research, Cambridge, MA 02140, Fax: 617-665-5682, fhu@wyeth.com, (2) Chemical and Screening Sciences-Pearl River, NY, Wyeth Research, (3) Drug Satefy and Metabolism-Andover, MA, Wyeth Research*

Osteoarthritis (OA) is a debilitating disease resulting from the breakdown of articular cartilage and characterized by chronic joint pain and inflammation. Current treatments, such as NSAIDs (including COX-2 inhibitors), although effective in relieving the pain of OA, fail to halt the progression of this disease. Matrix metalloproteinase-13 (MMP-13 or collagenase–3) efficiently and irreversibly cleaves type II collagen, the main structural component of the cartilage matrix, and is over-expressed in OA patient cartilage. Agents that inhibit this enzyme therefore offer a potential therapy that could alter the progression of osteoarthritis. The development of potent, selective and orally bioavailable biphenylsulfonamide carboxylate MMP-13 inhibitors will be presented.

MEDI 287

P1’ Modified sultam hydroxamates as potent MMP inhibitors

Ruowei Mo*, Dayton T. Meyer, Zelda R. Wasserman, Karl D. Hardman, Rui-Qin Liu, Maryanne B. Covington, Mingxin Qian, David D. Christ, James M. Trzaskos, Robert C. Newton, Carl P. Decicco, and Robert J. Cherney, Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box. 4000, Princeton, NJ 08543-4000, Fax: 609-252-6601*

Matrix metalloproteinases (MMPs) are zinc dependent proteases in the metzincin family and play key roles in matrix remodeling and destruction. They are found to be over-expressed in connective tissue associated with osteoarthritis, angiogenesis, periodontal disease, atherosclerosis and cancer. As a result, they are potential therapeutic targets for the treatment of many diseases. We designed and synthesized potent MMP-2, -9, and -13 inhibitors with good selectivity over MMP-1 and TACE. In this communication, we describe our efforts to optimize these novel sultam hydroxomates in the P1' position.

MEDI 288

Potent, selective and orally bioavailable inhibitors of tumor necrosis factor-α converting

enzyme (TACE): Discovery of novel indole, benzofuran, imidazopyridine and pyrazolopyridine P1' substituents

Zhonghui Lu[1], *Rajan Anand*[2], *Richard Liu*[2], *Maryanne Covington*[2], *Krishna Vaddi*[2], *Mingxin Qian*[2], *James J-W. Duan*[2], *and Gregory R. Ott*[2]. *(1) Discovery Chemistry, Bristol-Myers Squibb Company, P. O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6804, zhonghui.lu@bms.com, (2) N/A*

Tumor necrosis factor-α converting enzyme (TACE) has been the subject of intense interest as an interception point in the processing of TNF-α, a pro-inflammatory cytokine implicated in numerous inflammatory diseases. Small molecule inhibitors of TACE have been shown to be effective at suppressing levels of TNF-α in both cell assays and in vivo models. The development of TACE inhibitors selective against the structurally related proteins in the MMP and ADAM family has been a constant challenge. Recently, inhibitors based on novel β-benzamido hydroxamic acid scaffolds were found to be highly potent for TACE, potent in the cellular suppression of TNF-α and displayed oral bioavailability. Further investigation using these optimized platforms led to the discovery of novel heterocyclic P1' substituents. Optimized examples possess the requisite potency in enzyme and cellular assays, display outstanding selectivity and are orally bioavailabe in multiple species.

MEDI 289

Design and synthesis of remarkably selective, orally bioavailable inhibitors of tumor necrosis factor-α converting enzyme (TACE): Discovery of novel benzimidazole P1' moieties

Gregory R. Ott[1], *Naoyuki Asakawa*[2], ***Zhonghui Lu***[3], *Rajan Anand*[2], *Richard Liu*[2], *Maryanne Covington*[2], *Krishna Vaddi*[2], *Mingxin Qian*[2], *and James J-W. Duan*[2]. *(1) Cephalon, Inc, 145 Brandwine Parkway, West chester, PA 19380, gott@cephalon.com, (2) (3) Discovery Chemistry, Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6804, zhonghui.lu@bms.com*

Tumor necrosis factor-α converting enzyme (TACE) is the principal metalloprotease that processes the pro-form of tumor necrosis factor-α (TNF-α) to the soluble form. With the clinical success of anti-TNF-α biologics in diseases such as rheumatoid arthritis, TACE has attracted significant interest as an intervention point for small molecules to suppress the amount of circulating TNF-α. Most early TACE inhibitors were derived from inhibitors of structurally related matrix metalloproteases (MMPs) and hence, suffered from lack of TACE selectivity. Recently, several novel β-benzamido hydroxamic acid scaffolds were found to be highly potent for TACE, potent in the cellular suppression of TNF-α and displayed oral bioavailability in multiple species. Using the optimized scaffolds, further investigation of the P1' position has led to the discovery of novel benzimidazole P1' moieties. These inhibitors possess the requisite potency/oral bioavailability profiles and importantly, were remarkably selective over a wide panel of MMP and related ADAM proteases.

MEDI 289

Design and synthesis of remarkably selective, orally bioavailable inhibitors of tumor necrosis factor-α converting enzyme (TACE): Discovery of novel benzimidazole P1' moieties

*Gregory R. Ott[1], Naoyuki Asakawa[2], **Zhonghui Lu**[3], Rajan Anand[2], Richard Liu[2], Maryanne Covington[2], Krishna Vaddi[2], Mingxin Qian[2], and James J-W. Duan[2]. (1) Cephalon, Inc, 145 Brandwine Parkway, West chester, PA 19380, gott@cephalon.com, (2) (3) Discovery Chemistry, Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6804, zhonghui.lu@bms.com*

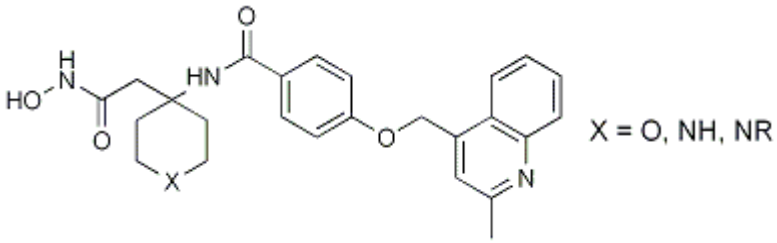
Tumor necrosis factor-α converting enzyme (TACE) is the principal metalloprotease that processes the pro-form of tumor necrosis factor-α (TNF-α) to the soluble form. With the clinical success of anti-TNF-α biologics in diseases such as rheumatoid arthritis, TACE has attracted significant interest as an intervention point for small molecules to suppress the amount of circulating TNF-α. Most early TACE inhibitors were derived from inhibitors of structurally related matrix metalloproteases (MMPs) and hence, suffered from lack of TACE selectivity. Recently, several novel β-benzamido hydroxamic acid scaffolds were found to be highly potent for TACE, potent in the cellular suppression of TNF-α and displayed oral bioavailability in multiple species. Using the optimized scaffolds, further investigation of the P1' position has led to the discovery of novel benzimidazole P1' moieties. These inhibitors possess the requisite potency/oral bioavailability profiles and importantly, were remarkably selective over a wide panel of MMP and related ADAM proteases.

MEDI 290

Synthesis and structure-activity relationship of a novel, achiral series of TNF-alpha converting enzyme inhibitors

***John L. Gilmore**[1], Bryan W. King[2], Cathy Harris[2], Thomas P Maduskuie[2], Stephen E. Mercer[1], Rui Quin Liu[3], Maryane B. Covington[2], Mingxin Qian[3], Maria D. Ribadeneria[2], Krishna G. Vaddi[2], James M. Trzaskos[3], Robert C. Newton[3], Carl P. Decicco[3], and James J - W. Duan[1]. (1) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000, john.gilmore@bms.com, (2) (3) Pharmaceutical Research Institute, Bristol-Myers Squibb Company*

TNF-alpha is a potent proinflammatory cytokine which when disregulated has been implicated in chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. The marketed anti-TNF biologics, Enbrel, Remicade, and Humira are effective in the treatment of these diseases by sequestering the soluble form of TNF- alpha. An alternate approach is to inhibit the release of soluble TNF- alpha via proteinase inhibitors such as TNF- alpha Converting Enzyme (TACE). We have discovered a novel, achiral series of compounds which are effective in inhibiting TACE. The synthesis and biological activity of these beta, beta - cyclic beta-amidohydroxamic acids will be presented.

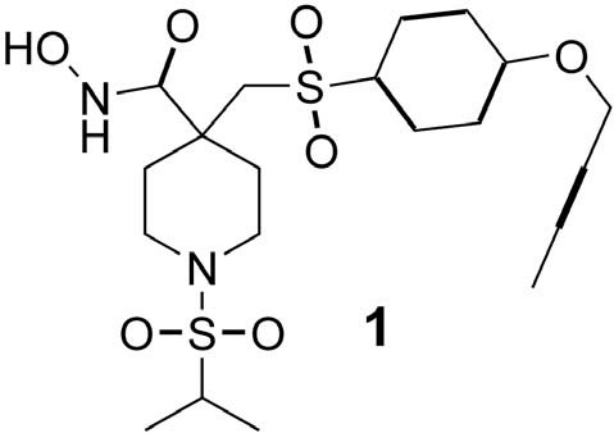


MEDI 291

Exploration of the TACE S1 pocket: Attempts toward achieving selectivity over MMP family members

Jeffrey S. Condon[1]*, Alexis Aplasca*[1]*, Eric Feyfant*[1]*, Diane Joseph-McCarthy*[1]*, Jeremy I. Levin*[1]*, Henry-Georges Lombart*[1]*, Frank E. Lovering*[1]*, Kaapjoo Park*[1]*, Jerauld Skotnicki*[1]*, LinHong Sun*[2]*, Qin Wang*[3]*, Weixin Xu*[1]*, Congmei Zeng*[2]*, Yuhua Zhang*[2]*, and Yi Zhu*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 200 Cambridgepark Dr, Cambridge, MA 02140, jscondon@wyeth.com, (2) Inflammation, Wyeth Research, (3) Drug Safety and Metabolism, Wyeth Research*

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine associated with many inflammatory diseases including rheumatoid arthritis (RA). TNF-α exhibits elevated levels in the synovium of RA patients, the level of which correlates to the observed degree of sinuvitis and bone erosion. It promotes inflammation and joint destruction by stimulating the expression of adhesion molecules, MMP's, angiogenesis factor and other pro-inflammatory cytokines. Anti-TNF therapies such as Enbrel® and Remicade® have validated TNF-α as a target for pharmaceutical intervention. TNF-α Converting enzyme (TACE) is a membrane bound zinc proteinase responsible for the cleavage of membrane bound TNF-α (pro-TNF-α) to create soluble TNF-α, and its inhibition is an interesting target in the prevention of these inflammatory diseases. Our work focuses on the development of small molecule inhibitors of TACE for the treatment of RA. Piperidine sulfone 1 has potent TACE inhibitory activity but shows a modest MMP selectivity profile. Herein we report the results of our efforts on the optimization of the MMP selectivity using a bio-structure guided approach



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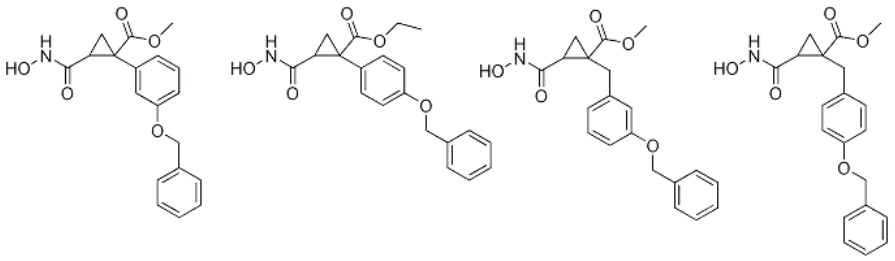
MEDI 292

Novel hydroxamates as highly potent TACE inhibitors: Part I – de novo design and discovery of two binding modes

Z. Zhu[1], *Robert Mazzola*[2], *B. McKittrick*[1], *Lisa Sinning*[2], *Daniel Lundell*[3], *Xiao-Da Niu*[3], *Peter Orth*[2], *and Zhuyan Guo*[2]. *(1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7152, zhaoning.zhu@spcorp.com, (2) Department of Medicinal Chemistry, Schering-Plough Research Institute, (3) Department of Inflammation and Infectious Diseases, Schering-Plough Research Institute*

Over expression of Tumor Necrosis factor - alpha (TNF-alpha) is directly associated with inflammation diseases such as rheumatoid arthritis and Crohn's disease. Inhibition of TNF-alpha ƒnConverting Enzyme (TACE) activity to control the level of TNF-alpha production has long been viewed as a promising way for treating related inflammatory diseases. Many of the known small molecule TACE inhibitors, most of which are related to a succinyl hydroxamate, contain three important structural motifs: a Zinc binding group, usually a hydroxamic acid, a hydrogen bond acceptor group placed 3 to 4 bonds away and a hydrophobic group attached somewhere in between. The backbones of these inhibitors are usually rigidified through cyclization. Several hydroxamates based on trans-cyclopropyldicarboxylate were designed to take into consideration these important binding elements and a group of compounds with closely related structures were examined for their TACE inhibitory activities (Fig. 1). A detailed account of inhibitor design and further SAR development for binding affinity and selectivity of the Mode B inhibitors will be discussed in the presentation.

Fig 1.



1 2 3 4

MEDI 293

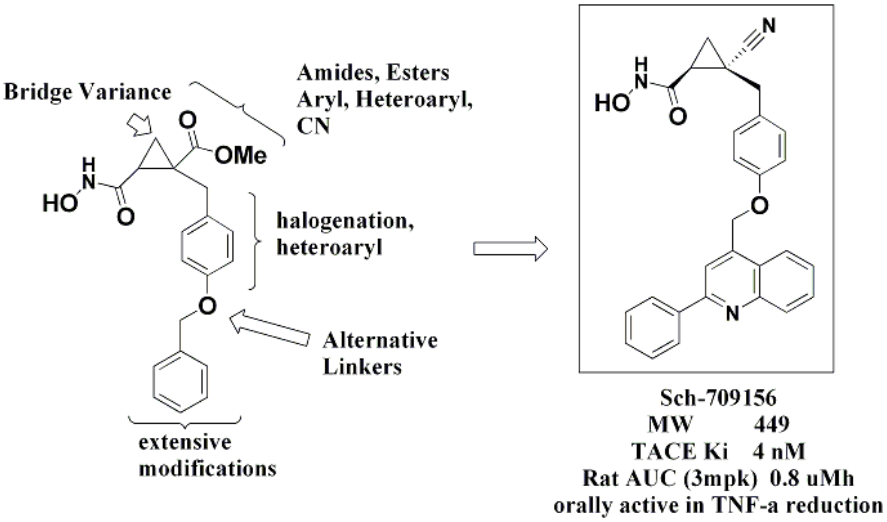
Discovery of novel hydroxamates as highly potent and selective TACE inhibitiors: Part II – SAR development of mode A inhibitors

Z. Zhu[1], ***Robert Mazzola***[2], *Lisa Sinning*[2], *Brian Lavey*[2], *Guowei Zhou*[2], *James Spitler*[2], *Shing-Chun Wong*[2], *Peter Orth*[2], *Zhuyan Guo*[2], *Jianshe Kong*[2], *Xian Liang*[2], *Jesse Wong*[2], *Joseph Kozlowski*[2], *B. McKittrick*[1], *Neng-Yang Shih*[2], *Jing Sun*[3], *Shu-Cheng Chen*[3], *Xiao-Da Niu*[3], *Lee Sullivan*[3], *and Daniel Lundell*[3]. *(1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7152, zhaoning.zhu@spcorp.com, (2) Department of Medicinal Chemistry, Schering-Plough*

Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, robert.mazzola@spcorp.com, (3) Department of Inflammation and Infectious Diseases, Schering-Plough Research Institute

Through a de novo design approach, a potent Tumor Necrosis Factor – alpha (TNF-alpha) inhibitor based on a trans-cyclopropyldicarboxylate scaffold was identified. A focused SAR development effort was launched to optimize the enzyme binding affinity, selectivity against other MMPs and ADAMs, and pharmacokinetic profile which led to the discovery of Sch-7091456; an orally active TACE inhibitor (Fig. 1). Detailed SAR information and biological data will be discussed in the presentation.

Fig. 1.



MEDI 294

Design, parallel chemical synthesis and in vitro characterization of novel hydroxamate-based prostaglandin H2 synthase inhibitors

***Jean Lee**, Department of Pharmaceutical and Medicinal Chemistry, Department of Pharmacy, Centre for Synthesis and Chemical Biology, Royal College of Surgeons in Ireland, 123, St. Stephens Green, Dublin 2, Dublin, Ireland, Fax: 00353-1-4022168, jlee@rcsi.ie*

Prostaglandin H2 synthase (PGHS), the first enzyme in the biotransformation of arachidonic acid to prostaglandins, has two active sites, a cyclooxygenase (COX), the target of aspirin, and a spatially and functionally distinct peroxidase (POX). The POX activity is independent of the COX activity, however the reverse does not hold. Inhibitors of the POX activity are of potential therapeutic value as unchecked peroxidase activity, leading to free radicals, contribute to disease progression despite NSAID administration. Aspirin irreversibly inhibits COX by acetylating a serine residue in the active site. Recently, we have produced a series of acetylating compounds, including triacetylsalicylhydroxamic acid (TriACSHA), a more potent irreversible acetylating agent than aspirin and based on a salicylhydroxamic acid scaffold. Similarly, recent work carried out in our laboratories has shown that anthranilic hydroxamic acid (AHA) is able to inhibit the peroxidase activity of PGHS. The presence of the hydroxamic acid group is essential as the carboxylic analogue has a significant reduced inhibitory activity.

A library of 30 AHA derivatives, displaying various substituents on the aromatic ring, was synthesised by parallel synthesis. Four potent peroxidase inhibitors with IC50's in the low μM range have been identified. Structure-Activity Relationships are being investigated, looking at the other randomisation points on this AHA core scaffold.

MEDI 294

Design, parallel chemical synthesis and in vitro characterization of novel hydroxamate-based prostaglandin H2 synthase inhibitors

***Jean Lee**, Department of Pharmaceutical and Medicinal Chemistry, Department of Pharmacy, Centre for Synthesis and Chemical Biology, Royal College of Surgeons in Ireland, 123, St. Stephens Green, Dublin 2, Dublin, Ireland, Fax: 00353-1-4022168, jlee@rcsi.ie*

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MEDI 295

Synthesis of 2,3-bis(nitroxy)propyl esters of naproxen, indomethacin, diclofenac and/or aspirin and pharmacogical evaluation of a novel gastro-protective NMI-1182 as a cyclooxygenase inhibitor endowed with nitric oxide donor (CINOD)

***Subhash P. Khanapure**, Michael E. Augustyniak, Vijay Dhawan, Richard A. Earl, James L. Ellis, Maiko Ezawa, David. S. Garvey, Rick D. Gaston, David. R. Janero, Madhavi G. Murty, David J. Schwalb, William S. Selig, Matthew J. Shumway, Andrzej M. Trocha, Shiow-Jyi Wey, Delano V. Young, Irina S. Zemtseva, and L. Gordon Letts, NitroMed, Inc, 125 Spring Street, Lexington, MA 02421, Fax: 781-274-8083, skhanapure@nitromed.com*

The recent voluntary withdrawal of the cyclooxygenase-2 (COX-2) selective inhibitors rofecoxib and valdecoxib from the market has renewed interest in the design and development of novel, effective, and gastro-tolerant anti-inflammatory drugs for the treatment of pain and inflammatory diseases such as arthritis. Nitric oxide (NO) targeted to the gastrointestinal tract has been shown to have gastroprotective properties due to its ability to stimulate the blood flow

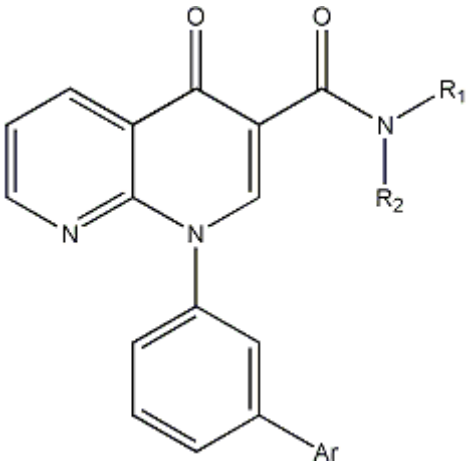
and inhibit the adhesion and infiltration of neutrophils that produce pro-inflammatory mediators. 2, 3-Bis(nitroxy)propyl esters of non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen, indomethacin, diclofenac, and aspirin have been synthesized and evaluated for their anti-inflammatory activity and gastrointestinal safety. Out of these compounds, NMI-1182 was identified as a novel gastroprotective anti-inflammatory agent with a reduced incidence of ulceration linked to cyclooxygenase inhibition. The synthesis and pharmacological evaluation of NMI-1182 will be presented.

MEDI 296

Substituted 1-biaryl-1,8-naphtyridin-4-one as potent and selective phosphodiesterase-4 inhibitors

Sébastien Laliberté[1]*, Daniel Guay*[1]*, Mario Girard*[1]*, Pierre Hamel*[1]*, Richard W. Friesen*[1]*, France Laliberté*[2]*, Zheng Huang*[2]*, Angela Styhler*[3]*, and Joseph A. Mancini*[2]*. (1) Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, QC H9R 4P8, Canada, sebastien_laliberte@merck.com, (2) Department of Biology, Merck Frosst Center for Therapeutic Research, (3) Department of Biology, Merck Frosst Centre for Therapeutic Research*

Intracellular modulation of cAMP levels by phosphodiesterase type 4 (PDE4) inhibitors represents a promising novel approach for the treatment of chronic inflammatory diseases such as asthma, COPD and rheumatoid arthritis. We report herein the results of a SAR study that led to the discovery of compounds that exhibit excellent *in vitro* activity against the truncated PDE 4B enzyme and in the LPS-stimulated TNF-α production assay in human whole blood. Furthermore, one of these compounds displays good activity in *in vivo* model of bronchoconstriction.



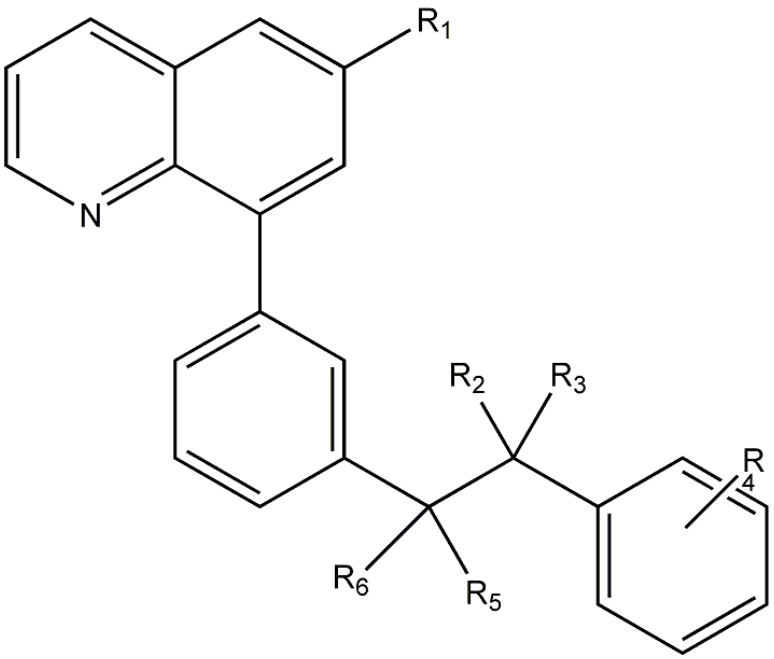
MEDI 297

8-Arylquinolines derivatives as potent PDE IV inhibitors

Patrick Lacombe[1]*, Denis Deschênes*[1]*, Daniel Dubé*[1]*, Laurence Dubé*[1]*, Michel Gallant*[1]*,*

Dwight Macdonald[1], Antony Mastracchio[1], Hélène Perrier[1], Zheng Huang[2], France Laliberté[2], Joseph A. Mancini[2], Paul Masson[2], Myriam Salem[2], Donald W. Nicholson[2], and Yves Girard[1]. (1) Department of Medicinal Chemistry, Merck Frosst Center for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, QC H9R 4P8, Canada, Fax: 514-428-4900, patrick_lacombe@merck.com, (2) Department of Biology, Merck Frosst Center for Therapeutic Research

Substituted 8-Arylquinoline analogs bearing a ethyl linked side chain were identified as potent inhibitors of the human PDE IV enzyme. The SAR is described herein as well as the pharmacokinetic profile and the in-vivo activity of key compounds in an ovalbumin-induced bronchoconstriction assay in conscious guinea pigs.



MEDI 298

Conformationally constrained dipeptidyl peptidase IV inhibitors in the α-aminoacyl amide series

Hong Dong[1], *Wallace T. Ashton[1], Leah B Reigle[1], Rosemary M. Sisco[1], Jinyou Xu[1], Lan Wei[1], Kathryn A. Lyons[1], Huaibing He[1], Barbara Leiting[2], Joseph K. Wu[2], Xiaoping Zhang[2], Reshma A. Patel[2], Frank Marsilio[2], Nancy A. Thornberry[2], and Ann E. Weber[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-5350, hong_dong@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories*

Some of the most promising current approaches for the treatment of type 2 diabetes are centered on glucagon-like peptide 1 (GLP-1), an incretin hormone that stimulates glucose-dependent insulin biosynthesis and secretion. However, GLP-1 is not active orally and is subject to rapid metabolic inactivation by dipeptidyl peptidase IV (DPP-IV). Inhibition of DPP-IV could thus improve glucose tolerance by enhancing the action of endogenous GLP-1. One

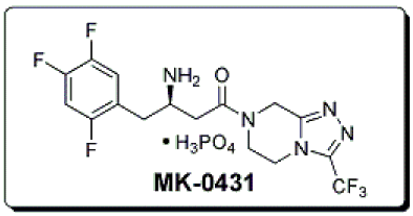
major class of DPP-IV inhibitors consists of α-aminoacyl amides of cyclic secondary amines such as pyrrolidine and its derivatives. Work from these laboratories has demonstrated that compounds in this class derived from L-phenylalanine, substituted at the *para* position with aryl or heteroaryl groups and/or with side chains at the β-position, are effective inhibitors of DPP-IV. We now report the synthesis and biological evaluation of conformationally constrained analogs in which the *ortho*-position is linked to the β-position by formation of a ring. Some simple prototypes were nonselective. However, modifications to stereochemistry, substitution, and ring size led to highly potent DPP-IV inhibitors with 1000-fold selectivity over related peptidases. Selected analogs were also evaluated for pharmacokinetics in rats.

MEDI 299

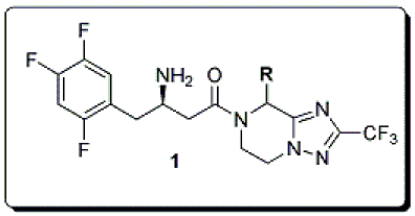
Design, synthesis, and biological evaluation of fused heterocycle-based beta-amino amides as potent, orally active DPP-IV inhibitors for the treatment of type 2 diabetes

Jennifer E. Kowalchick[1]*, Dooseop Kim*[1]*, Liping Wang*[1]*, Maria Beconi*[2]*, George Eiermann*[3]*, Huaibing He*[1]*, Barbara Leiting*[4]*, Kathryn A. Lyons*[1]*, Reshma A. Patel*[4]*, Sangita B. Patel*[1]*, Aleksandr Petrov*[3]*, Giovana Scapin*[1]*, Joseph K. Wu*[4]*, Nancy A. Thornberry*[4]*, and Ann E. Weber*[1]*. (1) Department of Medicinal Chemistry, Merck & Co., Inc, P.O. Box 2000, Rahway, NJ 07065, Fax: (732) 594-9545, jennifer_kowalchick@merck.com, (2) Preclinical Drug Metabolism, Merck & Co. Inc, (3) Department of Pharmacology, Merck & Co., Inc, (4) Department of Metabolic Disorders, Merck & Co., Inc*

Contemporary research efforts focus on therapy of glucagon-like peptide-1 (GLP-1), an incretin hormone that regulates glucose levels by stimulating insulin secretion and inhibiting glucagon secretion from the pancreas. These studies suggest encouraging new methods for the treatment of type 2 diabetes mellitus. Dipeptidyl peptidase IV (DPP-IV), a serine protease, cleaves the N-terminal His-Ala fragment of active GLP-1, rapidly rendering it inactive in vivo. Inhibition of DPP-IV raises levels of GLP-1 and thus enables the incretin to efficiently regulate blood glucose levels. Accordingly, DPP-IV inhibition is emerging as a new prospective treatment for type 2 diabetes. Recently, we reported the extensive SAR studies that led to the discovery of the current development compound MK-0431. Additional investigations have included the incorporation of a variety of fused-heterocycles into the beta-amino acid scaffold. Specifically, bicycles were synthesized from the reordering of the substituents around the triazole ring, along with substitution at the ƒÑ-position of the piperazine ring. Subsequent structure-activity relationship (SAR) studies of these analogs resulted in the discovery of a series of potent, orally active DPP-IV inhibitors 1 with outstanding pharmacokinetic profiles in various animal species. This poster presentation will focus on the design, synthesis, SAR, and biological profiles of these potent DPP-IV inhibitors.



MK-0431



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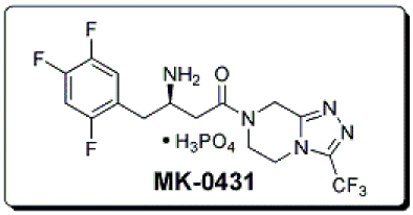
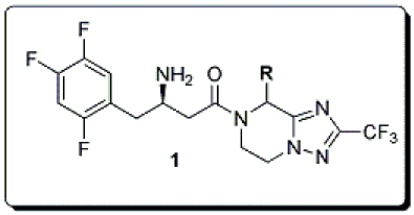
MEDI 299

Design, synthesis, and biological evaluation of fused heterocycle-based beta-amino amides as potent, orally active DPP-IV inhibitors for the treatment of type 2 diabetes

Jennifer E. Kowalchick[1], *Dooseop Kim*[1], *Liping Wang*[1], *Maria Beconi*[2], *George Eiermann*[3], *Huaibing He*[1], *Barbara Leiting*[4], *Kathryn A. Lyons*[1], *Reshma A. Patel*[4], *Sangita B. Patel*[1], *Aleksandr Petrov*[3], *Giovana Scapin*[1], *Joseph K. Wu*[4], *Nancy A. Thornberry*[4], *and Ann E. Weber*[1]. *(1) Department of Medicinal Chemistry, Merck & Co., Inc, P.O. Box 2000, Rahway, NJ 07065, Fax: (732) 594-9545, jennifer_kowalchick@merck.com, (2) Preclinical Drug Metabolism, Merck & Co. Inc, (3) Department of Pharmacology, Merck & Co., Inc, (4) Department of Metabolic Disorders, Merck & Co., Inc*

Contemporary research efforts focus on therapy of glucagon-like peptide-1 (GLP-1), an incretin hormone that regulates glucose levels by stimulating insulin secretion and inhibiting glucagon secretion from the pancreas. These studies suggest encouraging new methods for the treatment of type 2 diabetes mellitus. Dipeptidyl peptidase IV (DPP-IV), a serine protease, cleaves the N-terminal His-Ala fragment of active GLP-1, rapidly rendering it inactive in vivo. Inhibition of DPP-IV raises levels of GLP-1 and thus enables the incretin to efficiently regulate blood glucose levels. Accordingly, DPP-IV inhibition is emerging as a new prospective treatment for type 2 diabetes. Recently, we reported the extensive SAR studies that led to the discovery of the current development compound MK-0431. Additional investigations have included the incorporation of a variety of fused-heterocycles into the beta-amino acid scaffold. Specifically, bicycles were synthesized from the reordering of the substituents around the triazole ring, along with substitution at the ƒÑ-position of the piperazine ring. Subsequent structure-activity relationship (SAR) studies of these analogs resulted in the discovery of a series of potent, orally active DPP-IV inhibitors 1 with outstanding pharmacokinetic profiles in various animal species. This poster presentation will focus on the design, synthesis, SAR, and biological profiles of these potent DPP-IV inhibitors.





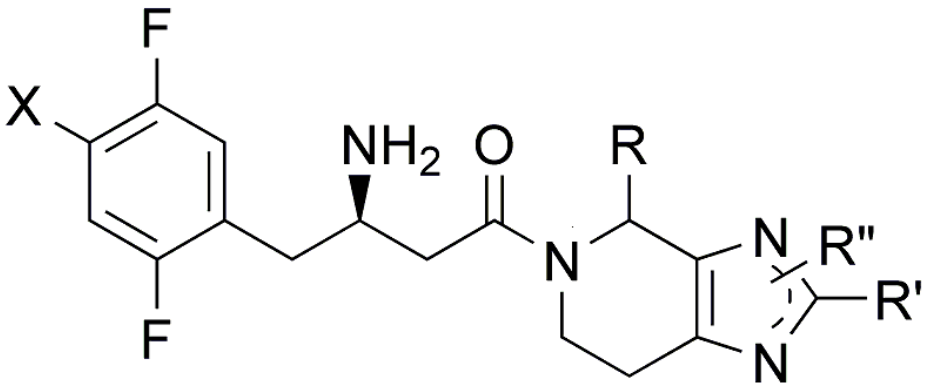
MEDI 300

Imidazopiperidine amides as dipeptidyl peptidase IV inhibitors for the treatment of diabetes

Ping Chen[1], *Charles G. Caldwell*[1], *Robert J. Mathvink*[1], *Barbara Leiting*[2], *Frank Marsilio*[3], *Reshma A. Patel*[2], *Xiaoping Zhang*[2], *Huaibing He*[1], *Kathryn A. Lyons*[1], *Nancy A. Thornberry*[2], *and Ann E. Weber*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-5790, ping_chen@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, (3) Department of*

Metabolic Disorders-Diabetes, Merck Research Laboratories

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L-cells in response to food intake. The active form of GLP-1 is a 30-amino acid peptide which stimulates insulin release while inhibiting hepatic glucose production. Administration of exogenous GLP-1 has been examined in patients having type-2 diabetes, with continuous subcutaneous infusion resulting in reduction of blood glucose levels. The active form of GLP-1 is rapidly inactivated, however, by dipeptidyl peptidase IV (DPP-IV), a serine protease which cleaves a dipeptide from the N-terminus. A small-molecule DPP-IV inhibitor which extends the lifetime of endogenously secreted GLP-1 provides an attractive target for the treatment of diabetes. This presentation will describe the synthesis and biological activity of a series of imidazopiperidine amide DPP-IV inhibitors.



MEDI 301

Discovery of potent DPP-IV inhibitors

*Yixian Chen, Steven Richards, Qi Shuai, **Jyoti Patel**, David Madar, Hong Yong, Zhonghua Pei, Thomas W. von Geldern, Kenton L. Longenecker, Kent Stewart, Tom Lubben, Steven Ballaron, Mike Stashko, James Trevillyan, and Hing Sham, Metabolic Disease Research Division, Abbott Laboratories, Dept. R47H, Bldg. AP-10-2, 100 Abbott Park Rd., Abbott Park, IL 60064, yixian.chen@abbott.com*

Small molecule inhibitiors of DPP-IV have been proven to improve glucose tolerance in diabetic patients. DPPIV inhibition protects the incretin GLP-1 from inactivation. GLP-1 stimulates insulin biosynthesis, inhibits glucagon secretion and slows post-prandial gastric emptying. We have discovered a series of proline based DPPIV inhibitors with P2 sulfonamide functionality. Earlier compounds in this series were potent inhibitors of DPPIV (IC50 < 10 nM) but lost activity in the presence of plasma. The sulfonamide groups were tolerated by the enzyme, and reduced the plasma shift. We will discuss the synthesis and SAR of these compounds, and present the crystal structures of representative compounds bound to hDPPIV.

MEDI 302

Xanthine mimetics as novel DPP4 inhibitors

***Ravi Kurukulasuriya**, Jeffrey J. Rohde, Bruce G. Szczepankiewicz, Fatima Z. Basha, Kenton Longenecker, Steven Ballaron, James, T. Link, Thomas Von Geldern, and Tom Lubben, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, Ravi.Kurukulasuriya@abbott.com*

A high throughput screen of the Abbott Laboratories library of compounds for potential DPP4 inhibitors revealed several Xanthine analogues showing low micro molar potency for the enzyme. Due to prior patent literature on Xanthines as potent DPP4 inhibitors, the development of Xanthine mimetics was actively pursued. The paper describes the discovery of several 5,5 and 5,6 fused Xanthine mimetics via novel Cu mediated cyclization chemistry which were found to be potent DPP4 inhibitors having low nano molar potency. The x-ray crystal structure of these novel compounds soaked with the enzyme reveal that the binding mode is similar to the corresponding Xanthine analogues.

MEDI 303

Acyl thiazolidides-novel potent DPP-IV inhibitors

***Qi Shuai**[1], Jyoti Patel[1], Irini Zanze[2], Jurgen Dinges[1], Paul E. Wiedeman[2], Zhonghua Pei[1], Melissa Michmerhuizen[2], Ethan Hoff[2], Douglas Kalvin[2], Thomas Von Geldern[3], Tom Lubben[3], Steven Ballaron[3], Mike Stashko[1], Brad Zinker[1], Stevan W. Djuric[1], David Beno[4], Anita Kempf-Grote[1], Amanda Mika[1], Tomas Farb[1], Matthew Perham[1], Andrew Adler[1], James Trevillyan[1], and Hing L. Sham[4]. (1) Metabolic Disease Research , GPRD, Abbott Laboratories, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, Qi.Shuai@abbott.com, (2) Medicinal Chemistry Technologies, R4CP. GPRD, Abbott Laboratories, (3) Global Pharmaceutical Research and Development, Abbott Laboratories, (4) Global Pharmaceutical Research and Development, Metabolic Disease Research, Abbott Laboratories*

Dipeptidyl-peptidase IV (DPP-IV) is a serine peptidase that inactivates bioactive peptides such as GLP-1 by cleaving N-terminal dipeptides. Because GLP-1 is a peptide that can stimulate insulin secretion, inhibit glucagon incretion and promote proliferation of pancreatic beta cells, inhibitors of DPP-IV represent a potential treatment for type II diabetes by prohibiting the degradation of GLP-1 and extending the duration of action of GLP-1.

We will discuss the discovery and SAR studies of the acyl thiazolidides as a novel class of DPP-IV inhibitors. The optimization of P1 and P2 sites of the acyl thiazolidides has lead to the discovery of very potent DPP-IV inhibitor such as **3a** (Kic=0.5 nM) and **1e** (Kic= 5 nM). **1e** exhibits a 100-fold selectivity of DPP-IV over related serine proteases DPP7, DPP8, POP and FAP-alpha. The PK profile of **1e** is promising ($t_{1/2}$ = 5.0 h, F= 57.6%, Vss=1.38 L/Kg , CLp=1.94 L/hr•Kg.). **1e** has also shown a greater than 90% inhibition of DPP-IV activity in vivo at 3 mpk and 10 mpk, an increase in the active GLP-1 level and a 34% reduction of the glucose level (10 mpk) in an OGTT. The synthesis of acyl thiazolidide analogs and their *in vitro* and *in vivo* biological data will be presented.

MEDI 304

Design and synthesis of potent inhibitors of protein tyrosine phosphatase 1b

Douglas P. Wilson[1], *Zhao-Kui Wan*[1], *Follows Bruce*[1], *Steven J. Kirincich*[1], *Alessandro F. Moretto*[1], *Rajeev Hotchandani*[1], *Junjun Wu*[2], *Weixin Xu*[2], *Diane Joseph-McCarthy*[1], *Kenneth Foreman*[1], *Dave Erbe*[3], *Zhang Yan-Ling*[3], *James Tobin*[3], *Steve Tam*[1], *and Jinbo Lee*[1]. *(1) Chemical and Screening Sciences, Wyeth, 200 Cambridge Park Drive, Cambridge, MA 02140, (2) Chemical and Screening Sciences, Wyeth Research, (3) Cardiovascular and Metabolic Diseases, Wyeth*

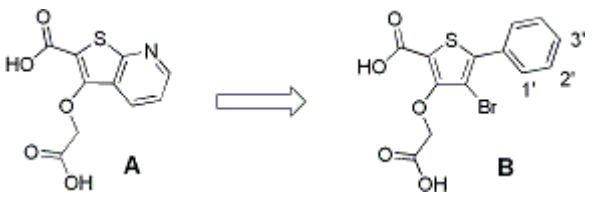
Protein Tyrosine Phosphatase 1b (PTP1b) is an intracellular protein tyrosine phosphatase expressed in insulin responsive tissues. This enzyme has been shown to be a negative regulator of both insulin and leptin receptor pathways. The phenotype of PTP1B knockout mice has further validated this enzyme as a potential therapeutic target for insulin resistance and type 2 diabetes. We here report the development of a series of highly efficient, low-nanomolar PTP1B inhibitors. These compounds were iteratively designed to gain potency and selectivity by reaching from the active site of PTP1B to the nearby second phosphotyrosine-binding site. The role of X-Ray crystallography and molecular modeling in this effort will be discussed.

MEDI 305

En route to potent PTP1b inhibitors: Discovery of a potent and selective thiophene diacid series

Zhao-Kui Wan[1], *Bruce Follows*[1], *Steven Kirincich*[1], *Douglas P. Wilson*[1], *Weixin Xu*[2], *Diane Joseph-McCarthy*[1], *Kenneth Foreman*[1], *Yan-Ling Zhang*[3], *Dave Erbe*[3], *James Tobin*[3], *Steve Tam*[1], *and Jinbo Lee*[1]. *(1) Chemical and Screening Sciences, Wyeth, 200 Cambridge Park Drive, Cambridge, MA 02140, Fax: 617-665-5682, zwan@wyeth.com, (2) Structrual Biology, Wyeth, (3) Cardiovascular and Metabolic Diseases, Wyeth*

Protein tyrosine phosphatase 1b (PTP1b) is an intracellular protein tyrosine phosphatase expressed found in insulin responsive tissues. It has been shown to be a negative regulator of insulin signaling pathway as demonstrated by studies on PTP1B knockout mice. Lack of PTP1b is associated with increased insulin sensitivity, lowered blood glucose levels and resistance to weight gain on a high-fat diet. Thus, developing small molecule inhibitors of this enzyme is of great interest for the treatment of type 2 diabetes. Probing the SAR of the scaffold of compound A (Ki = 230 μM) led to the discovery of a new and more potent lead, compound B (Ki = 3.2 μM) that was subsequently developed into the thiophene series of PTP1b inhibitors. Using structure-based design, a more than 50,000 fold improvement in potency was achieved. This poster will focus on the discovery and optimization of our PTP1b inhibitors, and the structural-activity relationship targeting interaction with Asp48/Arg47.



