Division of Medicinal Chemistry
Abstracts-234th ACS National Meeting
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Members:

On behalf of the executive committee of the Division of Medicinal Chemistry, I would like to thank all of the participants in our Boston Program. We look forward to a scientifically and professionally stimulating meeting.

One of the new initiatives the Division has undertaken is to offer a Lunch and Learn session on a case study in drug discovery and will cover the design, synthesis and development of Sprycel™ (Dasatinib). The session will be offered on Tuesday, August 21 from noon to 2 PM at the Boston Convention Center in Room 253A. There are a limited number of tickets that can be purchased for $20.00 (that partially cover the cost) when you register for the meeting. Please see the ad on page 42 and additional specifics on page 85 of the June 25, 2007 C&E News that has the preliminary program for Boston. In addition, more information on the session appears on page 10 of the Division Newsletter, *The Reaction Times*. Also please plan to attend the "Hall of Fame" reception on Wednesday evening at 5:30 in room 203 of the convention center. Four new members will be inducted into this group of outstanding scientists. New members are elected from nominations submitted by Division members, have received one of the awards associated with the Division (Smissman, Burger, Division of Medicinal Chemistry award), or have received an ACS award and presented their research to the Division.

As always, we look forward to your input and welcome your suggestions to improve our service to you

Sincerely,
Jim McCarthy
MEDI Chair

MEDI 1

Malaria as a world health problem

***Solomon Nwaka**, Special Programme for Research and Training in Tropical Diseases, World Health Organization, 1221 Geneva 27, Switzerland, Fax: +421 22 791 4854, nwakas@who.int*

Malaria is among humanity's largest - and oldest - health and developmental challenges. It kills more than a million people and causes another 300 million to 500 million cases of the disease every year. The humanitarian and economic costs associated with malaria are immense. The current state of drug therapy, and the challenges facing prevention of malaria will be discussed.

MEDI 2

Synthetic peroxides as antimalarials: Identification of a secondary ozonide (1,2,4-trioxolane) drug development candidate

***Jonathan L Vennerstrom**, Department of Pharmaceutical Sciences, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198-6025, Fax: 402-559-9543*

The discovery of artemisinin in 1971 initiated a new era in malaria chemotherapy. Although the clinically useful semisynthetic artemisinin derivatives are rapid acting and potent antimalarial drugs, they have short half-lives and must be administered over a period of 5-7 days, leading to noncompliance and recrudescence. With this in view, many synthetic peroxide antimalarials have been prepared. Yet, identification of synthetic peroxides that are easily synthesized, inexpensive, and with good biopharmaceutical properties has been surprisingly difficult. In this seminar, we document the pitfalls and progress made in this endeavor, and highlight the discovery of a secondary ozonide (1,2,4-trioxolane) drug development candidate.

MEDI 3

Recent developments in the medicinal chemistry of 4-aminoquinoline antimalarials: Identification of N-tert butyl Isoquine as a next generation 4-Aminoquinoline antimalarial drug

***Paul O'Neill**, Departments of Chemistry and of Pharmacology, University of Liverpool, The Robert Robinson Laboratories, Liverpool L69 7ZD, United Kingdom, P.M.oneill01@liverpool.ac.uk*

The developing World is desperate for new, safe, effective and affordable antimalarial drugs and has been since the demise of chloroquine (CQ) due to PfCRT mediated parasite resistance emergence in the 60's. The talk will provide an overview of recent developments in the medicinal chemistry of 4-aminoquinoline antimalarials and will then focus on the Isoquine series of 4-aminoquinolines. Using the 4-aminoquinoline amodiaquine (AQ) as our template we

have developed simple routes to novel rationally designed analogues that are highly effective against CQ resistant parasites. Importantly these are not metabolized to substrates for the resistance mechanism and cannot form reactive electrophilic quinoneimine metabolites associated with the drug-induced hepatotoxicity and agranulocytosis seen in humans taking amodiaquine. Interchange of the 3' hydroxyl and the 4' Mannich side-chain function of amodiaquine blocks quinoneimine formation and replacement of the diethylamino side chain with a t-butyl group blocks P450 mediated dealkylation to metabolites displaying cross resistance with CQ and retains the key physiochemical features of the parent drug required for activity against CQR parasites. GSK369796 was candidate selected based on excellent activity against human malaria P.falciparum isolates in vitro and rodent malaria parasites in vivo and an optimised synthetic route that delivered this novel synthetic quinoline in a two-step procedure from cheap and available starting materials. The molecule has a full industry standard pre-clinical development programme allowing first into man to proceed in 2007. Employing CQ and AQ as comparator molecules in the pre-clinical plan, the first pre-clinical dossier of GLP pharmacokinetic, toxicity and safety pharmacology has also been established for the 4-aminoquinoline antimalarial class.

MEDI 4

Peroxides for chemotherapy of malaria and cancer

***Gary H. Posner**, Department of Chemistry, The Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218, Fax: 410-516-8420, ghp@jhu.edu*

Widespread resistance has greatly diminished the utility of previously reliable antimalarial drugs. Artemisinins and related trioxanes are among the newest antimalarials, and combination therapy that includes a trioxane with at least one other drug is now usually recommended in malaria-endemic areas. Although potent and fast-acting, the clinically available monomeric trioxanes commonly fail to achieve a cure when administered alone. In an effort to improve antimalarial activity and to prevent metabolic inactivation, a series of dimeric compounds that contain two artemisinin moieties linked by a short non-hydrolyzable bridge was designed and synthesized. In contrast to the clinically used trioxane artesunate which prolongs mouse survival by 3 days or less, for several of our new trioxane dimers a single subcutaneous dose of 30 mg/kg cured P. berghei-infected mice. Other of our dimers cured after three consecutive daily oral doses of 30 mg/kg. No toxicity was noted. The result is structurally diverse new trioxane dimers, obtained in good yield in a straightforward and inexpensive few steps from plant-derived artemisinin, having potent antimalarial activity, efficacy and safety in curing malaria-infected mice. These trioxane dimers are promising candidates for further preclinical and human studies toward much-needed new drug development for antimalarial chemotherapy.