MEDI 306

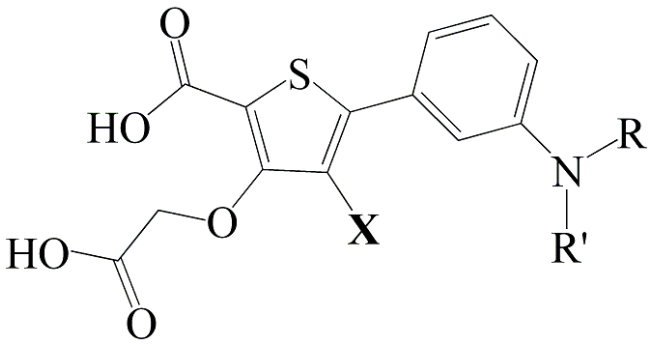
WITHDRAWN

MEDI 307

PTP1b inhibitors: Capturing interactions with Arg24

*Junjun Wu[1], **Rajeev Hotchandani**[1], Douglas P. Wilson[1], Eva Binnun[1], Alessandro Moretto[1], Zhao-Kui Wan[1], Bruce Follows[1], Steven Kirincich[1], Michael J Smith[1], Manus Ipek[1], Diane Joseph-McCarthy[1], Kenneth Foreman[1], Wei-Xin Xu[1], Yan-Ling Zhang[2], May Tam[2], Dave Erbe[2], James Tobin[2], Steve Tam[1], and Jinbo Lee[1]. (1) Department of Chemical and Screening Sciences, Wyeth, 200 CambridgePark Drive, Cambridge, MA 02140, (2) Department of Cardiovascular and Metabolic Diseases, Wyeth*

Protein tyrosine phosphatase 1b (PTP1b) is an important negative regulator of the insulin and leptin signaling pathways. Studies have shown that PTP1b knock out mice have increased sensitivity to both hormones, resulting in improved glucose tolerance and resistance to diet-induced obesity. Thus, PTP1b plays a vital role in insulin sensitivity and fuel metabolism and selective PTP1b inhibitors could provide therapeutic benefits for treatment of type-2 diabetes and obesity. This poster will describe our efforts in optimizing a novel series (1) of PTP1b inhibitors through medicinal chemistry guided by X-ray structural information and molecular modeling. Emphasis will be placed on the design and synthesis of analogs that capture the interaction with Arg24 of PTP1b, which has provided significant improvement in potency. Other aspects of drug design such as polar surface area, number of rotatable bonds and molecular weight will also be discussed.



X= Br, Cl, CH_3

1

MEDI 307

PTP1b inhibitors: Capturing interactions with Arg24

*Junjun Wu[1], **Rajeev Hotchandani**[1], Douglas P. Wilson[1], Eva Binnun[1], Alessandro Moretto[1], Zhao-Kui Wan[1], Bruce Follows[1], Steven Kirincich[1], Michael J Smith[1], Manus Ipek[1], Diane Joseph-McCarthy[1], Kenneth Foreman[1], Wei-Xin Xu[1], Yan-Ling Zhang[2], May Tam[2], Dave*

Erbe[2], James Tobin[2], Steve Tam[1], and Jinbo Lee[1]. (1) Department of Chemical and Screening Sciences, Wyeth, 200 CambridgePark Drive, Cambridge, MA 02140, (2) Department of Cardiovascular and Metabolic Diseases, Wyeth

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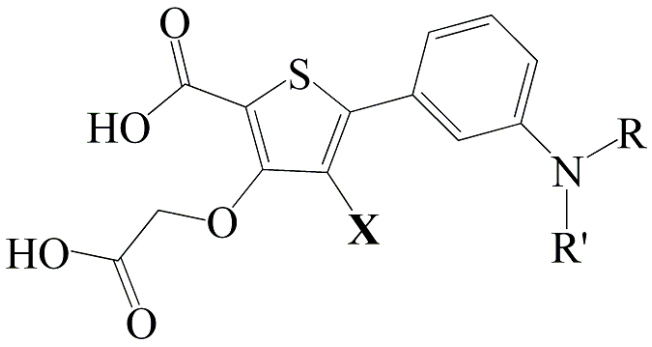

X= Br, Cl, CH_3

1

MEDI 308

Pharmacophore hypothesis for γ-secretase inhibitor and application in virtual screening

***Kristi Yi Fan[1]**, Xinyi Huang[2], Ann Aulabaugh[1], Eric Gundersen[1], Haas Kimberly[1], Boyd L. Harrison[1], J. Steven Jacobsen[3], Alan Katz[1], Anthony Kreft[1], Robert Martone[3], Scott C. Mayer[1], and Alex Porte[1]. (1) Chemical and Screening Sciences, Wyeth Research, CN8000, Princeton, NJ 08543, Fax: 732-274-4292, (2) Chemical and Screening Sciences, Wyeth Research, (3) NeuroSciences, Wyeth Research*

γ-secretase is a critical enzyme that cleaves the β-amyloid precursor protein (APP) and generates the C-terminus of Aβ. A high Aβ42 level is a major pathological feature of Alzheimer's disease (AD). Therefore the reduction of brain Aβ levels through the inhibition of γ-secretase is being pursued as an approach for AD therapy. We present here the first pharmacophore hypothesis for γ-secretase inhibitors in a ligand-based approach, using Catalyst/Hypogen 3D QSAR modeling program. The hypothesis was developed from a set of structurally diverse γ-secretase inhibitors that were screened in the radioligand cell-free γ-

secretase binding assay. The pharmacophore was further validated by a large set of test inhibitors in the literature and from our in-house program. The results showed that over 70% of the active inhibitors could be successfully identified by the model. The information contained in the hypothesis was then used for virtual screening of our 3D corporate database for possible new lead series.

MEDI 308

Pharmacophore hypothesis for γ-secretase inhibitor and application in virtual screening

Kristi Yi Fan[1]*, Xinyi Huang*[2]*, Ann Aulabaugh*[1]*, Eric Gundersen*[1]*, Haas Kimberly*[1]*, Boyd L. Harrison*[1]*, J. Steven Jacobsen*[3]*, Alan Katz*[1]*, Anthony Kreft*[1]*, Robert Martone*[3]*, Scott C. Mayer*[1]*, and Alex Porte*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, CN8000, Princeton, NJ 08543, Fax: 732-274-4292, (2) Chemical and Screening Sciences, Wyeth Research, (3) NeuroSciences, Wyeth Research*

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MEDI 309

Acylguanidines as small molecule BACE1 inhibitors: Exploration of the S1 pocket

Ping Zhou[1]*, Rajiv Chopra*[1]*, Derek C. Cole*[1]*, Jeffrey S. Condon*[1]*, Rebecca Cowling*[2]*, Kristi Fan*[1]*, Boyd L. Harrison*[1]*, Yun Hu*[3]*, Lee D. Jennings*[1]*, Guixian Jin*[1]*, Wei Liu*[4]*, Frank E. Lovering*[1]*, Michael S. Malamas*[1]*, Eric S. Manas*[1]*, Koi M. Morris*[1]*, Albert J. Robichaud*[5]*, Mohani N. Sukhdeo*[1]*, Jim Turner*[3]*, Junjun Wu*[1]*, and Jonanthan Bard*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 609-274-4505, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, (3) Department of Neuroscience, Wyeth Research, (4) (5) Chemical and Screening Sciences, Wyeth Research, Princeton*

Alzheimer's disease (AD), a progressive neurodegenerative disease and the most common form of dementia, can be attributed, at least in part, to the aggregation and neurotoxic properties of amyloid b-peptide (Ab) in the brain. Amyloid b-peptide (Ab) is produced by the sequential processing of amyloid precursor protein (APP) by two proteases, i.e., b- and g-

secretase. The novel aspartyl protease BACE1, (also called Asp2 or Memapsin2), has been identified as the enzyme responsible for processing of APP at the b-secretase cleavage site. Thus, BACE1 inhibition is an attractive approach for the treatment of AD. Herein, we will discuss the exploration of the diphenyl-pyrrole acylguanidine analog, a weak (IC50 = 3.7 mM) BACE1 inhibitor, identified via high–throughput-screening (HTS) hit. An in-house x-ray crystal structure of this hit complexed with BACE1 demonstrated that the acylguanidine moiety interacts with the two aspartic acids of catalytic active site of BACE1 through hydrogen bonding interactions. Initial SAR was focused on the S1 region of the binding pocket, to optimize the ligand/protein interaction. Replacing one of the phenyl groups with carbocyclic moieties appears to fill-up this region better than a phenyl group, resulting in a 6-fold increase of potency. Further modifications of the S1' region leads to even further enhancement of the potency. The synthesis, SAR and several x-ray structures will be presented.

MEDI 310

Acylguanidines as small molecule BACE1 inhibitors: Optimization of the S1' region

Mohani N. Sukhdeo[1]*, Rajiv Chopra*[1]*, Derek C. Cole*[1]*, Rebecca Cowling*[2]*, John W. Ellingboe*[1]*, Kristi Yi Fan*[1]*, Yun Hu*[3]*, Guixian Jin*[1]*, Lee D. Jennings*[1]*, Laura Lin*[1]*, Mei-Chu Lo*[1]*, Peter A. Lohse*[4]*, Michael S. Malamas*[1]*, Eric S. Manas*[1]*, William J. Moore*[4]*, Mary-Margaret O'Donnell*[4]*, Joseph R. Stock*[1]*, James Strand*[1]*, Steven Sukits*[1]*, Kristine Svenson*[1]*, M. James Turner*[3]*, Erik Wagner*[3]*, and Jonathan Bard*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 401 N.Middletown Road, M/S 222/2109, Pearl River, NY 10965, sukhdem@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, (3) Department of Neuroscience, Wyeth Research, (4) ArQule, Inc*

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that is the leading cause of dementia. Although the cause of AD is still unclear, evidence suggests that amyloid β-peptide (Aβ) (the predominant constituent of amyloid fibrils) aggregates, resulting in oligomerization, neuronal loss of function and plaque deposition. This amyloid hypothesis suggests that agents which decrease levels of Aβ should have therapeutic benefit in AD. Aβ is produced from membrane-bound β-amyloid precursor protein (APP) by sequential proteolytic cleavage by β-secretase (BACE1) and γ-secretase. Thus BACE1 is an attractive therapeutic target for the design of inhibitors of Aβ production. In this poster we will discuss the optimization of a weak HTS hit, which uses an unsubstituted acylguanidine moiety to form key interactions in the catalytic active site of BACE1, but leaves the S1' region unoccupied. We will describe our exploration of the S1' region using synthetic arrays designed with the help of docking calculations and in-house x-ray crystal structures, focusing on the identification of substituted acylguanidines that led to significant increases in potency.

MEDI 311

Acylguanidines as small molecule BACE1 inhibitors: Initial exploration of S1 and S2' pockets

Joseph R. Stock[1]*, Rajiv Chopra*[1]*, Derek C. Cole*[1]*, Jeffrey S. Condon*[1]*, Rebecca Cowling*[2]*, John W. Ellingboe*[1]*, Yun Hu*[3]*, Guixian Jin*[1]*, Laura Lin*[1]*, Mei-Chu Lo*[1]*, Frank E. Lovering*[1]*,*

Michael S. Malamas[1], Eric S. Manas[1], James Strand[1], Steven Sukits[1], Kristine Svenson[1], M. James Turner[3], Erik Wagner[3], Junjun Wu[1], and Jonathan Bard[3]. (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, Fax: 845-602-5561, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, (3) Department of Neuroscience, Wyeth Research

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that is the leading cause of dementia. Although the cause of AD is still unclear, evidence suggests that amyloid β-peptide (Aβ), the predominant constituent of amyloid fibrils, aggregates, resulting in oligomerization, neuronal loss of function and plaque deposition. This amyloid hypothesis suggests that agents which decrease levels of Aβ should have therapeutic benefit in AD. Aβ is produced from membrane-bound β-amyloid precursor protein (APP) by sequential proteolytic cleavage by β-secretase (BACE1) and γ-secretase. Thus BACE1 is an attractive therapeutic target for the design of inhibitors of Aβ production In this poster, we will describe our initial exploration of the S1 and S2' pockets, starting from a weak pyrrole acylguanidine high-throughput screening (HTS) hit. This exploration was facilitated by structure-based combinatorial libraries, designed using an x-ray crystal structure of the HTS hit complexed to BACE1. Because of the symmetrical nature of the HTS hit, monomers were selected which could potentially occupy either the S1 or S2' sites. Compounds with significant improvements in potency were then further analyzed both crystallographically and computationally in order to understand the binding mode. This poster will describe the SAR discovered through this approach, and how it was used as a starting point for further SAR development.

MEDI 312

Design and synthesis of pyrimidoindolone Caspase-3 inhibitors: Part 1 -- Phenoxy modifications

*Lisa M. Havran[1], **Chae-Koo Dan Chong**[1], Wayne E. Childers Jr.[1], Ann Aulabaugh[2], Helen Chan[3], Rebecca Cowling[4], Myles Fennel[3], Boyd L. Harrison[1], Wah-Tung Hum[1], Bhupesh Kapoor[1], Huai-Ping Ling[3], Ronald L. Magolda[1], Albert J. Robichaud[5], and Andrew Wood[6]. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, havranl@wyeth.com, chongc@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, Pearl River, (5) Chemical and Screening Sciences, Wyeth Research, Princeton, (6) Neuroscience, Wyeth Research, Princeton*

Cysteine-dependant aspartyl protease (Caspase) activation has been implicated as a part of the signal transduction pathway leading to apoptosis. As part of a program to develop a novel small molecule inhibitor of Caspase 3 as a treatment for ischemic stroke, a series of 3,4-dihydropyrimido(1,2-a)indol-10(2H)-ones (pyrimidoindolones) was identified as highly potent Caspase 3 inhibitors. In order to expand the SAR around the pyrimidoindolones, key regions were explored in a series of parallel synthesis libraries. While it was found that sulfonamide was needed to retain activity, this work showed that phenoxy region was amenable to substitution that could be used to modify the physiochemical profile of these molecules. The parallel synthesis effort, synthetic optimization, and SAR of these compounds will be discussed in detail.

MEDI 313

Design and synthesis of pyrimidoindolone Caspase -- 3 inhibitors: Part 3-Tricycle modifications

Lisa M. Havran[1], *Chae-Koo Dan Chong*[1], *Wayne E. Childers Jr.*[1], *Vasilios Marathias*[1], *James J. Bicksler*[1], *Ann Aulabaugh*[2], *Helen Chan*[3], *Seongeun Cho*[3], *Rebecca Cowling*[4], *Myles Fennel*[3], *Boyd L. Harrison*[1], *Wah-Tung Hum*[5], *Bhupesh Kapoor*[1], *Huai-Ping Ling*[3], *Ronald L. Magolda*[1], *Lidia Mosyak*[1], *Albert J. Robichaud*[6], *Gregory J. Tawa*[1], *Weixin Xu*[3], *Mei-Yi Zhang*[1], *and Andrew Wood*[7]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, havranl@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, Pearl River, (5) Chemical and Screening Sciences, Wyeth Research, Cambridge, (6) Chemical and Screening Sciences, Wyeth Research, Princeton, (7) Neuroscience, Wyeth Research, Princeton*

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MEDI 314

Design and synthesis of pyrimidoindolone Caspase-3 inhibitors: Part 2 -- Sulfonamide modifications

Lisa M. Havran[1], *Wayne E. Childers Jr.*[1], *Vasilios Marathias*[1], *Ann Aulabaugh*[2], *Helen Chan*[3], *Seongeun Cho*[3], *Rebecca Cowling*[4], *Myles Fennel*[3], *Boyd L. Harrison*[1], *Wah-Tung Hum*[1], *Bhupesh Kapoor*[1], *Huai-Ping Ling*[3], *Ronald L. Magolda*[1], *Lidia Mosyak*[1], *Albert J. Robichaud*[5], *Weixin Xu*[3], *and Andrew Wood*[6]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, havranl@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, Pearl River, (5) Chemical and Screening Sciences, Wyeth Research, Princeton, (6) Neuroscience, Wyeth Research, Princeton*

Cysteine-dependant aspartyl protease (Caspase) activation has been implicated as a part of the signal transduction pathway leading to apoptosis. As part of a program to develop a novel small molecule inhibitor of Caspase 3 as a treatment for ischemic stroke, a series of 3,4-dihydropyrimido(1,2-a)indol-10(2H)-ones (pyrimidoindolones) was identified as highly potent Caspase 3 inhibitors. In order to expand the SAR around the pyrimidoindolones and improve

the physiochemical profile of these molecules, key regions were explored using parallel synthesis techniques. A series of sulfonamide analogs was prepared that showed potent activity in in vitro assays of Caspase 3 inhibition. The design, synthesis and SAR of these compounds will be described.

MEDI 315

Identification and characterization of 3,4-dihydro-2H-pyrimido(1,2-a)indol-10-ones as caspase inhibitors

Paul J Dollings[1], *Ann Aulabaugh*[2], *Annette Banker*[2], *Helen Chan*[3], *Seongeun Cho*[3], *Rebecca Cowling*[4], *Arlene Dietrich*[1], *Li Di*[2], *George Ellestad*[2], *Myles Fennell*[3], *Xinyi Huang*[2], *Wah-Tung Hum*[5], *Donna Huryn*[6], *Guixian Jin*[6], *Bhupesh Kapoor*[6], *Teresa Kleintop*[6], *James LaRocque*[6], *Huai-Ping Ling*[3], *Vasilios Marathias*[6], *Franklin Moy*[6], *Susan Petusky*[6], *William S Somers*[6], *Gregory J. Tawa*[6], *Desiree Tsao*[6], *Andrew Wood*[7], *and Weixin Xu*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, Princeton, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, dollinp@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, Pearl River, (5) Chemical and Screening Sciences, Wyeth Research, Cambridge, (6) Chemical and Screening Sciences, Wyeth Research, (7) Neuroscience, Wyeth Research, Princeton*

The caspases (cysteinyl aspartate specific proteases) have been strongly implicated to play an essential role in apoptosis and are activated following ischemic injury. The utility of a small molecule caspase inhibitor for the treatment of ischemic injuries has not been fully understood due to inadequate pharmaceutical properties of the previously studied molecules. We have identified 3,4-dihydro-2H-pyrimido(1,2-a)indol-10-ones as potent, non-peptide inhibitors of the caspase family of enzymes. The pyrimidoindolones offer a greater opportunity to explore the therapeutic utility of caspase inhibition for the prevention of tissue damage following ischemic injury. This poster describes the synthesis of substituted 3,4-dihydro-2H-pyrimido(1,2-a)indol-10-ones, preliminary structure activity relationships and binding data as lead molecules for medicinal chemistry research.

MEDI 316

Thiophene acyl guanidines as BACE1 inhibitors

William R. Solvibile[1], *William F. Fobare*[1], *Eric S. Manas*[1], *Jonathan Bard*[2], *Jim Turner*[2], *Yun Hu*[2], *Erik Wagner*[2], *Albert J. Robichaud*[3], *Jerry Sun*[1], *Rajiv Chopra*[1], *Rebecca Cowling*[4], *Guixian Jin*[1], *and Michael S. Malamas*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, solvibw@wyeth.com, (2) Department of Neuroscience, Wyeth Research, (3) Chemical and Screening Sciences, Wyeth Research, Princeton, (4) Chemical and Screening Sciences, Wyeth Research, Pearl River*

Alzheimer's disease (AD), which affects over four million people in the U.S. and is the 4th leading cause of death in developed countries, is characterized by a decline in cognitive functions leading to, in latter stages, dementia and eventual death. One approach toward AD

therapeutics is reduction of β-amyloid (Aβ), a key neurotoxic component of the plaques and believed to play a central role in the pathogenesis of AD. Because Aβ is generated by the sequential proteolysis of β-amyloid precursor protein (APP) by β-secretase or BACE1 and γ-secretase, our chemistry efforts have focused on the identification and optimization of pharmacologically active small molecule inhibitors of BACE1. A BACE1 inhibitor containing a pyrrole substituted acyl guanidine pharmacaphore was identified through HTS and showed micromolar activity (IC_{50} = 3.3 μM) in a peptide cleavage assay (FRET). Using in-house x-ray crystal structures, SAR was developed through both traditional medicinal and combinatorial chemistries. The pharmacophore was further explored by changing the central ring from a pyrrole to a thiophene. This new scaffold created a common intermediate, which permitted SAR exploration through Suzuki couplings. The substituted thiophene compounds resulted in a 22-fold improvement in BACE1 inhibition in the FRET assay (e.g. IC_{50} of 3.3 μM to 148 nM). The synthesis and SAR of these compounds will be presented.

MEDI 317

Acylguanidines as inhibitors of BACE-1: Variation of pyrrole ring substituents extending into the S_1 and S_3 pockets

Lee D. Jennings[1], *Derek C. Cole*[1], *Joseph R. Stock*[1], *Rebecca Cowling*[2], *Eric S. Manas*[1], *Kristi Yi Fan*[1], *Ping Zhou*[1], *Michael S. Malamas*[1], *Rajiv Chopra*[1], *Frank E. Lovering*[1], *Erik Wagner*[3], *Jim Turner*[3], *Yun Hu*[3], *and Jonathan Bard*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Bldg 222/2110, Pearl River, NY 10965, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, (3) Department of Neuroscience, Wyeth Research*

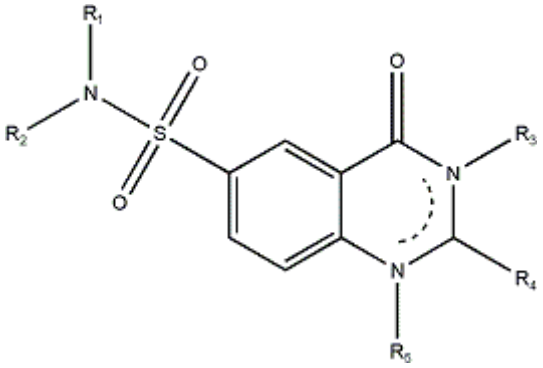
Alzheimer's Disease (AD) is a progressive, neurodegenerative disease of the brain. Experimental evidence suggests that the amyloid &beta-peptide (A&beta) is a predominant constituent of amyloid fibrils which cause plaque formation and lead to loss of neuronal function. Consequently, inhibition of A&beta peptide synthesis is a promising strategy for the treatment of Alzheimer's disease. BACE-1, an aspartic acid protease involved in the processing of the amyloid precursor protein, has been shown to have a major role in A&beta generation and is a current focus for AD therapeutics. A high throughput screening campaign identified an acylguanidine as an inhibitor of BACE-1 with low micromolar affinity. Preliminary analoging and an X-ray crystal structure of this lead complexed to BACE-1 revealed the key structural features of the ligand that enable binding to the enzyme. These studies also indicated pockets within the active site where there were clear opportunities to make further interactions and improve binding affinity to BACE-1. In an effort to address the optimization of the substituents on the pyrrole scaffold directed towards the S_1 and S_3 pockets, three combinatorial libraries were prepared using parallel synthesis and automated sample purification. Here we report the application of molecular modeling and X-ray crystallography to the design of these libraries and key discoveries made based on the assay of the products of these libraries.

MEDI 318

Design, synthesis and biological activity of novel quinazolinone-based Caspase 3 inhibitors

*Alexander Greenfield[1], **Cristina Grosanu**[1], Gregory J. Tawa[1], Wayne E. Childers Jr.[1], Boyd L. Harrison[1], Ronald L. Magolda[1], Albert J. Robichaud[2], Ann Aulabaugh[1], Helen Chan[3], Rebecca Cowling[1], Myles Fennel[3], Xinyi Huang[4], Wah-Tung Hum[1], Bhupesh Kapoor[1], Huai-Ping Ling[3], and Andrew Wood[5]. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Neuroscience, Wyeth Research, (4) Chemical and Screening Sciences, Wyeth Research, (5) Neuroscience, Wyeth Research, Princeton*

The caspases are a family of cysteine proteases that perform important functions in the cell life cycle. Caspase-3, a member of the effector caspases subtype has been found to be activated in models of apoptosis and cerebral ischemia, making it a potential therapeutic target for the treatment of several neurodegenerative diseases involving dysregulated cell death. Because of its role in ischemia, inflammation and apoptosis there is an everlasting interest in finding potent and selective inhibitors of Caspase-3 with drug-like properties. Our efforts focused on the development of quinazolinone-based analogs (1) and optimization of substitution patterns. The SAR of these molecules as well as an efficient ambient temperature variant of the Dimroth-type rearrangement as a simple entry into 2, 3-disubstituted quinazoline-4-ones which was developed in the course of the synthetic studies, will be presented and discussed.



MEDI 319

A computational methodology for calculating the relative binding free energies of caspase-3 inhibitors

***Gregory J. Tawa**[1], Paul J Dollings[2], Wayne E. Childers Jr.[1], Andrew Wood[3], Weixin Xu[4], Lidia Mosyak[1], Rebecca Cowling[5], Ann Aulabaugh[6], Bhupesh Kapoor[1], Huai-Ping Ling[4], Seongeun Cho[4], Albert J. Robichaud[2], Alan H. Katz[1], and William S Somers[1]. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4292, tawag@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Neuroscience, Wyeth Research, Princeton, (4) Neuroscience, Wyeth Research, (5) Chemical and Screening Sciences, Wyeth Research, Pearl River, (6) Chemical and Screening Sciences, Wyeth Research*

A methodology is derived for the calculation of covalent ligand-protein binding free energies in aqueous solution. The components of this methodology include molecular mechanics, dielectric continuum solvation and semi-empirical molecular orbital theory. We validate this method using a set of pyrimidoindolone (3,4-dihydropyrimido (1,2-a) indol-10 (2H)-one) Caspase-3 inhibitors. This series covalently binds to Caspase-3 via CYS 285 located in the S1 binding pocket. We show that the calculated binding free energies correlate well with experimentally determined Ki values. Analysis of the components of the binding free energy reveal that the majority of the ligand-protein interaction comes from the covalent bond. This is clearly demonstrated by a solid correlation between computed and experimental Ki values. Furthermore, we can improve these correlations by taking additional non-covalent effects into account such as ligand-protein desolvation and non-bonded interactions. Significantly, these non-covalent effects chiefly occur outside of the S1 binding pocket, i.e., S2, S3, and S4. These are regions were the differences between Caspase-3 and the other Caspases are largest. We believe this method can be a useful tool for assessing ligand-protein binding affinity prior to synthesis of proposed compounds.

MEDI 320

Caspase binding site differences and prescriptions for pan and selective inhibition

Gregory J. Tawa[1], *Paul J Dollings*[2], *Wayne E. Childers Jr.*[1], *Andrew Wood*[3], *Weixin Xu*[4], *Lidia Mosyak*[1], *Albert J. Robichaud*[2], *Alan H. Katz*[1], *and William S Somers*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4292, tawag@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Neuroscience, Wyeth Research, Princeton, (4) Neuroscience, Wyeth Research*

A series of published Caspase-DEVD aldehyde crystal structure complexes were aligned in an effort to determine the similarities and differences in binding sites for a variety of Caspase proteins. After aligning the complexes DEVD aldehyde was used as a probe to determine the identities of the binding site residues of the Caspases. The binding site residues were derived by analysis of the local Caspase environment around each residue of DEVD aldehyde. Residues within 4 A of D, E, V, and D, determine the S4, S3, S2, and S1 binding pockets of the various Caspases. Comparison of the binding site residues across the different Caspases reveals similarities in binding pockets S1 and S2, but some major differences in binding pockets S3 and S4. These similarities and differences provide a prescription for development of either pan or selective CASPASE inhibitors. They also allow for explanation of the binding selectivity of a variety of Caspase inhibitors published in the literature.

MEDI 321

Aza-peptide epoxides as inhibitors of caspases: How epoxide stereochemistry and prime side interactions influence reactivity and selectivity

Amy J. Campbell[1], *Juliana L. Asgian*[1], *Jowita Mikolajczyk*[2], *Karen E. James*[1], *Zhao Zhao Li*[1], *Özlem Dogan Ekici*[1], *Guy S. Salvesen*[2], *and James C. Powers*[1]. *(1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332, Fax: 404-894-2295, gte849y@mail.gatech.edu, (2) Program in Apoptosis and Cell Death Research,*

Burnham Institute

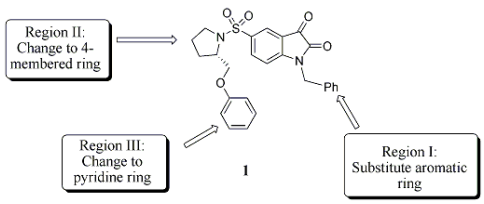
Caspases are members of an important clan of cysteine proteases, clan CD. Caspases 2, 3, 6, 7, 8, 9, and 10 are essential for completing the process of programmed cell death, also called apoptosis. Thus far, at least 12 human caspases have been identified. The synthesis of selective caspase inhibitors, particularly inhibitors selective for one caspase versus other caspases, has great significance towards elucidating useful information about the apoptotic cascade. Aza-peptide epoxides are a recently discovered class of clan CD cysteine protease inhibitors. These peptidyl inhibitors utilize the prime side of the active site in caspases. The prime side substituent increases the selectivity and reactivity of the aza-peptide epoxide inhibitors. Also, aza-peptide epoxides show varying degrees of reactivity and selectivity with respect to the stereochemistry of the epoxide warhead. This research will focus on how both of these influences, the prime side substituent and the stereochemistry of the epoxide, change the reactivity and selectivity of the aza-peptide epoxides with apoptotic caspases.

MEDI 322

N-Benzyl-isatin sulfonamide analogs as potent and selective caspase-3 inhibitors

***Robert H Mach**, Wenhua Chu, Zun Zhang, Chenbo Zeng, Justin Rothfuss, Zhude Tu, Yunxiang Chu, David E. Reichert, and Michael J Welch, Department of Radiology, Washington University School of Medicine, Division of Radiological Sciences, 510 S. Kingshighway Blvd., St. Louis, MO 63110, Fax: 314-362-9940, rhmach@wustl.edu*

Apoptosis, or programmed cell death, is a conserved process that is mediated by the activation of a series of cysteine aspartyl-specific proteases called caspases. While apoptosis plays a significant role in a wide variety of normal cellular processes, abnormal apoptosis is implicated in large number pathological conditions. Therefore, the development of compounds that can inhibit apoptosis may be utilized as new therapeutic drugs. Recently, the isatin compound, 1, has been identified as a potent and selective non-peptide inhibitor of caspases 3 and 7 in vitro (Lee et al., J. Med. Chem. 44: 2015-2026, 2001). Our goal was to extend the structure-activity relationship study of this class of compounds by incorporating the following changes: 1) substituting the para position of the N-benzyl group in order to determine if there are any substituent effects with respect to caspase-3 potency; 2) replacing the pyrrolidine ring with an azetidine ring; and, 3) replacing the benzene ring of the phenoxymethyl moiety with a pyridine ring. This series of N-benzyl isatin sulfonamide analogs were tested for potency and selectivity against a panel of caspases (1, 3, 6, 7, and 8) using standard Fluorometric assays. Several of our compounds were potent and selective inhibitors of caspase 3 (IC50 4 – 10 nM) and displayed approximately 1000-fold selectivity over caspases 1, 6, and 8. However, our compounds show 2-3 fold selectivity over caspase 7. Quantitative structure-activity relationship studies were also conducted in order to determine the molecular descriptors that determine to potency of this class of compounds for inhibiting caspase-3 activity.



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MEDI 322

N-Benzyl-isatin sulfonamide analogs as potent and selective caspase-3 inhibitors

***Robert H Mach**, Wenhua Chu, Zun Zhang, Chenbo Zeng, Justin Rothfuss, Zhude Tu, Yunxiang Chu, David E. Reichert, and Michael J Welch, Department of Radiology, Washington University School of Medicine, Division of Radiological Sciences, 510 S. Kingshighway Blvd., St. Louis, MO 63110, Fax: 314-362-9940, rhmach@wustl.edu*

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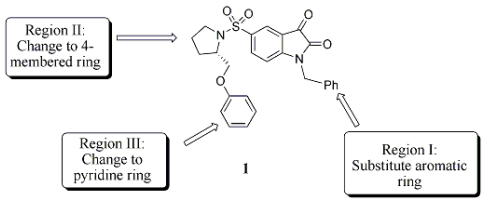


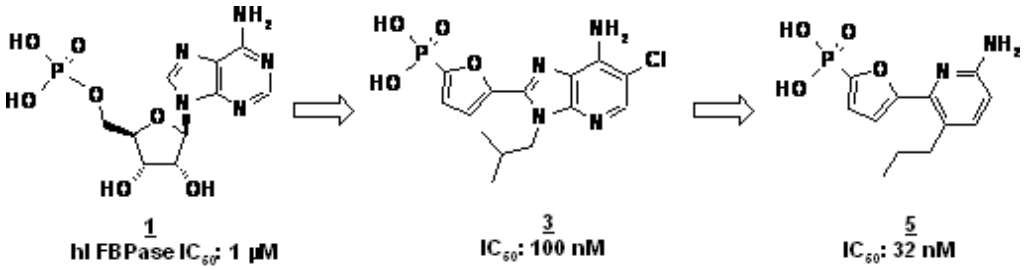
MEDI 323

Discovery of 2-aminopyridine inhibitors of FBPase

***K. Raja Reddy**, Mark D. Erion, Qun Dang, Srinivas R. Kasibhatla, Kevin Fan, M. Rami Reddy, and Paul D. van Poelje, Metabasis Therapeutics, Inc, 9390 Towne Centre Drive, San Diego, CA 92121, rajar@mbasis.com*

Increased flux through the gluconeogenesis (GNG) pathway has been implicated as the primary cause of the abnormally high hepatic glucose output (HGO) in type 2 diabetes (T2D). Enzymes in the GNG biochemical pathway represent potential targets for new therapies for T2D. Fructose-1,6-bisphosphatase (FBPase) is a rate-limiting enzyme of GNG and is allosterically regulated by adenosine monophosphate (AMP). Our research efforts were

directed to finding potent, specific inhibitors of FBPase that bind at the AMP allosteric binding site. The initial lead series was identified using structure-based drug design. Deaza-purine analogs of the lead AMP mimetic were made in order to improve potency by decreasing desolvation energy without loss of protein-inhibitor interactions. These efforts resulted in identification of key pharmacophores and discovery of several novel series of compounds that are potent and selective FBPase inhibitors (FBPIs). Herein, we present the design, synthesis, and SAR of deaza-purine analogs and related monocyclic FBPIs.



MEDI 324

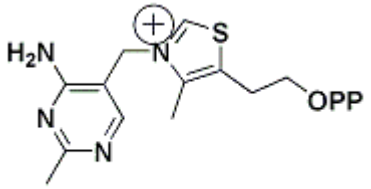
WITHDRAWN

MEDI 325

Thiamine mimetics as inhibitors of enzyme transketolase

Indrani Gunawardana[1], *Josh Ballard*[1], *Bryan Bernat*[1], *Steven A. Boyd*[1], *Barb Brandhuber*[1], *Kevin Condroski*[1], *Jason De Meese*[1], *Walter DeWolf*[1], *Stephen S. Gonzales*[1], *May Han*[2], *Tomas Kaplan*[1], *Yvan Le Huerou*[1], *Christine Lemieux*[1], *Todd T. Romoff*[1], *Darin Smith*[1], *Francis Sullivan*[1], *Allen A. Thomas*[1], *Solly Weiler*[2], *S. Kirk Wright*[2], *and Guy Vigers*[1]. *(1) Array BioPharma, 3200 Walnut Street, Boulder, CO 80301, igunawardana@arraybiopharma.com, (2) AVEO Pharmaceuticals*

Inhibition of the thiamine-utilizing enzyme transketolase (TK) has been linked with diminished tumor cell proliferation (Boros, et al.). Using structure-aided design, we synthesized thiamine mimetics which are highly potent TK inhibitors both *in vitro* and *in vivo*. In addition to optimizing for TK inhibition, we desired thiamine mimetics which could achieve cell penetration via passive diffusion or thiamine transporters (ThTr1 and ThTr2). Once inside the cell, such mimetics should be diphosphorylated by thiamine pyrophosphokinase (TPPK) to enable binding interactions with TK. To achieve these goals, optimization for multiple protein targets (i.e. TK, TPPK, and ThTr1/ThTr2) was required. Synthesis and SAR of thiamine mimetics with modifications of both the pyrimidine and thiazole rings will be described.



thiamine pyrophosphate

MEDI 325

Thiamine mimetics as inhibitors of enzyme transketolase

Indrani Gunawardana[1], *Josh Ballard*[1], *Bryan Bernat*[1], *Steven A. Boyd*[1], *Barb Brandhuber*[1], *Kevin Condroski*[1], *Jason De Meese*[1], *Walter DeWolf*[1], *Stephen S. Gonzales*[1], *May Han*[2], *Tomas Kaplan*[1], *Yvan Le Huerou*[1], *Christine Lemieux*[1], *Todd T. Romoff*[1], *Darin Smith*[1], *Francis Sullivan*[1], *Allen A. Thomas*[1], *Solly Weiler*[2], *S. Kirk Wright*[2], *and Guy Vigers*[1]. *(1) Array BioPharma, 3200 Walnut Street, Boulder, CO 80301, igunawardana@arraybiopharma.com, (2) AVEO Pharmaceuticals*

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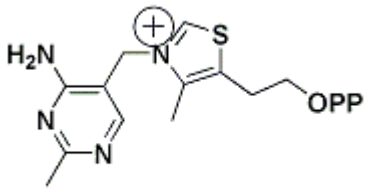


thiamine pyrophosphate

MEDI 326

Potent and selective thiamine antagonists that inhibit transketolase

Todd T. Romoff[1], *Josh Ballard*[1], *Bryan Bernat*[1], *Steven A. Boyd*[1], *Barb Brandhuber*[1], *Kevin Condroski*[1], *Jason De Meese*[1], *Walter DeWolf*[1], *Stephen S. Gonzales*[1], *Indrani Gunawardana*[1], *May Han*[2], *Yvan Le Huerou*[1], *Patrice Lee*[1], *Tomas Kaplan*[1], *Christine Lemieux*[1], *Robin Pedersen*[2], *Jed Pheneger*[1], *Greg Poch*[1], *Darin Smith*[1], *Francis Sullivan*[1], *Allen A. Thomas*[1], *Solly Weiler*[2], *S. Kirk Wright*[2], *and Guy Vigers*[1]. *(1) Array BioPharma, 3200*

Walnut Street, Boulder, CO 80301, Fax: 303-386-1420, tromoff@arraybiopharma.com, (2) AVEO Pharmaceuticals

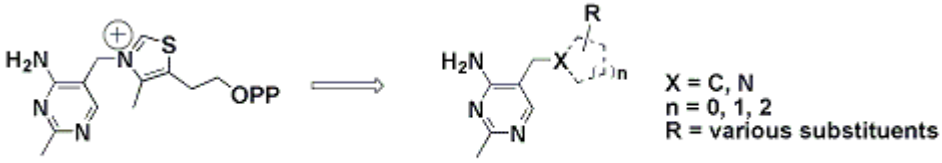
Tumor cells extensively utilize the pentose phosphate pathway for the synthesis of ribose. A key enzyme in this pathway, transketolase, has been suggested as a target for inhibition in the treatment of cancer. Compound 1, an analog of thiamine, the cofactor of transketolase, was subjected to a pharmacodynamic study in which nude mice with HCT-116 xenograft tumors were dosed with the compound. Transketolase activity was almost completely suppressed in blood, spleen, and tumor cells, and there was little effect on the activity of another thiamine-utilizing enzyme, &alpha-ketoglutarate dehydrogenase. Synthesis and SAR of transketolase inhibitors as well as molecular modeling of the active site of transketolase will be discussed.

MEDI 327

Non-charged thiamine analogues as inhibitors of enzyme transketolase

Allen A. Thomas[1]*, Josh Ballard*[1]*, Bryan Bernat*[1]*, Steven A. Boyd*[1]*, Barb Brandhuber*[1]*, Kevin Condroski*[1]*, Jason De Meese*[1]*, Walter DeWolf*[1]*, Stephen S. Gonzales*[1]*, Indrani Gunawardana*[1]*, May Han*[2]*, Tomas Kaplan*[1]*, Yvan Le Huerou*[1]*, Christine Lemieux*[1]*, Todd T. Romoff*[1]*, Francis Sullivan*[1]*, Solly Weiler*[2]*, S. Kirk Wright*[2]*, Guy Vigers*[1]*, and Darin Smith*[1]*. (1) Array BioPharma, 3200 Walnut St., Boulder, CO 80301, athomas@arraybiopharma.com, (2) AVEO Pharmaceuticals*

Inhibition of the thiamine-utilizing enzyme transketolase (TK) has been linked with diminished tumor cell proliferation (Boros, et al.). Most thiamine antagonists except thiamine thiazolone have a permanent positive charge on the B-ring, and it has been suggested that this charge is required for diphosphorylation by thiamine pyrophosphokinase (TPPK) to enable binding to TK. We sought neutral thiazolium replacements that would be substrates for TPPK, while not necessarily needing thiamine transporters (ThTr1 and ThTr2) for cell penetration. The synthesis and SAR including structure-based rationale drug design for highly potent non-thiazolium TK antagonists (A) will be presented.



thiamine pyrophosphate

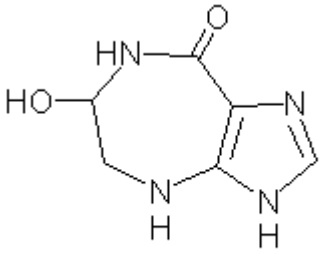
non-thiazolium antagonists (A)

MEDI 328

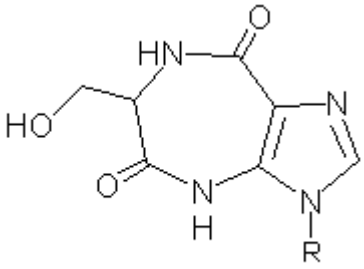
Analogues of azepinomycin as inhibitors of guanase: Synthesis and biochemical evaluation of a transition state analogue of the enzyme-catalyzed reaction

Ravi K. Ujjinamatada *and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, ravikum@umbc.edu*

Guanase (guanine deaminase, EC 3.5.4.3) is an important enzyme involved in purine salvage pathway. Inhibition of this enzyme has important implications in treatment of cancer, liver diseases, multiple sclerosis, and transplant rejections. Guanase catalyzes the hydrolysis of guanine to xanthine. Azepinomycin, a naturally occurring antitumor antibiotic, is a moderate inhibitor of guanase, and is considered a transition state analogue inhibitor of the enzyme. As part of an effort to explore the structure-activity relationships of azepinomycin so as to enhance its inhibitory potency against guanase, we present here the synthesis and biochemical evaluation of an analogues of azepinomycin (I), which possesses the structural features of the transition state of the enzyme-catalyzed reaction.



Azepinomycin



I

MEDI 329

Protein Arginine Deiminase 4: Synthesis of mechanism based inactivators

Yuan Luo *and Paul R. Thompson, Department of Chemistry & Biochemistry, University of South Carolina, 631 Sumter Street, Columbia, SC 29208, Fax: 803-777-9521, luo@mail.chem.sc.edu*

Protein Arginine Deiminase 4 (PAD4) is a transcriptional corepressor that has been implicated in the pathophysiology of Rheumatoid Arthritis (RA). While the enzyme is known to catalyze the post-translational conversion of Arginine to Citrulline in a number of proteins, little is known about its mechanism of catalysis, its in vivo role, or its role in the pathophysiology of RA. A goal of this work is to develop PAD4 selective inhibitors that can be used as pharmacological probes to study the in vivo role of PAD4. Inhibitors of this type may also ultimately prove to be useful RA treatments. Based on the initial kinetic and mechanistic characterization of human PAD4 accomplished in our laboratory, we have designed a series of halomethyl ketone derivatives of benzoylated ornithine as potential irreversible PAD4 selective inhibitors. Early efforts towards the syntheses of these compounds are reported.

MEDI 330

Straightforward route to a series of mammalian farnesyltransferase inhibitors based upon a simple ethylenediamine scaffold

Erin E. Pusateri[1]*, Matthew P. Glenn*[1]*, Sung-Youn Chang*[1]*, Said M. Sebti*[2]*, and Andrew D. Hamilton*[1]*. (1) Department of Chemistry, Yale University, 225 Prospect St., P.O. Box 208107, New Haven, CT 06520-8107, erin.pusateri@yale.edu, (2) Department of Biochemistry and Molecular Biology, University of South Florida*

In recent years, protein Farnesyltransferase (FTase) has been a major target in the search for novel anticancer agents. We have successfully developed a series of compounds that exhibit nanomolar inhibition of mammalian FTase *in vitro*. This series of inhibitors was designed utilizing a flexible ligand docking approach. These docking studies have predicted that inhibitors based upon a simple ethylenediamine scaffold will project functionality in such a way to easily access the four pockets of the active site of FTase. The straightforward synthesis of these compounds allows for efficient introduction of diversity in order to access a wide spectrum of inhibitors.

MEDI 330

Straightforward route to a series of mammalian farnesyltransferase inhibitors based upon a simple ethylenediamine scaffold

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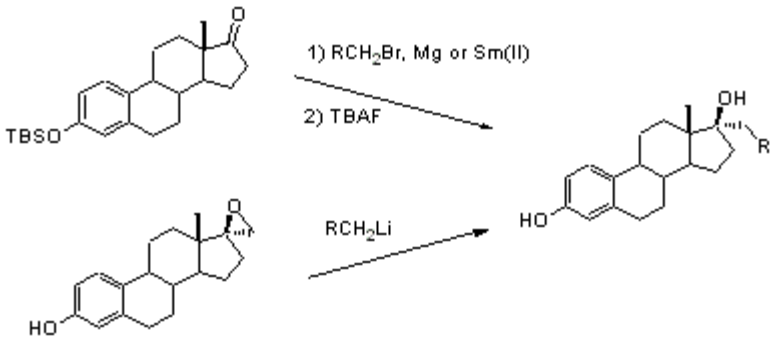
MEDI 331

Synthesis of 17 α-benzylestradiol derivatives for steroid sulfatase inhibition

Diane Fournier *and Donald Poirier, Medicinal Chemistry Division, Oncology and Molecular Research Center and Laval University, 2705 Laurier blvd, Québec, QC G1V 4G2, Canada, Fax: 1-418-654-2714, diane.fournier@crchul.ulaval.ca*

The inhibition of steroid sulfatase (STS) has potentially important therapeutical applications in the treatment of hormone-dependant cancers and of other diseases such as alopecia, acne and Alzheimer's disease. Previous work in our laboratory has shown that 17α-benzylestradiol derivatives were reversible inhibitors of STS and that the best inhibition was obtained with small hydrophobic groups on the benzyl moiety. Thus we sought to increase the potency of these compounds by synthesizing new derivatives with increased hydrophobicity and varying sizes and electronic distributions. Two main strategies were employed starting from estrone, that is alkylation of the 17-ketone and the opening of a 17β-oxirane. Highly hindered carbonyl at position 17 and functionnal group incompatibility brought us to use samarium chemistry in some cases. The 18 products obtained were then tested for inhibition of the transformation of E_1S (0.1 µM) into E_1 by STS and some compounds displayed a potency of ~ 50% at 10^{-7}M.



MEDI 331

Synthesis of 17 α-benzylestradiol derivatives for steroid sulfatase inhibition

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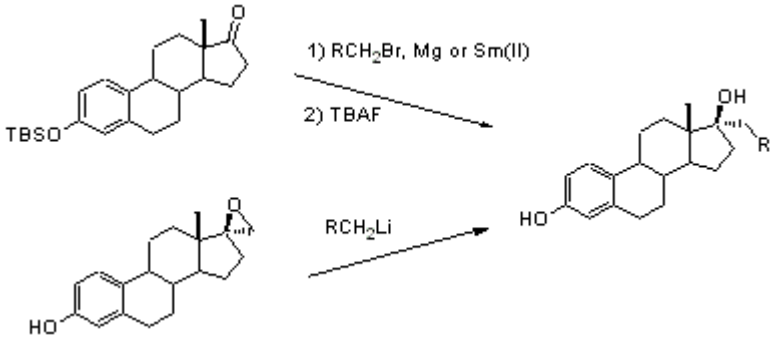
The inhibition of steroid sulfatase (STS) has potentially important therapeutical applications in the treatment of hormone-dependant cancers and of other diseases such as alopecia, acne and Alzheimer's disease. Previous work in our laboratory has shown that 17α-benzylestradiol derivatives were reversible inhibitors of STS and that the best inhibition was obtained with small hydrophobic groups on the benzyl moiety. Thus we sought to increase the potency of these compounds by synthesizing new derivatives with increased hydrophobicity and varying sizes and electronic distributions. Two main strategies were employed starting from estrone, that is alkylation of the 17-ketone and the opening of a 17β-oxirane. Highly hindered carbonyl at position 17 and functionnal group incompatibility brought us to use samarium chemistry in some cases. The 18 products obtained were then tested for inhibition of the transformation of E_1S (0.1 μM) into E_1 by STS and some compounds displayed a potency of ~ 50% at 10^{-7}M.



MEDI 332

Pharmacological characterization of a novel orally active neutrophil elastase inhibitor

Akemi Kuromiya[1]*, Hiroshi Okazaki*[2]*, and Jun-ichi Tsuji*[1]*. (1) Pharmacology & Microbiology Research Laboratories, Dainippon Pharmaceutical Co., Ltd, Enoki 33-94, Suita, Osaka 564-*

0053, Japan, Fax: +81-6-6337-5109, akemi-kuromiya@dainippon-pharm.co.jp, (2) Research Management, Dainippon Pharmaceutical Co., Ltd

Human neutrophil elastase (HNE), a serine proteinase, is capable of degrading a variety of extracellular matrix proteins in many tissues. As patients defective in HNE endogenous protein inhibitors show high prevalence of emphysema, a major condition in chronic obstructive pulmonary disease (COPD), HNE is believed to be a possible pathogenic factor in COPD. In our search for potent HNE inhibitors that prevent the progression of COPD, we have found compound A as a structurally new and orally active HNE inhibitor. Compound A strongly inhibited HNE activity in vitro (IC_{50}< 10 nM). In HNE-induced pulmonary injury model, oral administration of compound A potently inhibited pulmonary hemorrhage in a dose-dependent and long-lasting manner (ED_{50}< 3 mg/kg). In addition, in a model based on reverse passive Arthus reaction, compound A inhibited pulmonary hemorrhage (ED_{50}< 5 mg/kg) and white blood cells infiltration (ED_{50}< 3 mg/kg). These results suggest that compound A may be useful in the treatment of COPD.

MEDI 333

Design and synthesis of novel peptide-based orally active inhibitors of human neutrophil elastase

***Ryotaro Shiratake**, Takashi Deguchi, Yasunao Inoue, Noriyuki Imayoshi, Tomohiko Ueda, Kenji Suzuki, and Fuminori Sato, Chemistry Research Laboratories, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita 564-0053, Japan, ryotaro-shiratake@dainippon-pharm.co.jp*

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Patients with COPD have been shown to exhibit elevated levels of human neutrophil elastase (HNE). Therefore, HNE inhibitors have been investigated as potential therapeutic agents for the prevention of the progression of COPD. Although we have reported previously injectable highly water-soluble inhibitors of HNE for acute disorders such as ARDS at the 221st ACS meeting, these inhibitors were not orally active. In our search for potent orally active inhibitors of HNE, we have found a novel series of peptide-based inhibitors which would be useful for the treatment for COPD. The design, synthesis and structure-activity relationship of this series of inhibitors will be presented.

MEDI 334

WITHDRAWN

MEDI 334

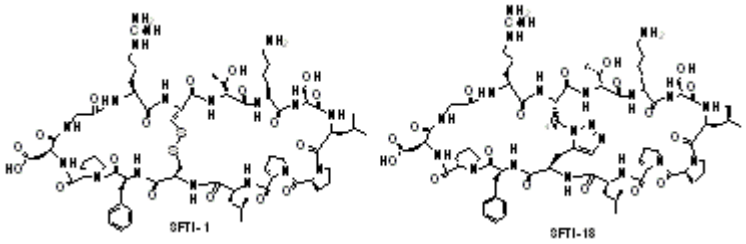
WITHDRAWN

MEDI 335

Synthesis and evaluation of analogs of sfti-1, potent inhibitors of the type II transmembrane serine protease, matriptase

Sheng Jiang[1]*, Peng Li*[2]*, Ya-Qiu Long*[3]*, Sheau-Ling Lee*[4]*, Cheng Yong Lin*[4]*, Robert B Dickson*[4]*, and Peter P. Roller*[5]*. (1) Lab of medicinal chemistry, NCI/NIH, Boyles street, NCI at Frederick, Frederick, MD 21702, Fax: 301-846-6033, sjiang@ncifcrf.gov, (2) Lab of Medicinal chemistry, NCI, (3) NC/NIH, (4) Lombardi Cancer Center, Georgetown University Medical Center, (5) Lab of medicinal Chemistry, NCI/NIH*

Matriptase, isolated from human breast cancer cells in culture, is a member of the emerging class of type II transmembrane serine proteases. Matriptase blockade could potentially modulate cell proliferation, motility, invasion, and differentiation of cells. A 14 amino acid peptide, termed sunflower trypsin inhibtor (SFTI-1) was isolated from sunflower seeds. SFTI-1 inhibited ß-trypsin with an impressive Ki of 1.0 nM, and it inhibited cathepsin G with a comparable Ki. Recently, our group synthesized SFTI-1 and found that it inhibited Matriptase with an impressive sub-nanomolar Ki of 0.92 nM. Here we report a series of analogs with redox-stable bicyclic linkages, such as the peptide, SFTI-18.

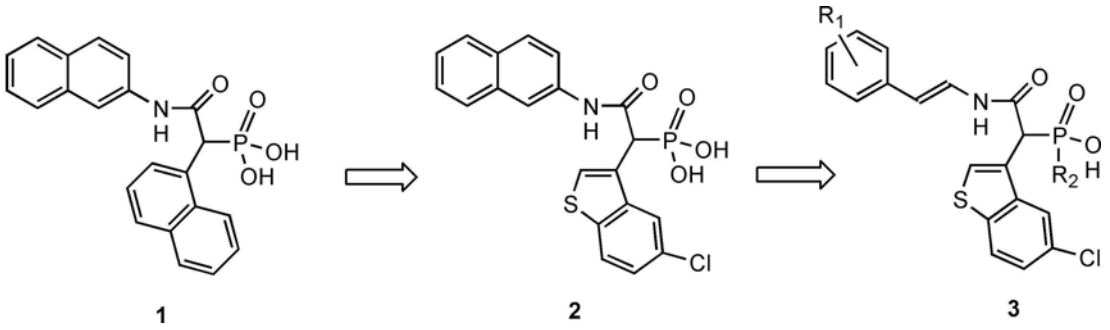


MEDI 336

Structure-based design of serine protease inhibitors: Discovery of selective chymase inhibitors containing a novel β-amidophosphonic acid recognition motif

Michael J. Hawkins[1]*, M. N. Greco*[1]*, E. T. Powell*[1]*, T. W. Corcoran*[1]*, L. De Garavilla*[1]*, J. A. Kauffman*[1]*, Y. Wang*[1]*, L. Minor*[1]*, E. Di Cera*[2]*, N. Sukumar*[2]*, Z-W. Chen*[2]*, A. O. Pineda*[2]*, F. S. Mathews*[2]*, and B. E. Maryanoff*[1]*. (1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477, Fax: 215-628-4985, mhawkins@prdus.jnj.com, (2) Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine*

Human chymase, a chymotrypsin-like serine protease present in the mast cell and released on activation, has been implicated in various pathological conditions associated with inflammation, including airway inflammation. We identified β-amidophosphonic acid **1** as a selective inhibitor of chymase (IC50 = 0.2 μM) through routine screening. We solved the X-ray crystal structure of **2**•chymase and used the information in a structure-based optimization protocol. Details of the interactions of **2** within the active site of chymase will be discussed. Compound **2** was efficacious in the standard sheep model of asthma. Further optimization of **2** led to a series of potent, selective, orally active chymase inhibitors, represented by **3**, from which we identified a suitable compound for preclinical development. Details of these studies will be presented.



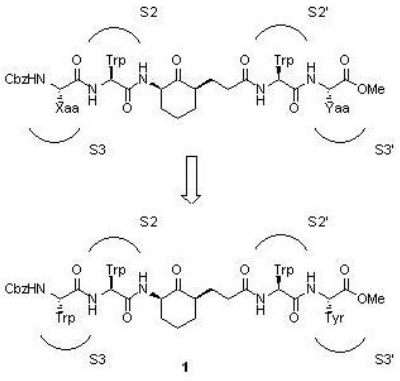
1 2 3

MEDI 337

Combinatorial library of inhibitors for serine protease plasmin: Binding specificity at S3 and S3' subsites

Fengtian Xue *and Christopher T. Seto, Department of Chemistry, Brown University, 324 Brook St., Providence, RI 02912*

A combinatorial library of 400 peptide-based inhibitors has been synthesized and screened against serine proteases plasmin. The inhibitors are constructed upon a Trp-cyclohexanone-Trp nucleus and are designed to probe binding specificity of the S3 and S3' subsites. The library was synthesized by “mix and split” solid-phase synthesis and was screened using positional scanning and deconvolution processes. The “hits” from the original library were resynthesized and characterized by solution-phase synthesis. This combinatorial library methodology has led to the discovery of inhibitors 1, which incorporates Trp at P3 position and Tyr at P3' position and has an IC50 value of 2.1 mM respectively. Data from screening of the library indicates that plasmin has a good specificity for Trp at the S3 subsite, and prefer to bind hydrophobic and aromatic amino acid such as Ala, Ile, Leu, Phe, Tyr, and Val at the P3 subsite.



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MEDI 337

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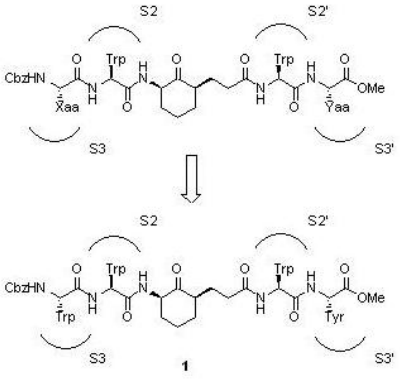


MEDI 338

Hitting more than one target: Inhibitors of serine- and metallo-β-lactamases

John D. Buynak[1]*, Hansong Chen*[1]*, Sukhakar Ganta*[2]*, and Anjaneyulu Sheri*[3]*. (1) Department of Chemistry, Southern Methodist University, Box 0314, Dallas, TX 75275-0314, Fax: 214-768-4089, jbuynak@mail.smu.edu, (2) Chemistry, Southern Methodist University, (3) Department of Medicinal Chemistry, University of Mississippi*

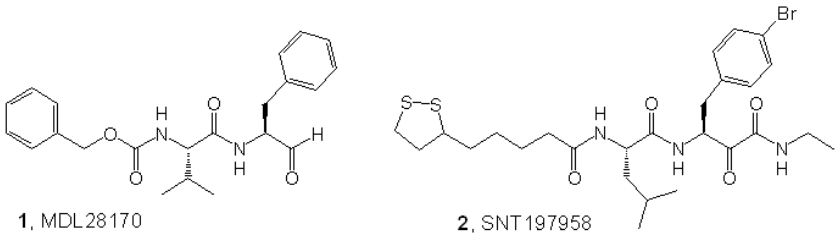
We have designed several series of compounds that simultaneously inactivate two bacterial resistance targets: the serine- and the metallo-β-lactamases. These enzymes represent the most imporant cause of penicillin resistance. Serine- and metallo-β-lactamases have different mechanisms of action and different active site architecture. However, both groups of enzymes recognize β-lactam antibiotics as a hydrolytic target. Thus, our design motif utilizes penicillin- and cephalosporin-derived scaffolds to insure recognition. We will discuss the synthesis, activity, and probably mechanism of action of these inhibitors.

MEDI 339

Cell permeable α-ketoamide calpain inhibitors for the treatment of Duchenne Muscular Dystrophy

Holger Herzner[1], *Reto Bolliger*[1], *Marco Henneböhle*[1], *Cyrille Lescop*[1], *Hervé Siendt*[1], *Philipp Weyermann*[1], *Andreas von Sprecher*[1], *Alexandre Briguet*[2], *Isabelle Cordier-Fruh*[2], *Michael Erb*[2], *Marc Foster*[2], *and Josef P. Magyar*[2]. *(1) Medicinal Chemistry Department, Santhera Pharmaceuticals AG, Hammerstrasse 25, CH-4410 Liestal, Switzerland, Fax: +41-61-906-8988, holger.herzner@santhera.com, (2) Biology Department, Santhera Pharmaceuticals AG*

Duchenne Muscular Dystrophy (DMD) is a recessive X-linked disorder which is characterized by progressive muscle wasting. Patients become usually wheelchair bound as teenagers and die at young age as a result of cardiac or respiratory failures. Mutations in the dystrophin gene lead to an absence of functional dystrophin, a protein linking the cytoskeleton to the cellular membrane. The lack of dystrophin decreases the muscle cell integrity: For example, lesions of the cellular membrane cause an increased influx of calcium into the cell leading to activation of the cystein protease calpain. The activation of calpain results in degradation of various sarcomeric proteins contributing to the deterioration of muscle cells. Inhibition of calpain is therefore a possible approach for the treatment of DMD by preventing the muscle cell degeneration cascade. Starting from known inhibitors like MDL-28170 1 we initiated a program to discover muscle cell permeable, stable calpain inhibitors. Peptide derived alpha-ketoamides like SNT197958 2 exhibited nanomolar activity in our in vitro assays as well as favorable pharmacological properties. Appropriate choice of the aminoterminal targeting group proved to be pivotal for activity in cultivated C2C12-myoblasts. Several of these covalent, reversible calpain inhibitors improved the muscle histology in mdx-mice, an animal model for Duchenne Muscular Dystrophy.



1, MDL28170 **2**, SNT197958

MEDI 340

Structural basis for the differential activity of fumagillin-type inhibitors towards type I and type II human methionine aminopeptidase

Anthony Addlagatta[1], *Xiaoyi Hu*[2], *Jun O. Liu*[2], *and Brian W. Matthews*[1]. *(1) Howard Hughes Medical Institute, Institute of Molecular Biology, Unierversity of Oregon, Eugene, OR 97403, Fax: (541) 346-5870, anthony@uoxray.uoregon.edu, (2) Johns Hopkins School of Medicine, Department of Pharmacology and Molecular Sciences*

Angiogenesis, the growth of new capillary blood vessels is not only important in physiological process but also for pathological process such as tumor progression and metastasis. The

natural products fumagillin, ovalicin and their synthetic analogue TNP-470, were previously shown to have potent anti-angiogenic activity. Methionine aminopeptidase type II (MetAP2) was identified as the molecular target of these fungal compounds. At the same time MetAP1, which shares a high degree of similarity with the type II enzyme was not affected. Lack of a mammalian MetAP1 structure limited the understanding of difference in specificity. We have determined the crystal structure of human MetAP1 at 1.1 Å. This structure for the first time suggests why the fumagillin based inhibitors do not target the type 1 MetAP.

MEDI 341

Practical synthesis and SAR study of aliskiren: An orally active human renin inhibitor

*Hua Dong, Zhi-Liu Zhang, Jia-Hui Huang, Rujian Ma, **Shu-Hui Chen**, and Ge Li, Chemistry Division, WuXi PharmaTech Co., Ltd, No.1 Building, 288 FuTe ZhongLu, WaiGaoQiao Free Trade Zone, Shanghai 200131, China, Fax: 86-21-50463718, chen_shuhui@pharmatechs.com, chen_shuhui@pharmatechs.com*

The renin-angiotensin system (RAS) is known to participate in the regulation of blood pressure, and intervention in this cascade has been the subject of intensive investigation as a treatment for hypertension and congestive heart failure. Angiotensinogen is the only known substrate for the renin enzyme and its conversion to Angiotensin I is the rate-limiting step in the cascade. Thus, inhibition of renin appears to be an ideal target for the development of antihypertensive drugs. In this poster, we describe a practical synthetic route for Aliskiren, an orally active human renin inhibitor selected for clinical development. In addition, a stereoselective synthesis of 4-hydroxy isomer of Aliskiren will also be reported.

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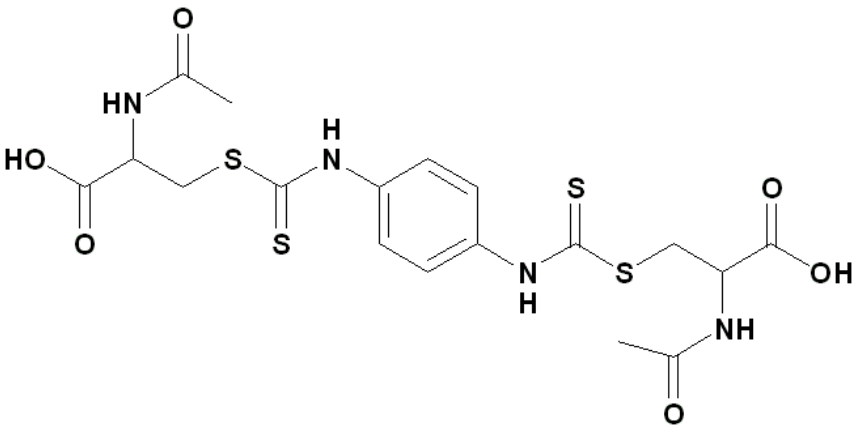
MEDI 342

2-Acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)

phenylthiocarbamoylsulfanyl]propionic acid – a novel irreversible glutathione reductase inhibitor

***Laura Carlson**, Teresa Seefeldt, Jocqueline Herman, and Xiangming Guan, Department of Pharmaceutical Sciences, South Dakota State University, Box 2202 C, Brookings, SD 57007, Fax: (605) 688-5993, Laurakcarlson@hotmail.com*

Glutathione reductase (GR) catalyses the reduction of the oxidized glutathione (GSSG) to the reduced glutathione (GSH). The enzyme is an attractive target for the development of antimalarial agents, agents to reduce malarial drug resistance and anticancer agents. In addition, inhibition of the enzyme has been employed as a tool in research for various purposes. We have identified 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethyl-sulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid as a novel irreversible GR inhibitor. The compound is more potent than N,N-bis(2-chloroethyl)-N-nitrosourea (BCNU), which is currently the most commonly employed irreversible GR inhibitor. The synthesis, enzyme inhibitory constants with yeast GR, and inhibition mechanism will be presented. The inhibitory selectivity of the compound was determined by investigating its effects on GSH-related enzymes such as glutathione peroxidase and glutathione-S-transferase.



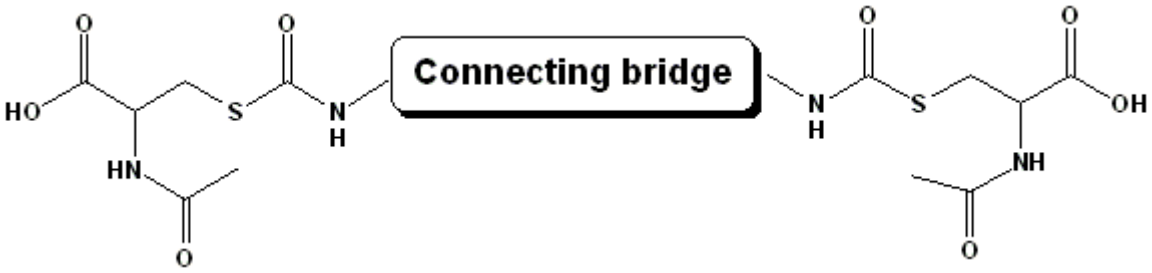
MEDI 343

2-Acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylcarbonylamino) phenylcarbamoylsulfanyl]propionic acid and its derivatives as a novel class of glutathione reductase inhibitors

***Teresa Seefeldt**, Chandradhar Dwivedi, Greg Peitz, Jocqueline Herman, Laura Carlson, Zhiling Zhang, and Xiangming Guan, Department of Pharmaceutical Sciences, South Dakota State University, Box 2202 C, Brookings, SD 57007, Fax: (605) 688-5993, Teresa.Seefeldt@sdstate.edu*

Glutathione reductase (GR) catalyses the reduction of oxidized glutathione to reduced glutathione. The enzyme is an attractive target for the development of antimalarial agents, agents to decrease malarial drug resistance, and anticancer agents. In addition, inhibition of the enzyme has been employed as a tool in research for various purposes. In this presentation, a rational strategy for the design of irreversible GR inhibitors will be presented. This strategy was based on the structure of a lead compound and the binding site for the

substrate GSSG. Based on this strategy, seven compounds were synthesized. All seven compounds exhibited more potent GR inhibitory activity than the lead. Among the compounds, 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylcarbonylamino) phenylcarbamoylsulfanyl]propionic acid was found to be the most potent inhibitor. The selectivity of inhibition, inhibitory parameters, and mechanism of inhibition will also be presented.

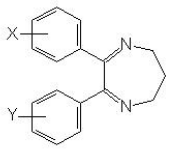


MEDI 344

Design, synthesis and evaluation of 2,3-diaryl-1,4-diazepines as potential antiproliferative agents

Ramachandran Ramajayam*, Rajani Giridhar, and Mange Ram Yadav, Department of Medicinal Chemistry, The M.S University of Baroda, Faculty of tech & Engg, Pharmacy department, Kalabhavan, P.O Box-51, Baroda 390001, India, ramajayam79@rediffmail.com*

The major challenge in cancer therapy is the destruction of malignant cells, sparing the normal tissues thereby reducing the side effects. 1,4- diazepines are now well established moieties for the management of cancer authenticated by earlier reports of anthramycin , a pyrrolobenzodiazepine analog. Recent reports of small molecules like a five/ sixmembered heterocyclic nucleus with di substituted diaryl system indicate anticancer activity. In the present work we report the synthesis of 2,3-diaryl-1,4-diazepines by reacting the substituted benzils with 1,3-propanediamine in the presence of glacial acetic acid as a one pot synthesis.In the proton NMR spectrum the methylene protons adjacent to the imine appears as a broad hump. Mass and elemental data are in conformity with the assigned structure. Biological studies are currently underway.



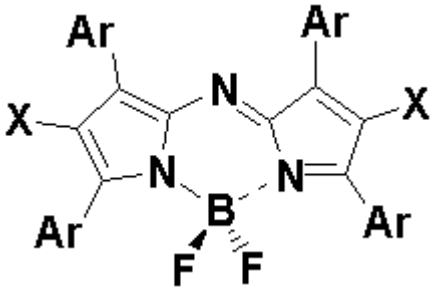
X,Y = Halogens, Alkyl, Nitro, Thiol etc

MEDI 345

A potent non-porphyrin class of photodynamic therapeutic agent

***Michael Hall**, William M Gallagher, and Donal F. O'Shea, Centre for Synthesis and Chemical Biology, Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland, donal.f.oshea@ucd.ie*

Photodynamic therapy (PDT) is an emerging treatment modality for a range of diseases including cancer. We have developed a series of non-porphyrin photodynamic therapeutic agents based on the BF2 chelated tetraarylazadipyromethenes chromophore class. Structural modification of the chromophore has allowed control of key photo-physical and pharmacological properties leading to environmentally targeted photodynamic action. Confocal laser scanning microscopy imaging has been used to examine the localization of the PDT agents in cytosolic compartments, with specific accumulation in the endoplasmic reticulum and to a lesser extent in the mitochondria. Light-induced toxicity assays, carried out over a broad range of human tumor cell lines, have displayed EC50 values in the nano-molar range with no discernable activity bias for a specific cell type. Our most active agents even retain significant activity under hypoxic conditions, while showing low to non-determinable dark toxicity. The photo-physical and biological characteristics of these PDT agents suggests that they have potential for the development of new anti-cancer therapeutics.



MEDI 346

Preparation of sulfonylaminocarboxylic acid N-arylamides as potential anti-tumor agents

***Karl J. Fisher**[1], Courtney A. Reubens[1], Edward M. Doerffler[1], Jeff K. Curtis[1], Mathew M. Abelman[1], Jennifer Davis Bergthold[1], Richard D. Gless[1], and Irwin Braude[2]. (1) Signature BioSciences, Inc, 1200 South 47th Street, Richmond, CA 94804, RNJGless@mindspring.com, (2) Compass Pharmaceuticals, LLC*

Compounds of the general class sulfonylaminocarboxylic acid N-arylamides were found to exhibit selective cytotoxicity to tumor cells when screened against patient tumor and patient normal cells obtained by processing tissue specimens from oncology patients undergoing therapeutic tissue resection. Lead compounds show good anti-tumor activity potency against a variety of tumor types. Aspects of synthesis, SAR, and screening are discussed.

MEDI 347

Design, synthesis and biological evaluation of novel small-molecule inhibitors of Bcl-2 and Bcl-xL proteins

Guoping Wang[1], *Zaneta Nilolovska-Coleska*[1], *Renxiao Wang*[1], *Jie Guo*[1], *Su Qiu*[2], *Wei Gao*[2], *Sanjeev Kumar*[1], *York Tomita*[3], *and Shaomeng Wang*[1]. *(1) Comprehensive Cancer Center and Department of Internal Medicine, The University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109, (2) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, (3) Lombardi Cancer Center, Georgetown University*

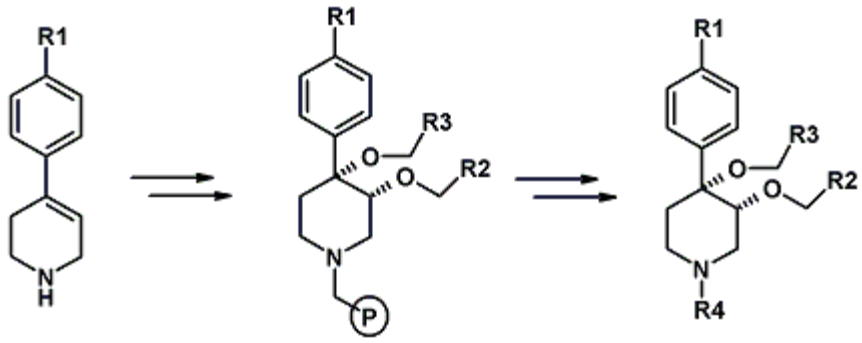
The antiapoptotic Bcl-2 family proteins play a significant role in human malignancies and other proliferative diseases and they have become attractive targets to discover effective anticancer therapies. Gossypol was recently identified as a potent Bcl-2 and Bcl-xL inhibitor. Based on the three-dimensional structure of gossypol in complex with Bcl-xL protein and computational structure-based modeling, a series of novel small-molecule inhibitors were designed and synthesized. A number of these new inhibitors show nanomolar binding affinities to Bcl-2 and/or Bcl-xL and are effective in inhibition of cell growth and induction of apoptosis in cancer cells with high levels of Bcl-2 and Bcl-xL proteins. We will present the design, synthesis, biochemical and biological testing of these potent and promising small-molecule inhibitors of Bcl-2/Bcl-xL.

MEDI 348

Small molecule inhibitors of Mdm2 as novel cancer therapeutics: From hit-to-lead generation to lead optimization

Kyungjin Kim[1], *Emily Liu*[1], *Steven G. Mischke*[1], *Andrew Schutt*[2], *Lyubomir T. Vassilev*[2], *and Bingbing Wang*[1]. *(1) Discovery Chemistry, Hoffmann-La Roche, Inc, 340 Kingsland Street, Nutley, NJ 07110, Fax: 973-235-6084, kyungjin.kim@roche.com, (2) Discovery Oncology, Hoffmann-La Roche, Inc*

The tumor suppressor p53 plays a central role in protection against the development of cancer. p53 is a transcription factor, which is tightly regulated by mdm2 at the cellular level. MDM2 binds p53 and inhibits its ability to transactivate p53-regulated genes. Inhibition of Mdm2-p53 interaction in tumor cells with wild-type p53 leads to accumulation of p53, cell cycle arrest and/or apoptosis. MDM2 antagonists, therefore, can offer a novel approach to cancer therapy. A series of piperidine derivatives was identified as small molecule inhibitors of mdm2. Herein hit-to-lead generation using an efficient synthetic approach in solid phase followed by lead optimization utilizing solid-supported reagents will be discussed.



MEDI 349

Structure-based design of potent, non-peptide small-molecule inhibitors of the MDM2-p53 interaction starting from an inactive lead

Shaomeng Wang[1]*, Ke Ding*[1]*, Yipin Lu*[1]*, Zaneta Nikolovska-Coleska*[1]*, Su Qiu*[1]*, Sanjeev Kumar*[1]*, Peter P. Roller*[2]*, York Tomita*[3]*, Krzysztof Krajewski*[2]*, and Jeffrey R. Deschamps*[4]*. (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, CCGC/3316, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0934, shaomeng@umich.edu, (2) Laboratory of Medicinal Chemistry, National Cancer Institute, NIH, (3) Lombardi Cancer Center, Georgetown University, (4) Laboratory of Structural Matters, Naval Research Laboratory*

The design of non-peptide small-molecule inhibitors of the MDM2 oncoprotein to target the p53-MMD2 interaction is being intensively pursued as an attractive strategy for anti-cancer drug design. We will present our structure-based design, chemical synthesis, detailed biochemical and biological characterization of a class of non-peptide small-molecule inhibitors of MDM2. The most potent small-molecule inhibitors bind to MDM2 protein with a low nanomolar affinity. They effectively inhibit cell growth in cancer cells with wild-type p53 and are highly selective to cancer cells with mutated or deleted p53. Importantly, they have no or minimal toxicity to normal cells. Our studies provide a convincing example that a structure-based strategy can be employed to design highly potent, non-peptide, small-molecule inhibitors that target protein-protein interaction, a very challenging area in chemical biology and drug design.

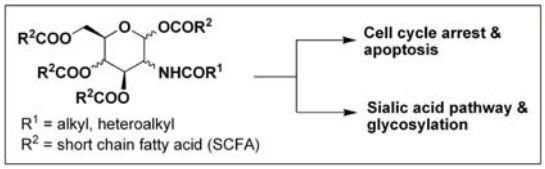
MEDI 350

Design and synthesis of novel SCFA-carbohydrate hybrids with anti-cancer properties

Kevin J. Yarema, ***Srinivasa Gopalan Sampathkumar****, Mark B. Jones, Kaoru Hida, Prasra Gomutputra, and Tony H. Sheh, Whitaker Biomedical Engineering Institute, The Johns Hopkins University, 3400 N Charles St Clark Hall 107, Baltimore, MD 21218, Fax: 410-516-8152, kjyarema@bme.jhu.edu, gopalan@bme.jhu.edu*

In this presentation, we report the design and synthesis of a series of small-molecule hexosamine analogs that carry a variety of functionalities at the N-acyl group and ester-linked short chain fatty acids (SCFAs) on the hydroxyl groups of the sugar and their cellular effects.

These compounds are designed to intervene against two of the hallmarks of cancer, specifically aberrant protein production and glycosylation. SCFAs, particularly butyrate, are small molecules capable of inducing cell cycle arrest resulting in the apoptosis of cancer cells. Despite its ability to inhibit cancer cells while not harming healthy cells, butyrate has poor pharmacological properties and has not achieved wide clinical use. We have developed novel butyrate pro-drugs that not only are used more efficiently by cells, but also contain a ‘pro-active' carrier molecule that possesses synergistic anti-cancer properties. Aberrant glycosylation, a second dominant feature of cancer cells, is caused by defects in carbohydrate metabolism and often impacts the sialic acid biosynthetic pathway which is capable of processing non-natural forms of N-acetylmannosamine (ManNAc). The ‘sialic acid engineering' methodology alters cellular properties and, of interest to this presentation, offers novel ways to kill cancer cells when combined in the same molecule with butyrate functionalities. These molecules induce cell cycle arrest and apoptosis with efficiencies 50-100 times compared to sodium butyrate and, at the same time, increase flux into the sialic acid pathway ~2,100 times more efficiently than ManNAc. Moreover, butyrate, when attached to other hexosamine-based carriers, offers analogs with tunable properties that can be agonistic, antagonistic or neutral to the SCFA activity.



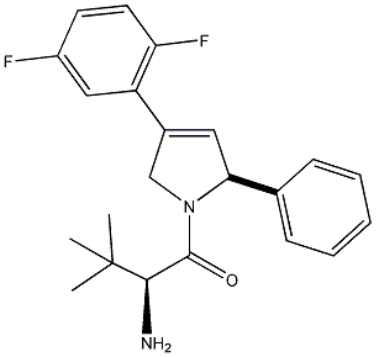
MEDI 351

Developing 2,4-diaryl 2,5-dihydropyrroles as a novel class of KSP kinesin inhibitors

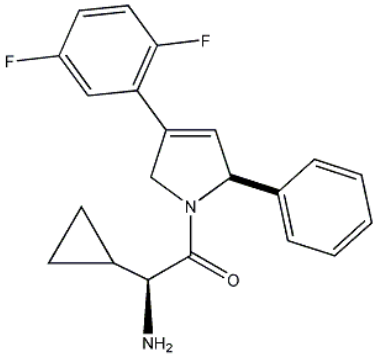
Kenneth L. Arrington[1]*, Robert M. Garbaccio*[2]*, Mark E. Fraley*[1]*, Christopher Cox*[2]*, Paul Coleman*[1]*, George D. Hartman*[3]*, William F. Hoffman*[4]*, Carolyn A. Buser*[5]*, Joe Davide*[5]*, Kelly Hamilton*[5]*, Huber Hans*[1]*, Nancy E. Kohl*[6]*, Robert B. Lobell*[5]*, Michael Schaber*[1]*, Weikang Tao*[5]*, Eileen S. Walsh*[6]*, Lawrence C. Kuo*[7]*, Thomayant Prueksaritanont*[3]*, Donald Slaughter*[8]*, and Cathy Shu*[8]*. (1) Department of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, West Point, PA 19486, Fax: 215-652-6345, kenneth_arrington@merck.com, (2) Department of Medicinal Chemistry, Merck & Co., Inc, (3) Departments of Medicinal Chemistry, Bone Biology and Endocrinology, Drug Metabolism, and Pharmacology, Merck Research Laboratories, (4) Medicinal Chemistry, Merck and Co. Inc, (5) Department of Cancer Research, Merck & Co., Inc, (6) Department of Cancer Research, Merck Research Laboratories, (7) Department of Structural Biology, Merck & Co., Inc, (8) Department of Drug Metabolism, Merck & Co., Inc*

Kinesin Spindle Protein (KSP) is a mitotic kinesin which plays an essential role in the formation of the mitotic spindle generated during mitosis. Inhibition of KSP causes the collapse of the bipolar spindle, which subsequently induces mitotic arrest and apoptosis. Therefore, small molecule KSP inhibitors are regarded as potential, novel chemotherapeutics. We present herein a novel class of KSP inhibitors centered around a 2,4 diaryl 2,5 dihydropyrrole nucleus. Rapid analog synthesis proved vital to the evolution of the series, facilitating the identification of molecules featuring enhancement in both potency and physical properties. The strategic

design elements, SAR, and two distinct synthetic routes will be presented.



Compound 1



Compound 2

MEDI 352

Novel thiazole compounds that inhibit myosin phosphatase activity and human cancer cell proliferation

Scott C Grindrod[1]*, Masumi Eto*[2]*, and Milton L. Brown*[1]*. (1) Department of Chemistry, University of Virginia, McCormick Rd, Charlottesville, VA 22904, sg9v@virginia.edu, (2) Center for Cell Signaling, University of Virginia*

Members of the PPP superfamily of protein phosphatases are important signaling targets in anticancer research. Development of selective inhibitors of protein phosphatase 1 C (PP1C), specifically myosin light chain phosphatase (MLCP), would provide insight into the function of MLCP, a member of the PPP superfamily. A series of 2-aminothiazoles was synthesized and tested for activity against MLCP function and MCF7 cell proliferation. MLCP inhibition data demonstrated that a guanidine moiety on the exocyclic nitrogen of the thiazole was critical to the compounds ability to inhibit the enzyme and could be rationalized by molecular docking into the PP1C crystal structure. Correlation of MLCP IC_{50} and GI_{50} of MCF7 breast cancer cells for a series of these novel compounds showed that increased MLCP inhibition directly correlates to reduction in MFC7 cell proliferation.

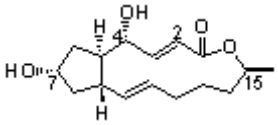
MEDI 353

Determining the mechanisms of action of anticancer natural products

Nwanne O. Anadu*, Mark Cushman, and Vincent Jo Davisson, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907*

Brefeldin A (BFA) is an anticancer natural product isolated from *Eupenicillium brefeldianum*. It causes a reversible disassembly of the Golgi complex however the induction of apoptosis is independent of the Golgi disruption. The relationship between BFA's known targets and

apoptosis induction is yet to be elucidated. Identifying the drug's intracellular targets is key to defining the mechanism of its anticancer activity. BFA immobilized on solid support, allowed isolation of proteins that bound to the drug. HCT 116 human colon cancer cell lysates were incubated with drug conjugated affinity beads, and interacting proteins were isolated in a pull-down assay and analyzed by current proteomic methods. Using 2D gel electrophoresis, we profiled the cellular response of HCT 116 cells to BFA. This global analysis identifies all proteins affected by drug treatment. We generated a differential map that indicated proteins with changed expression levels in response to drug, outlining the targeted biological pathway (s).