MEDI 5

Hemozoin formation as a target for antimalarial drug design

***Michael K. Riscoe**, Jane X. Kelly, Martin J. Smilkstein, and Rolf W. Winter, Medical Research Service, Mail Code: RD-33, Portland V.A. Medical Center, 3710 S.W.U.S. Veterans' Hospital Road, Portland, OR 97239, Fax: 503-721-1084, riscoem@ohsu.edu*

The Plasmodium parasites that cause malaria attack and invade red blood cells and devour hemoglobin to derive amino acids necessary for their survival. Hemoglobinolysis liberates an enormous amount of free heme in the parasite's digestive vacuole. The heme is detoxified by conversion into dimers which spontaneously form an macromolecular aggregate known as “hemozoin”. We have designed and synthesized acridones that accumulate in the digestive vacuole, form soluble complexes with heme, and prevent the process of hemozoin formation. We have also built into these molecules the ability to sensitize multidrug resistant parasites to the quinolines, quinine and chloroquine. My presentation will detail pertinent structure-activity profiles of these “merged acridones” together with in vivo evidence of their efficacy alone and in combination with the quinolines in a mouse model of malaria. Studies of certain synthetic intermediates that exhibited unexpected and potent antiplasmodial activity will also be discussed.

MEDI 6

Recent approaches to the treatment of stroke and cerebral ischemia

***Wayne E. Childers Jr.** and Boyd L. Harrison, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, childew@wyeth.com*

Stroke is the second leading cause of death worldwide, with an estimated 5.7 million deaths attributed to this disease in 2005 according to the World Health Organization. In the US alone, approximately 700,000 new and recurrent stroke cases occur each year and the annual cost of caring for the 5.5 million survivors is estimated at over $58 billion. Despite nearly two decades of anti-ischemic research, only one drug, the thrombolytic agent Altepase™, is currently approved for use in acute ischemic stroke. However, the limitations inherent in that agent (relatively short therapeutic window, the need to rule out the presence of hemorrhage and the risk of inducing a life-threatening hemorrhage) emphasize the genuine need for safe, efficacious and widely applicable drugs that possess a wide therapeutic window. In the past, compounds targeting various aspects of the ischemic cascade have demonstrated neuroprotective efficacy in pre-clinical animal models of stroke but have failed in the clinic. However, new mechanistic approaches are emerging that target not only neuroprotection but neuroregeneration as well. This presentation will review some of the more recent approaches and mechanistic targets currently under investigation in the quest for an effective drug to treat this debilitating disease.

MEDI 7

JNK signalling pathway after MCAo: Neuroprotective effect of JNK inhibitor peptide (D-JNKI1)

***Tiziana Borsello**, Biol. Neurodeg. Disorders Lab, Istituto di ricerche Farmacologiche "Mario Negri", Via Eritrea 62, Milano ITALY 20157, Italy, Fax: +39 02 3546277, borsello@marionegri.it, and M. Repici, Cellular Biology and Morphology Department, University of Lausanne, Lausanne CH-1005, Switzerland*

Activation of c-Jun N-terminal kinase (JNK) occurs in ischemia. The biological action of JNK could be inhibited by the JNK inhibitor peptide (D-JNKI1) that contains TAT-cell entry sequence linked to JBD20 sequence (from JIP1/IB1 scaffold protein), and has been designed to block the interaction between JNK and its targets. We showed strong protection by using D-JNKI1 in two models of middle cerebral artery occlusion: transient occlusion in adult mice and permanent occlusion in 14 days old rats. In the former model, intracerebroventricular administration as late as 6 h post-occlusion reduced the lesion volume by more than 90%, a protection that was maintained for at least 14 days and was accompanied by behavioral sparing. In the latter model, systemic delivery reduced the lesion by 78% at 6 h post-ischemia, and by 49% at 12 h. Protection correlated with prevention of increase in c-Jun activation and caspase-3 activation. Taken together these data suggest that D-JNKI1 is a unique and potent neuroprotective agent. However, comprehensive molecular machinery that modulates this powerful protection remains unclear. To clarify this point, we investigated the JNK molecular cascade activation in cerebral ischemia and the D-JNKI1 effects on this cascade. c-Jun activation starts 3h after ischemia and peaks at 6 h in the ischemic core, while in the penumbra it starts at 1h and peaks at 6h. The 6h JNK activation peak correlates well with that of P-c-jun. D-JNKI1 markedly prevented the increase of P-c-Jun in both core and penumbra and powerfully inhibited caspase-3 activation in the core. These results indicate that targeting the JNK cascade in a very specific way, using the TAT cell-penetrating peptide, offers a promising therapeutic approach for ischemia, raising hopes for human neuroprotection.