MEDI 353

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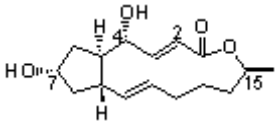


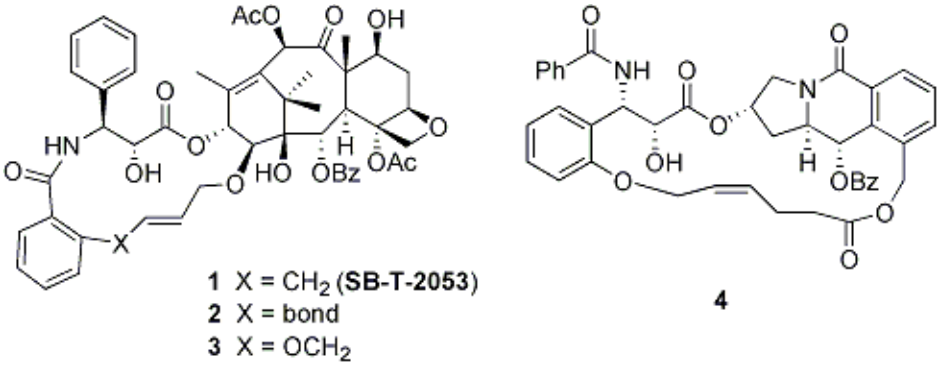
MEDI 354

Design, synthesis and evaluation of novel macrocyclic paclitaxel analogs and a de novo paclitaxel mimic

Liang Sun*[1], Raphaël Geney[1], Yuan Li[1], Kan Ma[2], and Iwao Ojima[3]. (1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, Fax: 631-632-7942, liasun@ic.sunysb.edu, (2) Institute of Chemical Biology & Drug Discovery,*

State University of New York at Stony Brook, (3) Institute of Chemical Biology & Drug Discovery and Department of Chemsitry, State University of New York at Stony Brook

Paclitaxel (Taxol®) currently serves as one of the most important drugs in cancer chemotherapy. A plausible pharmacophore for paclitaxel-like microtubule-stabilizing agents suggests that the complex baccatin core could be replaced by a structurally simpler scaffold that retains its essential features. Thus, baccatin-free paclitaxel-mimics could be developed based on the bioactive conformation of paclitaxel at the binding site of β-tubulin. SB-T-2053 (1), a conformationally restrained novel paclitaxel analog that mimics the “REDOR-Taxol” conformation, exhibits a strong potency comparable to paclitaxel. Two novel macrocyclic paclitaxel analogs (2 and 3) were synthesized to see if either one has a better fit than 1. We further designed a novel baccatin-free paclitaxel mimic (4) that can take the “REDOR-Taxol” conformation. Molecular modeling studies, synthesis and biological evaluation of these novel macrocyclic compounds will be presented.



1 X = CH_2 (**SB-T-2053**)
2 X = bond
3 X = OCH_2

4

MEDI 355

Hydrophobic derivates of 5-(hydroxymethyl)isophthalic acid that selectively induce apoptosis in leukaemia cells but not in fibroblasts

***P. Gustav Boije af Gennäs**, Anna Galkin, Anu Surakka, Timo Ruotsalainen, Päivi Tammela, Jari Yli-Kauhaluoma, Kaarina Sivonen, and Pia Vuorela, Faculty of Farmacy, University of Helsinki, P.O.Box 56, (Viikinkaari 5 E), FIN-00014 University of Helsinki, Finland, Fax: +358-9-191 59556, boije@mappi.helsinki.fi*

Apoptosis or programmed cell death is a highly organized physiological process to destroy unwanted cells. Defective apoptosis regulation is associated with many diseases, for example in cancer and autoimmunity diseases. Since new apoptosis modulating molecules are widely sought, we embarked on the synthesis of ten new hydrophobic derivates of 5-(hydroxymethyl) isophthalic acid. Cancerous leukaemia cells (HL-60) and non-malignant fibroblasts (Swiss 3T3) were incubated with these compounds and morphologically evaluated. The changes in mitochondrial membrane potential (Äøm) and caspase-3 activity assay confirmed the results. Cytotoxicity was determined using the lactate dehydrogenase (LDH) cytotoxicity assay and mutagenicity with miniaturized Ames-test. There were two potent selective apoptosis inducers found having IC50 values 41 µM and 23 µM, respectively in leukaemia cells (HL-60) while effects on fibroblast (Swiss 3T3) were insignificant. Reduction of Äøm and increase in caspase-3 activity were observed in the HL-60 cells. Neither of the compounds was cytotoxic or mutagenic.

MEDI 356

Organic arsenicals as carcinostatic agents

***Mingzhang Gao**, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, Room L3-202, Indianapolis, IN 46202, Fax: 317-278-9711, migao@iupui.edu, and Ralph A. Zingaro, Department of Chemistry, Texas A & M University*

The synthesis of compounds of the type **B-SAsR_2** is described. B is a biological compound such as sugar, lipid, amino acid, or oligopeptide and R is a short chain alkyl group. The typical example was shown in Fig. 1, which was synthesized via five-step reaction from D-(+)-xylose. These molecules show significant carcinostatic activity in vivo, in the PS388 and L1210 (leukemia) test systems, and in vitro in the NCI 60 tumor human cell assay and in a number of cancer cell cultures. These molecules are innocuous against normal cell cultures and tolerated with no ill effects in live animal tests (mice and dogs). Clinical trials are in the planning stage.

Fig. **1**

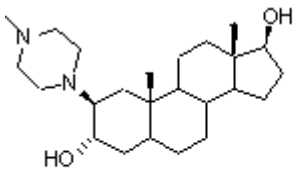
MEDI 357

Steroidal antileukemic agents: Synthesis and biological evaluation of a family of 2b-aminoandrostane-3a,17b-diols on HL-60 cells

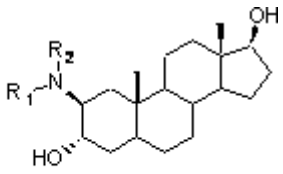
***Jenny Roy**[1], Dominic Thibeault[2], and Donald Poirier[2]. (1) Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center (CHUQ-CRCHUL) and Université Laval, Québec, Canada, CHUL Research Center, 2705 Laurier Boulevard, Québec, QC G1V 4G2, Canada, Fax: 418-654-2761, Jenny.roy@crchul.ulaval.ca, (2) Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center, (CHUQ-CRCHUL) and Université Laval, Québec, Canada*

Leukemia is the most commonly occurring cancer for children. Many therapeutic agents are available but they are highly toxic and induce several side effects. Recent studies have identified the C-19 steroid **1** as a potential antileukemic agent. With an efficient procedure that we have developed for the aminolysis of hindered steroidal epoxides, we synthesized a series

of HY analogs. Hence, the opening of 2,3a-epoxy-5a-androstan-17b-ol with primary and secondary amines generated seventy 2b-aminosteroids **2** with different functionnalization for SAR study. The antileukemic activity was evaluated in HL-60 cells model assay and twenty of the seventy compounds tested were more antiproliferative than HY and displayed over 88 % cell growth inhibition at 10 µM. Three representative compounds rapidly induced apoptosis in the leukemia cells whereas cell differentiation assay is under progress. The chemical synthesis and biological evaluation will be presented in detail.



1 (HY)



2

MEDI 357

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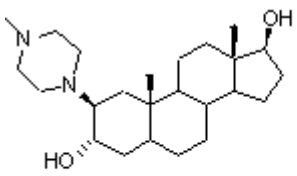
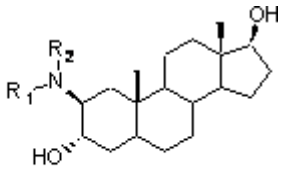


1 (HY)



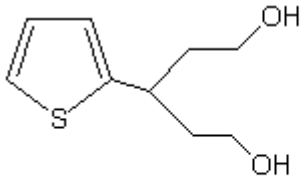
2

MEDI 358

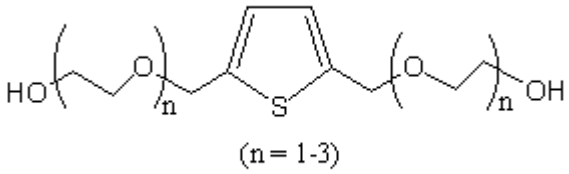
Dialcohols containing a thiophene core: Synthesis and biological evaluations

***Brahmi Shukla**, Rajesh Kavali, Ravi K. Ujjinamatada, and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, brahmi@umbc.edu*

Prompted by a recent report (Saenz, M. T., *et al. Farmaco* **1998**, *53*, 448-9) that dialcohols from the unsaponifiable fraction obtained from virgin olive oil exhibit strong cytostatic activity against human epithelial cell line (McCoy cells) using 6-mercaptopurine as a positive control, we set out to synthesize a number of dialcohols containing a thiophene ring as the core moiety. We report herein the synthesis and biological activities of these dialcohols. Our synthetic endeavor, coupled with modern spectroscopic methods, has uncovered an error in the reported structure of an intermediate (*J. Am. Chem. Soc.* **1954**, *76*, 2731), which will also be discussed.



I



II

MEDI 359

Synthesis and structure-activity relationships of boronic acid chalcone bioisosteres of combretastatin A-4

***Yali Kong**[1], Jolanta Grembecka[2], Michael C Edler[3], Ernest Hamel[3], and Milton L. Brown[1]. (1)*

Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904-4319, yk4n@virginia.edu, (2) Molecular physiology & Biological Physics, University of Virginia, (3) Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute at Frederick

In this study, we determined and synthesized chalcones grafted onto a boronic acid combretastatin scaffold. We systematically evaluated the position effects of the carbonyl towards inhibition of tubulin polymerization and cancer cell proliferation. Using molecular docking and volume mapping, we predicted relative binding interactions for the novel analogues. Our study identified a boronic acid chalcone with cytotoxicity towards 19 human cancer cell lines in the 10-200 nM range. Finally, SAR reveal the importance of carbonyl positioning in these novel compounds in regard to tubulin depolymerization.

MEDI 360

Synthesis and biological activity of combretastatin derivatives

***Kristin Odlo**, Trond Vidar Hansen, Pål Rongved, and Jo Klaveness, School of Pharmacy, University of Oslo, PO BOX 1068, Blindern, N-0316 Oslo, Norway, Fax: +4722855947, kristin.odlo@farmasi.uio.no*

Combretastatins belong to a class of natural products isolated from the South African tree *Combretum caffrum*. This class of compounds has been identified as competitive inhibitors of the colchicine binding site on β-tubulin. The non-complex structures and high affinity of combretastatins for the colchicine binding site make the combretastatins attractive lead compounds in the development of new tubulin inhibitors. Thus, novel compounds derived from the combretastatin family are of interest as anticancer agents. Furthermore, the presence of one or several phenolic hydroxyl groups and methyl ethers in the combretastatins spurred our interest in examining their ability to scavenge radicals and inhibit lipoxygenases, since radicals are important in the development of cancer and atherosclerosis.

MEDI 361

Synthesis and SAR of potent N-substituted pipecolic acid derivatives of hemiasterlin that are very poor substrates for P-glycoprotein-mediated drug efflux

***Shawn Schiller**, Hongsheng Cheng, James J Kowalczyk, Galina Kuznetsov, Bruce A. Littlefield, Diana Liu, Véronique Marceau, Cheryl Rowell, Boris M. Seletsky, Edward M. Suh, Karen TenDyke, Murray Towle, and Hu Yang, Eisai Research Institute, Andover, MA 01810, Fax: 978-657-7715, shawn_schiller@eisai.com*

The tripeptide marine natural product, hemiasterlin, which was isolated from several marine sponges (*Auletta* sp., *Cymbastela* sp., *Hemiasterella minor*, and *Siphonochalina* sp.) has been shown to exhibit potent cytotoxicity against a variety of cancer cell lines *in vitro* via a tubulin-depolymerizing antimitotic mechanism. It has also exhibited activity *in vivo* in a limited number of animal models. The relatively simple structure of hemiasterlin and its potent antimitotic activity make it an ideal candidate for structural modification. In order to fully evaluate the potential of hemiasterlin as an anticancer drug, we embarked on the synthesis and biological

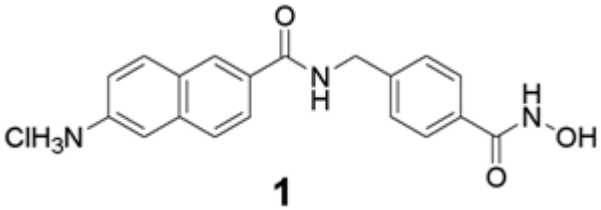
evaluation of a number of analogs. Optimization of the N-terminal amino acid of hemiasterlin resulted in compounds with high potency against numerous human cancer cell lines *in vitro* with low susceptibility to p-glycoprotein (PgP) mediated drug efflux. Here we present structure activity relationships (SAR) obtained from the biological evaluation of a series of N-substituted pipecolic acid derivatives of hemiasterlin. Several of these derivatives exhibited substantially less susceptibility to PgP than clinically used antimicrotubule agents such as paclitaxel or vinblastine. One analog in particular, E7974, has also shown significant *in vivo* antitumor activity in a variety of tumor xenograft models, including taxane resistant models. This property suggests a potential clinical advantage over existing drugs, including anti-tubulin agents, which are largely ineffective against multidrug resistant tumors.

MEDI 362

New histone deacetylase inhibitors: Benzamide derivatives with a 2-hydroxyethylamino group

*Yasuo Nagaoka, Taishi Maeda, and **Shinichi Uesato**, Department of Biotechnology, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan, Fax: +81-6-6388-8609, ynagaoka@ipcku.kansai-u.ac.jp, uesato@ipcku.kansai-u.ac.jp*

Histone deacetylase (HDAC) inhibitors are promising antitumor candidates because they inhibit cell cycle propagation and induce apoptosis of human tumor cells by activating tumor suppressor genes such as p21/WAF1, p27 and GADD45. Previously we found a novel HDAC inhibitor *N*-hydroxybenzamide **1** which showed a significant survival rate (T/C%, 185) in a murine P388 leukemia model. In the present study, we further tried to modify the structure of **1** in order to improve its physicochemical properties as well as the tumor-antiproliferative activities. Thus, we have synthesized benzamide derivatives with a 2-hydroxyethylamino moiety instead of the carbonylamino segment. Some derivatives exhibited water-solubility and a HDAC-inhibiton comparable with those of SAHA and MS-275.



1

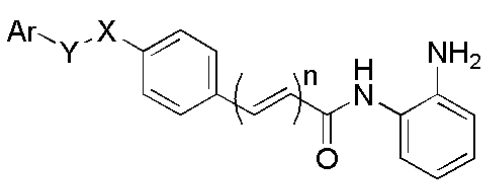
MEDI 363

Design and synthesis of arylamino-(2-aminophenyl)-benzamides or cinnamides (A) and heteroaryl -N-(2-aminophenyl)-benzamides (B) as a novel class of histone deacetylase inhibitors

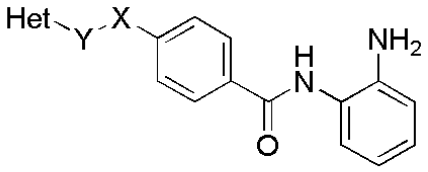
***Nancy Zhihong Zhou*[1], *Oscar Moradei*[1], *Stéphane Raeppel*[1], *Silvana Leit*[1], *Sylvie Frechette*[1], *Frédéric Gaudette*[1], *Isabelle Paquin*[1], *Giliane Bouchain*[1], *Naomy Bernstein*[1], *Franck*

Raeppel[1], Oscar Saavedra[1], Soon Hyung Woo[1], Arkadii Vaisburg[1], Marielle Fournel[2], Ann Kalita[2], Aihua Lu[2], Marie-Claude Trachy-Bourget[2], Pu T. Yan[2], Jianhong Liu[2], Zuomei Li[2], Gabi Rahil[2], Robert Macleod[2], Jeffrey Besterman[2], and Daniel Delorme[1]. (1) Department of Medicinal Chemistry, Methylgene Inc, 7220 Frederick-Banting, Montreal, QC H4S2A1, Canada, Fax: (514) 337-0550, zhoun@methylgene.com, (2) Department of Biology, Methylgene Inc

Abstract—Inhibition of histone deacetylases (HDACs) is emerging as a new strategy in human cancer therapy. We have designed and synthesized novel arylamino-(2-aminophenyl)-benzamides or cinnamides (A) and heteroaryl -N-(2-aminophenyl)-benzamides (B), non-hydroxamate small molecule HDAC inhibitors, as a novel anti-cancer therapeutic. Those compounds selectively target certain specific class I HDAC enzymes at IC50's of submicromolar concentrations in vitro and induce hyperacetylation of histones in cultured human cancer cells. In vivo, some of those compounds significantly inhibit growth of human tumors in xenograft models.



A



B

n = 0 or 1
X = CH_2, Y = NH
X = NH, Y = CH_2

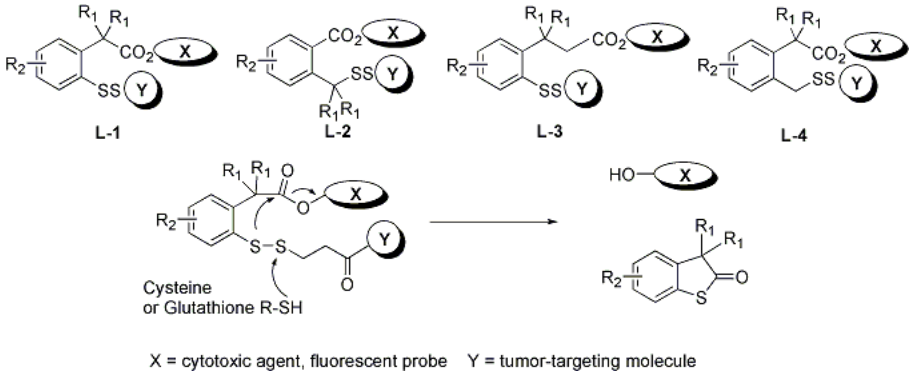
MEDI 364

Synthesis and evaluation of a new class of disulfide-containing linkers for efficient intracellular release of anticancer agents

***Jin Chen**[1], Xianrui Zhao[1], Shuyi Chen[1], Stanislav Jaracz[1], and Iwao Ojima[2]. (1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, jinchen2@ic.sunysb.edu, (2) Institute of Chemical Biology & Drug Discovery and Department of Chemsitry, State University of New York at Stony Brook*

A new class of disulfide-containing linkers for tumor-targeting prodrugs has been designed and synthesized. The novel disulfide linker contains a carboxylic acid group and an active ester terminus. A tumor-targeting prodrug is formed by coupling the carboxylic acid terminus to an anticancer drug (eg. taxoid) and reacting the active ester with a tumor-targeting molecule (eg. monoclonal antibody). A monoclonal antibody second-generation taxoid conjugate (KS-77-SB-T-1214) has been prepared through such a linker. These bifunctional linkers could be applied to a variety of tumor-targeting molecules and cytotoxic agents. A series of model experiments have been performed and proved the designed release mechanism, i.e., disulfide bond cleavage by a thiol, fast intramolecular thiolactonization, and the release of a free cytotoxic agent. The mechanism of the release process, including pH dependence and substituent

effects, will be discussed.



MEDI 365

Structure elucidation of novel chloromethylpyridyl purine nucleoside analogues and related compounds

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Since the report of Neplanocin A, a carbocyclic analogue of adenosine with potent antitumor and antiviral activity, several carbocyclic nucleoside analogues of purine, pyrimidine and related nucleic acid bases have been investigated as potential chemotherapeutic agents. We have also investigated several aromatic nucleoside analogues of Neplanocin A and especially the ortho- and meta-analogues have shown good adenosine deaminase substrate activity and anticancer properties. In order to investigate further the structure-activity-relationship (SAR) of this class, we have designed and synthesized several new chloromethylpyridyl purine nucleoside analogues as potential anticancer and antiviral agents. In the present study 6-chloropurine was reacted with 2,6-bis(chloromethyl)pyridine in dimethyl formamide and potassium carbonate medium to furnish N9-[(chloromethyl)pyridylmethyl]-6-chloropurine, and N7-[(chloromethyl)pyridylmethyl]-6-chloropurine. By changing the molar ratios of the reagents, the reaction time and temperature we have succeed to isolate the symmetrical N9-N9-pyridylmethyl-6-chloropurine dimer and asymmetrical N9-N7-dimer. Structure elucidation of these isomers was done with the proton NMR and UV spectroscopy. These results and adenosine deaminase studies of N9-[(hydroxymethyl)pyridylmethyl]adenine will be presented.

MEDI 365

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MEDI 366

Synthesis and biological evaluation of purealin and analogues as cytoplasmic dynein heavy chain inhibitors

Guangyu Zhu[1]*, Fanglong Yang*[1]*, Raghavan Balachandran*[2]*, Peter Hook*[3]*, Richard B. Vallee*[3]*, Dennis P. Curran*[1]*, and Billy W. Day*[2]*. (1) Department of Chemistry, University of Pittsburgh, 234 Chevron Science Center, Pittsburgh, PA 15260, guz2@pitt.edu, (2) Department of Pharmaceutical Sciences, University of Pittsburgh, (3) Departments of Pathology and of Anatomy and Cell Biology, College of Physicians and Surgeons, Columbia University*

Cytoplasmic dynein plays an important role in the transport of cargo in cells, nuclear envelope breakdown, and formation and proper execution of the mitotic spindle. Little is known about the structural requirements of small molecule cytoplasmic dynein heavy chain inhibitors. We report here the synthesis of purealin, a natural product isolated from the sea sponge *Psammaplysilla purea* known to inhibit axonemal dynein heavy chain, and a small library of purealin analogues, as well as their abilities to inhibit cytoplasmic dynein heavy chain and cell growth. The library showed effective antiproliferative activity against a mouse leukemia cell line, but selective activities against human carcinoma cell lines. Purealin and some of the analogues inhibited the ATPase activity of isolated cytoplasmic dynein heavy chain. They also showed the inhibitory effects on microtubule-stimulated ATPase of recombinant dynein motor domain. The inhibitory effect of purealin was concentration-dependent. The pattern of inhibition was found to be uncompetitive, supporting the hypothesis that purealin does not compete for ATP binding. These data illustrate small molecule inhibitors of cytoplasmic dynein that could prove to be useful tools for investigation of the cellular function of cytoplasmic dynein are an achievable goal. Also, the results suggest the possibility of using dynein heavy chain inhibitor as a potential chemotherapeutic agent.

MEDI 367

Structure based design and synthesis of core binding factor alpha inhibitors: A new target for anti-leukemic agents

Kristin M. Graf[1]*, Jolanta Grembecka*[2]*, Miki Newman*[2]*, John H. Bushweller*[2]*, and Milton L. Brown*[1]*. (1) Department of Chemistry, University of Virginia, McCormick Rd, P.O. Box 400319, Charlottesville, VA 22904, kmg4u@virginia.edu, (2) Department of Molecular Physiology and Biological Physics, University of Virginia*

Core binding factors (CBFs) are heterodimeric transcription factors consisting of a DNA-binding subunit (CBFα) and a non-DNA binding subunit (CBFβ). Mutations in the gene that encodes CBFα have been shown to disrupt normal hematopoietic function and are closely linked to several forms of leukemia. As the interaction between CBFα and CBFβ is crucial for transcription to occur, inhibition of this dimerization represents a promising therapeutic strategy. LUDI screening and extensive docking of ligands with CBFα led to the development of a 5-furan-1,2,4-triazole-3-thione as a potential small molecule inhibitor of CBFα/β interactions. Synthetic efforts to date have focused on isosteric replacements of the furan ring and atoms within the triazole ring. Fluorescence resonance energy transfer (FRET) studies were used to validate the molecular docking experiments and determine the binding affinity of each compound as well as its ability to inhibit dimerization of CBFα with CBFβ.

MEDI 368

Hydrophylic 3-carboranyl thymidine analogues (3CTAs) for boron neutron capture therapy (BNCT)

Sureshbabu Narayanasamy[1]*, B. T. S. Thirumamagal*[1]*, Jayaseharan Johnsamuel*[1]*, Cecilia Carnrot*[2]*, Ashraf S Al-Madhoun*[3]*, Guirec Y Cosquer*[1]*,* ***Youngjoo Byun***[1]*, Achintya K. Bandyopadhyaya*[1]*, Staffan Eriksson*[2]*, and Werner Tjarks*[1]*. (1) Division of Medicinal Chemistry & Pharmacognosy, College of Pharmacy, The Ohio State University, 500 W. 12th Avenue, 416 Parks Hall, Columbus, OH 43210, narayanasamy.1@osu.edu, byun.12@osu.edu, (2) Department of Molecular Biosciences, Division of Veterinary Medical Biochemistry, Swedish University of Agricultural Sciences, Uppsala, Sweden, (3) Division of Cardiology, Vascular Biology Laboratory, University of Ottawa Heart Institute, Ottawa, Canada*

Boron Neutron Capture Therapy (BNCT) is a binary system for the treatment of cancer. In order for this therapy to be effective, the targeted cancer cells must attain a sufficient concentration of boron-10 and, thus, delivery systems for this non-radioactive isotope have to be developed that selectively target tumor cells. Boronated nucleosides have been considered as very attractive BNCT agents because of their potential metabolic properties, which could result in their selective accumulation and retention in tumor cells. Previously, we have synthesized various types of 3-carboranyl substituted thymidine analogues (3CTAs), which have the potential to fulfill the basic requirements as boron delivery agents for BNCT. Here, we describe the concise synthetic methods for the synthesis of novel 3CTAs hydrophylically enhanced either with additional nucleoside moieties or cyclic and acyclic alcohol functions. NMR and MS spectroscopy confirmed the structures of all synthesized compounds. Binding patterns of these novel 3CTAs to the active site of thymidine kinase 1 (TK1) was analyzed in docking studies using the crystal structure of TK1. TK1 substrate characteristics of all new 3CTAs were determined in enzyme assays using recombinant TK1 preparations. Results of this preliminary biological evaluation indicated that some of the novel 3CTAs might have similar or even superior potential as BNCT agents than 3CTAs previously reported.

MEDI 369

Liposomal formulations of carboranyl cholesterol derivatives for boron neutron capture therapy (BNCT)

B. T. S. Thirumamagal[1]*, Xiaobin B. Zhao*[1]*, Danold W. Golightly*[2]*, Joseph. M. Backer*[3]*, Robert J. Lee*[1]*, and Werner Tjarks*[1]*. (1) Division of medicinal chemistry & Pharmacognosy, College of Pharmacy, The Ohio State University, columbus, OH 43210, srinivasaraghava.2@osu.edu, (2) Department of Civil and Environmental Engineering, The Ohio State University, OH, USA, (3) SibTech, Inc, Newington, CT 06111, USA*

Boron neutron capture therapy is a binary therapeutic method for the treatment of high-grade brain tumors. It is based on the capture of thermal neutrons by the 10B nucleus in the tumors. Irradiation of tumor-localized 10B with low energy neutrons produces high linear energy He and Li ions that cause irreversible lethal damage to tumor cells. Both particles have limited ranges in tissue of about one cell diameter and therefore, their destructive effect is localized to the 10B containing tumor.The successful treatment of cancer by BNCT requires the selective delivery of 15-30µg of 10B-containing compounds to malignant tumor tissue Here we report the synthesis of novel carboranyl derivatives of cholesterol for encapsulation into liposomes. In these structures, the carborane moiety partially replaces the carbocyclic steroidal skeleton of the cholesterol molecule. The results of structural and physicochemical analyses of these new boron carriers will be presented. These highly lipophilic compounds were incorporated with high efficiency in the lipid bilayers of both folate receptor-targeted and non-targeted liposomes having particles sizes in the range of 60 – 110 nm. The results of in vitro studies of folate receptor-targeted liposomes containing novel carboranyl cholesterols using KB cells will be presented

MEDI 370

Synthesis and characterization of new titanium and palladium chloroquine complexes with antitumoral activity

Maribel Navarro[1]*, Nayarit Prieto-Peña*[1]*, Miriam Arsenak*[2]*, and Peter Taylor*[2]*. (1) Centro de Química, Instituto Venezolano de Investigaciones Científicas, Carretera Panamericana Km 11, Altos de Pipe, Caracas 1020-A, Venezuela, Fax: (58212)5041350, mnavarro@ivic.ve, (2) Centro de Medicina Experimental, Instituto Venezolano de Investigaciones Científicas*

As a part of our research, we have been using a strategy based on the observation that coordination of drug such as chloroquine with known biological activities to transition metals can result in remarkable enhance of the biological activity. Compound of chloroquine attached to different transition metals (Ru, Rh, Au, etc) have been showed to be effective against Malaria. But their activity as antineoplastic agents have been very littler explored. Thus, there is interest in enhancing the efficacy of this organic drug with potential anticancer activity by incorporating novel transition metals into its structure. We initiated our research modifying chloroquine with palladium and titanium as a metal would modified the CQ. In this presentation, we will describe the synthesis and characterization of the new complexes [Ti(CQ) Cl3]Cl(1), [Ti(CQ)2Cl2]Cl2(2), [TiCp(CQ)2Cl]PF6 (3 Pd(CQ)2Cl2(4). Additionally, some

promising cytotoxicity results have been obtained with these complexes against the four cell lines PANC-1, SKBR-3, MDA-MB231, HT29. All the results will be discussed. Supported by IVIC and FONACIT.

MEDI 371

Investigation of 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid's effect on intracellular glutathione reductase, glutathione, and cell growth with monkey kidney cells

***Yong Zhao**, Teresa Seefeldt, Jocqueline Herman, Laura Carlson, and Xiangming Guan, Department of Pharmaceutical Sciences, South Dakota State University, Box 2202 C, Brookings, SD 57007, Fax: 605-688-5993, yzhao518@yahoo.com.cn*

2-Acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino) phenylthiocarbamoylsulfanyl]propionic acid has been identified as a novel potent inhibitor of yeast glutathione reductase (GR). GR catalyses the reduction of the oxidized glutathione (GSSG) to the reduced glutathione (GSSG). The enzyme is an attractive target for the development of antimalarial agents, agents to decrease malarial drug resistance and anticancer agents. In addition, inhibition of the enzyme has been employed as a tool in research for various purposes. This poster presentation will demonstrate that 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl] propionic acid also inhibits mammalian intracellular GR. The effects of the compound on intracellular levels of GSSG and GSH will also be presented. In addition, the cytotoxicity of the compound on monkey kidney cell line was evaluated.

MEDI 372

Dihydroquinazolinones: Dual action inhibitors of cancer cell proliferation and angiogenesis

***Gary M. Chinigo**[1], Rachel Leal[2], Michael Elder[1], Ernest Hamel[3], Susan L. Mooberry[4], and Milton L. Brown[1]. (1) Department of Chemistry, University of Virginia, McCormick Rd, Charlottesville, VA 22904, Fax: 434-924-0798, gmc8s@virginia.edu, (2) Southwest Foundation for Biomedical Research, (3) Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, (4) Department of Physiology and Medicine, Southwest Foundation for Biomedical Research*

A series of novel biphenyl substituted 2,3-dihydroquinazolinones have been evaluated as inhibitors of human colon cancer cell proliferation. Mechanistic studies reveal these compounds to be potent inhibitors of tubulin polymerization as well as angiogenesis. Herein, we report the multistep syntheses and SAR of these compounds for effects on 3H-colchicine displacement, tubulin depolymerization, human endothelial and colon cancer cell proliferation. Although structurally simple, the most active analogs display cancer cell cytotoxicities on the order of combretastatin, vinca alkaloids, and other tubulin binding natural products.

MEDI 373

SC-2-71: A novel small molecule dual inhibitor of human cancer cell proliferation and angiogenesis

Akunna M. Iheanacho[1], *Scott M. Capitosti*[1], *Todd P. Hansen*[1], *Gary M. Chinigo*[1], *W. Nathaniel Brennen*[2], *Rachel M. Leal*[3], *Maiko Sakai*[1], *Tamara D. Stoops*[4], *Susan L. Mooberry*[3], *Robert A Sikes*[2], *Carlton A. Cooper*[2], *and Milton L. Brown*[1]. *(1) University of Virginia, Department of Chemistry, McCormick Road, Charlottesville, VA 22904, ami3k@virginia.edu, (2) Department of Biological Sciences, Laboratory for Cancer Ontogeny and Therapeutics, (3) Department of Physiology and Medicine, Southwest Foundation for Biomedical Research, (4) Experimental and Molecular Therapeutics, University of Virginia Cancer Center*

Increased expression levels of class III beta tubulin and P-glycoprotein have been implicated as important mechanisms of paclitaxel resistance in ovarian and breast cancer patients. We have discovered a series of substituted 2-aryl-2,3-dihydro-4-quinazolinones that are effective against cancer cell lines where beta III expression levels are elevated. Several mechanistic experiments were performed in an effort to examine the relationship between beta III tubulin levels and sensitivity to SC-2-71. Interestingly, SC-2-71 also demonstrated both potent in vitro anti-proliferative activity and in vivo anti-angiogenic activity. SC-2-71 inhibited intracellular microtubules, caused greater than a 30% increase in G2 arrest, and was a poor substrate for P-glycoprotein. Altogether, our data demonstrates that SC-2-71 targets both endothelial and cancer cell types. Further, this class of analogues may serve as promising leads for the development of agents to treat cancers for which a poor prognosis correlates to increased microvessel density, beta III tubulin and P-glycoprotein expression.

MEDI 374

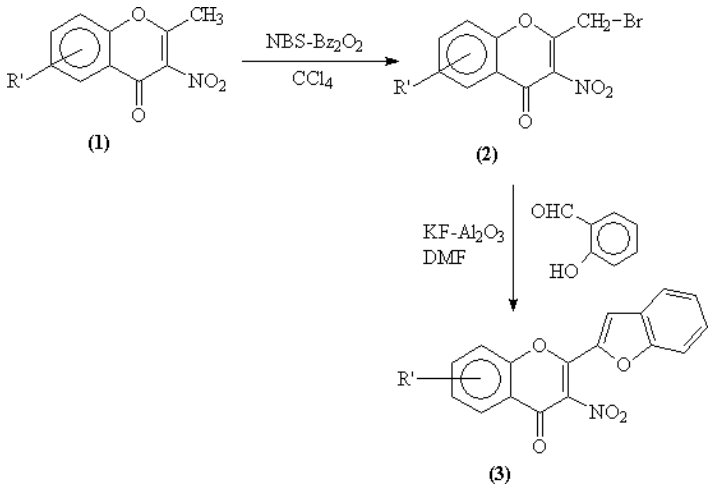
Synthesis and anti-cancer activity of 2-(2-benzofuranyl)-3-nitro-4h(1)-benzopyran-4-ones

Papa Rao Chebrolu *and Rakesh Masna, O.U.P.G.College(Osmania University), Osmania University, MIRZAPUR, Medak District, Andhra Pradesh-502249, Mirzapur 502249, India, chebrolupr@yahoo.com*

2-Heteryl-4H(1)benzopyran-4-ones have been reported to exhibit varied biological properties such as anti-cancer, cardio-vascular, anti-tumour and anti-allergic activities. Literature indicated that compounds in which the carbonyl flanked by a nitro group such as in 3-nitro-4-hydroxycoumarins exhibit excellent anaphylactic activity.

In view of the above biological properties exhibited by the suitably substituted 4H (1)-benzopyran-4-ones, we are prompted to synthesize the title compounds in very good yields. The potential synthon, 2-methyl-3-nitro-4H(1)benzopyran-4-one (1) reacts with N-bromosuccinimide and dibenzoyl peroxide in carbon tetrachloride to give 2-bromomethyl derivative (2) which further reacts with salicylaldehyde in the presence of potassium fluoride and alumina in dimethyl formamide produces 2-(2-benzofuranyl)-3-nitro-4H(1)benzopyran-4-

one(3). The compounds thus synthesized are screened for their anti-cancer activity the results of which will be discussed.



MEDI 375

Synthesis and anti-tumor activity of fluorocyclopentenyl-pyrimidines

Lak Shin Jeong[1]*, Long Xuan Zhao*[1]*, Mikyung Yun*[1]*, Won Jun Choi*[1]*, Sang Kook Lee*[1]*, Kang Man Lee*[1]*, Young B Lee*[2]*, and Chang H. Ahn*[2]*. (1) Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, 11-1 Seodaemun-ku, Daehyun-dong, Seoul, South Korea, Fax: 82-2-3277-2851, lakjeong@mm.ewha.ac.kr, (2) Rexahn Coporation*

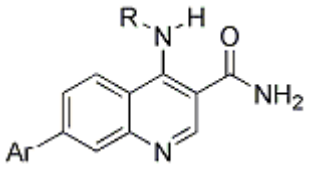
On the basis of potent biological activity of neplanocin A, we have recently discovered the carbocyclic nucleoside, fluoro-neplanocin A, which is a potent inhibitor of S-adenosylhomocysteine hydrolase. Fluoro-neplanocin A was about twice more potent than neplanocin A and showed novel type II irreversible mechanism of action, but was highly cytotoxic. Thus, it is of great interest to synthesize the corresponding pyrimidine derivatives of fluoro-neplanocin A and to evaluate their antitumor activity. First, the key carbasugar, 3-hydroxymethylcyclopentenone with various protective groups was stereoselectively synthesized, starting from D-ribose in 7 steps and 45-50% overall yields via the stereoselective formation of the tertiary allylic alcohol enforced by the bulkiness of the protective group and oxidative rearrangement of the tertiary allylic alcohol under mild conditions. The key carbasugar was converted to fluoro-cyclopentenone using electrophilic vinyl fluorination, which was modified to the various fluorocyclopentenyl-pyrimidines via a Mitsunobu condensation. Among compound tested, cytosine derivative exhibited in vivo antitumor activity as well as potent in vitro anticancer activity. Synthesis and biological activity of the target nucleosides will be presented in detail.

MEDI 376

Synthesis and biological evaluation of novel anilinoquinoline *c-fms* inhibitors

Terrence L. Smalley Jr.[1]*, Wendy Y. Mills*[1]*, Stanley D. Chamberlain*[1]*, Lee Kuyper*[1]*, Sab A. Randhawa*[2]*, John A. Ray*[1]*, Vicente Samano*[1]*, and Lloyd Frick*[1]*. (1) Medicinal Chemistry, GlaxoSmithKline, Inc, Five Moore Drive, Research Triangle Park, NC 27709, Fax: 919-315-0430, terry.l.smalley@gsk.com, (2) Medicinal Chemistry, GlaxoSmithKline*

Macrophage colony stimulating factor (M-CSF) is a potent pro-inflammatory mediator which drives the proliferation and differentiation of monocytes to macrophages. Stimulation of M-CSF, through its receptor *c-fms* (CSF-1R), a member of the receptor tyrosine kinase family of growth factor receptors, leads to accumulation of macrophages which may produce deleterious biological effects. Several disease states have been proposed to be effected by aberrant M-CSF signaling, including osteoarthritis, Alzheimer's disease, atherosclerosis and cancer. We identified 4-anilino-7-arylquinoline-3-carboxamides as *c-fms* inhibitors through high-throughput screening. Optimization at the C4 anilino position and the C7 aryl position yielded potent, metabolically stable inhibitors.

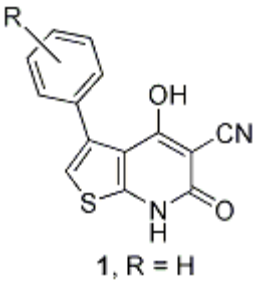


MEDI 377

Discovery and SAR studies of thienopyridones: A class of small molecule AMPK activators

Rajesh R. Iyengar[1]*, Gang Zhao*[1]*, Andrew S. Judd*[1]*, Lemma Kifle*[1]*, Ning Cao*[1]*, William J. Chiou*[1]*, Barbara L. Cool*[1]*, Heidi S. Camp*[1]*, Ernst U. Frevert*[1]*, Teresa M. Turner*[2]*, Jinrong Liu*[2]*, Ye Huang*[2]*, Kennan C. Marsh*[2]*, Amanda K. Mika*[1]*, Matthew A. Perham*[1]*, Bradley A. Zinker*[1]*, Hing L. Sham*[1]*, and Philip R. Kym*[1]*. (1) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division, 100 Abbott Park Road, Abbott Park, IL 60064-6101, Fax: 847-938-1674, rajesh.iyengar@abbott.com, (2) Preclinical Safety, Abbott Laboratories, Global Pharmaceutical Research Division*

Activation of AMP-activated protein kinase (AMPK) is implicated in a number of metabolic pathways such as stimulation of hepatic fatty acid oxidation, inhibition of lipogenesis, cholesterol, fatty acid and triglyceride synthesis, stimulation of skeletal muscle fatty acid oxidation, glucose uptake and control of insulin secretion by pancreatic cells. A small molecule activator of AMPK is proposed to significantly impact this energy homeostasis. We identified a densely functionalized thienopyridone 1 as an AMPK activator (Rat Liver AMPK EC50 = 38 mM) from high throughput screening of the Abbott library. We developed a robust, diversifiable three-step synthesis to access the thienopyridones that proved amenable to scale-up. A systematic evaluation of substitution around this ring system quickly identified key structural elements of the pharmacophore. Subsequent modifications were successful in improving the potency, ultimately resulting in sub-micromolar AMPK activators.



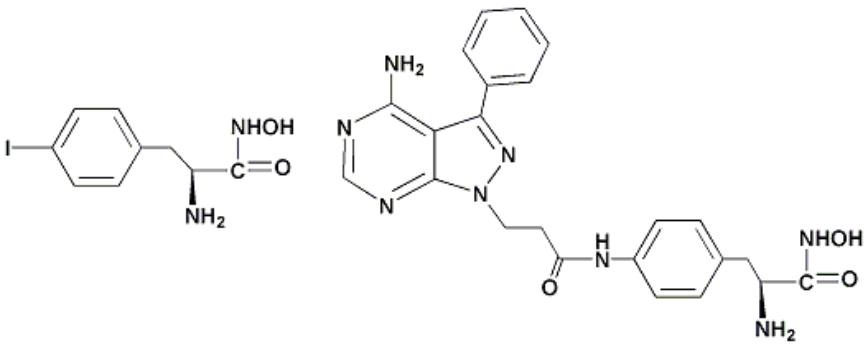
1, R = H

MEDI 378

Synthesis and evaluation of hydroxamate derivatives as metal-mediated inhibitors of Csk

Xianfeng Gu[1]*, Yuehao Wang*[2]*, Anil Kumar*[1]*, Gonquin Sun*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5048, xfgusky@yahoo.com, (2) Department of Cell and Molecular Biology, University of Rhode Island*

In order to explore the possibility of designing metal-mediated inhibitors against protein tyrosine kinases, a class of tyrosine and phenylalanine hydroxamate derivatives were synthesized (25 compounds) and evaluated for their ability to inhibit C-terminal Src kinase (Csk), a model tyrosine kinase, in the presence of cobalt. Tyrosine hydroxamate (IC_{50} = 9.5 μM) and phenylalanine hydroxamate (IC_{50} = 15.5 μM) inhibited Csk only in the presence of $CoCl_2$. The presence of bulky groups (e.g., Cl, Br, I) or pyrazolopyrimidine on the phenyl ring enhanced the inhibitory potency (IC_{50} = 2.0-6.3 μM), possibly due to the presence of interactions between these groups and a hydrophobic pocket in the enzyme. The substitution of amino group of hydroxamate with akyl or aryl groups or removal of α-amino group significantly reduced the inhibitory potency. These data suggest that specific functional groups are required for metal-binding affinity and inhibitors with better inhibitory profile can be designed.



MEDI 379

A novel dual inhibitor of HER1 and HER2 protein tyrosine kinases

Harold Mastalerz[1]*, Pierre Dextraze*[1]*, Ashvinikumar Gavai*[1]*, Walter Johnson*[1]*, Francis Lee*[2]*, Simone Oppenheimer*[2]*, Edward Ruediger*[1]*, James Tarrant*[1]*, Gregory Vite*[1]*, Dolatrai Vyas*[1]*, Tai W. Wong*[2]*, Guifen Zhang*[1]*, and Hongjian Zhang*[3]*. (1) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702, harold.mastalerz@bms.com, (2) Oncology Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, (3) PCO, Bristol-Myers Squibb Pharmaceutical Research Institute*

HER1 and HER2 are receptor tyrosine kinases of the EGF receptor family that have been clinically validated as rational targets for cancer therapy. Their frequent co-expression in a variety of tumor types and their capacity to form heterodimers with other members of the EGFR family provides a strong rationale for simultaneous targeting both receptors. This poster describes the structure-activity relationships of a new series of 5-subsitituted pyrrolo[2,1-f] [1,2,4]triazine dual HER1/HER2 inhibitors that lead to compounds with excellent potency and selectivity in in vitro biochemical and cell-based assays. These results are presented together with in vivo data for selected lead compounds.

MEDI 380

4-Arylpyridines as selective c-jun-N-terminal kinase-3 (JNK-3) inhibitors

Niklas Plobeck[1]*, B-M. Swahn*[1]*, J. Viklund*[1]*, and Y. Xue*[2]*. (1) Department of Medicinal Chemistry, AstraZeneca R&D Södertälje, SE-15185 Södertälje, Sweden, (2) Structural Chemistry Laboratory, AstraZeneca R&D Mölndal*

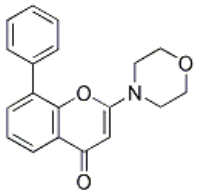
The c-jun N-terminal kinases (JNKs), also called stress activated protein kinases, belong to the mitogen-activated protein kinase (MAPK) family, which regulate signal transduction in response to environmental stress. For treating neurodegenerative diseases such as stroke, Alzheimer's and Parkinson's disease it could be beneficial to find JNK-3 isoform selective compounds. The three JNK isoforms share more than 90% amino acid sequence identity and the ATP pocket >98%. It has therefore been a challenge to find JNK-3 over JNK-1 isoform selective ATP competitive inhibitors. Here we will report structure modifications of an initial screening lead compound from a new structure class which led to a new series of 4-arylpyridines with improved binding potency and selectivity. The modification strategy was based on information from X-ray structures of inhibitors bound to the enzyme. Synthesis, binding data and structure activity relationships (SAR) will be presented.

MEDI 381

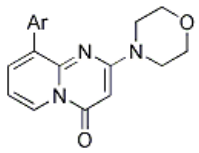
Design and synthesis of novel DNA-dependent protein kinase (DNA-PK) inhibitors

Olivier R. Barbeau[1]*, Bernard T. Golding*[2]*, Roger J. Griffin*[2]*, Ian R. Hardcastle*[2]*, Graeme C. M. Smith*[3]*, and Caroline Richardson*[3]*. (1) School of Natural Sciences - Chemistry, Northern Institute for Cancer Research, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, United Kingdom, Fax: 01912228591, olivier.barbeau@ncl.ac.uk, (2) Northern Institute for Cancer Research, School of Natural Sciences - Chemistry, (3) KuDOS Pharmaceuticals Limited*

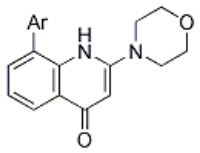
DNA-dependent protein kinase (DNA-PK), a member of the PI3-kinase related kinase (PIKK) family, is a multi-component serine/threonine protein kinase that plays a key role in the repair of mammalian DNA double-strand breaks (DSBs). Kinase-selective DNA-PK inhibitors could be used to gain an understanding of the role of DNA-PK. In addition, by impeding DNA DSB repair, selective DNA-PK inhibitors have potential application as radio- and chemo-potentiators in the treatment of cancer. Using LY294002 as a template for inhibitor design, a number of potent DNA-PK inhibitors have been developed. Structure-activity relationships have been determined for these structural classes and potent and selective inhibitors have been identified. Subsequent structure-activity studies conducted suggested that modifications to the core heterocycle would be tolerated. This discovery leaded to the synthesis of a range of analogues based on two new scaffolds, namely pyridopyrimidin-4-one (**1**) and quinolin-4-one (**2**). Within these series, compounds bearing a dibenzothiophene (**1a** and **1b**) or dibenzofuran (**2a** and **2b**) group exhibit potent DNA-PK activity (IC_{50} values in the range 10-50 nM). The chemistry, optimisation and biological evaluation will be reported in detail.



LY294002



1
1a ; Ar = dibenzofuran-4-yl
1b ; Ar = dibenzothiophen-4-yl



2
2a ; Ar = dibenzofuran-4-yl
2b ; Ar = dibenzothiophen-4-yl

MEDI 381

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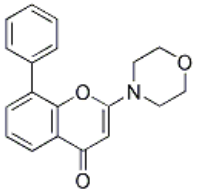
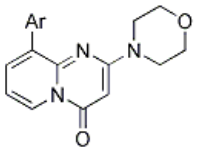
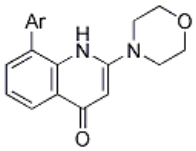
chemistry, optimisation and biological evaluation will be reported in detail.



LY294002



1
1a ; Ar = dibenzofuran-4-yl
1b ; Ar = dibenzothiophen-4-yl



2
2a ; Ar = dibenzofuran-4-yl
2b ; Ar = dibenzothiophen-4-yl

MEDI 382

Discovery of the VEGFR-2 inhibitor BAY 57-9352: The synthesis and SAR of thieno- and furopyridazine analogs

Julie A. Dixon[1]*, Warren Brini*[1]*, Stephen J. Boyer*[1]*, Frederick Ehrgott*[1]*, Zhenqui Hong*[1]*, Harold C. Kluender*[1]*, Rico C. Lavoie*[1]*, Xin Ma*[1]*, Raymond Reeves*[1]*, Tiffany Turner*[1]*, Wai Wong*[1]*, Yanlin Zhang*[1]*, James Elting*[2]*, Randall M. Jones*[2]*, Mark McHugh*[2]*, and Guochang Zhu*[2]*. (1) Department of Chemistry Research, Bayer HealthCare Pharmaceuticals Corporation, 400 Mogan Lane, West Haven, CT 06516, Fax: 203-812-6182, (2) Department of Cancer Research, Bayer HealthCare Pharmaceuticals Corporation*

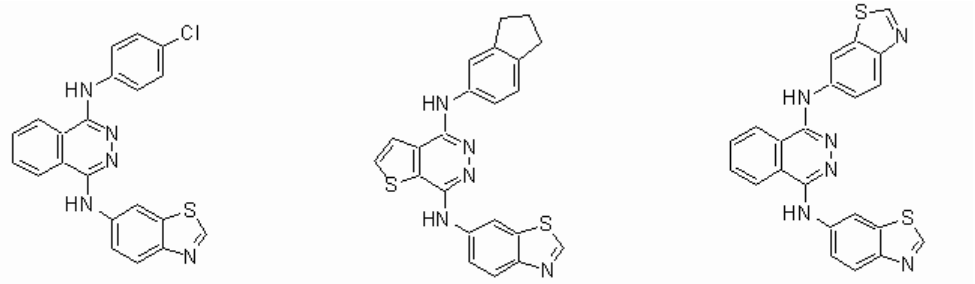
Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase VEGFR-2 are key mediators of angiogenesis. Since the growth of new blood vessels is an important step in tumor progression, inhibition of VEGFR-2 has become a major area of research for the treatment of solid tumors. We recently disclosed the furopyridazine BAY 57-9352, a potent, orally active VEGFR-2, PDGFR, and c-kit inhibitor currently in Phase I clinical trials. In this poster, we wish to report the later stage optimization leading to BAY 57-9352. The synthesis and evaluation of alternative cores (thieno- and furo-pyridazines) will be described. Analogs defining the scope of the upper aniline fragment and lower pyridyl fragment SAR, particularly compounds incorporating polar moieties directed at increasing solubility, will be presented.

MEDI 383

Discovery of the VEGFR-2 inhibitor BAY 57-9352: Combinatorial synthesis of dianilino phthalazine, thienopyridazine, and furopyridazine analogs

Dhanapalan Nagarathnam[1]*, Ning Su*[1]*, T. Joe*[2]*, H. N. Hatoum-Mokdad*[2]*, Jacques Dumas*[1]*, W. C. Wong*[2]*, C. Brennan*[2]*, Danielle Holmes*[1]*, Stephen J. Boyer*[1]*, Jennifer M. Burke*[1]*, Julie A. Dixon*[1]*, X. Ma*[2]*, Frederick Ehrgott*[1]*, Y. Zhang*[2]*, Harold C. Kluender*[1]*, I. Enyedy*[2]*, James Elting*[3]*, Randall M. Jones*[3]*, and Guochang Zhu*[3]*. (1) Department of Chemistry Research, Bayer HealthCare Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516, Fax: 203-812-6182, dhanapalan.nagarathnam.b@bayer.com, (2) Bayer HealthCare, Pharmaceutical Division, (3) Department of Cancer Research, Bayer HealthCare Pharmaceuticals Corporation*

Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase VEGFR-2 are key mediators of angiogenesis. Since the growth of new blood vessels is an important step in tumor progression, inhibition of VEGFR-2 has become a major area of research for the treatment of solid tumors. We recently disclosed the furopyridazine BAY 57-9352, a potent, orally active VEGFR-2, PDGFR, and c-kit inhibitor currently in Phase I clinical trials. In this poster, we wish to report a combinatorial chemistry program on the synthesis and evaluation of dianilino- phthalazine, thienopyridazine, and furopyridazine libraries. These efforts led to the identification of highly potent replacements for the lower pyridyl fragment. Compounds 1-3 are representative examples from this series, demonstrating potent VEGFR-2 inhibitory activity in vitro.



1
VEGFR-2 IC_{50} = 22 nM

2
VEGFR-2 IC_{50} = 7 nM

3
VEGFR-2 IC_{50} = 21 nM

MEDI 384

Discovery of the VEGFR-2 inhibitor BAY 57-9352: The synthesis and SAR of phthalazine and isoquinoline analogs

Wendy Lee[1]*, Stephen J. Boyer*[1]*, Catherine R. Brennan*[1]*, Jennifer M. Burke*[1]*, William Collibee*[1]*, Jacques Dumas*[1]*, Holia Hatoum-Mokdad*[1]*, Danielle Holmes*[1]*, Zhenqui Hong*[1]*, Harold C. Kluender*[1]*, Dhanapalan Nagarathnam*[1]*, Robert N. Sibley*[1]*, Ning Su*[1]*, Wai Wong*[1]*, James Elting*[2]*, Randall M. Jones*[2]*, Mark McHugh*[2]*, and Guochang Zhu*[2]*. (1) Department of Chemistry Research, Bayer HealthCare Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516, wendy.lee.b@bayer.com, (2) Department of Cancer Research, Bayer HealthCare Pharmaceuticals Corporation*

Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase VEGFR-2 are key mediators of angiogenesis. Since the growth of new blood vessels is an important step in tumor progression, inhibition of VEGFR-2 has become a major area of research for the treatment of solid tumors. We recently disclosed the furopyridazine BAY 57-9352, a potent, orally active VEGFR-2, PDGFR, and c-kit inhibitor currently in Phase I clinical trials. In this poster, we wish to report early lead generation efforts leading to the discovery of BAY 57-9352. The synthesis and evaluation of phthalazine and isoquinoline analogs will be described. Exploration of the lower pyridyl fragment in both series led to the identification of the 2-carboxamidopyridyl moiety as a preferred hinge-binding element.

MEDI 385

Identification and development of azolidinone vinyl-fused benzene derivatives, as potent and selective PI3Kg inhibitors, orally active in models of rheumatoid arthritis

Thomas Rueckle[1], *Tania Grippi-Vallotton*[1], *Maurizio Maio*[1], *David Covini*[1], *Vincent Pomel*[1], *Fabienne Burgat-Charvillon*[1], *Dennis Church*[1], *Jeffrey Shaw*[1], *Wolfgang Sauer*[1], *Jasna Klicic*[1], *Vladimir Sherbukhin*[1], *Anna Quattropani*[1], *Jerome Dorbais*[1], *Gwenaelle Desforges*[1], *Delphine Valognes*[1], *Montserrat Camps*[2], *Christian Chabert*[2], *Corine Gillieron*[2], *Bernard Francon*[3], *Dominique Perrin*[3], *Didier Leroy*[3], *Denise Gretener*[3], *Anthony Nichols*[3], *Hong Ji*[2], *Felix Rintelen*[2], *Vittoria Ardissone*[4], *Chiara Ferrandi*[4], *Pierre-Alain Vitte*[5], *Susanna Carboni*[5], *Rocco Cirillo*[4], *Matthias K. Schwarz*[1], *and Christian Rommel*[2]. *(1) Department of Chemistry, Serono Pharmaceutical Research Institute, 14, Chemin des Aulx, 1228 Plan-les-Ouates, Geneva, Switzerland, thomas.ruckle@serono.com, (2) Department of Signal Transduction, Serono Pharmaceutical Research Institute, (3) Department of Bioscreening, Serono Pharmaceutical Research Institute, (4) Department of Pharmacology, LCG-RBM Serono International S.A, (5) Department of Pharmacology, Serono Pharmaceutical Research Institute*

PI3Kgamma plays a crucial role in mediating leukocyte chemotaxis as well as mast cell degranulation, mainly in response to G-protein coupled receptor activation and hence represents a high value target for autoimmunity and inflammation. Exploiting the interface of Molecular Medicine, Medicinal Chemistry and Experimental Pharmacology, we have developed potent and selective small molecule PI3Kg inhibitors, that upon oral treatment suppress the progression of joint inflammation and cartilage damage in murine models of RA, reproducing the protective effects exhibited by PI3Kg deficient mice. SAR of two generations of inhibitors, supported by X-ray crystallography and structure based design, has led to the identification of the lead compound AS-605240 (Ki = 7.8 nM), active in animal models of cell recruitment, mast cell activation and inflammation.

MEDI 386

Design and synthesis of a novel class of potent and highly isoform selective PI3Kg inhibitors

Vincent Pomel[1], *David Covini*[1], *Dennis Church*[1], *Jeffrey Shaw*[1], *Jasna Klicic*[1], *Delphine Valognes*[1], *Montserrat Camps*[2], *Christian Chabert*[2], *Corine Gillieron*[2], *Bernard Francon*[3], *Dominique Perrin*[3], *Didier Leroy*[3], *Denise Gretener*[3], *Anthony Nichols*[3], *Pierre-Alain Vitte*[4], *Susanna Carboni*[4], *Christian Rommel*[2], *Matthias K. Schwarz*[1], *and Thomas Rueckle*[1]. *(1) Department of Chemistry, Serono Pharmaceutical Research Institute, chemin des Aulx 14, 1228 Geneva, Switzerland, Fax: ++41-22-706-9565, vincent.pomel@serono.com, (2) Department of Signal Transduction, Serono Pharmaceutical Research Institute, (3) Department of Bioscreening, Serono Pharmaceutical Research Institute, (4) Department of Pharmacology, Serono Pharmaceutical Research Institute*

Small molecule inhibitors targeting class Ib PI3K isoforms have vast potential use for the treatment of inflammatory, autoimmune disorders and cardiovascular diseases. However, the lack of specificity, isoform selectivity and poor biopharmaceutical profile of PI3K inhibitors has so far hampered rigorous disease-oriented and pharmacologically relevant target validation. PI3Kgamma plays a crucial role in mediating leukocyte chemotaxis as well as mast cell

degranulation, mainly in response to G-protein coupled receptor activation and hence represents a high value target for autoimmunity and inflammation. In the course of our efforts to develop PI3Kgamma inhibitors we have identified thiazolidine-diones containing furanyl-phenol moieties as highly potent and selective PI3Kgamma inhibitors. Focussed SAR studies supported by X-ray crystallography and structure based design have led to the identification of the lead compound (6), an orally available small molecule that selectively inhibits the PI3Kgamma isoform as well as its biochemical pathway in cells. In-vivo evaluation of (6) in models of peritonitis shows its anti-inflammatory potential.

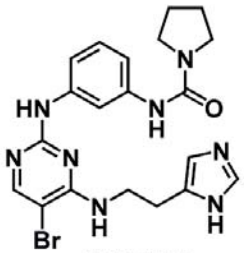
MEDI 387

Identification of potent and selective inhibitors of rhosphoinositide-dependent kinase-1 (PDK1)

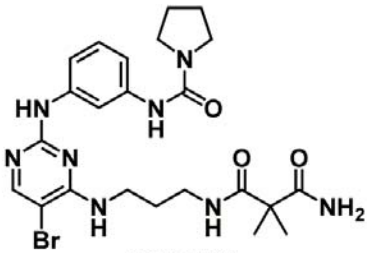
Damian O. Arnaiz[1]*, Richard I. Feldman*[2]*, Judi Bryant*[1]*, Brad O. Buckman*[1]*, Zheng Chang*[1]*, Seock-Kyu Khim*[1]*, Dirk Kosemund*[1]*, Shendong Yuan*[1]*, Marc Adler*[1]*, Bruno Alicke*[3]*, Sandra L. Biroc*[3]*, Elena Ho*[3]*, Dao Lentz*[3]*, Mark A. Polokoff*[3]*, Jun Shen*[3]*, Babu Subramanyam*[3]*, Janette Walters*[3]*, Marc Whitlow*[1]*, James M. Wu*[2]*, Daguang Zhu*[2]*, Monica J. Kochanny*[1]*, and Gary B. Phillips*[1]*. (1) Department of Chemistry, Berlex Biosciences, 2600 Hilltop Dr, Richmond, CA 94804, Fax: 510-669-4310, Damian_Arnaiz@Berlex.com, (2) Department of Cancer Research, Berlex Biosciences, (3) Department of Pharmacology, Berlex Biosciences*

The PI 3-Kinase/ PDK1/Akt signaling pathway plays a key role in cancer cell growth, survival, and tumor angiogenesis and represents a promising target for anti-cancer drugs. High-throughput screening using a PDK1 mediated AKT2 activation assay identified several compounds with activity less than 500 nM. The most potent was compound **1** (IC_{50} = 27 nM). Further testing determined that this compound was an inhibitor of PDK1. Although **1** was a potent inhibitor, it had poor selectivity against other kinases, and non-optimal ADME properties. Optimization of the aniline at C-2 afforded **BX-912** which had improved potency (IC_{50} = 6 nM) and selectivity against other kinases. **BX-912** also had good pharmacokinetic properties after iv dosing, but was not orally bioavailable. Optimization of the histamine sidechain at C-4 afforded **BX-320**. **BX-320** was less potent (IC_{50} = 25 nM) than **BX-912**, but had superior selectivity and pharmacokinetic properties. **BX-320** inhibited the growth of LOX melanoma tumors in the lungs of nude mice.

1



BX-912



BX-320

MEDI 388

Discovery and development of p38 MAP kinase inhibitors derived from pyrrolo[2,1-*f*][1,2,4]triazines

John Hynes Jr.[1], *Alaric Dyckman*[1], *Tianle Li*[1], *Shuqun Lin*[1], *Stephen T Wrobleski*[1], *Hong Wu*[1], *Derek Loo*[2], *Kim W McIntyre*[2], *Gary L Schieven*[2], *Rosemary Zhang*[2], *Kathleen M Gillooly*[2], *Sidney Pitt*[2], *Ding Ren Shen*[2], *David J Shuster*[2], *Arthur Doweyko*[3], *John Sack*[3], *Joel C. Barrish*[1], *John H. Dodd*[1], *and Katerina Leftheris*[1]*. (1) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6601, john.hynes@bms.com, (2) Department of Immunology, Pharmaceutical Research Institute, Bristol-Myers Squibb, (3) Department of Macromolecular Structure, Pharmaceutical Research Institute, Bristol-Myers Squibb*

Overproduction of cytokines such as TNF-α and IL-1β regulated by the p38 pathway are implicated in a wide variety of inflammatory diseases, including rheumatoid arthritis (RA). A focused screening of the BMS compound collection revealed a new class of p38 MAP kinase inhibitors with sub-micromolar inhibition of p38-α. Further SAR studies to improve in vitro activity will be presented along with results from in vivo studies in rodent models of inflammation (acute and chronic). Chemical synthesis, profiling, and X-ray co-crystallization data will also be presented.

MEDI 389

Design, synthesis, and SAR of new pyrrolo[2,1-f][1,2,4]triazines as potent p38 MAP kinase inhibitors

Stephen T Wrobleski[1], *Shuqun Lin*[1], *Alaric Dyckman*[1], *John Hynes Jr.*[1], *Tianle Li*[1], *Hong Wu*[1], *Kim W McIntyre*[2], *Gary L Schieven*[2], *Rosemary Zhang*[2], *Kathleen M Gillooly*[2], *Sidney Pitt*[2], *Ding Ren Shen*[2], *David J Shuster*[2], *Arthur Doweyko*[3], *John Sack*[3], *Joel Barrish*[1], *John Dodd*[1], *and Katerina Leftheris*[1]*. (1) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, P.O. Box 4000, Princeton, NJ 08543-4000, stephen.wrobleski@bms.com, (2) Department of Immunology, Pharmaceutical Research Institute, Bristol-Myers Squibb, (3) Department of Macromolecular Structure, Pharmaceutical Research Institute, Bristol-Myers Squibb*

Targeted inhibition of the MAP kinase p38α has emerged as a promising strategy for the treatment of rheumatoid arthritis, as well as other inflammatory diseases, primarily due to the role of p38α in the release of the proinflammatory cytokines TNFα and IL-1β. We wish to report additional results toward the design and development of a new class of potent, small molecule inhibitors of p38α based on the pyrrolo[2,1-f][1,2,4]triazine nucleus. These efforts have led to the discovery of new inhibitors that upon binding to p38α, have been demonstrated to cause reorganization of the activation loop to a DFG-out conformation. X-ray co-crystallography results as well as synthesis, SAR, and relevant in vivo data for these compounds will be presented.

MEDI 390

Structure active relationship of substituted imidazo(2,1-b)thiazoles: Novel, selective p38 MAP kinase inhibitors

D. Vensel[1], *Mark A. Ashwell*[1], *Syed M. Ali*[1], *V. Antonenko*[1], *R. Graceffa*[1], *M. Harris*[1], *M. Kaselj*[1], *E. Kelleher*[1], *J. Liu*[1], *J-M. Lapierre*[1], *Y. Liu*[1], *M. O'Donnell*[1], *R. Selliah*[1], *Manish Tandon*[1], *W. Wrona*[1], *K. Bresciano*[2], *K. Caserta*[2], *H. Chan*[2], *T. Gannett*[2], *S. Jones*[2], *P. Leydon*[2], *S. Mcdonald*[2], *A. Naper*[2], *L. Saraswat*[2], *A. Tyler*[3], *M. Warren*[2], *and S. Zhu*[2]. *(1) Medicinal Chemistry, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, (2) Biology, ArQule Inc, (3) Bioanalytical, ArQule Inc*

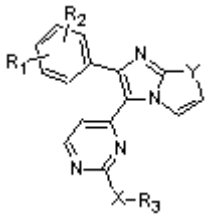
Novel imidazo(2,1-b) thiazoles have been identified as potent inhibitors of p38 MAP kinase. Structure activity relationships employed in the optimization of the series will be described. This work led to the discovery of potent, selective, in vivo active inhibitors of TNFa production, a cytokine that has been implicated in pathogenesis of rheumatoid arthritis.

MEDI 391

Design, synthesis and biological evaluations of novel substituted imidazooxazoles as potent p38 MAP kinase inhibitors

Yanbin Liu[1], *Mark A. Ashwell*[1], *Syed M. Ali*[1], *V. Antonenko*[1], *R. Graceffa*[1], *M. Harris*[1], *M. Kaselj*[1], *E. Kelleher*[1], *J. Liu*[1], *M. O'Donnell*[1], *R. Selliah*[1], *Manish Tandon*[1], *D. Vensel*[1], *W. Wrona*[1], *J-M. Lapierre*[1], *K. Bresciano*[2], *K. Caserta*[2], *H. Chan*[2], *T. Gannett*[2], *S. Jones*[2], *P. Leydon*[2], *S. Mcdonald*[2], *A. Naper*[2], *L. Saraswat*[2], *A. Tyler*[3], *M. Warren*[2], *and S. Zhu*[2]. *(1) Medicinal Chemistry, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, yliu@arqule.com, (2) Biology, ArQule Inc, (3) Bioanalytical, ArQule Inc*

A series of novel, selective, orally active imidazo(2,1-b)oxazoles have been developed as potent inhibitors of p38 MAP kinase with demonstrated in vivo suppression of the production of TNFa. p38 MAP kinase signaling pathways mediate the over expression of pro-inflammatory cytokines in many inflammatory diseases such as Rhematoid Arthritis (RA). Compounds that inhibit p38 MAP kinase and the production of the cytokine-TNFa have potential for the treatment of RA and other inflammatory diseases. The synthesis and structure-activity relationships (SAR) are described

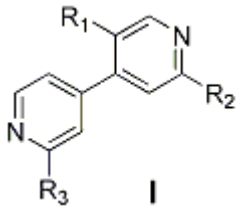


MEDI 392

Design, synthesis and SAR of bipyridine derivatives as potent and selective p38 kinase inhibitors

Seifu Tadesse[1], *Fang-Tsao Hong*[1], *Nuria Tamayo*[1], *Lillian Liao*[1], *David Powers*[2], *Yan-Yan Yudor*[2], *Violeta Yu*[2], *Ming Wong*[3], *Brad Henkle*[3], *Scot Middleton*[3], *Rashid Syed*[2], *Tim Harvey*[2], *Randall Hungate*[1], *and Celia Dominguez*[1]. *(1) Department of Chemistry Research & Discovery, Amgen Inc, One Amgen Center Drive, Thousand oaks, CA 91320, Fax: 805 480 1346, stadesse@amgen.com, (2) Department of HTS and Molecular Pharmacology, Amgen Inc, (3) Inflammation, Amgen Inc*

The p38 MAP kinase plays a crucial role in regulating the production of several important pro-inflammatory cytokines, for example TNF-a and IL-1b. Blocking this enzyme may offer an attractive therapy for treating arthritis and other inflammatory diseases. Here we report the identification of a novel class of potent inhibitors of p38 MAP kinase. In this poster we present our synthetic studies toward a series of bipyridine derivatives I, and discuss their biological activity.



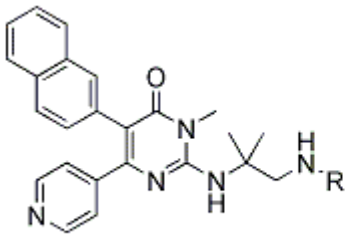
I

MEDI 393

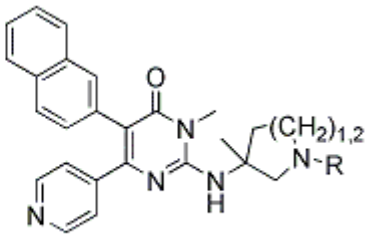
Evaluation of p38a inhibitors with improved metabolic stability

Daniel M Retz[1], *Gilbert M Rishton*[1], *Celia Dominguez*[1], *Graham Yang*[2], *Scott Middleton*[3], *Min Wong*[3], *and David Powers*[4]. *(1) Chemistry Research and Development, Amgen, 1 Amgen Center Dr, Thousand Oaks, CA 91320, dretz@amgen.com, (2) Pharmacokinetics and Drug Metabolism, Amgen, (3) Inflammation Pharmacology, Amgen, (4) HTS Molecular Pharmacology, Amgen*

P38α is a member of mitogen-activated protein kinase (MAPK) family of kinases responsible for the biosynthesis of the proinflammatory cytokines TNFα and IL-1B. These cytokines play a role in the initiation and progression of autoimmune inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. To expand the SAR of pyrimidone based p38α inhibitors developed in our group, a series of dimethylethylenediamines (1), 3-aminopyrrolidines and 3-aminopiperidines (2) were synthesized. The preparation, biological evaluation and pharmacokinetic properties of these series will be presented.



(1)



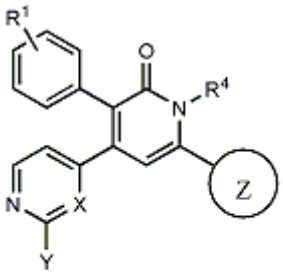
(2)

MEDI 394

Synthesis and SAR of 6-(carbocycle)-substituted 2-pyridones as potent and selective p38 kinase inhibitors

Fang-Tsao Hong[1], *Seifu Tadesse*[1], *Nuria Tamayo*[1], *Lillian Liao*[1], *Martin Goldberg*[1], *Cuo-Qiang Cao*[1], *David Powers*[2], *Yan-Yan Yudor*[2], *Violeta Yu*[2], *Ming Wong*[3], *Brad Henkle*[3], *Scot Middleton*[3], *Rashid Syed*[2], *Tim Harvey*[2], *Randall Hungate*[1], *and Celia Dominguez*[1]. *(1) Department of Chemistry Research & Discovery, Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, Fax: 805-480-1337, fhong@amgen.com, (2) Department of HTS and Molecular Pharmacology, Amgen Inc, (3) Inflammation, Amgen Inc*

Activation of the p38 MAP kinase cascade has been demonstrated to play important roles in inflammatory cellular responses to external stress. Several small molecule p38 inhibitors have been shown to suppress the production of the proinflammatory cytokines such as interleukin 1b (IL-1b) and tumor necrosis factor (TNF-a) in animal models, and therefore provide an attractive way for treatment of various autoimmune disorders. Our program goal is to identify small molecule p38 inhibitors as therapeutic agents for rheumatoid arthritis (RA). In this poster we report our synthetic efforts toward a novel series of 2-pyridone derivatives I, and highlight their biological activities as p38 inhibitors.



I

X = CH, N; Y = NHR;
Z = N-carbocycles

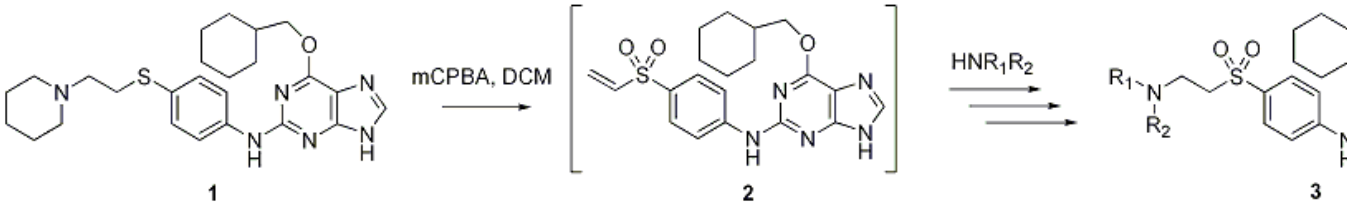
MEDI 395

Searching for potent CDK2 inhibitors using a variant of the Cope elimination

Andrew Henderson[1], *Yuzhu Cheng*[2], *Nicola J. Curtin*[2], *Jane A. Endicott*[3], *Bernard T. Golding*[1], *Roger J. Griffin*[1], *Ian R. Hardcastle*[1], *David R. Newell*[2], *Martin E. M. Noble*[3], *and Lan-Zhen Wang*[2]. *(1) Northern Institute for Cancer Research, School of Natural Sciences - Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, United Kingdom, Fax: 0191 222 8591, andrew.henderson@ncl.ac.uk, (2) Northern Institute for Cancer Research, Paul O'Gorman Building, (3) Department of Biochemistry, Laboratory of Molecular Biophysics*

Cyclin-dependent kinases (CDKs) are members of the protein kinase family of enzymes that aid in the regulation of the cell cycle. Aberrant control of CDKs, resulting in the loss of orderly

cell cycle progression, has therefore been directly associated with the molecular pathology of cancer. As a result, inhibitors of CDKs possess therapeutic potential in the treatment of proliferative disorders, including cancer. Guided by X-ray crystallographic studies, the discovery of potent *N* ^{2}-aryl substituted *O* ^{6}-cyclohexylmethylguanine based inhibitors of CDK2 has been achieved. A novel synthetic approach, whereby a vinyl sulfone species (**2**) generated *in situ* through a variant of the Cope elimination, was reacted with various amines, enabled the preparation of a series of sulfone-based inhibitors with the generic structure **3** using a multiple-parallel synthesis approach. The chemistry, optimisation and biological evaluation of this series of inhibitor will be reported in detail.



MEDI 395

Searching for potent CDK2 inhibitors using a variant of the Cope elimination

Andrew Henderson[1]*, Yuzhu Cheng*[2]*, Nicola J. Curtin*[2]*, Jane A. Endicott*[3]*, Bernard T. Golding*[1]*, Roger J. Griffin*[1]*, Ian R. Hardcastle*[1]*, David R. Newell*[2]*, Martin E. M. Noble*[3]*, and Lan-Zhen Wang*[2]*. (1) Northern Institute for Cancer Research, School of Natural Sciences - Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, United Kingdom, Fax: 0191 222 8591, andrew.henderson@ncl.ac.uk, (2) Northern Institute for Cancer Research, Paul O'Gorman Building, (3) Department of Biochemistry, Laboratory of Molecular Biophysics*

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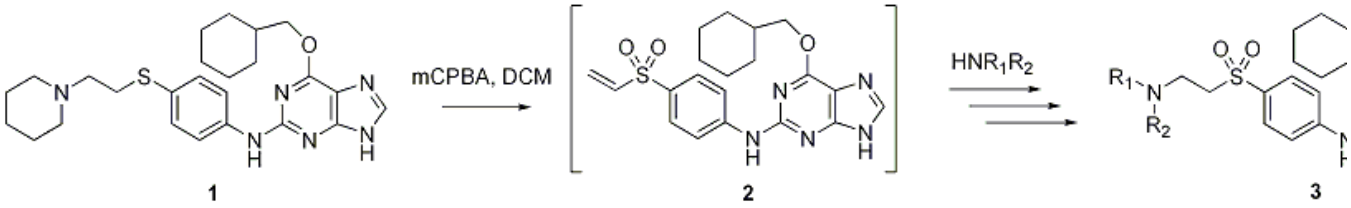


MEDI 396

Evolution of CDK2/CyclinA recruitment site small molecule inhibitors from a potent peptide lead

Georgette M. Castanedo[1], *Kevin Clark*[1], *Shumei Wang*[1], *Mengling Wong*[1], *Dineli Wickramasinghe*[2], *Nerissa Mendoza*[2], *James Marsters*[1], *and Daniel P. Sutherlin*[1]. *(1) Department of Medicinal Chemistry, Genentech, Inc, 1 DNA way, South San Francisco, CA 94080, (2) Department of Biooncology, Genentech, Inc*

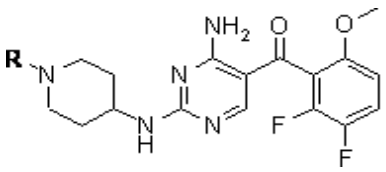
The CDK2/CyclinA complex plays an important role in the cell cycle and is a viable cancer target. We pursued CDK2/CyclinA recruitment site inhibitors as opposed to those at the CDK2 active site. Peptides that mimic endogenous substrates and inhibitors of the complex have been reported to bind to the recruitment site in the nanomolar range and produce selective killing of cancer cells in vitro/vivo. The chemistry program began with an octa-peptide lead (IC50=12nM), which was investigated through alanine scanning. A meta-chlorophenylalanine substitution discovered through unnatural amino acid replacement improved potency approximately ten fold. C and N-terminal truncations yielded a tetra-peptide (IC50=4mM), a significant loss in activity when compared to the lead. Combining optimized residues from a tetra-peptide SAR search with rigidification of the peptide backbone, the original activity was recovered (IC50=47nM). Potency was maintained while replacing two positively charged groups with neutral moieties resulting in a small molecule inhibitor (IC50=22nM).

MEDI 397

2,4-Diamino-5-ketopyrimidines as potent and selective CDK inhibitors: Further exploration of the 2-amino substituents

Binh T. Vu[1], *Xin-jie Chu*[1], *Qingjie Ding*[1], *Gerald Kaplan*[1], *Dave Barkovitz*[1], *John Mullin*[1], *John Moliterni*[1], *Nan Jiang*[1], *Sung-sau So*[1], *Christine Lukacs*[1], *Bradford Graves*[1], *Xuefeng Yin*[2], *Jianping Chen*[2], *Wanda DePinto*[2], *and Allen Lovey*[1]. *(1) Discovery Chemistry, Hoffmann-La Roche, Inc, 340 Kingsland Street, Nutley, NJ 07110, binh_t.vu@roche.com, (2) Discovery Oncology, Hoffmann-La Roche, Inc*

The cyclin-dependent kinases (CDKs) play an important role in cell cycle regulatory pathways. CDK inhibitors have been developed as therapeutic agents in treatment of cancer. We recently disclosed a new class of potent and selective CDK inhibitors based on the 2,4-diamino-5-ketopyrimidine core. A member of this class of compounds has been selected for clinical development (1). It is highly selective against CDK1, CDK2 and CDK4 (Ki <10 nM), potent in cellular assays (IC50 0.05-0.60 ƒÝM) and efficacious in a variety of xenograft tumor models. In this presentation, the chemistry and SAR of 2-(piperidin-4-ylamino)-substitution (R) will be reported and discussed.



1

MEDI 398

Synthesis of 2,4-diamino-5-ketopyrimidines as novel and potent CDK inhibitors: Utilization of a facile metal/halogen exchange initiated by isopropyl magnesium chloride

John Moliterni[1], *Xin-Jie Chu*[1], *David Bartkovitz*[1], *John Mullin*[1], *Qingjie Ding*[1], *Binh Vu*[1], *Nan Jiang*[1], *Gerald Kaplan*[1], *Sung-Sau So*[1], *Christine Lukacs*[1], *Brad Graves*[1], *Wanda DePinto*[2], *Xuefeng Yin*[2], *Yingsi Chen*[3], *Allen Lovey*[1], *Yi Ren*[4], *Ping Wang*[4], *and Corey Brumsted*[4]. *(1) Department of Discovery Chemistry, Hoffmann-La Roche Inc, 340 Kingsland Street, Nutley, NJ 07110, Fax: 973-235-2448, (2) Department of Discovery Oncology, Hoffmann-La Roche Inc, (3) Department of Discovery Technologies, Hoffmann-La Roche Inc, (4) Department of Chemical Synthesis, Hoffmann-La Roche Inc*

The cyclin-dependent kinases (CDKs) play a key role in regulating the cell cycle process. Deregulation of CDK function occurs with high frequency in many human tumors. A small molecule inhibitor of the CDK family would serve to return cells to their normal functions and could represent a therapy for cancer. We have recently reported a new class of potent CDK inhibitors based on the 2,4-diamino-5-ketopyrimidine template. Herein, we report a novel synthesis of key intermediates leading to active and potent analogs. Alternate synthetic approaches will be presented and the process chemistry for preparing a clinical candidate will be discussed.

MEDI 399

Design and synthesis of 4-alkylamino-2-anilinoquinazoline as potential antitumor agents

Grace Shiahuy Chen[1], *Ming-Hsieh Chuang*[1], *Meng-Ling Chen*[2], *Tsai-Ni Hsieh*[2], *and Ji-Wang Chern*[2]. *(1) Department of Applied Chemistry, Providence University, 200 Chung-Chi Road, Shalu 43301, Taiwan, Fax: 886-4-26327554, grace@pu.edu.tw, (2) School of Pharmacy, National Taiwan University*

Abnormal CDK control and consequent loss of cell cycle checkpoint function have been directly linked to the molecular pathology of cancer. Till now, most of CDK2 inhibitors came from microbial and natural products, high throughput screening, and combinational libraries. A potent CDK2 inhibitor should contain both hydrogen bonding with Asp86 and hydrophobic interaction with Val18 and Gly11 exist. Quinazoline derivatives have been reported to possess various biological activities, and several quinazoline compounds have been advanced to market. Based on the shape-similarity to known CDK2 inhibitors, we designed quinazolines containing anlino and cycohexylamino groups for potential CDK2 inhibitors. The in vitro cytotoxicitic data showed that the designed compounds were potent antiproliferative agents.

Most of the prepared compounds have GI50 value around 1 μM against A549, HT-29, and HepG2 cancer cell lines. Among them, two compounds possess GI50 values of about 30 nM against HepG2 cancer cell line.

MEDI 400

2,4-Diamino-5-ketopyrimidines: Synthesis and structure-activity relationships of a series of novel and potent CDK inhibitors

*Xin-Jie Chu[1], **David Bartkovitz**[1], John Mullin[1], John Moliterni[1], Binh T. Vu[1], Qingjie Ding[1], Nan Jiang[1], Gerald Kaplan[1], Gino Sasso[1], Sung-Sau So[1], Christine Lukacs[1], Bradford Graves[1], Wanda DePinto[2], Xuefeng Yin[2], Yingsi Chen[3], and Allen Lovey[1]. (1) Department of Discovery Chemistry, Hoffmann-La Roche Inc, 340 Kingsland Street, Nutley, NJ 07110, xin-jie.chu@roche.com, david.bartkovitz@roche.com, (2) Department of Discovery Oncology, Hoffmann-La Roche Inc, (3) Department of Discovery Technologies, Hoffmann-La Roche Inc*

The cyclin-dependent kinases (CDKs) are essential for regulation of the cell cycle in proliferating cells. The inhibition of CDKs has emerged as an important theme in anticancer research. We have recently reported a new class of potent CDK inhibitors based on a novel 2,4-diamino-5-ketopyrimidine core. This series was derived through a rational template design and our optimization resulted in analogs that are highly potent against CDK1, CDK2 and CDK4 (Ki <10 nM) but essentially inactive against a panel of other major protein kinases (Ki >5,000 nM). The compounds exhibited potent *in vitro* cellular activity against a variety of tumor cell lines, including HCT116 (colon) and H460A (lung), with IC50 values between 0.05-0.60 μM. Moreover, a number of these compounds have demonstrated significant *in vivo* anti-tumor activity in a variety of tumor models. These findings have led to the selection of one of these compounds as a candidate for clinical development. In this presentation, the synthesis of this class of CDK inhibitors will be described as well as a discussion of the SAR that led to the selection of the clinical candidate.