MEDI 8

Design, synthesis and neuroprotective effects of azulenyl nitrone spin traps in animal models of cerebral ischemia

***David A. Becker**, Chemistry and Biochemistry, Florida International University, University Park, Miami, FL 33199, Fax: 305-348-3772, beckerd@fiu.edu*

Much interest has centered on the potential of nitrone spin traps to counter free radical-mediated damage in biological systems. A large corpus of evidence points to oxidizing radicals as contributors to the pathological consequences of cerebral ischemia. Consideration of such evidence has led to the development of the Mitsubishi drug edaravone, a free radical scavenging agent currently in use to treat stroke victims in Japan. In 2006, notwithstanding encouraging results in animal models, the Renovis/AstraZeneca nitrone NXY-059 failed in late Phase III human ischemic stroke trials. The Ginsberg/Becker groups have been actively investigating the neuroprotective effects of azulenyl nitrones, a novel class of nitrones that have demonstrated promising results in models of cerebral ischemia. The stilbazulenyl nitrone

STAZN confers neuroprotection at extremely low doses. Perspectives on the genesis, preparation and efficacy of azulenyl nitrones in animal models of cerebral ischemia will be presented.

MEDI 9

Design and synthesis of novel SHh agonists: SAR and biological evaluation in a cerebral ischemia model

Simon N. Haydar[1]*, David Albers*[2]*, Shirley brunton*[3]*, Tammy Dellovade*[2]*, Boyd L. Harrison*[4]*, Warren D. Hirst*[5]*, Ronald L. Magolda*[4]*, Menelas Pangalos*[5]*, Peter H. Reinhart*[5]*, Lee L. Rubin*[2]*, and Dane M. Springer*[1]*. (1) Department of Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, haydars@wyeth.com, (2) Curis Inc, Cambridge, MA 02138, (3) Evotec OAI, Abingdon OX14 4SD, United Kingdom, (4) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, (5) Wyeth Research, Discovery Neuroscience, Princeton, NJ 08543*

The vertebrate protein Sonic Hedgehog (SHh) plays critical roles in embryonic development of the nervous system. In the adult nervous system, hedgehog activators have been shown to promote neuroprotection and regeneration in several models of neural disorders such as stroke, Parkinson's disease and peripheral neuropathy. We have developed small molecule activators of hedgehog signaling. The synthesis and structure activity relationship of these molecules will be discussed. These novel compounds were shown to be efficacious in a model of stroke (rat temporary middle cerebral artery occlusion (tMCAO) and are potential novel therapeutics in the treatment of acute stroke.

MEDI 10

Necroptosis inhibition as a therapeutic strategy for cerebral ischemia

Gregory D Cuny*, Laboratory for Drug Discovery in Neurodegeneration, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne St, Cambridge, MA 02139, Fax: 617-768-8606, gcuny@rics.bwh.harvard.edu*

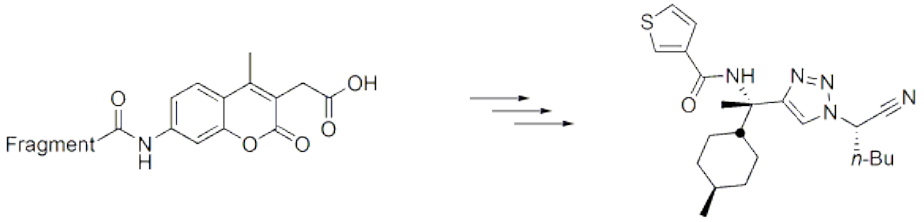
Necrosis represents types of cell death morphologically and mechanistically distinct from apoptosis. It is the prevalent form of acute cell death in many pathologies, including cerebral ischemia. Few attempts, however, have been made to develop therapeutics specifically targeting necrosis because of the conventional notion that it is a non-regulated response to overwhelming stress. This concept is directly challenged by recent studies demonstrating the existence of regulated caspase-independent cell death mechanisms with morphological features resembling necrosis. Previously, one type of necrosis has been described and termed necroptosis. The identification of molecules capable of inhibiting necroptosis will assist in elucidating caspase-independent cell death pathways, their roles in disease patho-physiology and provide lead compounds for therapeutic development. The discovery and optimization of three distinct chemical series of necroptosis inhibitors will be summarized in this presentation. In addition, a current working model of the necroptosis cell death pathway will also be presented.

MEDI 11

Substrate Activity Screening (SAS): A fragment-based method for the identification of nonpeptidic protease inhibitors

Andrew W. Patterson[1], *Hiroaki Inagaki*[2], *Warren J. L. Wood*[3], *Hiroyuki Tsuruoka*[2], *Rishi K. Jain*[4], *and Jonathan A. Ellman*[1]. *(1) Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720-1460, andypat@berkeley.edu, (2) Daiichi Sankyo, Co., Ltd, Tokyo, Japan, (3) Physiology and Pharmacology, Oregon Health and Science University, Portland, OR 97239-3098, (4) Novartis Institute for Biomedical Research, Cambridge, MA*

We have developed a new fragment-based method for the rapid development of nonpeptidic protease inhibitors, Substrate Activity Screening (SAS). This method consists of three steps: (1) a library of N-acyl aminocoumarins with diverse, low molecular weight N-acyl groups is screened to identify protease substrates using a simple fluorescence-based assay, (2) the identified N-acyl aminocoumarin substrates are optimized by rapid analogue synthesis and evaluation, and (3) the optimized substrates are converted to inhibitors by replacement of the aminocoumarin with mechanism-based pharmacophores. The SAS method was successfully applied to cathepsin S, a cysteine protease implicated in autoimmune diseases. Upon screening an N-acyl aminocoumarin library, two nonpeptidic substrate classes were identified and subsequently optimized to substrates with >10,000-fold improvements in cleavage efficiency for each class. Select substrates were then converted to novel inhibitors with nanomolar affinity to cathepsin S. One scaffold yielded a 15 nM nitrile inhibitor with >1,000-fold selectivity over related proteases.