MEDI 401

Synthesis and identification of [1,3,5]triazine-pyridine biheteroaryl as a novel series of potent cyclin-dependent kinase inhibitors

*Gee Hong Kuo[1], **Alan DeAngelis**[1], Stuart Emanuel[1], Aihua Wang[1], Yan Zhang[1], Peter J. Connolly[2], Xin Chen[1], Robert H. Gruninger[1], Catherine Rugg[1], Angel Fuentes-Pesquera[1], Steven A. Middleton[1], Linda Jolliffe[1], and William V. Murray[1]. (1) Drug Discovery Division, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, 1000 Route 202, P.O. Box 300, Raritan, NJ 08869, Fax: 908-203-8109, gkuo@prius.jnj.com, adeangel@prdus.jnj.com, (2) JNJPRD, Raritan, NJ*

Based upon previous studies, we identified pyrazine-pyridine A as a potent VEGF inhibitor and pyrimidine-pyridine B as a modest CDK inhibitor. A proposed combination of the pyrimidine moiety from CGP-60474 and the pyrimidine moiety from compound B led to the discovery of [1,3,5]triazine-pyridine as a new series of potent CDK inhibitors. Palladium-catalyzed C-C bond (particularly the Negishi coupling reaction) and C-N bond formation reactions were used to

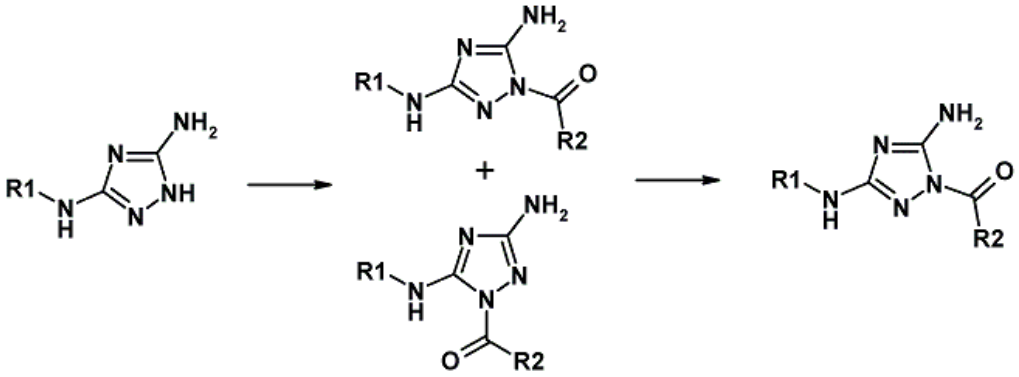
assemble various triazine-heteroaryl analogs effectively. Among them, compound 20 displayed high inhibitory potency at CDK1 (IC50 = 0.021 mM), CDK2, and CDK5; and with submicromolar potency at CDK4, CDK6 and CDK7. Compound 20 also displayed high potency at GSK-3b (IC50 = 0.020 mM) but with weak or no inhibitions toward twelve non-CDK kinases. It demonstrated potent antiproliferative activity on various tumor cell lines, including HeLa, HCT-116, U937 and A375, and it appears that 20 is not a substrate of P-glycoprotein. In U937 cells, 20 induced apoptosis dose dependently via activation of caspases. At 150 mg/kg and 125 mg/kg i.p. treatments of 20, each produced a significant survival increase in A375-bearing mice along with one out of six 57-day survivor for each dose. Molecular docking studies were conducted in an attempt to enhance the understanding of the observed SAR.

MEDI 402

Chemoselective synthesis of 1,2,4-triazole derivatives using solid-supported reagents as selective inhibitors of cyclin-dependent kinase 4 (Cdk4)

Kyungjin Kim[1]*, Li Chen*[2]*, Yingsi Chen*[3]*, Wanda Depinto*[4]*, Allen Lovey*[1]*, Warren McComas*[1]*, Qing Xiang*[3]*, and Xuefeng Yin*[4]*. (1) Discovery Chemistry, Hoffmann-La Roche, Inc, 340 Kingsland Street, Bldg. 123, Nutley, NJ 07110-1199, Fax: 973-235-6084, kyungjin.kim@roche.com, (2) Roche R&D Center at China, Hoffmann-La Roche, Ltd, (3) Discovery Technologies, (4) Pre-clinical Oncology*

A series of 1,2,4-triazaole derivatives was identified as selective inhibitors of cyclin-dependent kinase 4 (CDK4). A novel synthetic pathway using a combination of solid-supported reagents and microwave-assisted technology was explored to facilitate SAR development. Polymer-supported activated ester acylation reagents were prepared from a variety of commercially available aromatic carboxylic acids with polymer-supported HOBt. Utilizing microwave technology to accelerate reaction rates, N-acylation reactions were successfully explored. A simple purification method to isolate the N1 from N2 regioisomer of the 1,2,4-triazole scaffold was developed. Herein we will also discuss some analogs with low nanomolar activity toward CDK4 as well as greater than 10-fold selectivity against CDK1 and CDK2.

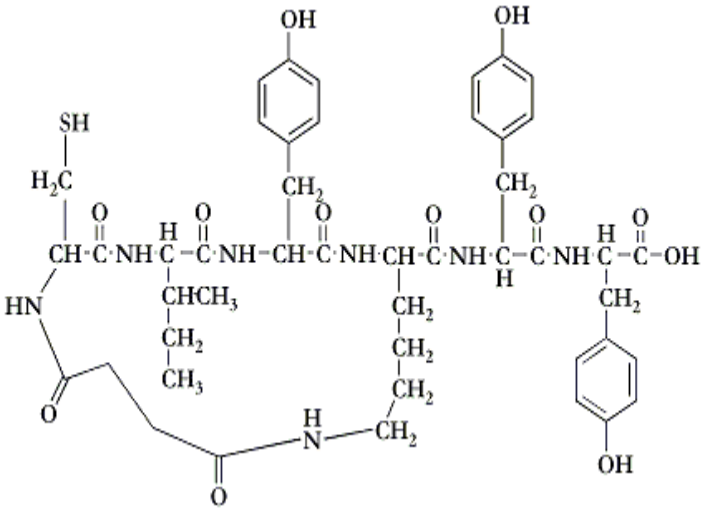


MEDI 403

Conformationally constrained peptide analogs of ClYKYY as inhibitors of Src tyrosine kinase

Guofeng Ye[1]*, Anil Kumar*[1]*, Yuehao Wang*[2]*, Gongqin Sun*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5048, guofengye@mail.uri.edu, (2) Department of Cell and Molecular Biology, University of Rhode Island*

Peptide Ac-CIYKYY was a weak inhibitor (IC_{50} = 400 μM) of polyE4Y phosphorylation by active Src as shown by the radioactive kinase assay. Peptide Ac-CIYKF(NO_2)Y, in which the nitrophenylalanine is located at Y_5 position, exhibited a significantly higher inhibitory potency (IC_{50} = 0.53 μM) by approximately 750-fold *versus* Ac-CIYKYY. Conformationally constrained derivatives of these compounds were synthesized by solid-phase methods to determine whether the presence of the constrained ring has any effect in inhibitory potency. Due to the presence of three tyrosine residues and one lysine in the $C_1I_2Y_3K_4Y_5Y_6$, there were several opportunities for linking side chains of amino acids. Four types of conformational constraints were introduced by linking head to tail, *C*-terminal to side chain, *N*-terminal to side chain, and side chain to side chain of the amino acids. The structure-activity relationships of these analogs and the comparison of their inhibitory potency with parent linear peptides are discussed.



MEDI 404

N-Heteroaromatic-peptide conjugates as Src kinase inhibitors

Anil Kumar[1]*, Yuehao Wang*[2]*, Gonquin Sun*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5048, kanilkadian@mail.uri.edu, (2) Department of Cell and Molecular Biology, University of Rhode Island*

Src kinase exists as intriguing therapeutic target for drug discovery with respect to cancer and osteoporosis. Although selective inhibitors competitive with ATP have been synthesized for specific protein kinases, the process of inhibitor development is labor intensive due mainly to the presence of a large number of protein kinases that show a conserved ATP binding site. The main objective of this study was to exploit the ATP-binding site molecular recognition motif

in combination with other recognition motifs. 3-Phenylpyrazolopyrimidine derivative, substituted with an alkyl carboxylic acid at N^1 endocyclic amine, exhibited weak inhibitory potency (IC_{50} = 250 μM). Additionally, the radioactive kinase assay using polyE4Y as the substrate suggested that peptides YIYGSFK (IC_{50} = 570 μM) and Ac-CIYKYY (IC_{50} = 400 μM) were weak inhibitors of polyE4Y phosphorylation by active c-Src. More than fifty N-heteroaromatic-peptide conjugates were synthesized using 3-pyrazolopyrimidine derivative as an ATP mimic and CIYKYY and YIYGSFK as peptide substrates. The carboxylic acid of substituted 3-phenylpyrazolopyrimidines was attached to the side chain of different amino acids in the peptide template. Two N-terminal substituted 3-phenylpyrazolopyrimidine-peptide conjugates, 3-phenylpyrazolopyrimidine-CIYKYY (IC_{50} = 0.38 μM) and 3-phenylpyrazolopyrimidine-YIYGSFK (IC_{50} = 2.7 μM), inhibited the polyE4Y phosphorylation by active Src significantly higher than parent compounds, N-heteroaromatics and peptides. This study suggests a synergistic inhibition effect of the conjugation of the ATP mimic with the peptide by possibly creating favorable interactions between the conjugate and the kinase domain. Molecular modeling studies of 3-phenylpyrazolopyrimidine-CIYKYY conjugate with Src suggested that the pyrazolopyrimidine ring binds to the ATP binding site and the peptide occupies the exterior space of the N-lobe in the kinase domain creating some new bonding interactions. This study suggests that weak inhibitors of Sc kinase can be conjugated to generate potent lead inhibitors that may be used for further optimization.

MEDI 405

Converting a weak peptide inhibitor of Src kinase to potent peptide inhibitors by systemic structural modification

Anil Kumar[1]*, Yuehao Wang*[2]*, Gongqin Sun*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5048, kanilkadian@mail.uri.edu, (2) Department of Cell and Molecular Biology, University of Rhode Island*

The design, synthesis, and evaluation of new compounds against Src tyrosine kinases are attractive due to the association of Src tyrosine kinases activity with several diseases including cancer and osteoporosis. In contrast to ATP binding site, a few peptides have been identified as substrates for Src tyrosine kinases. Most of these peptide substrates are rather weak inhibitors with K_m in high micromolar or in millimolar range. The best examples from these studies are peptides, Ac-YIYGSFK and Ac-CIYKYY, which were reported to be inhibitors of Src. Our radioactive kinase assay showed that Ac-YIYGSFK (IC_{50} = 570 μM) and Ac-CIYKYY (IC_{50} = 400 μM) were weak inhibitors of polyE4Y phosphorylation by active c-Src. We investigated whether by functional group modifications in the side chains of amino acids in Ac-CIYKYY, the inhibitory activity can be improved. The purpose of this study was to understand the structure-activity relationship of these compounds in order to develop novel Src inhibitors. Peptide Ac-CIYKF(NO_2)Y, in which the nitrophenylalanine is located at position 5, exhibited a significantly higher inhibitory potency (IC_{50} = 0.53 μM) by approximately 750-fold versus Ac-CIYKYY. Additionally, compounds with substituted halogens exhibited significantly high

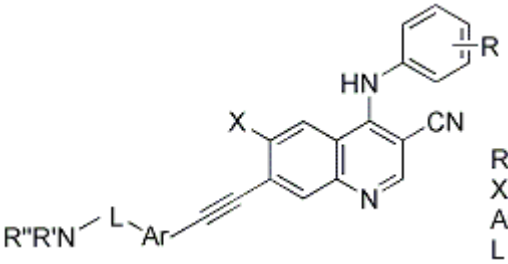
inhibitory potencies in the order of I > Cl > F. For example, Ac-ClYKF(4-I)Y exhibited (IC_{50} = 0.78 μM) approximately 510-fold higher inhibitory potency than Ac-ClYKYY. Molecular modeling studies showed that the intramolecular hydrogen bonding of the amino group of the K4 with hydroxyl group of Y5 in Ac-ClYKYY is eliminated when the hydroxyl group is substituted with nitro group or halogens. It appears that the free amino group of the lysine is required for the interaction with the kinase domain of Src and generating inhibition. These results suggest that it is possible to convert a weak peptide inhibitor of Sc kinase to potent peptide inhibitors by systemic structural modifications.

MEDI 406

New Src kinase inhibitors Part I: 4-Anilino-7-ethynyl-3-quinolinecarbonitriles

Biqi Wu[1]*, Ana Carolina Barrios Sosa*[1]*, Diane H. Boschelli*[1]*, Frank Boschelli*[2]*, Erick E. Honores*[1]*, Jennifer M. Golas*[2]*, and Yanong D. Wang*[1]*. (1) Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, (2) Discovery Oncology, Wyeth Research*

Src, a non-receptor tyrosine kinase, has a key role in signaling pathways controlling cell proliferation and migration. Small molecule Src inhibitors have been extensively studied for the treatment of various diseases. We previously reported that 4-anilino-7-ethynyl-3-quinolinecarbonitriles are Src kinase inhibitors. In order to optimize this Src inhibitory activity, new 4-anilino-7-ethynyl-3-quinolinecarbonitriles with a pyridine, phenyl or thiophene ring containing basic water solubilizing groups were prepared. Here we present the synthesis and structure-activity relationships of these new analogs. Potent activity was observed with compounds where R is 2,4-diCl-5-OMe, X is OMe or OEt, Ar is pyridine and R”R'N is dimethylamine or N-methylpiperazine.



R = 2,4-diCl-5-OMe and 3,4,5-triOMe
X = OMe, OEt and H
Ar = pyridine, phenyl and thiophene
L = CH_2, CH_2CH_2 and CO

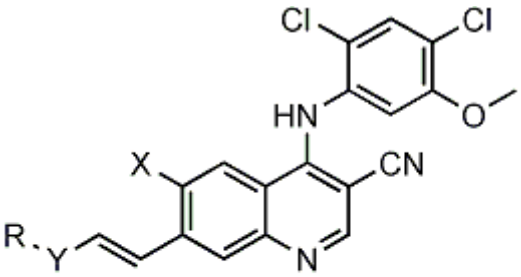
MEDI 407

New Src kinase inhibitors Part II: 4-Anilino-7-vinyl-3-quinolinecarbonitriles

Erick E. Honores[1]*, Ana C. Barrios Sosa*[1]*, Diane H. Boschelli*[1]*, Frank Boschelli*[2]*, Jennifer M. Golas*[2]*, Yan Wang*[1]*, Yanong D. Wang*[1]*, and Biqi Wu*[1]*. (1) Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, honoree@wyeth.com, (2) Discovery Oncology, Wyeth Research*

Src tyrosine kinase is involved in several cell-signaling pathways. Therefore, Src inhibition

could prove to be efficacious for the treatment of cancer and other diseases. We recently identified C-7 vinyl substituted 3-quinolinecarbonitrile derivatives as potent Src kinase inhibitors. Following this lead, additional analogs were synthesized. We report here further functionalization of the C-7 vinyl substituted analogs by introducing various basic water solubilizing groups and the structure-activity relationships of these compounds.



X= H, OMe, OEt
Y= phenyl, pyridine, thiophene, furan
R= $(CH_2)_nNR'R''$, $CONR'R''$
n = 0 - 2

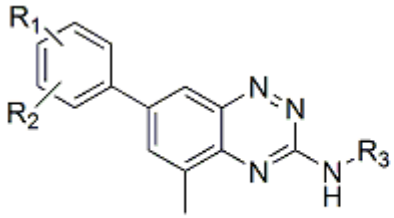
MEDI 408

Discovery of a benzotriazine scaffold as a new class of novel src kinase inhibitors

*W. Wrasidlo[1], E. Dneprovskaia[1], X. Gong[1], G. Noronha[1], J. Hood[2], K. Barrett[2], R. Soll[1], G. Li[3], W. Liao[3], Y. Zhou[3], and **V.P. Pathak**[1]. (1) Medicinal Chemistry, TargeGen Inc, 9393 Towne Centre Drive, San Diego, CA 92121, Fax: 858-678-0762, wrasidlo@targegen.com, pathak@targegen.com, (2) In-vitro Biology, TargeGen Inc, (3) WuXi PharmaTech Co. Ltd*

Src is a prototype member of the src family of tyrosine kinases and plays a key role in vascular permeability, tumor progression and metastasis. Increased levels of src activity are observed in a variety of cancers including metastatic colorectal, pancreatic and ovarian cancers. Due to their the involvement in cell signaling pathways, src family inhibitors may be useful therapeutics for the treatment of cancers and other diseases including myocardial infarction, osteoporosis, stroke, and neurodegeneration.

Using a focused library approach, elaboration of the 3-amino-7-phenyl-benzo[1,2,4]triazine core 1 resulted in potent, low nM src inhibitors, generation of preliminary SAR, and identification of permissible substitution of R1 and R2 about the C-7 phenyl group and of R3 on 3-amino as substituted aryl/heteroaryl groups. The synthesis and src activity of these analogs will be discussed.



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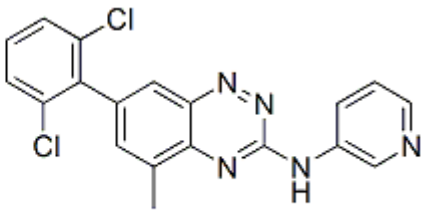


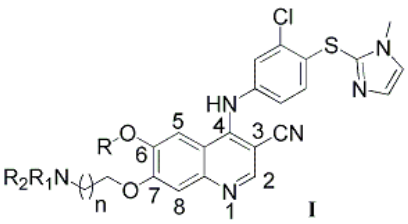
Src IC_{50} 27 nM

MEDI 409

Design and synthesis of 4-anilino-3-quinolinecarbonitrile with C-7 substituted amines as potent inhibitors of MEK kinase

Minu Dutia[1], *Dan M. Berger*[1], *Yan Wang*[2], *Nancy Torres*[1], *Leïla Abrous*[1], *Dennis W. Powell*[1], *Robert Mallon*[3], *Donald Wojiciechowicz*[3], *Steven Kim*[3], *Larry Feldberg*[3], *and Karen Collins*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, dutiam@wyeth.com, (2) Chemical & Screening Sciences, Wyeth Research, (3) Discovery Oncology, Wyeth Research*

The Ras-Raf-MEK1-MAPK signaling cascade transmits mitogenic stimuli from growth factor receptors and activated Ras to the cell nucleus. Inappropriate Ras activation is associated with ~30% of all human cancers, making the downstream kinase components (Raf and MEK1) attractive targets for pharmaceutical intervention. Using a high throughput, non-radioactive ELISA method developed to detect Raf and/or MEK1 kinase inhibitors, we identified a series of 6,7-dialkoxy substituted quinolinecarbonitriles I as potent inhibitors of MEK1. While displaying potent in vitro activity versus enzyme and selected cell lines, these compounds were poorly soluble in aqueous media and were not orally active in vivo. In an effort to address these issues, we prepared analogs II with substituted amines at the C7 position. A number of novel analogs in this series possess significantly improved water solubility and enhanced oral bioavailability. In this presentation, we will discuss the synthesis, pharmacological properties and biological activities of this series. In addition we will describe the in vivo activity of one compound against nude mouse xenografts.



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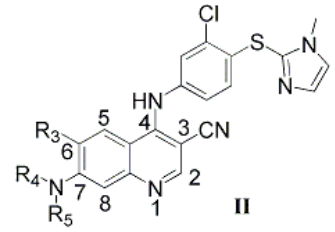


II

R_3 = alkoxy , F
NR_4R_5 = substituted piperazines, piperidines, alkyldiamines, heterocycles.

MEDI 410

New approaches for targeting protein-protein interactions: Dual surface phage-display

***Indraneel Ghosh**, Srivats Rajagopal, Thaddeus J. Smith, and Aaron Goldman, Department of Chemistry, University of Arizona, 1306 E. University Blvd., Tucson, AZ 85721-0041, Fax: 520-621-8407, ghosh@email.arizona.edu*

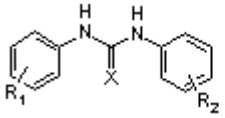
Mini-protein libraries biased towards amino-acid residues found at so-called “hotspots” were incorporated into the beta-sheet region of a thermostable protein scaffold that binds IgG. The library of over a billion variants with a minimal 12 amino acid basis set were first selected for binding IgG, to ensure structural conservation, and subsequently to a test protein, thrombin, to evolve a thrombin-binding function. Several of the de novo selected thrombin binding mini-proteins were found to inhibit thrombin activity by an allosteric mechanism through a di-tyrosine motif. Small molecules derived from the de novo discovered structured epitope also resulted in thrombin inhibition. We have also utilized this approach for the identification of novel inhibitors of beta-amyloid aggregation. We believe that this new dual surface selection strategy is general and will have utility in evolving new bi-functional proteins without compromising structure. Furthermore, the discrete beta-sheet epitopes identified by this methodology lends itself to the rational design of small-molecule mimics.

MEDI 411

Small molecule inhibitors against mitochondrial permeability transition pore (mPT)

***Yong-Qian Wu**[1], Sean Hamilton[1], Doug Wilkinson[2], Ling Wei[1], Larisa Serdyuk[3], Mike Fuller[1], J Alt[1], Joseph Steiner[1], Larry Williams[1], Camilo Rojas[2], and Gregory S. Hamilton[1]. (1) Guilford Pharmaceuticals Inc, 6611 Tributary St., Baltimore, MD 21224, wuy@guilfordpharm.com, (2) Guilford Pharmaceuticals, Inc, (3) Department of Research, Guilford Pharmaceuticals Inc*

Abnormal regulation of apoptosis resulting from mitochondrial dysfunction and subsequent release of Cyt c may lead to cell death in a variety of human disorders. Although one of the mechanisms by which Cyt c is released through the induction of the mitochondria permeability transition (mPT) in response to stress is controversial, agents showing inhibition against mPT induction have clearly demonstrated therapeutic potential for the treatment of the diseases such as cardiac ischemia-reperfusion injury and neurodegenerative diseases. We herein disclosure our discovery of a new class of molecules, N, N'-diaryl ureas and cyanoguanidines, as inhibitors against stress-induced mitochondrial swelling, and subsequent release of Cyt c. Compound synthesis and preliminary biological results will be discussed.



X= O, NCN

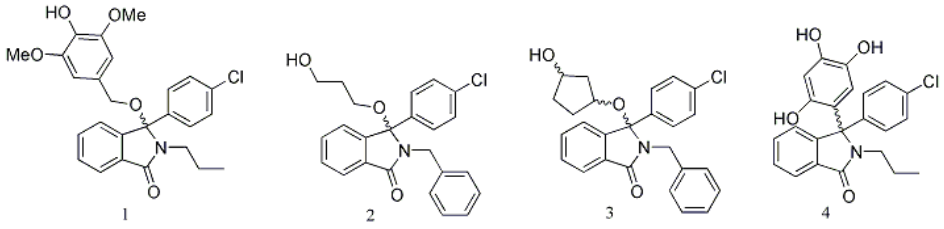
MEDI 412

Isoindolinone based inhibitors of the MDM2-p53 protein-protein interaction

***Stuart J. Kemp**[1], Ian R. Hardcastle[1], Shafiq U. Ahmed[2], Noar A. Atatreh[1], Paul Barrett[3], Jane A. Endicott[3], Bernard T. Golding[1], Roger J. Griffin[1], Jan Gruber[3], Claire Hutton[2], John Lunec[2],*

Martin E. M. Noble[3], Rebecca J. Reid[1], Christiane Riedinger[3], and Lynette A. Smyth[1]. (1) Northern Institute for Cancer Research, School of Natural Sciences - Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, United Kingdom, s.j.kemp@ncl.ac.uk, (2) Northern Institute for Cancer Research, Medical School, (3) Department of Biochemistry, Laboratory of Molecular Biophysics

The MDM2 oncoprotein directly binds the p53 tumour suppressor protein negatively regulating p53. In normal cells the balance between active p53 and inactive MDM2-bound p53 is maintained by an autoregulatory feedback loop. *Mdm2* gene amplification and subsequent p53 inactivation has been observed in a wide range of tumours. Inhibition of the MDM2-p53 protein-protein complex by small molecule inhibitors is expected to reactivate normal p53 pathways in cells overexpressing MDM2, consequently exerting an anti-cancer effect. Recently, potent small molecule inhibitors of the MDM2-p53 interaction have been identified e.g. the Nutlins [*Science* **2004***, 303*, 844] and the benzodiazepinediones [*J. Med. Chem.* **2005***, 48*, 909]. Our previous studies using structure-based design approaches have resulted in the identification of novel small molecule inhibitors of the MDM2-p53 interaction, based on an isoindolinone scaffold [*Bioorg. Med. Chem. Lett.* **2005***, 15*, 1515] e.g. **1** (IC_{50} = 5.3 μM) and **2** (IC_{50} =15.9 μM). NMR structural studies have indicated a plausible binding mode for **2** which has been used to design improved inhibitors e.g. **3** (IC_{50} = 3 μM). The synthesis of **4** (IC_{50} = 530 nM) proceeded by an unexpected mechanism resulting in a novel class of mdm2-p53 inhibitors.



MEDI 413

Development of an allosteric inhibitor of the protein-protein interaction between RUNX1 and CBF beta

Michael J. Gorczynski[1], Miki Newman[2], Jolanta Grembecka[2], Yunpeng Zhou[2], Takeshi Corpora[2], Jae-Pil Jeon[3], P. Paul Liu[3], Mohini Sridharan[4], Ryan Lilien[4], Bruce R. Donald[4], John H. Bushweller[2], and ***Milton L. Brown***[1]*. (1) Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904, Fax: 434-924-0798, mjg6d@virginia.edu, (2) Department of Molecular Physiology and Biological Physics, University of Virginia, (3) National Genome Research Institute, National Institute of Health, (4) Department of Computer Science, Dartmouth College*

Core binding factors play critical roles in hematopoiesis and are frequent targets of chromosomal translocations commonly found in leukemia. The inv(16) fuses the heterodimerization domain of CBF beta to a portion of SMMHC. The binding of this fusion protein to RUNX1 is essential for the hematopoietic blockage mediated by this fusion protein; therefore this interaction represents a viable target for the development of a protein-protein

interaction inhibitor. Lead compounds have been identified using LUDI, NMR, and a FRET assay. A library of compounds was synthesized and several of the compounds effectively inhibited the binding of RUNX1 to CBF beta. A number of these compounds have been tested in vitro and are active. In silico docking of these molecules to CBF beta clearly shows that these compounds bind at a site close to the binding interface for RUNX1 on CBF beta and therefore, function as allosteric inhibitors of this protein-protein interaction.

MEDI 414

1,2-Oxazines as NO prodrugs

Harinath Chakrapani *and Eric J. Toone, Department of Chemistry, Duke University, B 120 Levine Science Research Center, Duke University, Durham, NC 27708, harinath@chem.duke.edu*

Nitric oxide mediated biological events include regulation of smooth muscle relaxation, inhibition of platelet activation, neurotransmission, and control of gene regulation. However, the role of Nitric oxide is enigmatic due to its sometimes contradictory role in several biological processes. However, a closer look suggests that the effects can be accounted for based on the timing, location, and concentration of NO. Hence, the need to better understand the mechanism(s) by which NO exerts its bioactivity and to apply this understanding to the development of therapeutic agents that mimic the effects of endogenous nitric oxide. Exogenous donors of NO have been routinely used in many of these studies to help understand the nature of NO-related bioactivity. 1,2-Oxazines are hetero Diels-Alder adducts of C-Nitroso compounds (CNOs). CNOs spontaneously generate NO at room temperature and show NO-related bioactivity even at nanomolar concentrations. We synthesize and study the NO-related bioactivity of several substituted 1,2-Oxazines as candidates for NO prodrugs with the aim of controlling the rate of NO release by influencing the rate of cycloreversion.

MEDI 415

Modeling the binding of DAG-lactones to protein kinase C at the lipid interface

Megan L. Peach[1]*, Ji-Hye Kang*[2]*, Yongmei Pu*[3]*, Nancy E. Lewin*[3]*, Peter M. Blumberg*[3]*, Marc C. Nicklaus*[2]*, and Victor E. Marquez*[2]*. (1) Basic Research Program, SAIC Frederick, Inc, National Cancer Institute, 376 Boyles Street, Frederick, MD 21702, mpeach@helix.nih.gov, (2) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health, (3) Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institutes of Health*

Protein kinase C (PKC) isozymes play important roles in many cell-signaling processes. In response to the second messenger diacylglycerol (DAG), PKC translocates to the cell membrane, where its regulatory C1 domain partially inserts as it binds DAG, leading to activation of the kinase domain. DAG and related synthetic ligands have three pharmacophore sites, however docking has shown that only two of these interact directly with the C1 domain, leaving the third as an "orphan" of unknown function. We used DAG-lactones with altered functionality at the two carbonyl pharmacophores (C=O $\rightarrow$ CH2 or C=O $\rightarrow$ C=S) to probe the

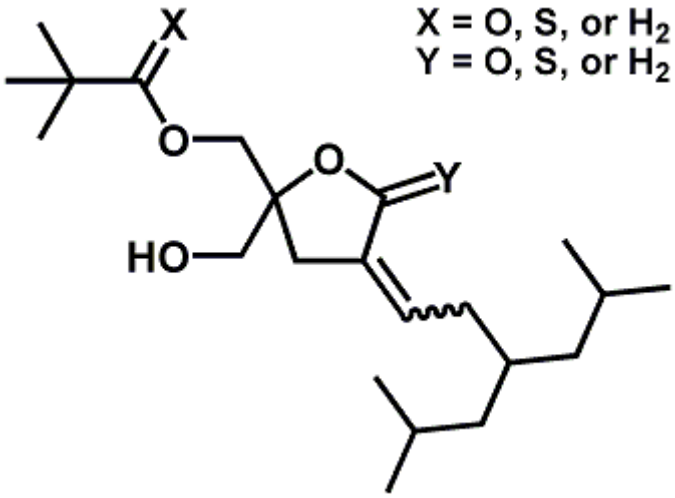
polar interactions between ligand, C1 domain, and phosphatidylserine lipid. We present results from molecular dynamics simulations illustrating why the lower-dielectric medium of the bilayer is necessary for stable binding of DAG-lactones to the C1 domain, and suggesting a role for the "orphan" pharmacophore in mitigating the energetic penalty of inserting the backbone of the C1 domain into the lipid interface.

MEDI 416

Exploration of the sn-1 and sn-2 carbonyl functionalities reveals the essential role of the sn-1 carbonyl at the lipid interface in the binding of DAG-lactones to protein kinase C

Ji-Hye Kang[1], *Megan L. Peach*[2], *Yongmei Pu*[3], *Nancy E. Lewin*[3], *Peter M. Blumberg*[3], *and Victor E. Marquez*[1]. *(1) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health, 376 Boyles Street, Frederick, MD 21702, jhkang@ncifcrf.gov, (2) Basic Research Program, SAIC Frederick, Inc, (3) Laboratory of Cellular Carcinogenesis & Tumor Promotion, National Institutes of Health*

The synthesis of DAG-lactones with altered functionality (C=O → C=S or C=O → CH_2) at the *sn-1* and *sn-2* carbonyl pharmacophores were synthesized and used as probes to scrutinize the individual role of each carbonyl in binding to PKC. The Δ(ΔG°) values calculated from the dissociation constants for the new ligands relative to parent DAG-lactones showed that the loss in binding affinity is more pronounced when the *sn-1* carbonyl is converted to the less polar thiocarbonyl or methylene group. These results suggest that the hydrated *sn-1* carbonyl is engaged in very strong hydrogen bonding interactions with the charged phosphate groups and organized water molecules at the lipid interface; and point to the existence of a third unknown binding site, which resides at this lipid interface.



MEDI 417

Synthesis and characterization of p-hydroxyphenobarbital O-glucuronide isolated from mouse urine

***Adnan Ahmed Kadi**, Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh, 11451, Saudi Arabia, Fax: +966-1-4676220, akadi@ksu.edu.sa, William H. Soine, Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, and Michael Hindle, Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University*

The isolation and characterization of p-hydroxyphenobarbital (p-OHPB) glucuronide from mouse urine, the development of sensitive LC-APCI-MS and LC-ESI-MS methods for its detection, and its chemical synthesis starting from phenobarbital is described. p-OHPB glucuronide was purified using solid phase extraction and semi-preparative HPLC. Approximately 3mg of purified material was obtained. LC-MS mobile phase compositions were 30:70 methanol : 0.01M trifluoracetic acid and 24:76 acetonitrile : 0.05M formic acid for APCI and ESI, respectively. APCI and ESI spectra gave ions at m/z 425 $[M + H]^+$ and 423 $[M - H]^-$ in the positive and negative ion modes, respectively. 1H and 13C NMR confirmed the structure of the purified compound. Synthetic p-OHPB glucuronide was obtained by the condensation of p-OHPB and methyl 2,3,4-tri-O-acetyl-1-O-(trichloroacetimidoyl)-α-D-glucopyranosyluronate using boron trifluoride and the subsequent deprotection with potassium carbonate. LC-MS and NMR data confirmed the structure. ƒ" configuration was confirmed with a J=6.7 value for the anomeric proton.

MEDI 418

Design and synthesis of novel phsophoramidate prodrugs as SH2 domain inhibitors

***Rong Huang**, Department of Medicinal Chemistry & Molecular Pharmacology, Purdue University, 201 South University Streeet, West Lafayette, IN 47906, rongh@pharmacy.purdue.edu, and Richard F. Borch, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue Cancer Center, Purdue University*

Specific Src SH2 domain inhibitors can be a potentially attractive therapy for cancer, osteoporosis, and immune diseases. Investigation of SH2 domain inhibitors has identified the cognate sequence pYEEI to which the Src SH2 domain binds, and several potent peptides that incorporate pY have been reported. However, those compounds had several undesirable features: poor cell membrane permeability, poor selectivity and instability. The phosphoramidate prodrug strategy is applied to offer cell permeability and selective intracellular activation based on previous studies in our laboratory. The preliminary computational modeling indicated that a cis-enediol containing a pY and a hydrophobic side chain at the C-terminal nicely fit in the two binding pockets. A series of cis-enediol peptidomimetic phosphate analogues are being synthesized to explore the potency, selectivity, and stability of SH2 domain inhibitors. Current efforts include the optimization of cis-enediol phosphates synthesis and in vitro biological evaluation. Based on the binding assay results, novel phosphoramidate prodrugs will be synthesized and tested in cell-based assay.

MEDI 419

Examination of methoxy- and hydroxy-containing phosphonomethylphenylalanine residues in Grb2 SH2 domain-binding peptides

Won Jun Choi[1], *Sang-Uk Kang*[2], *Karen M. Worthy*[3], *Lakshman Bindu*[3], *Robert J. Fisher*[3], *and Terrence R. Burke Jr.*[2]. *(1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, Frederick, MD 21702, (2) Laboratory of Medicinal Chemistry, CCR, NCI, (3) Protein Chemistry Laboratory, SAIC-Frederick*

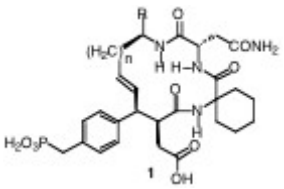
Replacement of phosphotyrosyl (pTyr) residues in SH2 domain-binding peptides with the hydrolytically stable phosphonomethylphenylalanine (Pmp) results in reduction of binding affinity. This may be attributed to loss of protein-ligand interactions incurred by substituting the pTyr phosphoryl ester oxygen with a methylene group. In order to potentially reinstate these lost interactions, analogues of Pmp were prepared by introducing methoxy and hydroxy groups onto the Pmp phenyl ring. The design, synthesis and evaluation of these new Pmp analogues will be reported.

MEDI 420

High affinity Grb2 SH2 domain-binding macrocycles derived from ring-closing metathesis of alkenylglycine residues with beta-vinyl phosphotyrosyl mimetics

Fa Liu[1], *Shinya Oishi*[2], *Rajeshri G. Karki*[1], *Zhen-Dan Shi*[1], *Karen M. Worthy*[3], *Lakshman Bindu*[3], *Melissa Maderia*[1], *Marc C Nicklaus*[1], *Joseph J Barchi Jr.*[1], *Robert J. Fisher*[3], *and Terrence R. Burke Jr.*[1]. *(1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, Bidg.376 Boyles Street, Frederick, MD 21702, Fax: 301-846-6033, liuf@ncifcrf.gov, (2) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institute of Health, (3) Protein Chemistry Laboratory, SAIC-Frederick*

Conformational constraint through macrocyclization is a potentially useful way to reduce entropy penalties associated with binding of peptides to proteins and thereby achieve affinity enhancement. Presented in the current work will be an application of this methodology to Grb2 SH2 domain-binding peptidomimetics of type 1. The design, synthesis and biological evaluation of this family of macrocycle will be covered.



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MEDI 421

Design and synthesis of beta-aminomethylene phosphotyrosyl mimetics and their use in the preparation of macrocyclic Grb2 SH2 domain binding inhibitors

Sang Uk Kang[1], *Karen M. Worthy*[2], *Lakshman Bindu*[2], *Rajeshri G. Karki*[1], *Marc C. Nicklaus*[1], *Robert J. Fisher*[2], *and Terrence R. Burke Jr*[1]. *(1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, (2) Protein Chemistry Laboratory, SAIC-Frederick*

Previously, we employed ring closing metathesis (RCM) to prepare high affinity Grb2 SH2 domain binding macrocycles that were characterized by their good efficacy in whole cell systems. Ring closure for these macrocycles was achieved at the beta-position of phosphotyrosyl (pTyr) mimicking residues. More recently, we have designed beta-aminomethylene containing p-Tyr mimetics intended to allow macrocycliaztion through amide bond formation rather than RCM reactions. The stereoselective synthesis and the use of these novel pTyr mimetics will be presented.

MEDI 422

Design, synthesis and biological evaluation of lsofylline (LSF) analogs as a possible treatment for Type 1 diabetes

Peng Cui[1]*, Meng Chen*[2]*, Zandong Yang*[2]*, Jerry.L Nadler*[2]*, and Timothy L. Macdonald*[1]*. (1) Department of Chemistry, University of Virginia, McCormick Rd, P.O.Box 400319, Charlottesville, VA 22904, Fax: 434-982-2302, pc3n@virginia.edu, (2) Division of Endocrinology, Department of Medicine, University of Virginia*

Lisofylline (LSF, 1-(5-R-hydroxyhexyl)-3,7-dimethylxanthine), an anti-inflammatory agent, can protect beta-cells from Th1 cytokine-induced dysfunction and reduce the onset of Type 1 diabetes in non-obese diabetic (NOD) mice. However, due to the poor oral bioavailability and weak potency, its clinical development has been limited. Our goal is to develop novel agents using LSF as a base molecule that will be more potent, selective and orally bioavailable. Our synthetic strategy is two fold. First, we held the side chain moiety (5-R-hydroxyhexyl) constant while substituting a variety of nitrogen-contained heterocyclic compounds. After investigating the core structures, we successfully identified phthalhydrazide as a lead for further optimization. The analog with this core structure showed satisfactory stability, bioavailability and safety as well as beneficial effects in human islets. Our current synthetic work is focused on optimization of the side chain structure, which will be presented.

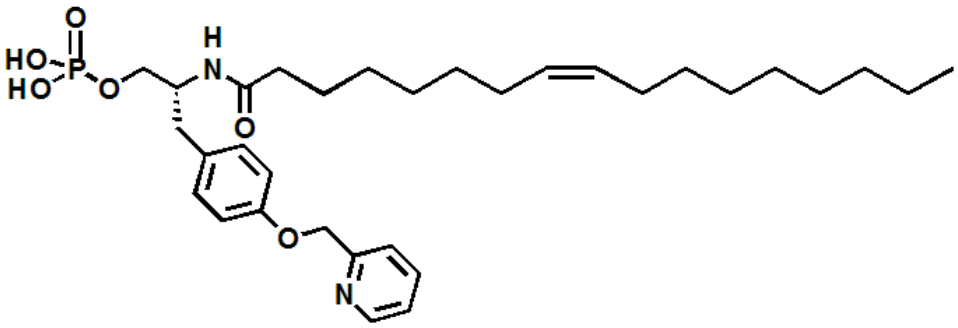
MEDI 423

Structure activity relationship studies of receptor-selective lysophosphatidic acid antagonists

Karen M. Carter[1]*, William F. McCalmont*[1]*, Brian H. Heasley*[1]*, Kevin R. Lynch*[2]*, and Timothy L. Macdonald*[1]*. (1) Department of Chemistry, University of Virginia, P.O. Box 400319 McCormick Road, Charlottesville, VA 22904, kmc4f@virginia.edu, (2) Department of Molecular Genetics and Biology andPharmacology, University of Virginia*

Lysophosphatidic acid (LPA; 1-acyl-2-sn-glycerol-3-phosphate) is an endogenous phospholipid mediator that stimulates cellular proliferation, migration and survival by binding to its cognate G-protein-coupled receptors. The precise physiological roles of each LPA receptor have yet to be fully characterized in part due to a lack of receptor subtype-specific ligands. In our lab, a library of receptor-subtype antagonists at LPA1 and LPA3 has been prepared. The antagonist pharmacophore has been established and contains four distinct regions: an aryl benzyloxy region, phosphate head group, ethanolamine backbone, and an acyl chain. Systematic

development of structure activity relationships of these regions has resulted in the discovery of potent and metabolically stable LPA receptor-subtype selective antagonists. Lead optimization persists in order to develop a viable antagonist for use in the elucidation of disease states associated with LPA with its receptors and ultimately resulting in the development of therapeutic candidates.



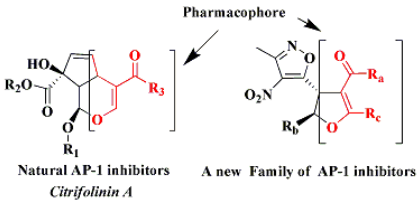
MEDI 424

Chloroketones as oxygen nucleophiles in the preparation of transcriptional factor inhibitors

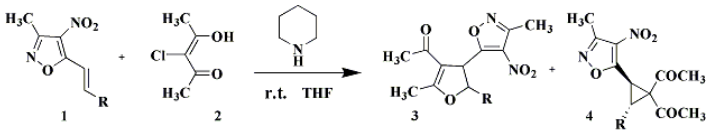
Vivekananda Reddy Konda, *Department of Pharmaceutical and Medicinal Chemistry, Centre for Synthesis and Chemical Biology, Royal College of Surgeons in Ireland, 123, St. Stephen's Green, Dublin 2, Dublin, Ireland, Fax: ++353-1-4022168, vrkonda@rcsi.ie, and Mauro F. A. Adamo, Department of Pharmaceutical and Medicinal Chemistry, Centre for Synthesis and Chemical Biology*

Transcriptional factor AP-1 plays an important role in the genesis of tumour, peculiarly in skin cancer. Aim of the present study is to find molecules capable of inhibiting AP-1 and use them as anti-tumour or chemo-preventive agents.

We have synthesised a new family of potentially active AP-1 inhibitors modelled on a natural product template (Scheme 1). During the studies on the reactivity of isoxazole 1, we found that 1 reacted with 3-chloroacetylacetone 2 in the presence of 2 equivalent of piperidine, to give, dihydrofuran 3 in 85% isolated yield (Scheme 2). Importantly, dihydrofuran 3 was obtained as the cis stereoisomer exclusively. We studied the behaviour of nine electronically different alkene substrates under the established reaction condition. In all cases dihydrofuran products were obtained in excellent isolate yields, obtaining in this way a small family of compounds. This simple methodology is modular and allows the introduction of diversity in efficient way.



Scheme 1



Scheme 2

MEDI 425

Inhibition of hypoxia inducible factor (HIF) hydroxylases

***Ana Conejo-Garcia**, Benoit M. R. Lienard, Michael McDonough, Luke McNeill, Kirsty Hewitson, and Christopher J. Schofield, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom, Fax: +44 (0)1865 275674, ana.conejo-garcia@chem.ox.ac.uk*

The mammalian hypoxic response is mediated by hypoxia-inducible factor (HIF), an α,β−heterodimeric transcription factor. The post-translational hydroxylation of HIFα is catalyzed by enzymes of the iron(II)- and 2-oxoglutarate-dependent dioxygenase family. In humans, three prolyl hydroxylase isoenzymes (PHD1-3) and an asparagine hydroxylase [factor inhibiting HIF (FIH)] have been identified. Here we report on selective HIF hydroxylase inhibitors and studies on their mechanism of action with a view to developing therapeutic agents that modulate the HIF pathway for medicinal application.

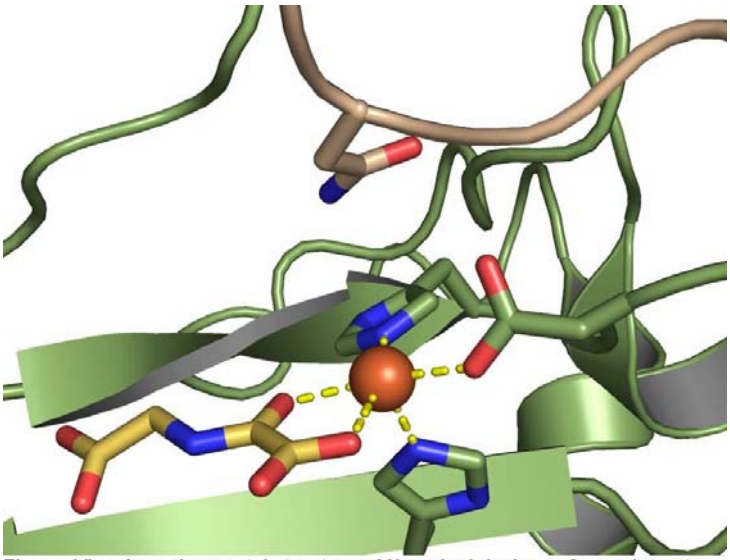


Figure. View from the crystal structure of N-oxalyolglycine, a 2-oxoglutarate analogue, complexed at the active site of FIH, a HIFa asparaginyl hydroxylase.

MEDI 426

IL-9 stimulates MUC4 transcription in respiratory epithelial cells

***Gautam Damera**, Baoyun Xia, and Goverdhan Sachdev, Department of Medicinal Chemistry, University of Oklahoma, College of Pharmacy, 1110N Stonewall Avenue, Oklahoma city, OK 73117, Fax: 405-271-7505, gautam-damera@ouhsc.edu*

MUC4 a membrane bound mucin, has been identified as a possible ligand for activation of ErbB-2, a receptor tyrosine kinase instrumental in modulating epithelial cell proliferation. In this study, we investigated the possible role of IL-9 a cytokine predominant in airway inflammatory states on MUC4 expression using an airway epithelial cell line NCI-H650. Presence of IL-9 receptor in NCI-H650 cells was established by immunohistochemical methodology using rabbit polyclonal anti-human IL-9R antibody. Maximal MUC4 levels were established at 25ng/ml after 2h of IL-9 exposure by realtime PCR. Western blotting analyses using a mouse monoclonal MUC4 antibody revealed a corresponding increase in MUC4 glycoprotein expression. Nuclear run on experiments indicated transcriptional regulation. Pretreatments with a JAK-3-specific inhibitor WHI-P131 substantially reduced IL-9 modulated MUC4 expression in a dose dependent fashion. These results implicate a potential role for IL-9 in MUC4 expression and airway epithelia cell restitution in airway inflammatory states. Supported by NIH:HL34012.

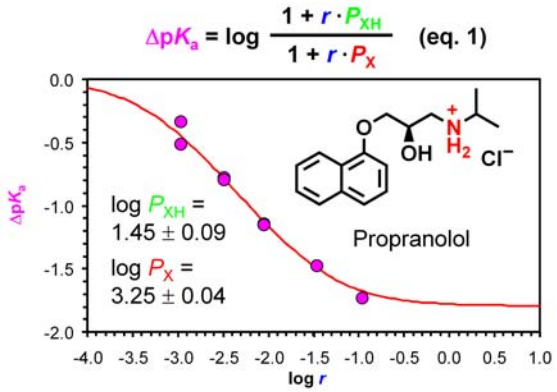
MEDI 427

Determination of liposome-water partition coefficients of pharmaceutical drugs using a simple laboratory titrator

***Arno Kraft**, Nicola M. Howarth, Rebecca Evans, Agnes A. Yeboah, and Leonard Gouzin, Chemistry, School of Engineering & Physical Sciences, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, United Kingdom, Fax: 44-131-4513180, a.kraft@hw.ac.uk*

Ionization constant, pK_a, and partition coefficient, log P, are two important physicochemical properties for any ionizable pharmaceutical drug. While the octanol–water partition coefficient is much more commonly employed in medicinal chemistry, there is an increasing interest in liposome–water partition coefficients, since phospholipid liposomes are much better mimics of a cell membrane than octanol. Unfortunately, highly purified phospholipids are also extremely expensive.

In this poster, we will discuss a simple and cost-effective potentiometric method for determining liposome–water partition coefficients for a range of monoprotic drugs. Titrations have been carried out with phosphatidyl choline of varying purity (96%, 86%, 25%). While cheaper phospholipids contain varying amounts of titratable impurities (fatty acids or phosphatidyl ethanolamine), these can be taken into account in the analysis of titration curves. The pK_a of the drug changes in the presence of a partitioning medium compared to an aqueous solution (eq. 1). The extent of the change, ΔpK_a, depends on the liposome-to-water ratio r, the log P_{XH} of the protonated and the log P_X of the deprotonated drug, both of which are obtained by curve fitting of the experimental data to eq. 1.



MEDI 428

Functional nanoliter chemical microarray for ultra high throughput screening and kinase profiling

Kurumi Y. Horiuchi[1]*, Yuan Wang*[1]*, Scott L. Diamond*[2]*, Stefan A. Kucharewicz*[1]*, and Haiching Ma*[1]*. (1) Reaction Biology Corp, One Great Valley Parkway, Suite 8, Malvern, PA 19355, Fax: 610-722-0246, kurumi@reactionbiology.com, (2) Department of Chemical Engineering, University of Pennsylvania*

Combining a chemical compound microarray and a proprietary aerosol deposition technology, we have created a functional chemical microarray system for ultra HTS. This platform can run over 6000 solution-phase reactions per microarray. Each reaction center containing chemical compound is printed in 1 nL volume, and a simple and rapid piezo-deposition delivers enzyme targets to activate each reaction center. In this study, we have applied this system for kinase profiling using a combination of solution-phase enzyme reaction, with either protein or peptide substrates, and solid-phase ELISA detection. The data demonstrate high sensitivity and linear detection. Kinetic parameters obtained using this system agreed with published data. Using this platform, high quality data for IC50 determination and selectivity study of kinase inhibitors are obtained. Multiple replications of chemical compound microarrays make kinase profiling easier and cost-effective, since each microarray can be used for different enzyme target.

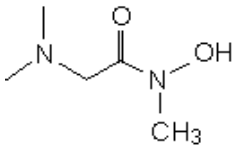
MEDI 429

Kinetic investigation of hydroxamic acids as ester hydrolysis catalysts for nucleic acid triggered prodrug activation (NATPA) systems

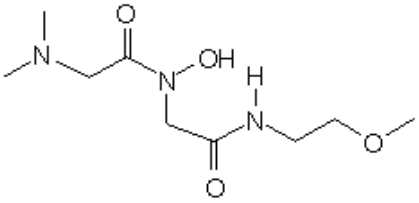
Bereket Y. Oquare *and J. S. Taylor, Department of Chemistry, Washington University, St. Louis, MO 63130-4899, byoquare@artsci.wustl.edu*

We have recently described a new approach to chemotherapeutic drugs in which a disease specific mRNA molecule is used to trigger the activation of a prodrug, otherwise known as nucleic acid triggered prodrug activation (NATPA) (1,2). Our first prototype made use of imidazole to catalyze the hydrolysis of ester-based prodrugs and probes, but was not very efficient. It has been reported that N-methyl-2-dimethylaminoacetohydroxamic acid (cat 1) is a

better catalyst than imidazole for the hydrolysis of active esters at biological pH (3). This poster focuses on a kinetic investigation of the hydrolysis of p-nitrophenyl and coumarin esters of N-Boc-protected amino acids by hydroxamic acid catalyst 1 and the related hydroxamic acids 2 and 3. (1) Ma, Z; Taylor, John-Stephen, PNAS, U.S.A, 2000, 97, 11159-1163, (2) Ma, Z; Taylor, John-Stephen, Bioconjugate Chem., 2003, 14, 679-683, (3) Ono, Mitsunori et al; Tetrahedron Letters, 1989, 30, 207-210.



1



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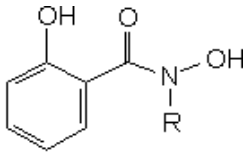


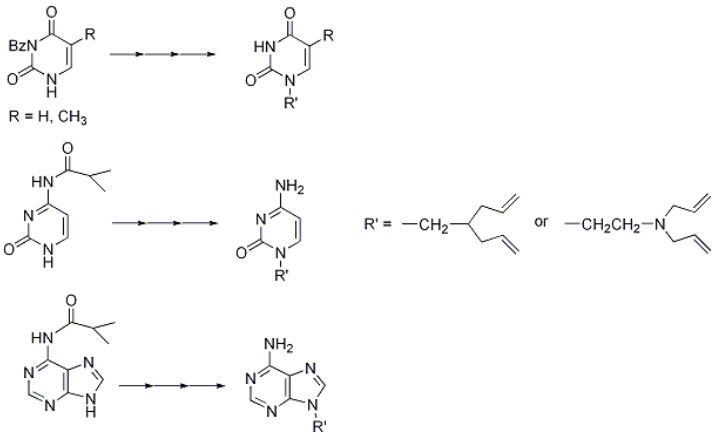
3a R=H
b R=CH_3

MEDI 430

Syntheses of non-conjugated dienes with nucleic bases attached: Varying the distance between the diene and the nucleic base

*Fares A. Fares, Rania Shatila, and **Kamal H. Bouhadir**, Department of Chemistry, American University of Beirut, Bliss Street, Beirut 11-0236, Lebanon, ff03@aub.edu.lb, kb05@aub.edu.lb*

The importance of synthetic methods for the preparation of synthetic oligodeoxynucleotides (ODNs) has increased remarkably during the last decade, because of their potential use in therapeutic applications, such as antisense & antigene, and diagnostic applications, such as biosensors & microarrays. One critical requirement for synthetic ODNs is their stability in biological environments, and hence, reasonable half-life in vivo. One possible approach to synthetic neutral ODNs is the copolymerization of non-conjugated dienes containing nucleic acid bases with sulfur dioxide to form polysulfones. Sulfones are neutral, achiral, and isolelectronic analogues of phosphodiesters that are stable to both chemical and biochemical degradations. We report, herein, the syntheses of a series of non-conjugated dienes with nucleic bases attached utilizing two different synthetic protocols. One protocol utilizes the Mitsunobu reaction to couple the protected nucleic base to the desired alcohol. These molecules are attractive intermediates for the synthesis of polysulfone nucleic acids.



MEDI 431

Effects of solvation on the chemistry of amino acid complexes of copper

***David A. Gallagher**, CAChe Group, Fujitsu America Inc, 15244 NW Greenbrier Parkway, Beaverton, OR 97006-5733, Fax: 503-531-9966, dgallagher@cachesoftware.com, and Londa Borer, Department of Chemistry, California State University Sacramento*

Copper (II) is an essential part of enzymes such as catecholoxidases and tyrosinases. Hence, there is considerable interest in the chemistry of copper with proteins and amino acids.

A conveniently simple model system, copper diglycinate, exists as both cis and trans isomers. While the cis isomer forms in aqueous solution, it is easily converted to the trans form on heating in the solid state. Some authors have suggested that although the trans isomer is more thermodynamically stable, the cis isomer is the kinetic product in aqueous solution. However, quantum chemistry studies reveal a different explanation.

Models of potential reaction pathways from simple intramolecular isomerization to water-catalyzed isomerization in solution, are compared with experimental observations and offer new insights into the coordination chemistry of copper with amino acids.

MEDI 432

In silico virtual ligand screening as a powerful tool to discover side effects of marketed and novel drugs

***William H. Bisson**[1], Anton Cheltsov[1], Jiyun Chen[2], James T. Dalton[2], Xiao-kun Zhang[3], and Ruben Abagyan[1]. (1) Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, wbisson@scripps.edu, (2) Division of Pharmaceutics, College of Pharmacy, The Ohio State University, (3) Oncodevelopmental Biology, The Burnham Institute*

Widely used traditional drug discovery technologies often do not perform well when applied to novel drug targets. They suffer from inadequate diversity, low hit rates, and might produce leads, which are toxic and/or exhibit poor bioavailability. Recently, it has been shown that by exploiting informations about the known side effects of marketed drugs, it is possible to generate drug leads with enhanced selectivity towards the observed side-effect target and with superior bioavailability and toxicity profile. Here, we propose a methodology, which enables to discover leads, based on known drugs, to a given protein target.We demonstrated its application for the discovery of novel non-steroidal antagonists against the human androgen receptor.Homology modeling was combined with virtual screening to produce a set of models able to discriminate known androgen antagonists from other binders. A library of marketed drugs was then docked into the best models, and selected compounds were assayed in vitro.Several marketed drugs were identified as mild androgen receptor antagonists in correlation with their clinical endocrinal side effects.

MEDI 433

Biotopology of Huntington's disease

*Demet Gurel, Chemistry and Physics, Touro College, 27 West 23 Street, New York, NY 10010, demetg@touro.edu, and **Okan Gurel**, IBM, 630 First Avenue, New York, NY 10016, protein@attglobal.net*

Huntingtin (Htt) is implicated in Huntington's disease (HD). Htt is a 3144 amino acid long monomer. Its mutated form is the extended-Htt by additional 103 Q(Gln-Glutamine) at the N-terminal. [1] Christopher A. Ross and his colleagues using extensions of 16Q and of 44Q experimentally determined that, while 16Q extension does not result in alterations, 44Q alters the conformation of the monomer, and fibrillation occurs. [2] Ross, et al. modelled fibrillation by alluding to helical formation (Figure 5). We showed that the conformation of Htt, DO(18-30), transforms to the conformation of the extended-Htt by addition of 103Q, DO(20-30). [3] In this presentation, we discuss the helical formation of DO(20-30) which fibrillates. We refer to the topology of 68 C(Cyc-Cysteine) and 186 P(Pro-Proline) residues and propose their role in conformational changes of extended-Htt. By comparing the rotational energies of DO(18), -10, and DO(20), -12, we conclude that pathological DO(20) is more stable than DO(18). [1] The Huntington's Disease Collaborative Research Group (1993) Cell 72, 971-983. (Fig.4, p.974-975). [2] Michelle A. Poitier, et al., The Journal of Biological Chemistry, v.277, n.43, Issue October 25, 2002, pp.41032-41037. [3] O. Gurel and D. Gurel, Polymer Preprints, v.40, n.2, August 1999. pp.1146-1147.

MEDI 434

Multivalent fertilinβ oligopeptides: The dependence of fertilization inhibition on length and density

***Younjoo Lee**, Department of Chemistry, Stony Brook University, Stony Brook, NY 11794, lee.younjoo@gmail.com*

The sperm protein fertilinβ, a member of the ADAM family of proteins is implicated in sperm-egg binding in all mammals studied to date. Multivalent inhibitors containing the three-amino acid binding sequence of fertilinβ, ECD, have been shown previously to be more effective inhibitors of fertilization than their monovalent counterparts. In this work, we probed sperm-egg interactions by examining the potency of fertilization inhibition by polymers that contained from 3 to 70 ECD pharmacophores in densities ranging from 10-100%. Evaluation of the polymer potency revealed that two multivalent contacts are sufficient for maximal inhibition, and that the distance between ECD pharmacophores required is 7-9 monomers. We conclude that inhibition requires recruitment of two receptors on the egg surface into an inhibitory complex.

MEDI 434

Multivalent fertilinβ oligopeptides: The dependence of fertilization inhibition on length and density

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lee.younjoo@gmail.com

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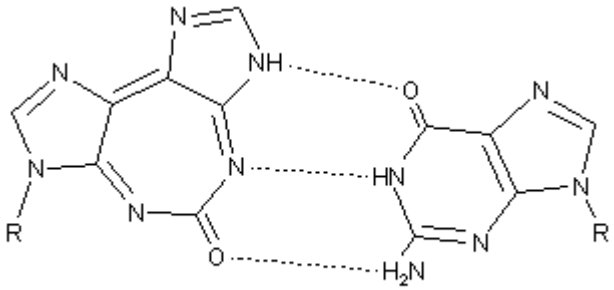
MEDI 435

Synthesis of a novel tricyclic nucleobase analogue containing a diimidazodiazepine nucleus with potential selectivity

Jules Guei *and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, jguei1@umbc.edu*

Recent efforts to expand the genetic alphabet have resulted in a variety of unnatural bases with unique base-pair motifs derived from their hydrogen-bonding or hydrophobic characteristics. Much less attention, however, is devoted to designing nucleobases that have enhanced base-pair selectivity based on both H-bonding and hydrophobic interactions. We report here the synthesis and base-pair hydrogen-bonding studies of a novel tricyclic nucleobase analogue (1) that has a potential selectivity to base-pair with guanine.



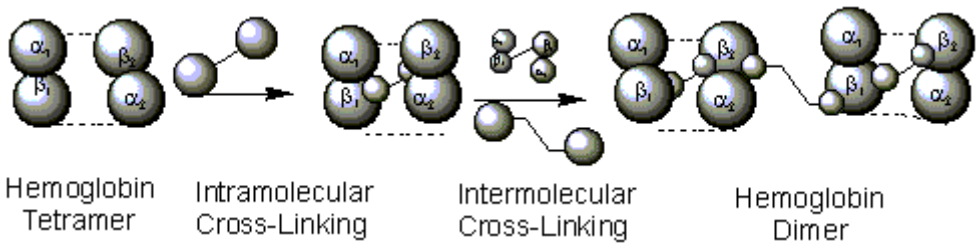
1 **G**

MEDI 436

Oligomerization of β-cleft cross-linked human hemoglobin: Synthesis, intramolecular cross-linking, and intermolecular coupling studies with polyfunctional organic reagents

Hongyi Cai*, Timothy A. Roach, and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland,Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, hongyi1@umbc.edu*

Current efforts to develop blood substitutes based on cell-free hemoglobin are directed toward (a) tuning its oxygen affinity to afford adequate oxygen delivery from lung to tissues via covalent cross-linking with an appropriate reagent that mimicks the hemoglobin's natural allosteric modifier 2,3-diphosphoglycerate (DPG), and (b) increasing the steric bulk of the cross-linked hemoglobin to allow its retention in circulation for prolonged periods of time as well as to prevent its facile seeping through the endothelium and the subsequent interaction with nitric oxide, which results in vasoconstriction, and hence, the elevated blood pressure. As part of a program to address the current problems facing the blood substitute research, we report here the results of our studies on sequential intramolecular cross-linking and intermolecular coupling of human hemoglobin, employing a variety of polyfunctional organic reagents.



MEDI 437

Novel neomycin conjugates for multi-recognition of DNA

Bert Willis *and Dev P. Arya, Department of Chemistry, Clemson University, 461 Hunter, Clemson, SC 29634, albertw@clemson.edu*

We have previously shown that neomycin can be conjugated with intercalating or groove binding moieties which significantly stabilize nucleic acids. The presented research results entertain multiple recognition pathways by the synthetic incorporation of groove – binding and intercalating moieties with neomycin. Viscometric and spectroscopic techniques for studying duplex DNA binding support a multi – recognition – based binding mode. The recognition of duplex nucleic acids by such conjugates provide further insight on the interactions that govern ligand binding and illustrate the potential for applications of such conjugates capable for multi-recognition of nucleic acids.

MEDI 438

Novel boron containing gadolinium texaphyrins

Achintya K. Bandyopadhyaya[1]*, Lamine A. Diop*[2]*, and Werner Tjarks*[1]*. (1) Division of Medicinal Chemistry & Pharmacognosy, College of Pharmacy, The Ohio State University, 500 W 12th Avenue, 416 Parks Hall, Columbus, OH 43214, bandyopadhyaya.1@osu.edu, (2) Collège Universitaire de Saint-Boniface, Winnipeg, Manitoba, Canada*

Texaphyrins have been discussed as potential cancer therapeutic agents. Motexafin, a gadolinium metal containing texaphyrin is currently in clinical studies as a cancer chemotherapeutic agent, as a MRI agent, and as a X-radiation sensitizer. Gadolinium

texaphyrins substituted with boron clusters could lead to novel cancer therapeutic and diagnostic agents in particular for use in combined gadolinium and boron neutron capture therapy (Gd/B NCT). Synthetic progresses towards novel boron and gadolinium containing texaphyrins, their characterization by MS and UV-vis spectrocsopy, and the results of their preliminary biological evaluation will be discussed.

MEDI 439

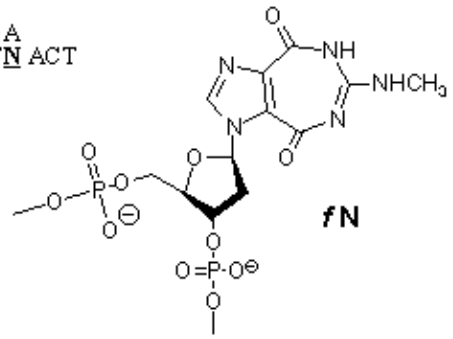
Transcription of a DNA template incorporated with a "fat" nucleotide: Studies of base-pair specificity and primer extension using Klenow fragments exo$^-$ and exo$^+$

Ning Zhang[1], *Anila Bhan*[2], *and Ramachandra S. Hosmane*[1]. *(1) Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, nzhang@umbc.edu, (2) Biosciences, GE Healthcare, Piscataway, New Jersey 08855*

Studies of incorporation of modified nucleotides are important in light of the heightened current interest in expanding the genetic alphabet, coupled with the scope for gaining valuable information on interactions between nucleic acid templates and polymerases, which ultimately determine the fidelity of replication in living systems. We report here the results of our studies on transcription of a DNA template incorporated with a novel "fat" nucleotide (1), using Klenow fragments exo$^+$ and exo$^-$. Our data show that 1 can base-pair with C, A or G, but not with T, although C appears to be the preferred base. The data also suggest that the primer extension is greatly inhibited after insertion of C, A, or G in the complementary strand against a "fat" nucleotide in the template strand. DNA primer and template employed in the experiments:

5'-/5Cy5/TAA TAC GAC TCA CTA TAG GGA GA
ATT ATG CTG AGT GAT ATC CCT CTN ACT

Where, Cy5 is a fluorophore, and N is G or *f*N



MEDI 440

Novel approach for diagnostics of genetic material applying auto-fluorescent N^2,N3-etheno-adenosine

Bilha Fischer *and Einat Sharon, Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel, Fax: 972-3-5351-250, bfischer@mail.biu.ac.il*

The natural bases of DNA are not useful as fluorescent probes for diagnostics because of their extremely low quantum yields. Current methods for labeling DNA/RNA by large extrinsic

fluorescent probes suffer from many limitations. Therefore, we propose a solution based on the incorporation of auto-fluorescent and base-pairing nucleotide analogues into nucleic acids. Specifically, we designed a novel analogue: N^2,N3-etheno-adenosine, **1**, representing a minor modification of adenosine. We developed three short, facile, and regiospecific syntheses of **1**. In addition, we measured the absorption and emission spectra of **1** at various pH values. We found **1** suitable for fluorescence detection based on its fluorescence at physiological pH, λ_{max}420 nm, φ0.03,and τ2.26 ns.Furthermore, we demonstrated the conserved adenine H-bonding pattern of **1** by determining its proton equilibria, base-pairing with other nucleobases, and incorporation into RNA by RNA polymerase. Therefore, we propose **1** as a promising alternative to the limited staining methods for diagnostics of genetic material. [A US patent application was filed on January 24, 2005]

MEDI 441

Synthesis and biological activity of novel polyhydroxy steroids

Katharine L. Bowdy *and Branko S. Jursic, Department of Chemistry, University of New Orleans, 2000 Lakeshore Drive, New Orleans, LA 70148, kbowdy@uno.edu*

Polyhydroxy steroids have consistently attracted much attention in the recent literature primarily due to their cytotoxicity against human tumor cells. These highly oxygenated steroids are abundant in marine organisms, especially starfish, which have provided a wide variety of biologically active steroids. Unfortunately, the synthesis of the polyhydroxy steroids isolated from nature generally involves complex multi-step and stereoselective syntheses. Since little is known about their mechanism of action, it remains unclear which moieties of the steroids are responsible for their biological activity. Therefore, the efficient synthesis from cholesterol and diosgenin of novel polyhydroxy steroids which are structurally similar to these biologically active natural products will be presented along with their biological activity.

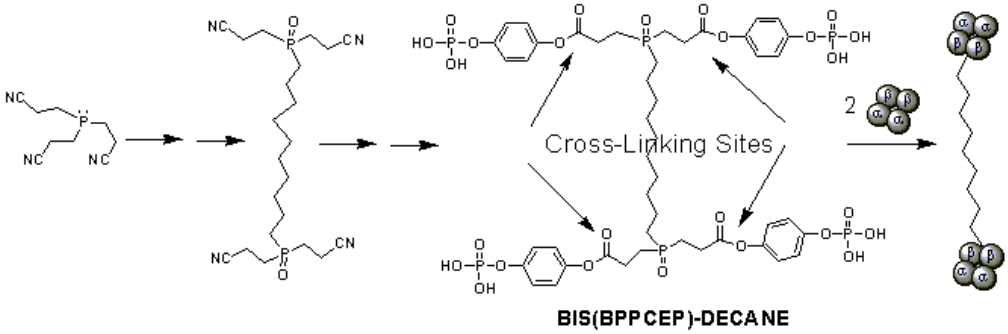
MEDI 442

An approach toward the synthesis of a multifunctional organic reagent to effect simultaneous intramolecular cross-link and intermolecular cross-bridge between two molecules of hemoglobin

Margaret Dabek*, Timothy A Roach, and Ramachandra S. Hosmane, Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-1148, mdabek1@umbc.edu*

Intramolecular cross-linking of cell-free human hemoglobin with an appropriate organic reagent is known to tune its oxygen affinity to allow adequate oxygen delivery from lung to tissues as well as enhance the retention time of hemoglobin in circulation. However, the modified hemoglobin still suffers from facile filtration through the endothelial lining and subsequent reaction with the vasorelaxing nitric oxide (NO), resulting in elevated blood pressure. Our goal is to prevent this undesired filtration by increasing the size of modified hemoglobin via oligomerization. To this end, we have outlined a novel approach which involves the synthesis

of a polyfunctional organic reagent, called Bis(BPPCEP)-Decane, which would simultaneously modify and dimerize the hemoglobin, as schematically represented below. The current status of research on organic synthesis and hemoglobin cross-linking studies of this reagent will be presented.



MEDI 443

Synthetic high affinity ligands: Molecular targeting agents

Saphon Hok[1]*, Rod L. Balhorn*[2]*, Michael E. Colvin*[2]*, Michele H. Corzett*[2]*, Monique Cosman*[2]*, Gerald L. DeNardo*[3]*, Sally J. Denardo*[3]*, Cheryl E. Dolan*[2]*, Leslie M. Hanna*[1]*, Edmond Y. Lau*[2]*, Felice C. Lightstone*[2]*, Arutselvan Natarajan*[3]*, and Julie Perkins*[1]*. (1) Chemistry and Materials Science, Lawrence Livermore National Laboratory, 7000 East Avenue, Livermore, CA 94551, hok2@llnl.gov, (2) Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, (3) Department of Internal Medicine, University of California, Davis Medical Center*

Synthetic High Affinity Ligands (SHALs) are being developed as molecular targeting agents for the delivery of radionuclides to radiation-sensitive cancers in the complex background of the human body. SHALs are multivalent synthetic ligands designed to bind to a protein tumor marker with high affinity and specificity as an alternative to traditional radio-immunotherapy agents. Here, the design, synthesis and in vitro and in vivo affinity of SHALs designed specifically to target the Non-Hodgkins Lymphoma tumor marker, HLA-DR10, will be presented. The effect of increasing multivalency on the affinity of SHALs for their protein target and the broad application of SHALs toward other protein targets will also be discussed. This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract W-7405-Eng-48.

MEDI 443

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MEDI 444

Inhibition of protein glycation by Rutin's metabolites

***Ihab F Halaweish**, Daniel Cervantes Laurean, and Fathi T Halaweish, Chemistry & Biochemistry, South Dakota State University, 121 Shepard Hall, Box 2202, Brookings, SD 57707, Fax: 605-688-6364, ihab.halaweish@sdstate.edu*

Protein glycation involves the non-enzymatic reaction between a reducing sugar and the amino group of a lysine residue. Initial protein glycation through a series of reactions leads to formation of advanced glycation end products (AGEs), which has been implicated in a number of diseases such as diabetes, Alzheimer's and the ageing process. It was important to establish whether inhibition of AGEs by rutin and/or its metabolites, was due to metal chelation or to inhibition of glycation. Development of AGEs inhibitors has a potential application as therapeutic agents in several diseases. AGEs formation was monitored by fluorescence and protein crosslinking model where ADP-ribose was incubated with histone, which occurs many times faster than using glucose. The data show that rutin's metabolites effectively inhibited the formation of AGE biomarkers protein-linked fluorescence and protein crosslinking. Rutin metabolites containing vicinyl dihydroxyl groups, i.e., 3,4-DHT, 3,4-DHPAA, inhibited formation of AGEs adducts, in a dose-dependent manner whereas non-vicinyl dihydroxyl group containing metabolites, i. e., HVA and m-HPAA were not effective. These studies demonstrate that rutin metabolites can inhibit AGEs formation in vitro. These effects likely contribute to the beneficial health effects associated with rutin consumption.

MEDI 445

Incorporation of boronic acid fluorescent reporters into DNA for aptamer selection

***Na Lin**[1], Zhen Huang[1], Craig Altier[2], Lynette Johnston[2], Nicolas Carrasco[1], Hao Fang[1], Jun Yan[1], Siming Wang[1], and Binghe Wang[1]. (1) Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, 33 Gilmer St. SE, Atlanta, GA 30303, (2) College of Veterinary Medicine, North Carolina State University*

It is well known that cell surface saccharide structures as part of glycosylated proteins and peptides are characteristic signatures of different cell types. Such characteristic saccharide structures might be considered the zip code for cell addressing. This is especially important in developing new diagnostics. For example, altered protein glycosylation or the expression of certain glycoproteins has been associated with the development and progression of many types of cancers. In this project, we are interested in developing fluorescence sensors based on boronic acid-modified DNA aptamers that can specifically recognize differences in glycosylation patterns of various glycoproteins. Such sensors can be used for the early detection of cancer, among other things. In this presentation, we will discuss our successful effort in this area.

MEDI 446

Design, synthesis and evaluation of conformationally restricted Smac mimetics as inhibitors of IAP family proteins

Haiying Sun[1]*, Dongguang Qin*[1]*, Zaneta Nikolovska-Coleska*[1]*, Chao yie Yang*[1]*, Sanjeev Kumar*[1]*, Wei Gao*[1]*, Su Qiu*[1]*, Jianfeng Lu*[1]*, York Tomita*[2]*, Peter P. Roller*[3]*, and Shaomeng Wang*[1]*. (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, (2) Lombardi Cancer Center, Georgetown University, (3) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health*

Smac/DIABLO (second mitochondria-derived activator of caspase or direct IAP binding protein with low pI) is a protein released from mitochondria in response to apoptotic stimuli. It interacts with the BIR3 domain of XIAP, cIAP-1 and cIAP-2 and a single BIR domain in ML-IAP and functions as a direct endogenous inhibitor of IAP proteins. In recent studies, it has been shown that short Smac peptides can bind to the recombinant XIAP BIR3 domain protein with the same affinities as the mature Smac protein. In order to overcome the intrinsic limitations of Smac peptides such as poor in vivo stability and poor bioavailability, we have designed and synthesized a series of conformationally constrained bicyclic Smac mimetics. Our most potent Smac mimetics have binding affinities 100-folds better than the Smac AVPI peptide. These compounds effectively overcome the inhibition of the activity of caspase-9 and -3 by XIAP BIR3 protein in cell-free functional assays. Importantly, they potently inhibit cell growth in a number of cancer cell lines with high levels of IAP proteins and have good selectivity to normal cells. We wish to present the structure-based design, synthesis, biochemical and biological characterization of these highly potent, non-peptide, drug-like small-molecule Smac mimetics.

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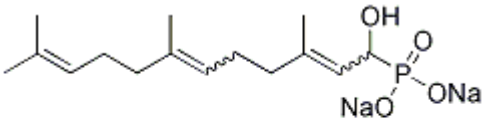
MEDI 447

Synthesis and biological evaluation of all α-hydroxyfarnesylphosphonate geometric isomers on RAS farnesylation

Jose S. Yu[1]*, Andrew J. Wiemer*[2]*, Raymond J. Hohl*[3]*, and David F. Wiemer*[1]*. (1) Department of Chemistry, University of Iowa, Iowa City, IA 52242, Fax: 319-335-1270, jose-yu@uiowa.edu, (2) Molecular Biology Program, University of Iowa, (3) Department of Internal Medicine, University of Iowa*

The Ras family of small GTPases plays a key role in a vast network of cell signaling, and mutated Ras has been linked to ~30% of all human cancers. To become biologically active, these proteins must undergo farnesylation through a reaction with farnesyl pyrophosphate (FPP) catalyzed by farnesyl transferase (FTase, EC 2.5.1.58); inhibition of this process might be exploited to impede Ras oncoprotein function. One approach to inhibition of FTase utilizes nonhydrolyzable analogs of FPP. The paradigm of this strategy involved the development of E,E-α-hydroxyfarnesylphosphonate (α-HFP, 1), from commercially available E,E-farnesol, as a potent inhibitor of FTase in vitro. We will discuss an efficient synthesis of the remaining three olefin isomers of α-HFP (2-4) and the effects of olefin geometry on Ras farnesylation.



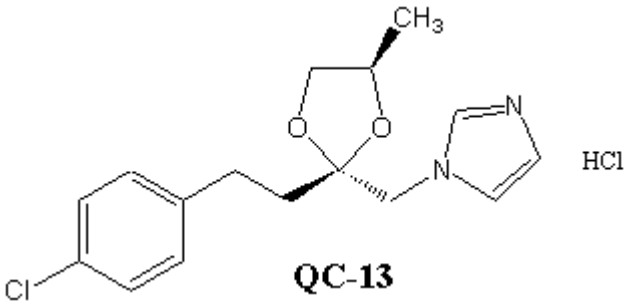
1 *2E,6E*-α-HFP **2** *2Z,6E*-α-HFP
3 *2E,6Z*-α-HFP **4** *2Z,6Z*-α-HFP

MEDI 448

Imidazole—dioxolane compounds as heme oxygenase inhibitors with enhanced selectivity for HO-1

Jason Z. Vlahakis[1]*, Robert T. Kinobe*[2]*, James F. Brien*[2]*, Kanji Nakatsu*[2]*, and Walter A. Szarek*[1]*. (1) Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, ON K7L 3N6, Canada, vlahakis@chem.queensu.ca, (2) Department of Pharmacology and Toxicology, Queen's University*

Several imidazole—dioxolane compounds were synthesized and evaluated as novel inhibitors of heme oxygenase (HO). A number of these analogues showed enhanced activity for HO over other heme-dependent enzymes (such as nitric oxide synthase, soluble guanylyl cyclase, and cytochromes P450). In addition, these compounds were found to be highly selective for the HO-1 isozyme (stress induced), and had substantially less inhibitory activity on the HO-2 isozyme (constitutive). One of the compounds, **QC-13**, exhibits an IC_{50} value of 0.6 ± 0.2 mM for HO-1 (rat spleen) and approximately 394 mM for HO-2 (rat brain), with a selectivity index approaching 657. Structure—activity relationships of various analogues with respect to the inhibition of HO and other enzymes will be presented. These drugs are anticipated to become very useful tools in elucidating the physiological/pathological roles of HO (and thus carbon monoxide) in mammalian and other biological systems.



QC-13

MEDI 449

Design and synthesis of stealth polymeric nanospheres and applications to the delivery of bioactive agents

Oluyomi A. Okunola*, Department of Chemistry, Howard University, 525 College Street, Washington, DC 20059, yom200@yahoo.com, and Emmanuel O. Akala, Department of Pharmaceutical Sciences, School of Pharmacy, Howard. University*

New drugs for different therapeutic purposes are being developed daily. However, their successful administration is limited by problems such as poor water-solubility, toxicity, instability en route to the site of action and rapid clearance. Biodegradable polymeric stealth nanospheres are being developed to circumvent these problems. The nanospheres are stable to opsonization by plasma proteins, resistant to clearance in the liver by the mononuclear phagocyte system, and have long half-lives in the blood. Targeting moieties can be tethered to the nanospheres for site-specific distribution in biological systems, especially for transport across the blood-brain barrier and tumor targeting. We have designed and synthesized (via free-radical dispersion polymerization) hydrolyzable biodegradable stealth nanospheres network consisting of hydrophobic cores, crosslinked by a pH-sensitive hydrolyzable

crosslinker, with hydrophilic polymer on their surfaces. They have been characterized for particle size, surface morphology, and functionality. These nanospheres are suitable for the delivery of different classes of bioactive agents.

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Design and synthesis of stealth polymeric nanospheres and applications to the delivery of bioactive agents

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MEDI 450

Synthesis and biological evaluation of novel heterocyclic compounds as SMN2 promoter activators for the potential treatment of spinal muscular atrophy

*J. Singh[1], **J Thurmond**[1], B Pease[1], M Rao[1], M Palomo[1], G Pai[1], L Bedell[1], M Keyvan[1], R Mishra[1], J Zhang[1], E Onua[1], E Bjarnadottir[2], M Haraldsson[2], T Andresson[2], T Gunnseinsdottir[2], P Atlason[2], G Sigthorsson[2], G Bragason[3], M Thorsteinsdottir[3], and M Gurney[2]. (1) deCODE Chemistry, 2501 Davey Road, Woodridge, IL 60517, Fax: 630-783-4646, jsingh@decode.com, jthurmond@decode.com, (2) deCODE genetics, Inc, (3) Encode*

Spinal Muscular Atrophy (SMA) is an inherited neuromuscular disorder caused by deletion of the telomeric copy of the survival motor neuron (SMN1) gene with loss of SMN protein. SMN2, the centromeric copy, which differs from SMN1 by a translationally silent single nucleotide mutation (C->T), leads to mis-splicing of the SMN2 mRNA and consequently mostly truncated SMN protein is produced, although some full-length protein is produced as well. Increasing the activity of the SMN2 gene, by producing additional full-length SMN protein, provides a promising strategy for the treatment of SMA. Utilizing a cell-based SMN2 promoter assay, a series of 2,4-diaminoquinazolines analogs have been identified as potentially useful compounds. deCODE's medicinal chemistry approach coupled with identification of potential

barriers, has led to identification of nanomolar, metabolically stable, orally bioavailable and brain permeable series of analogs. Highlights of the medicinal chemistry effort towards lead optimization and SAR for this scaffold will be described.

MEDI 451

Synthesis and polymerization of a functionalized caprolactone monomer for biomedical applications

***J. Michelle Leslie**, Rajesh Kumar Mishra, and Edward Turos, Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, SCA 400, Tampa, FL 33620, jmleslie@helios.acomp.usf.edu*

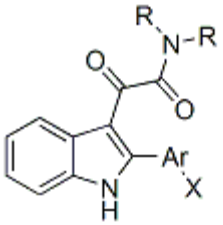
Polycaprolactone is known to be biodegradable/bioresorbable and non-toxic. These properties make polycaprolactone a good candidate for use in drug delivery. By building functionality into the caprolactone monomer, a "handle" whereby drug molecules can be attached is introduced. A caprolactone bearing functionality at the 4-position has been synthesized and subsequently polymerized using Novozym-435 as the catalyst.

MEDI 452

Development of SPECT imaging agents for the peripheral benzodiazepine receptor

***Idriss Bennacef**[1], Coliin N. Haile[2], Andrei O. Koren[3], J.K. Staley[4], Ronald M Baldwin[5], frederic Bois[1], Anne Schmidt[6], and Gilles D Tamagnan[3]. (1) Yale School of Medicine, 950 Campbell Avenue, West Haven, CT 06516, idriss.bennacef@yale.edu, (2) Yale School of Medecine, (3) Institute for Neurodegenerative Disorders, (4) Department of Psychiatry, VA Medical Center 116A2, Yale University, (5) Vanderbilt University, (6) Central Research Division, Pfizer Inc*

The peripheral benzodiazepine receptor (PBR) is expressed in both peripheral and central nervous system (CNS). Although it plays a critical role in the cell, less is known about the pathophysiological involvement of PBR. It could be a target suitable for therapeutic indications such as cancer, inflammation and auto-immune diseases, and neurodegenerative diseases. With the aim of visualizing PBR in vivo by single photon emission computed tomography (SPECT) or positron emission tomography (PET), we have undertaken the synthesis of new PBR ligands bearing iodine or fluorine based on the indolylglyoxamide structure. We report here the synthesis of new halogenated indolylglyoxamides displaying binding affinity Ki in the range 6.2-41 nM and lipohilicity log D 1.7-2.3. The most potent and selective ligands were radiolabeled with radioiodine for use as SPECT probes.