>150 Diverse fluorogenic *N*-acyl aminocoumarin substrates screened

K_i = 15 nM
Selectivity > 1000-fold

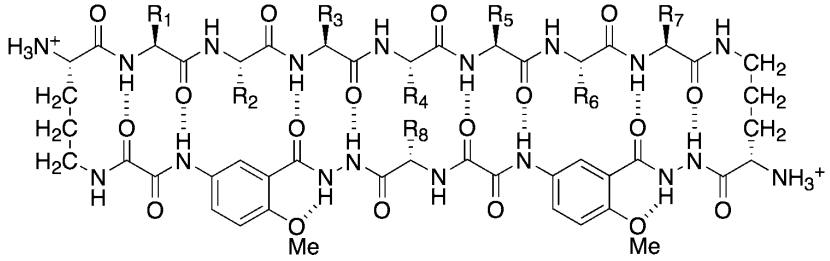
MEDI 12

Protein β-sheet quaternary interactions: From mimicry to molecular recognition

Omid Khakshoor *and James S. Nowick, Department of Chemistry, University of California, Irvine, Irvine, CA 92697-2025, Fax: 949-824-9920, khakshoo@uci.edu*

To better understand and control β-sheet interactions between disease-related proteins, our research group is developing chemical models of protein β-sheets. Recently, we developed 54-membered-ring cyclic peptides that mimic protein quaternary β-sheet structure in water through interchain β-sheet interactions. These cyclic peptides, which contain the unnatural amino acid Hao on one edge and a heptapeptide β-strand on the other edge, form β-sheet dimers that further associate to form tetrameric β-sheet sandwiches. This paper describes two

ongoing studies of the interaction between these peptides and β-sheet peptides and proteins. The first focuses on inhibiting β-amyloid formation with cyclic peptides containing complementary heptapeptide β-strands. The second focuses on binding a soluble protein (a protein G variant) with a cyclic peptide containing a complementary heptapeptide β-strand.



MEDI 13

Peptidomimetic modulators of bacterial quorum sensing

Sarah A. Fowler *and Helen E. Blackwell, Department of Chemistry, University of Wisconsin-Madison, 1101 University Ave., Madison, WI 53706-1322, sajewell@wisc.edu*

We seek to design, synthesize, and evaluate peptidomimetic ligands as new probes to modulate bacterial quorum sensing (QS). There is an urgent, global need for new antimicrobial therapies, and the regulation of QS has emerged as a highly attractive target. QS is a process of bacterial intercellular communication. Using signaling molecules and their cognate receptors, bacteria monitor their population density and regulate group behaviors, such as virulence and biofilm formation. We hypothesize that peptidomimetics of these ligands could represent valuable tools to modulate QS and attenuate pathogenesis. In Gram-positive bacteria, these ligands are short peptides; thus we designed *N*-substituted glycine oligomer, or peptoid, mimics. We have prepared focused libraries of linear and macrocyclic peptoids and peptide-peptoid hybrids (peptomers) in high yield and purity utilizing microwave-assisted reaction conditions. This talk will present our on-going characterization of these ligands in QS assays in *Staphylococcus aureus*.

MEDI 14

3-Hydroxy-4-tridecanone is the quorum sensing small molecule CAI-1 that controls virulence in Vibrio cholerae

*Douglas A. Higgins[1], **Megan E. Pomianek**[2], Christina M. Kraml[3], Ronald K. Taylor[4], Martin F. Semmelhack[2], and Bonnie L. Bassler[5]. (1) Department of Molecular Biology, Princeton University, Lewis Thomas Laboratory, Washington Road, Princeton, NJ 08544, (2) Department of Chemistry, Princeton University, Frick Laboratory, Washington Road, Princeton, NJ 08544, Fax: 609-258-6746, pomianek@princeton.edu, (3) AccelaPure Corporation, Newark, DE 19702, (4) Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, NH 03755, (5) Howard Hughes Medical Institute, Chevy Chase, MD 20815-6789*

Quorum sensing is a process by which groups of bacteria control collective behaviors according to population density. Many of these collective behaviors, including virulence factor production and biofilm formation, play significant roles in the development of infection in human hosts. Such is the case with the bacterium Vibrio cholerae, the causative agent of the disease cholera. To date, the chemical structure of V. cholerae autoinducer-1 (CAI-1) that mediates System 1 quorum sensing in this species has not been identified. In this work, we determine the structure of CAI-1, as isolated from cell supernatants, to be 3-hydroxy-4-tridecanone. We implement a straightforward synthetic strategy to easily access CAI-1 and a variety of structural analogs. Using chemically-synthesized CAI-1, we show that this small molecule initiates quorum sensing behavior in V. cholerae and has a pronounced effect on the formation of the toxin-coregulated pilus crucial to V. cholerae virulence. Our results demonstrate that CAI-1, a small molecule of a novel structural type for bacterial autoinducers, exerts direct control of virulence in V. cholerae through the System 1 quorum sensing circuit.