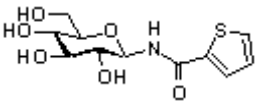
A= phenyl, pyridine
X = F, I
R = Et, Bu, Hex, $(CH_2)_2OCH_3$

MEDI 453

Synthetic approaches to cell proliferation inhibitors

Sarah L Rawe[1]*, Violeta Zaric*[2]*, Kathy M O' Boyle*[2]*, and Paul V Murphy*[1]*. (1) Department of Chemistry, University College Dublin, Belfield, Dublin 4 D4, Ireland, Fax: +353-1-7162127, sarah.rawe@ucd.ie, (2) Conway Institute of Biomolecular and Biomedical Research, University College Dublin*

The synthesis, structural analysis and biological evaluation of a range of novel thiophene-glucose conjugates will be described. Some compounds show activity as inhibitors of endothelial cell proliferation.



MEDI 454

Multi-step preparation of PET imaging probes in integrated microfluidic circuits

Guodong Sui[1]*, Cheng-Chung Lee*[2]*, Nagichettiar Satyamurthy*[1]*, James R. Heath*[3]*, Michael E. Phelps*[1]*, Stephen R. Quake*[4]*, and Hsian-Rong Tseng*[1]*. (1) Crump Institute for Molecular Imaging and Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, 700 Westwood Plaza, Los Angeles, CA 90095, Fax: 310-2068975, gsui@mednet.ucla.edu, (2) Department of Bioengineering, California Institute of Technology, (3) Division of Chemistry and Chemical Engineering, California Institute of Technology, (4) Department of Bioengineering, Stanford University*

We demonstrate that the [18F]radiolabeled Positron Emission Tomography (PET) imaging probe, 2-deoxy-2-[18F]fluoro-D-glucose (FDG), can be synthesized in a highly efficient manner in an integrated microfluidic device. Three sequential processes—concentration of [18F] fluoride, radiofluorination, and hydrolytic deprotection— were performed to produce FDG in a radiochemical yield of 30%, with 98% radiochemical purity. Using this integrated microfluidic chip, the total production time for FDG is 14 min—a significant improvement over the conventional method (50 min) using commercial automated synthesizers. These results not only constitute a proof of principle for performing sequential processes for chemical synthesis

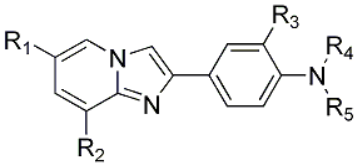
on the nanogram scale but also provide the impetus to employ integrated microfluidics chips to generalize, accelerate, diversify and lower the cost in the preparation of radiolabeled imaging probes.

MEDI 455

Structure-activity relationship study of IMPY derivatives as candidate radioligands for β-amyloid

Lisheng Cai[1]*, Lisa Nichols*[2]*, Jessica Cuevas*[1]*, Sebastian Temme*[1]*, Mary M. Herman*[3]*, Robert B. Innis*[2]*, and Victor W. Pike*[1]*. (1) PET Radiopharmaceutical Sciences, Molecular Imaging Branch, National Institute of Mental Health, 10 Center Drive, Bldg 10, B3C346, Bethesda, MD 20892, Fax: 301-480-5112, cail@intra.nimh.nih.gov, (2) Molecular Imaging Branch, National Institute of Mental Health, (3) Clinical Brain Disorders Branch, National Institute of Mental Health*

We have evaluated the tertiary amines, [18F]FEM-IMPY [N-(2-fluoroethyl)-4-(6-iodo-H-imidazo [1,2-a]pyridin-2-yl)-N-methylbenzeneamine] and its 3-fluoropropyl analog, [18F]FPM-IMPY, as beta-amyloid radioligands [1]. However, metabolism is rapid via de-alkylation of the tertiary aromatic amino group, culminating in defluoridation and high uptake of radioactivity in bone. With a view to avoiding rapid defluoridation, we decided to make use of 'isosteric' and 'isoelectronic' effects in the design of further analogs of IMPY. One set of analogs are secondary amines in which a methyl group is 'shifted' from the tertiary amine nitrogen to the nearest ortho ring position. The second set have a thiol ether instead of iodine in the 6-position. The third set combines both strategies. Through this in vitro evaluation, promising candidates have been identified as potential PET radioligands. The SAR study identifies that the binding site typical of 6-OH-BTA-1 (PIB) is a relatively small site, with only the 6-position in IMPY derivatives tolerating substantial structural change.



IMPY Derivatives, **1**

R_1 = F, Cl, Br, I, SEt, SCH_2CH_2OH, SCH_2CONH_2, OH, OCH_3

R_2 = H, CN

R_3 = H, Me, Br

R_4 = H, Me

R_5 = Me, CH_2CH_2F, $CH_2CH_2CH_2F$

MEDI 455

Structure-activity relationship study of IMPY derivatives as candidate radioligands for β-amyloid

Lisheng Cai[1]*, Lisa Nichols*[2]*, Jessica Cuevas*[1]*, Sebastian Temme*[1]*, Mary M. Herman*[3]*, Robert B. Innis*[2]*, and Victor W. Pike*[1]*. (1) PET Radiopharmaceutical Sciences, Molecular Imaging Branch, National Institute of Mental Health, 10 Center Drive, Bldg 10, B3C346, Bethesda, MD 20892, Fax: 301-480-5112, cail@intra.nimh.nih.gov, (2) Molecular Imaging Branch, National Institute of Mental Health, (3) Clinical Brain Disorders Branch, National Institute of Mental*

Health

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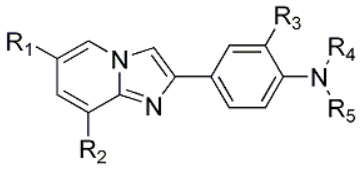


IMPY Derivatives, **1**

R_1 = F, Cl, Br, I, SEt, SCH_2CH_2OH, SCH_2CONH_2, OH, OCH_3

R_2 = H, CN

R_3 = H, Me, Br

R_4 = H, Me

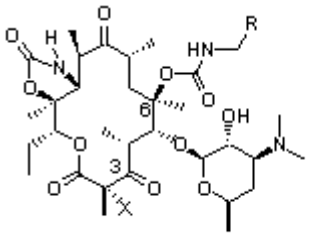
R_5 = Me, CH_2CH_2F, $CH_2CH_2CH_2F$

MEDI 456

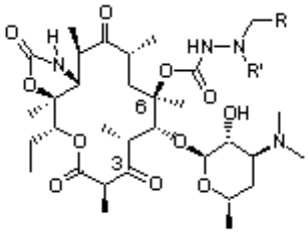
Synthesis and antimicrobial properties of novel C-6 alkoxycarbamate ketolides

***Xiaodong Xu**, Todd Henninger, Darren Abbanat, Karen Bush, Barbara Foleno, Jamese Hilliard, and Mark Macielag, Antimicrobial Agents Research Team, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, 1000 Route 202, Raritan, NJ 08869, Fax: 908-203-8109, xxu@prdus.jnj.com*

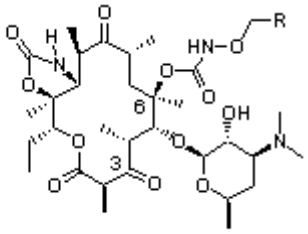
Ketolides are C-3-keto derivatives of erythromycin A with excellent activity against most macrolide-resistant respiratory tract pathogens. We recently identified a series of novel ketolides (I) in which the heteroaryl group is attached to the macrolactone ring via a C-6 carbamate linkage. The best compounds in this series displayed in vitro and in vivo activities comparable to ot better than the marketed ketolide antibiotic telithromycin (Ketek). Subsequently, we have reported on the extension of this approach to novel ketolides with the preparation of a series of C-6 carbazate ketolides (II). As part of our continuing investigations in this area we have now prepared C-6 alkoxycarbamate ketolides of general structure III. The synthesis and structure-activity relationships of this new series will be discussed and compared with the results from previous series.



I (X = H, F)



II



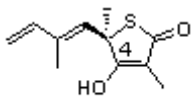
III

MEDI 457

Synthesis of 4-position hydrophilic derivatives of thiolactomycin as antitubercular agents

Pilho Kim[1]*, Yong-Mei Zhang*[2]*, Gautham Shenoy*[1]*, Ujjini Manjunatha*[1]*, Helena Boshoff*[1]*, Quynh-Anh Nguyen*[1]*, Michael Goodwin*[1]*, Darcie Miller*[3]*, Stephen White*[3]*, Ken Duncan*[4]*, Charles O. Rock*[2]*, Clifton E. Barry III*[1]*, and Cynthia S. Dowd*[1]*. (1) Tuberculosis Research Section, NIAID/National Institutes of Health, Rockville, MD 20852, Fax: 301-402-0993, pkim@niaid.nih.gov, (2) Department of Infectious Diseases, St. Jude Children's Research Hospital, (3) Department of Structural Biology, St. Jude CHildren's Research Hospital, (4) GlaxoSmithKline*

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the most deadly infectious diseases; infecting one-third of the world's population, 8 million new cases and 2-3 million deaths each year. MDR-TB, HIV/TB coinfection, and current lengthy TB regimen issues consequently require new drug development for TB treatment. Given that cell wall biosynthesis is a proven target for TB chemotherapeutic development, our effort for TB drug discovery started from thiolactomycin (TLM). TLM is known to inhibit key condensing enzymes in bacterial cell wall biosynthesis. According to a cocrystal structure of TLM and E. coli FabB, analogous to M. tb. condensing enzymes, the 4-position hydroxyl group of TLM is thought to point toward the binding site of the phosphopantetheine portion of the malonyl-ACP substrate. Thus, in order to achieve an increase in activity against M. tb, synthesis of 4-position hydrophilic derivatives of TLM have been explored. To better understand this binding site, SAR of the TLM 4-position will be discussed.



Thiolactomycin (TLM)

MEDI 458

Synthesis and binding profile of a novel series of (S)-2β-substituted-4',4"-difluorobenztropine analogs

Mu-Fa Zou[1]*, Jianjing Cao*[1]*, Theresa Kopajtic*[2]*, Raj Desai*[2]*, Jonathan L. Katz*[2]*, and Amy H. Newman*[1]*. (1) Medicinal Chemistry Section, NIDA-IRP, NIH, DHHS, 5500 Nathan Shock Dr,*

Baltimore, MD 21224, mzou@intra.nida.nih.gov, (2) Psychobiology Section, NIDA-IRP, NIH, DHHS

Extensive studies on cocaine, benztropine, and their respective analogs have revealed that these dopamine uptake inhibitors not only have distinct structural requirements for binding to the dopamine transporter (DAT), but also have different behavioral profiles in animal models of cocaine abuse. Although the benztropines bind with high affinity to the DAT without substitution in the 2-position of the tropane ring, only a substituent in the S-configuration is tolerated at DAT, in direct contrast to cocaine and its analogues that must have the 2-position substituent in the R-configuration. Interestingly, simple (S)-2β-carboalkoxy 4',4"-difluorobenztropines produce cocaine-like discriminative stimulus effects in rats, unlike benztropine and analogues in which substitution is made at the tropane N or 3-position. To further investigate SAR at the 2-position, we designed and synthesized a novel series of S-2-substituted 4',4"-difluorobenztropines. Evaluation for binding to the DAT, NET, SERT and muscarinic M1 receptors revealed that these compounds represent some of the highest affinity and most DAT selective ligands reported to date.

MEDI 458

Synthesis and binding profile of a novel series of (S)-2β-substituted-4',4"-difluorobenztropine analogs

Mu-Fa Zou[1]*, Jianjing Cao*[1]*, Theresa Kopajtic*[2]*, Raj Desai*[2]*, Jonathan L. Katz*[2]*, and Amy H. Newman*[1]*. (1) Medicinal Chemistry Section, NIDA-IRP, NIH, DHHS, 5500 Nathan Shock Dr, Baltimore, MD 21224, mzou@intra.nida.nih.gov, (2) Psychobiology Section, NIDA-IRP, NIH, DHHS*

Extensive studies on cocaine, benztropine, and their respective analogs have revealed that these dopamine uptake inhibitors not only have distinct structural requirements for binding to the dopamine transporter (DAT), but also have different behavioral profiles in animal models of cocaine abuse. Although the benztropines bind with high affinity to the DAT without substitution in the 2-position of the tropane ring, only a substituent in the S-configuration is tolerated at DAT, in direct contrast to cocaine and its analogues that must have the 2-position substituent in the R-configuration. Interestingly, simple (S)-2β-carboalkoxy 4',4"-difluorobenztropines produce cocaine-like discriminative stimulus effects in rats, unlike benztropine and analogues in which substitution is made at the tropane N or 3-position. To further investigate SAR at the 2-position, we designed and synthesized a novel series of S-2-substituted 4',4"-difluorobenztropines. Evaluation for binding to the DAT, NET, SERT and muscarinic M1 receptors revealed that these compounds represent some of the highest affinity and most DAT selective ligands reported to date.

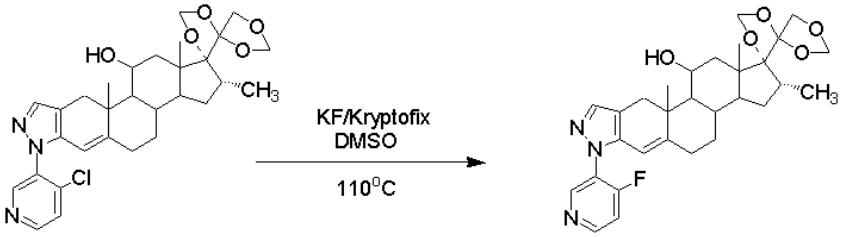
MEDI 459

Microwave-enhanced nucleophilic fluorination in the synthesis of fluoropyridyl derivatives of [3,2-c]pyrazolo-corticosteroids

Michael G.C. Kahn*, Emmanuel Konde, Francis Dossou, and Robert M. Hoyte, Department of*

Chemistry, SUNY College at Old Westbury, 223 Store Hill Road, Old Westbury, NY 11568, Fax: 516-876-2757

Fluoropyridyl derivatives of [3,2-c]pyrazolo-corticosteroids prepared by conventional thermal nucleophilic halogen exchange reactions with chloropyridyl precursors have been shown to have high affinity for the glucocorticoid receptor (GR) and to be highly active glucocorticoids. These fluorinated glucocorticoids are thus considered to be excellent candidates for imaging of GR containing tissues when labeled with fluorine-18. However, the conventionally heated halogen exchange reactions were found to proceed at rates too slow for feasible applications in radiosynthesis. We have applied microwave-heating methods to these reactions and found that significant rate enhancements can be realized. This results in significantly higher conversion to fluorinated products within the first hour of reaction, which is important to radiolabeling with short-lived isotopes. Thus, there is improved potential for application of halogen exchange reactions to the synthesis of fluorine-18 labeled glucocorticoids. The results of our kinetic investigation of these microwave-enhanced reactions will be presented and their potential application to the synthesis of GR based imaging agents will be discussed.



Conventional Heating: 15% conversion at 60min

Microwave Heating: 45% conversion at 60min

MEDI 460

Focused design and synthesis of novel neuroprotectors (cognition-enhancers) in series of glutamate receptors ligands

***Nikolay S. Zefirov**, Department of Chemistry, University, Vorob'evy Gory, Moscow 119992, Russia, Fax: 7(095)939-02-90, zefirov@org.chem.msu.ru, and Sergey O. Bachurin, Institute of Physiologically Active Compounds Russ Akad. Sci*

Efficient protection against diverse group of neurological disorders related to glutamate excitotoxicity can be achieved via specific blockade of calcium ions influx via activated NMDA-receptor (NMDAR). In the present study the neuroprotective and behavioral properties of glutamate receptors ligands in series of novel flexible analogs of model neuroprotector MK-801 have been studied. It was revealed that some dibenzylamine analogs of MK-801 exhibit strong glutamate-stimulated Ca-uptake blocking property and anti-NMDA activity. NT-1505 also showed ampakines-like activity positively modulating AMPA-induced currents on isolated neurons. Cognition-enhancing properties of this compound were studied in animal model of AD-type dementia, simulated by cholinotoxin AF64A in Morris water maze test. The computer docking of MK-801 and its flexible analogs on NMDAR-channel site elucidated the crucial role of the hydrogen bond formed between these compounds and asparagine residue in segment TMII, known to constitute the Mg2+-block site in NMDAR.

MEDI 461

6 Angstroms role in opioid receptor agonist analgesics

***Lin Hu**, Institute of Applied Chemistry, East China Jiaotong University, Shuang Gang Road, Nanchang 330013, China, haiyanhulin@netzero.com, Hanhong Xu, Key Lab of Pesticide and Chemical Biology, South China Agricultural University, and Gang Hu, Department of Chemistry, University of Science and Technology of China*

The molecule structures about tramadol and other 20 opioid receptor agonist analgesics were optimized by chemical structure software MOPAC. The essential structure parameters such as molecular refractivity (MR), calculated n-octanol/water partition coefficients (ClogP) as well as d_{NC} (the distance between nitrogen atom and the longest carbon atom in the nearest phenyl at stereo molecule structure with minimized energy) ware calculated. Putting molecular parameters of 21 compounds as net input and letting opioid receptor combine constants as net output set up artificial neural network. The result elucidate that the d_{NC} is the most important effect factor in all structure parameters and the d_{NC} at high activity opioid receptor agonist analgesics is about 6 angstroms.this finding is helpful to the analgesics molecule design.

MEDI 462

NMR-based screening in drug discovery and design

***Philip Hajduk**, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, philip.hajduk@abbott.com*

NMR-based screening has become a powerful tool in the pharmaceutical industry, having its greatest impact in lead validation and characterization and the application of fragment-based approaches to drug design. This presentation will describe various strategies for NMR-based screening and fragment-based drug design and will highlight applications in the design of inhibitors of several protein targets. Lessons learned from more than a decade of experience in fragment-based screening will also be described.

MEDI 463

Fragment-based lead discovery and optimization using the SHAPES strategy

***Christopher A. Lepre**, Vertex Pharmaceuticals, 130 Waverly Street, Cambridge, MA 02139, lepre@vrtx.com*

The SHAPES strategy uses NMR spectroscopy to screen libraries of compounds comprised of the molecular fragments most commonly found in known drugs. Current ligand-detected NMR methods use modest quantities of protein, may be applied to targets of unlimited size and do not require isotopic labeling. The SHAPES hits are used to direct a search for more elaborate and potent analogs, and they can be synthetically linked with the aid of structural models derived from x-ray crystallography or computational studies. This presentation will discuss the

successful application of the SHAPES strategy to lead discovery and optimization with several targets: Jnk3 MAP kinase, MAPKAP-K2, and human fatty acid binding protein (ALBP).

MEDI 464

Fragment-based drug discovery through tethering

***Daniel A. Erlanson**, Department of Chemistry, Sunesis Pharmaceuticals, Inc, 341 Oyster Point Blvd., South San Francisco, CA 94080, Fax: 650-266-3501*

Building drugs from small molecular fragments offers key advantages over traditional methods: greater diversity can be probed more rapidly, and fragments are less likely to contain interfering functionalities. At Sunesis we have developed Tethering, which can experimentally identify fragments that bind site-specifically to a target of interest. In Tethering, a fragment's affinity for the protein target is boosted by a reversible covalent bond, allowing even compounds that bind weakly to be identified through mass-spectrometry. Structural characterization of fragment-protein complexes often reveals new and unanticipated modes of binding. In this session I will discuss applications of Tethering to discover inhibitors of thymidylate synthase and IL-2. A second-generation technology, Tethering with Extenders, facilitates not only identification of fragments but also their assembly into inhibitors using dynamic combinatorial chemistry. I will discuss how we have used this method to discover potent small molecule inhibitors of caspase-3, caspase-1, and kinases.

MEDI 465

Case studies in fragment-based lead discovery

***Miles S. Congreve**, Astex Technology, 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA, United Kingdom, Fax: +44-1223-226201, m.congreve@astex-technology.com*

Libraries of low molecular weight compounds or ‘fragments' have been generated and screened using protein-ligand x-ray crystallography. This screening process (called PyramidTM) has resulted in fragment hits being identified for a broad range of therapeutic targets. A number of case studies are outlined in which structure-based drug design approaches are used, starting from protein-fragment crystal structures, to rapidly and efficiently identify potent drug-like lead compounds. Low nanomolar potency lead compounds have been discovered using this approach for the kinase enzymes, p38 MAP kinase and cyclin-dependent kinase 1 and 2 (CDK1, CDK2). Also described are highly potent leads for the blood coagulation serine protease target thrombin. In vivo results for a CDK anti-cancer agent, selected for pre-clinical studies and derived from hits identified using PyramidTM, are also outlined.

MEDI 466

Structure-guided drug discovery for protein kinases using fragment-based lead identification/lead optimization

***Stephen K Burley**, Structural GenomiX, Inc, 10505 Roselle Street, San Diego, CA 92121, Fax: 858-558-6079, sburley@stromix.com*

Structural GenomiX, Inc. (SGX) has developed an integrated target-to-lead platform that combines high-throughput X-ray crystallography with a fragment-based approach to lead identification/optimization. The proprietary FAST™ (Fragments of Active Structures) process exploits crystallographic screening to detect, visualize, and identify small ligands (MW 150-200) that are bound to the target protein. Each member of the FAST™ fragment/scaffold library was designed to be amenable to rapid chemical elaboration at two or three points of chemical diversity using high-throughput organic synthesis. Initial lead optimization involves using our knowledge of the co-crystal structure of the target-fragment complex and advanced computational chemistry tools to guide synthesis of small focused linear (one-dimensional) libraries. These linearly elaborated fragments/scaffolds are then evaluated with in vitro biochemical and cellular assays and co-crystallography. Thereafter, optimal variations at each point of chemical diversity are combined to synthesize focused combinatorial (two- or three-dimensional) libraries that are again examined with assays and co-crystallography. (The potential chemical diversity of the fully elaborated FAST™ fragment/scaffold library far exceeds 160 million compounds.) These focused combinatorial libraries typically contain multiple novel compounds of low molecular weight (<350) that bind the target protein at low nM IC50 and already display considerable selectivity. Thereafter, compound series are prioritized for further medicinal chemistry and compound development efforts using the results of in vitro and in vivo ADME and in vitro toxicology studies in concert with structural information. Successful applications of the FAST™ fragment-based lead discovery/optimization process will be presented for both protein kinases (Syk and Gleevec-resistant BCR-ABL) and proteases (Factor VIIa).

MEDI 467

Understanding the role of fluorine in rational drug design

***Sandro Mecozzi**, School of Pharmacy and Department of Chemistry, University of Wisconsin, 777 Highland Ave, Madison, WI 53705, Fax: 608-262-5345, smecozzi@pharmacy.wisc.edu*

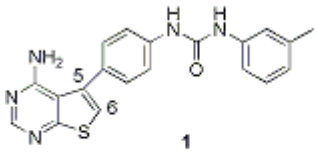
Scientific and commercial interest in fluorinated drugs has burgeoned in the last two decades. Notwithstanding, an explanation for the action of fluorinated substituents on drug efficacy has remained elusive. We have found that some of the properties of fluorinated drugs can be ascribed to the ability of fluorine to engage in intermolecular interactions. We have found that both aliphatic and aromatic organic fluorine can significantly engage in electrostatic and hydrogen bond interactions. In the attempt to understand the sometimes confusing action of fluorinated substituents in drugs, we have also looked at the importance of the degree of substitution on the carbon atom bearing a fluorine functionality. We will provide evidence of the change in the ability of organic fluorine to engage in intermolecular interactions based upon the nature of the groups attached to the fluorine-bound carbon atom. Furthermore, we will provide evidence of the importance of the substitution pattern in fluorine-containing aromatic molecules and on the differences in binding abilities of mono-, di-, and trifluoromethyl functionalities.

MEDI 468

Thienopyrimidine ureas as novel, potent multi-targeted receptor tyrosine kinase inhibitors

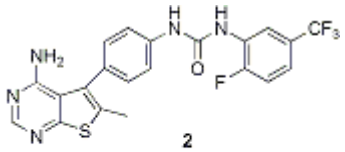
Yujia Dai[1], *Yan Guo*[1], *Robin R. Frey*[1], *Zhiqin Ji*[1], *Michael L. Curtin*[1], *Asma A. Ahmed*[2], *Daniel H. Albert*[1], *Lee Arnold*[2], *Shannon S. Arries*[1], *Teresa Barlozzari*[2], *Joy L. Bauch*[1], *Jennifer J. Bouska*[1], *Peter F. Bousquet*[2], *George A. Cunha*[2], *Keith B. Glaser*[1], *Jun Guo*[1], *Junling Li*[1], *Patrick M. Marcotte*[1], *Kennan C. Marsh*[1], *Maria D. Moskey*[2], *Lori J. Pease*[1], *Kent D. Stewart*[1], *Vincent S. Stoll*[1], *Paul Tapang*[1], *Neil Wishart*[2], *Steven K. Davidsen*[1], *and Michael R. Michaelides*[1]. *(1) Global Pharmaceutical Research & Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-935-5165, yujia.dai@abbott.com, (2) Global Pharmaceutical Research & Development, Abbott Bioresearch Center*

A series of novel thienopyrimidine-based receptor tyrosine kinase inhibitors has been discovered. Investigation of structure-activity relationships (SARs) at the 5- and 6-positions of the thienopyrimidine nucleus led to a series of biaryl ureas (e.g., compounds **1** and **2**) that potently inhibit all of the VEGF and PDGF receptor tyrosine kinases. A KDR homology model suggests that these compounds bind to the “inactive conformation” of the enzyme with the urea portion extending into the back hydrophobic pocket adjacent to the ATP-binding site. A number of compounds have been identified as displaying excellent *in vivo* potency. In particular, compounds **1** and **2** possess favorable PK profiles and demonstrate potent antitumor efficacy against the HT1080 human fibrosarcoma xenograft tumor growth model.



1

KDR: IC_{50} = 3 nM
cKit: IC_{50} = 6 nM
FLT3: IC_{50} = 3 nM



2

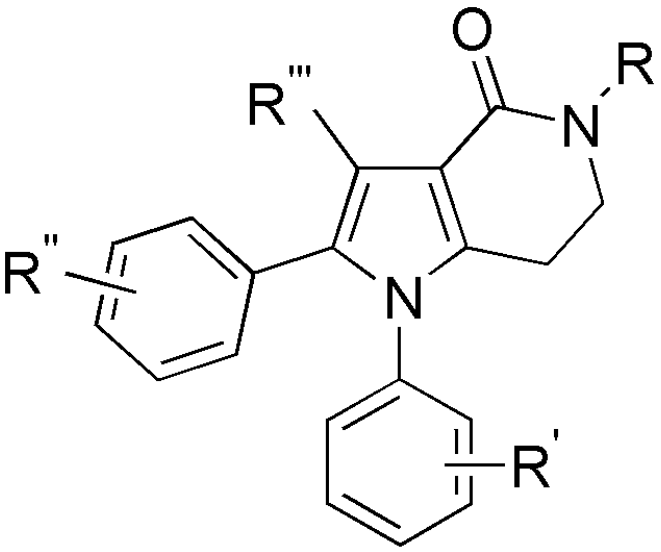
KDR: IC_{50} = 45 nM
cKit: IC_{50} = 182 nM
FLT3: IC_{50} = 27 nM

MEDI 469

Constrained analogs of CB-1 antagonists for the treatment of obesity: Design, synthesis, and pharmacology of 1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one derivatives

Roger A. Smith[1], *Soongyu Choi*[1], *Zhonghua Zhang*[1], *Susan Tomlinson*[1], *Harold C. Kluender*[1], *Rico C. Lavoie*[2], *Jianmei Fan*[1], *Stephen J. O’Connor*[1], *Brent L. Podlogar*[1], *Zahra Fathi*[3], *Anish Konkar*[3], *Su-Ellen Brown*[3], *Astrid A. Ortiz*[3], *Jennifer Natoli*[3], *Dawn Kelly-Sullivan*[3], *Lucinda Milardo*[3], *Stacy Hudgins*[3], *Christian Raphalides*[3], *Jennifer Evenski*[3], *Susan Jenkins*[4], *and Ronald Mays*[4]. *(1) Department of Chemistry Research, Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516, Fax: 203-812-6182, roger.smith.b@bayer.com, (2) Department of Chemistry Research, Bayer HealthCare Pharmaceuticals Corporation, (3) Department of Metabolics Disorders Research, Bayer Pharmaceuticals Corporation, (4) Department of Research Technologies, Bayer Pharmaceuticals Corporation*

During the last decade, antagonists of the cannabinoid type 1 receptor (CB-1) have emerged as a highly promising strategy for the treatment of obesity. The 1,5-diaryl-pyrazole rimonabant (SR-141716, Sanofi-Aventis) is the most characterized CB-1 antagonist, and is currently in Phase III clinical trials. In this report, we describe constrained analogs of rimonabant, designed with the aid of molecular modeling, with the target derivatives incorporating a 1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one scaffold. Synthesis methodology was developed and applied for the preparation of more than fifty of these pyrrolopyridinone derivatives, and several compounds with CB-1 receptor binding activity in the low nanomolar range were identified. Structure–activity relationships for the *in vitro* pharmacology as well as effects on food intake and body weight will be described.



MEDI 470

Implementation of an anesthetized rat cardiovascular safety model as a SAR tool to guide triaging of novel MCHR1 antagonists

Andrew J Souers[1], *James S. Polakowski*[2], *Thomas J. Campbell Jr.*[2], *Jason A. Segreti*[2], *Jennifer C. Freeman*[1], *Ju Gao*[1], *Rajesh Iyengar*[1], *Andrew S. Judd*[1], *John K. Lynch*[1], *Mathew M. Mulhern*[1], *Anil Vasudevan*[3], *Dariusz Wodka*[3], *Gang Zhao*[1], *Michael E. Brune*[1], *Eugene N. Bush*[4], *Robin Shapiro*[1], *Victoria E. Knourek-Segel*[4], *Brian A. Droz*[4], *Sevan Brodjian*[1], *Brian D. Dayton*[1], *Christopher A Ogiela*[1], *Dennis G. Fry*[1], *Lisa E. Hernandez*[5], *Kennan C. Marsh*[5], *Hing L. Sham*[1], *Christine A. Collins*[1], *and Philip R. Kym*[1]. *(1) Metabolic Disease Research, Abbott Laboratories, Global Pharmaceutical Research Division, Dept. R4MF, BLDG AP-10, 100 Abbott Park Road, Abbott Park, IL 60064-6099, Fax: 847-938-1674, andrew.souers@abbott.com, (2) Integrative Pharmacology, Abbott Laboratories, Global Pharmaceutical Research Division, (3) Medicinal Chemistry Technology, Abbott Laboratories, Global Pharmaceutical Research Division, (4) Global Pharmaceutical Research and Development, Metabolic Disease Research, Abbott Laboratories, (5) Preclinical Safety, Abbott Laboratories, Global Pharmaceutical Research Division*

Efforts at identifying novel MCHr1 antagonists for the treatment of obesity culminated in the

initial development of several orally efficacious compounds. However, these compounds suffered from cardiovascular toxicity when administered intravenously in an anesthetized dog. In order to circumvent this problem, we incorporated cardiovascular testing as the first in vivo assay for compounds of interest following the establishment of receptor affinity, functional activity, and hERG selectivity. Screening up to ten compounds per week, over 130 compounds from multiple classes were evaluated, and structure activity relationships of the parameters responsible for cardiovascular liabilities were established. The chemistry team was then able to triage lead series' depending on their effects in the assay, and ultimately identified a compound class with excellent cardiovascular safety and good in vitro parameters. Subsequent optimization afforded a more advanced compound that combined cardiovascular safety with oral efficacy in a chronic model for weight loss, thus providing the foundation for ongoing studies.

MEDI 471

Design, synthesis and binding affinity of some chiral nonsteroidal selective androgen receptor modulators: Bicalutamide analogues of A-ring modified molecules

Renukadevi Patil[1]*, Scott J. Fisher*[2]*, Michael L. Mohler*[1]*, Casey Bohl*[2]*, James T. Dalton*[2]*, and Duane D. Miller*[1]*. (1) Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, 847 Monroe Ave, Memphis, TN 38163, Fax: 901-448-6828, rpatil1@utmem.edu, (2) Division of Pharmaceutics, College of Pharmacy, The Ohio State University*

Prostate cancer is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. The growth of the prostate tumors is stimulated by androgens, the male sex hormones. The androgen receptor (AR) is an important member of the nuclear hormone receptor super family of ligand dependent intracellular transcription factors and is responsible for mediating the physiological actions of the endogenous steroidal androgens testosterone (T) and 5ƒÑ-dihydrotestosterone (DHT). The AR plays a critical role in normal male development and maintenance of secondary sexual characteristics such as hair, muscle mass, bone mass, strength, fat distribution and spermatogenesis. The present study described the design, synthesis, and binding affinity of a series of chiral nonsteroidal selective androgen receptor modulators (SARMs) of bicalutamide analogues, which have different heterocyclic moieties on A-ring and replacement of the bicalutamide sulfonyl by oxygen. The AR binding affinities of these SARMs were measured in a competitive binding assay with the radiolabeled high-affinity AR ligand, [3H]mibolerone. Also, we studied FlexX docking and examined three-dimensional quantitative structure-activity relationship (QSAR) of the SARMs for the androgen receptor (AR) using comparative molecular field analysis.

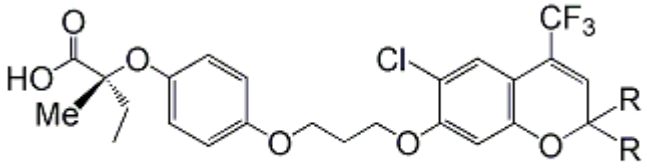
MEDI 472

Design and synthesis of potent and subtype-selective PPARα agonists

Ranjit C Desai[1]*, Edward Metzger*[1]*, Joel P. Berger*[2]*, Karen L. MacNaul*[2]*, Gaochao Zhou*[2]*, Tian-quan Cai*[3]*, Arun K. Agrawal*[4]*, Samuel D. Wright*[3]*, David E. Moller*[2]*, James V. Heck*[1]*,*

Peter T. Meinke[1], and Soumya P. Sahoo[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, Mail Code RY800-C112 P. O. Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-9556, ranjit_desai@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, (3) Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, (4) Department of Drug Metabolism, Merck Research Laboratories

The peroxisome proliferator-activated receptors (PPARs) are members of nuclear hormone receptor gene family of ligand activated transcriptions factors and are classified into three subtypes. Of the three known isoforms (α, β and γ), PPARα regulates the expression of genes encoding for proteins involved in lipid and lipoprotein metabolism. Hypercholesterolemia and hypertriglyceridemia are associated with coronary heart disease (CHD) the leading cause of death in the developed world. Fibrate class antihyperlipidemic drugs for examples fenofibrate and clofibrate provide effective means of lowering plasma triglyceride and raising HDL in humans. Though effective, fibrates are relatively weak PPARα agonists and their subtype-selectivity is poor. With the objective of identifying potent and selective PPARα agonists, a systematic approach was planned as an extension of our work in the dual PPAR α/γ agonists area. The efforts that led to the discovery, design and evaluation of 1 as a potent, highly selective, and in-vivo efficacious PPARα agonist will be the focus of the presentation.



1 R = O, Me

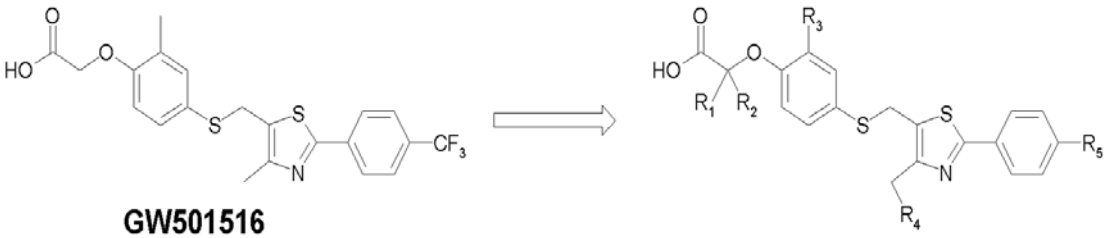
MEDI 473

From selective PPAR ligands to PPAR pan-agonists

***Stephen Rafferty**, Nuclear Receptor High-Throughput Chemistry, GlaxoSmithKline, Five Moore Dr, P.O. Box 13398, Research Triangle Park, NC 27709, swr78127@gsk.com, Pierette Banker, Medicinal Chemistry, GlaxoSmithKline, Brad R. Henke, MV CEDD Medicinal Chemistry, GlaxoSmithKline, Millard H. Lambert, Computational, Analytical and Structural Sciences, Glaxo SmithKline, William Oliver Jr., Department of Metabolic Diseases, GlaxoSmithKline, and Daniel D. Sternbach, Drug Discovery M&V CEDD, GlaxoSmithKline*

The **P**eroxisome **P**roliferator-**A**ctivated **R**eceptors (**PPAR**s) comprise a family of ligand-activated transcription factors belonging to the nuclear receptor gene superfamily. Three mammalian PPAR subtypes, commonly known as PPARa, PPARg and PPARd were originally cloned as orphan receptors. PPARa has been demonstrated to be involved in modulation of lipid metabolism; PPARg is involved in regulating insulin sensitivity; and PPARd treatment has been shown to increase HDL and decrease LDL. Given these beneficial effects, it would seem very attractive to design a single ligand that activates the three PPAR subtypes, a PPAR Pan-agonist. Starting with GW501516, a known PPARd-selective agonist, a PPAR Pan-agonist series was achieved by extending off the thiazole-Me-group as shown below (R4). The synthetic design, SAR, and *in vivo* studies for this series will be presented, with the *in vivo* data suggesting that treatment with a PPAR Pan-agonist may offer distinct advantages over

traditional therapy with a selective PPAR ligand.



GW501516
PPARδ Agonist

PPAR Pan-Agonist

MEDI 474

Identification and X-ray crystal structure of an ERR-alpha inverse agonist reveals a new mechanism of nuclear receptor antagonism

*Robert T. Nolte, Liping Wang, Lisa A. Orband-Miller, James M. Way, Julio J. Martin, Ana Maria Roa, Laura Vela, Aaron B. Miller, Timothy M. Willson, and **William J. Zuercher**, Discovery Research, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, william.j.zuercher@gsk.com*

The estrogen-related receptor-α (ERRα) is a potential therapeutic target for the treatment of metabolic diseases such as obesity or diabetes. The development of an ERRα FRET assay and its subsequent use in a high throughput screen has identified an ERRα inverse agonist, GSK9069. A detailed description of crystal structures of unliganded receptor and GSK9069-bound ERRα will be described. The latter structure includes a dramatic rearrangement which may constitute a novel mechanism of receptor deactivation applicable to other nuclear receptor family members.

MEDI 475

Potent and selective benzimidazole glucagon receptor antagonists for the treatment of type 2 diabetes

***Ronald M. Kim**[1], Jiang Chang[1], Elizabeth Rouse[1], Maria Beconi[2], Ed Brady[3], Maria Candelore[4], Qing Dallas-Yang[4], Victor Ding[4], Jasminka Dragovic[1], Guoqiang Jiang[4], Zhen Lin[1], Peggy McCann[3], Sajjad Qureshi[4], Richard Saperstein[3], Deborah Szalkowski[4], Sharon Tong[1], Laurie Tota[4], Michael Wright[4], Xiaodong Yang[4], Song Zheng[1], Milton Hammond[1], James Tata[1], Kevin Chapman[1], Bei Zhang[4], and Emma Parmee[1]. (1) Department of Medicinal Chemistry, Merck and Co., Inc, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-9473, ron_kim@merck.com, (2) Department of Drug Metabolism, Merck and Co., Inc, (3) Department of Pharmacology, Merck and Co., Inc, (4) Department of Metabolic Disorders, Merck and Co., Inc*

Glucagon and insulin are the main counterregulatory hormones that control glucose homeostasis. Glucagon increases glucose levels by inducing hepatic glycogenolysis and gluconeogenesis. In type 2 diabetics, inappropriately high glucagon levels contribute to

hyperglycemia. Recently, small molecule antagonists of the glucagon receptor have been shown to block the action of glucagon in animals and in man and to significantly lower blood glucose levels in animal models of diabetes. Glucagon receptor antagonists therefore show great potential as novel agents for the treatment of type 2 diabetes. We have developed a series of highly potent and selective benzimidazole glucagon receptor antagonists. Several of the compounds are low-nanomolar inhibitors and show excellent oral activity, blocking glucagon-induced glucose excursion in animal models. The development of the series will be presented and the in vivo profiling of one compound will be highlighted.

MEDI 476

2-Phenyl-4-piperazinylbenzimidazoles as inhibitors of the Gonadotropin Releasing Hormone (GnRH) Receptor

Jeffrey C. Pelletier[1]*, Murty Chengalvala*[2]*, Josh Cottom*[2]*, Irene Feingold*[3]*, Lloyd Garrick*[1]*, Daniel Green*[1]*, Diane Hauze*[1]*, Christine Huselton*[4]*, James Jetter*[1]*, Wenling Kao*[1]*, Gregory S. Kopf*[2]*, Joseph T. Lundquist IV*[1]*, Charles Mann*[1]*, John Mehlmann*[1]*, John Rogers*[1]*, Linda Shanno*[2]*, and Jay Wrobel*[5]*. (1) Department of Chemical & Screening Sciences, Wyeth Research, 500 Arcola Rd., Collegeville, PA 19426, Fax: 484-865-9399, pelletj@wyeth.com, (2) Department of Women's Health & Bone, Wyeth Research, (3) Department of Drug Safety and Metabolism, Wyeth Research, (4) Drug Safety and Metabolism, Wyeth Research, (5) Chemical and Screening Sciences, Wyeth Research*

Gonadotropin Releasing Hormone (GnRH) triggers the release of follicle stimulating hormone (FSH) and leuteinizing hormone (LH) into the general circulation where they can act on the gonads of both genders to produce sex steroids. Antagonists of the GnRH receptor have found clinical use as therapeutics for endometriosis and prostate cancer as well as other sex hormone sensitive diseases. All GnRH antagonists to date have been peptides that need to be administered via parenteral routes. Only recently have small molecule GnRH inhibitors started to emerge as potential orally available therapeutics. We will disclose the discovery of a series of compounds based on a novel structural template, 2-phenyl-4-piperazinylbenzimidazole, as small molecule antagonists of the GnRH receptor with excellent in vitro human and rat activity as well as serum LH reduction capabilities in rats following oral administration. Structure activity relationships and pharmacokinetics will be discussed.