MEDI 15

Inhibition of Hsp47 by triphenylmethylamides induces apoptosis in melanoma

Benjamin J. Leslie*, Department of Chemistry, The University of Illinois At Urbana-Champaign, Roger Adams Laboratory, 600 S. Mathews Ave Box 110-5, Urbana, IL 61801, Fax: 217-244-8024, bleslie@uiuc.edu, and Paul J. Hergenrother, Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801*

Melanoma, cancer that arises from pigment-producing melanocytes, is the most aggressive and deadly form of skin cancer. Properties of parent melanocytes result in a cancer type that is notoriously resistant to anticancer drugs and has an extremely high propensity for metastasis. As traditional S- and M-phase arrestors are ineffective against melanoma, new protein targets are needed in order to combat this disease. We have recently discovered a class of small molecules, triphenylmethylamides (TPMAs), that potently induce G1 cell cycle arrest and apoptosis in cultured melanoma cells. We have used affinity chromatography followed by mass spectrometry based peptide identification to identify the molecular target of TPMAs. This presentation will detail recent findings that suggest that TPMAs bind to Hsp47 (a chaperone for (pro)collagen folding) in vitro and in vivo and that inhibition of Hsp47 leads to G1 arrest and apoptosis through induction of the unfolded protein response.

MEDI 16

Inhibitors of the FBP-FUSE interaction as potential anticancer agents

Pauline N. Wyrembak*[1], Matthew P. Glenn[1], Demetrios T. Braddock[2], and Andrew D. Hamilton[1]. (1) Department of Chemistry, Yale University, 225 Prospect St, New Haven, CT 06520-8107, (2) Department of Pathology, Yale University School of Medicine, New Haven, CT 06510*

Deregulated or elevated expression of c-myc has been implicated in a wide array of human carcinomas making it an attractive target for molecular chemotherapy. Several experiments have shown that disruption of far-upstream element (FUSE) binding protein (FBP) function

may lead to the inhibition of c-myc driven tumors. FBP regulates c-myc expression through its interaction with single-stranded FUSE located upstream of the c-myc promoter. Here, we report the design and synthesis of compounds that target the FBP-FUSE protein-DNA interaction. Initial inhibitors based on a lead ligand display micromolar affinity in vitro and predominantly target the DNA binding domain of FBP as determined by HSQC NMR experiments. Alternative approaches to disrupt this interaction were also explored. Inhibitors identified through multiple strategies will be further optimized towards increasing potency and specificity to provide a set of molecular probes that will be used to validate FBP as a target for anti-cancer therapy.

MEDI 17

Photocontrol of ionotropic glutamate receptors: From design to in vivo application

Matthew Volgraf[1]*, Stephanie Szobota*[2]*, Pau Gorostiza*[2]*, Claire Wyart*[2]*, Ehud Y. Isacoff*[2]*, and Dirk Trauner*[1]*. (1) Department of Chemistry, University of California, Berkeley, 610 Latimer Hall, Berkeley, CA 94720, volgraf@berkeley.edu, (2) Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA CA*

General approaches for the optical control of a ligand-gated ion channel of central importance in neuroscience, the ionotropic glutamate receptor (iGluR), are described. Using structure-based design, an agonist is covalently tethered to the protein through an azobenzene moiety, to create a light-activated channel. Alternatively, a non-tethered photochromic ligand has been developed that functions as a reversibly caged neurotransmitter for the control neural activity. The application of these tools in cultured hippocampal neurons and zebrafish larvae will also be discussed.

MEDI 18

Next-generation contraceptives: The discovery of non-steroidal progesterone receptor modulators

Andrew Fensome[1]*, Andrea Adams*[2]*, William Adams*[2]*, Reinhold Bender*[1]*, Thomas Berrodin*[3]*, Rajiv Chopra*[1]*, Jeff Cohen*[3]*, Mark A. Collins*[1]*, Lin Deng*[2]*, Horace Fletcher III*[1]*, Phyllis Gallucci*[4]*, Valerie Hudak*[1]*, Christine Huselton*[2]*, Susan Lockhead*[2]*, Karl Malakian*[1]*, Michael Marella*[1]*, Edward Melenski*[1]*, Casey C. McComas*[1]*, Cheryl Mugford*[2]*, Layne Norlund*[4]*, Andrea Olland*[1]*, David Ruble*[4]*, Louise Russo*[3]*, Ov Slayden*[5]*, Kristine Svenson*[1]*, Eugene A. Terefenko*[1]*, Raymond Unwalla*[1]*, Jianyao Wang*[2]*, James Wilhelm*[1]*, Scott Wolfrom*[1]*, David Yates*[4]*, Matthew Yudt*[3]*, Zhiming Zhang*[3]*, Puwen Zhang*[1]*, Richard C. Winneker*[3]*, and Jay Wrobel*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, fensoma@wyeth.com, (2) Biotransfomation Division, Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (4) BioResources, Wyeth Research, Collegeville, PA, (5) Division of Reproductive Sciences, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR*

Oral contraceptives (OC) have been widely used for the past four decades; however, currently available therapies are not appropriate for all women. Contraindication, due to the small increased risk of thromboembolism for example, prevents some women from starting on these therapies; still others who begin using OC's discontinue their use due to hormonal side effects, commonly associated with the estrogenic component of the drug regimen. Hence there is still a need to provide improved medications for wider general use than the currently available OC's.

We have pursued the discovery of non-steroidal progesterone receptor (PR) modulators as a single therapeutic agent with potential for use in contraception and reproductive disorders. Several of these compounds have moved into development, including Tanaproget, the first non-steroidal PR modulator studied in the clinic.

This talk will focus on the discovery, SAR and pharmacological characterization of PR modulators, including both agonists and antagonists, which have progressed into the Development Pipeline at Wyeth for use in contraception.

MEDI 19

Transition state analysis of the chemical and enzymatic prenylation reactions

***Mark D. Distefano**, Departments of Chemistry and Medicinal Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, MN 55455, Fax: 612-626-7541, diste001@umn.edu, Stepan Lenevich, Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, and Christopher J Cramer, Department of Chemistry and Supercomputing Institute, University of Minnesota, Minneapolis, MN 55455-0431*

Protein prenylation involves the attachment of C15 (farnesyl) or C20 (geranylgeranyl) groups to proteins and is catalyzed by a class of enzymes known as prenyltransferases. The observation that inhibition of Ras farnesylation arrests the growth of tumor cells has been the motivating factor in developing inhibitors of prenyltransferases that can serve as anticancer drugs; currently several candidates are in Phase 3 clinical trials. We are interested in using kinetic isotope effect (KIE) measurements to determine the transition state (TS) structure for the enzyme catalyzed reaction since knowledge of the TS structure may allow the selectivity and affinity of inhibitors of these enzymes to be improved. Here, using a primary 13C KIE and a secondary 2H KIE measured via mass spectrometry, a TS structure for the protein farnesyltransferase enzyme catalyzed reaction was computed; a density functional level of electronic structure theory using the mPW1N functional in combination with the 6-31+G(d) basis set was employed for those calculations. The results indicate that the enzyme effects catalysis via an “exploded” TS structure.

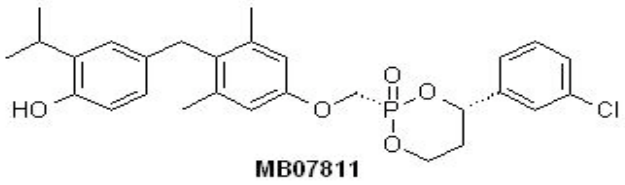
MEDI 20

MB07811: A liver-selective thyroid receptor agonist prodrug for the treatment of hyperlipidemia

***Serge H. Boyer**[1], Hongjian Jiang[1], Jason D. Jacintho[1], M. Venkat Reddy[1], Haiqing Li[1], Wenyu Li[1], William G. Schulz[1], Jennifer L. Godwin[1], Scott J. Hecker[1], Edward E. Cable[2], Bruce R. Ito[2],*

James Fujitaki[2], Patricia D. Finn[2], Bao-Hong Zhang[2], Jinzhao Hou[2], Paul D. van Poelje[2], David Linemeyer[2], and Mark D. Erion[3]. (1) Department of Medicinal Chemistry, Metabasis Therapeutics, Inc, 11119 North Torrey Pines Rd, La Jolla, CA 92037, Fax: 858-622-5573, boyer@mbasis.com, (2) Department of Biosciences, Metabasis Therapeutics, Inc, La Jolla, CA 92037, (3) Research & Development, Metabasis Therapeutics Inc, La Jolla, CA 92037

Thyroid hormone receptors (TRs) are a long-recognized target for hyperlipidemia, yet the therapeutic potential of selective TRß1 agonists remains unrealized in humans due to their concomitant undesired cardiovascular side effects. To increase the therapeutic index, phosphonic acid (PA) TR agonists were synthesized that were able to exploit the poor distribution of PA-based drugs to extra-hepatic tissues. Several PA TR agonists demonstrated excellent binding affinities (TRß1, Ki < 10 nM) and significant cholesterol lowering effects (cholesterol-fed rat, 0.2 mg/kg i.p.). Poor oral bioavailability of the lead PA MB07344 prompted synthesis of prodrugs, leading to identification of HepDirect prodrug MB07811 (rat ED50 = 0.5 mg/kg p.o.; F = 39%). Unlike T3 and the non-liver-selective TR agonist KB-141, MB07811 significantly reduced cholesterol and triglycerides (both serum and hepatic) in normal rats and diet-induced obese mice at doses devoid of effects on the heart, thyroid hormone axis, body weight, and glycemia.



MB07811

MEDI 21

Novel small molecule agonists of the integrin CD11b/CD18 as in vivo chemical biology probes

*Jack Rosa, M. Amin Arnaout, and **Vineet Gupta**, Department of Medicine, Nephrology Division, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Room 8224, Charlestown, MA 02129, Fax: 617-726-5669, vineet_gupta@hms.harvard.edu*

The integrin CD11b/CD18 is the predominant Beta2 (β2) integrin receptor in leukocytes and plays a central role in mediating pro-inflammatory functions of these cells. In vivo, the binding of integrin CD11b/CD18 to its physiologic ligands is carefully controlled and this integrin is expressed in a low affinity (inactive) conformation on the surface of circulating cells. Additionally, the interaction between CD11b/CD18 integrin and its physiologic ligands is of low affinity, which poses a challenge in the development of cell-based adhesion assays for the high throughput screening (HTS) environment. We recently developed a simple, novel cell-based HTS assay for screening a library of small molecules against CD11b/CD18. Using this assay, we screened >20,000 compounds and identified several unique small molecule agonists, some of which showed good selectivity for CD11b/CD18 over a highly related integrin CD11a/CD18 in secondary assays. Here, we will describe the use these agonists as in

vivo chemical biology probes in mouse and zebrafish models of human disease for selectively modulating the function of integrin CD11b/CD18. We will also discuss the insights gained in using such small molecules for functional modulation of cell surface receptors in vivo as well as the challenges that lie ahead.

MEDI 22

Discovery of potent and selective leukotriene A4 hydrolase inhibitors

***Cheryl A. Grice**, Frank U. Axe, Scott D. Bembenek, Christopher R. Butler, Fawn Coles, Paul J. Dunford, James P. Edwards, Anne M. Fourie, Lars Karlsson, Kathleen Lundeen, Jason Riley, Brad M. Savall, Kevin Tays, Jianmei Wei, Kacy Williams, and Xiaohua Xue, Johnson & Johnson Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121*

The pro-inflammatory mediator leukotriene B_4 (LTB_4) is a potent chemoattractant and activator of neutrophils and a chemoattractant of eosinophils and macrophages. Improper LTB_4 regulation is thought to play a role in numerous inflammatory diseases. The generation of LTB_4 in vivo is regulated by the action of leukotriene A_4 hydrolase (LTA_4H), a key enzyme in the arachidonic acid cascade, which stereospecifically catalyzes the transformation of the unstable epoxide, LTA_4 to the diol LTB_4. We wish to disclose our initial efforts to identify orally active inhibitors of LTA_4H in an effort to advance a compound into Phase I clinical trials. This work focuses on the development of a series of benzoxazoles, benzthiazoles and benzimidazoles. The SAR, in vitro and in vivo activity as well as pharmacokinetic profiles of selected inhibitors will be discussed.

MEDI 23

Multivalent muscarinic antagonists for the treatment of overactive bladder (OAB)

***Adam D. Hughes**[1], Kay H. Chin[2], Sharath S. Hegde[3], Craig O. Husfeld[1], Jeffrey R. Jasper[2], Yuhua Ji[1], Kristin E. King[2], Tae Weon Lee[2], Li Li[1], Mathai Mammen[2], Alexander J. McNamara[3], Trevor K. Mischki[1], Glenmar P. Obedencio[3], Tess Pulido-Rios[3], Tod Steinfeld[2], Shelley M. Sweazey[3], and Richard D. Wilson[1]. (1) Medicinal Chemistry, Theravance, Inc, 901 Gateway Blvd, South San Francisco, CA 94080, Fax: 650-808-6120, ahughes@theravance.com, (2) Molecular and Cellular Biology, Theravance, Inc, South San Francisco, CA 94080, (3) Pharmacology, Theravance, Inc, South San Francisco, CA 94080*

Overactive bladder (OAB) currently affects approximately 33 million adults in the U.S. and more than 100 million worldwide. Symptoms include urgency, frequency, urge incontinence and nocturia.

The mainstay of overactive bladder drug therapy is muscarinic acetycholine receptor (mAChR) antagonists. The mAChR population in the bladder smooth muscle (detrusor) is primarily composed of M2 and M3 subtypes with the former predominating in number (60-80%). There is increasing evidence that the predominant M2 receptor also mediates detrusor contraction indirectly by reversing sympathetically mediated relaxation.

The presentation will discuss how multivalent approaches to drug design have been used to achieve high M2 receptor subtype selectivity which was translated to in vivo efficacy in a disease relevant model and the identification of a potential development candidate, THRX-326151.

MEDI 24

Discovery of BI 1356: A highly potent and long-acting DPP-IV inhibitor with a xanthine scaffold

Frank Himmelsbach[1], *Klaus Dugi*[2], *Matthias Eckhardt*[1], *Holger Fuchs*[3], *Ulrike Graefe-Mody*[3], *Brian Guth*[4], *Elke Langkopf*[1], *Ralf Lotz*[4], *Michael Mark*[5], *Herbert Nar*[6], *Peter Sieger*[4], *Moh Tadayyon*[5], *and Leo Thomas*[5]. *(1) Department of Chemical Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany, Fax: +49-7351-83-7657, frank.himmelsbach@bc.boehringer-ingelheim.com, (2) Department of Therapeutic Area Metabolism, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany, (3) Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany, (4) Department of Drug Discovery Support, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany, (5) Department of Metabolic Research, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany, (6) Department of Lead Discovery, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany*

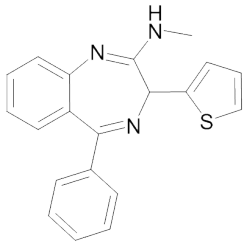
Dipeptidyl peptidase IV (DPP-IV) is a serine protease which specifically cleaves dipeptides after a penultimate N-terminal proline or alanine. DPP-IV is involved in the degradation of a number of peptides, most notably of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 exerts a potent glucose-dependent insulinotropic action and thereby contributes to the maintenance of glycaemic control. In addition, it inhibits glucagon release from pancreatic alpha-cells and in animal models has been shown to preserve beta-cell mass. Therefore, DPP-IV inhibitors are a promising new class of antidiabetic agents with a low risk of hypoglycaemia and a potential for disease modification. Here, we describe the discovery process that started with a micromolar screening hit and, after optimization of the key substituents at N1, N-7 and C-8 of the xanthine, culminated in the identification of BI 1356 (IC50 = 1 nM) that is currently in Phase IIb clinical trials. The SAR, in vivo characterization and the X-ray structure of BI 1356 in complex with DPP-IV will be discussed.

MEDI 25

Optimized synthesis of 2-methylamino-pyridodiazepines, potent and selective inhibitors of *Helicobacter pylori* Murl

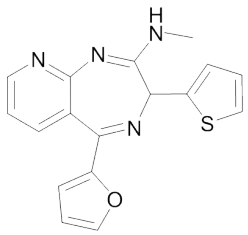
Pamela J. Hill*, Gregory S. Basarab, Bolin Geng, Lawrence MacPherson, George Mullen, and Alexander Satz, Infection Discovery, AstraZeneca, R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451, pam.hill@astrazeneca.com*

Helicobacter pylori, a Gram-negative bacterium, has been shown to cause gastritis and gastric ulcers, and has been linked to some gastric cancers. High-throughput screening efforts had previously identified benzodiazepines as selective inhibitors of *H. pylori* glutamate racemase (MurI), an enzyme essential for cell-wall biosynthesis. An analog program was carried out to increase enzyme inhibitory potency, improve antibacterial activity, and optimize physical properties for oral administration. The HTS hit (**I**) was transformed into an advanced lead compound (**II**) with improved physical properties. The precedented synthetic methods for making benzodizepines involves many steps and the use of toxic reagents. An alternative, more robust synthesis was designed to allow for the rapid synthesis of a larger range of analogs including the incorporation of heteroatoms into the benzodiazepine core.



I

H. pylori IC50 = 1.7uM
H. pylori MIC = 0.5µg/mL
Protein Binding = 99.7%
Solubility = 0.06µM
LogD = 4.1



II

H. pylori IC50 = 2.0uM
H. pylori MIC = 0.25µg/mL
Protein Binding = 82%
Solubility = 1360µM
LogD = 1.9

MEDI 26

Development of hydroxy hydantoins, a novel class of MMP-12 inhibitors, for treatment of COPD

Kristina Stenvall*, Balint Gabos, Michael Lundkvist, Magnus Munck af Rosenschöld, Matti Lepistö, and Igor Shamovsky, Department of Medicinal Chemistry, AstraZeneca, S-221 87 Lund, Sweden, Fax: +4646338399, Kristina.Stenvall@astrazeneca.com*

Matrix metalloproteinases (MMPs) belong to a family of zinc-containing enzymes that regulate the turnover of extra-cellular matrix proteins and activity of a number of pro-inflammatory mediators. Abnormal enzymatic activity of macrophage metalloelastase (MMP-12), one member of the MMP superfamily, is implicated in the development of cigarette smoke-induced emphysema, a hallmark of chronic obstructive pulmonary disease (COPD). Inhibition of MMP-12 therefore represents an attractive therapeutic strategy in the treatment of COPD. The clinical utility of broad-spectrum MMP inhibitors has been limited by musculoskeletal side effects and lack of selectivity is one possible explanation to this adverse effect, although the mechanism remains unclear. Most known MMP inhibitors possess a hydroxamic acid moiety, a strong Zn (II)-binding group, which leads to their high-affinity binding to the enzymatic sites of MMPs. Hydroxy hydantoins, a novel class of MMP inhibitors, interacts with the enzymes via a weak Zn (II)-binding group and the development of potent MMP-12 inhibitors from this series will be presented.

MEDI 27

Discovery of selective and potent T-type calcium channel antagonists

***Zhi-Qiang Yang**, Department of medicinal Chemistry, Merck, 770 Sumneytown Pike, West Point, PA 19486, Zhiqiang_yang@merck.com*

T-type calcium channels are low-voltage activated ion channels that play an important role in regulating a variety of biological processes, both peripherally and in the CNS. Several drugs such as mibefradil, ethosuximide, and pimozide have been reported to inhibit T-type calcium channels; however, their poor selectivity makes it difficult to conclusively determine the consequences of T-type calcium channel inhibition. Here, we report for the first time a class of truly selective and potent T-type channel antagonists derived from 1, 4-substituted piperidines. These inhibitors were identified though HTS screening followed by lead optimization to minimize hERG and L-type calcium channel activities. SAR and in vivo data of key compounds will be discussed in detail.

MEDI 28

Synthesis and characterization of dapagliflozin, a potent selective SGLT2 inhibitor for treatment of diabetes

***William N. Washburn**[1], Wei Meng[1], Bruce A. Ellsworth[1], Alexandra Nirschl[2], Peggy J. McCann[1], Manorama Patel[1], Ravindar N. Girotra[1], Gang Wu[1], Philip M. Sher[1], Scott A. Biller[1], Prashant P. Deshpande[3], Deborah L. Hagan[4], Joseph R. Taylor[4], Mary Obermeier[5], William G. Humphreys[6], Ashish Khanna[7], James G. Robertson[8], Aiying Wang[8], Song Ping Han[8], John R. Wetterau[4], Evan Janovitz[7], Oliver Flint[9], and Jean M. Whaley[4]. (1) Metabolic Diseases Chemistry, Bristol-Myers Squibb, Research and Development, PO Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3550, washburw@bms.com, (2) Discovery Chemistry, Bristol-Myers Squibb Company, Princeton, NJ 08543-5400, (3) Process R & D, Bristol-Myers Squibb, Princeton, NJ 08543, (4) Metabolic Research Department, Bristol-Myers Squibb, Princeton, NJ 08534, (5) Metabolism and Pharmacokinetics Department, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (6) Department of Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, (7) Pharmaceutical Candidate Optimization, Bristol-Myers Squibb, Princeton, NJ 08543, (8) Department of Metabolic Research, Bristol-Myers Squibb Company, Princeton, NJ 08543-5400, (9) Drug Safety Evaluation, Bristol-Myers Squibb Company, Princeton, NJ 08543-5400*

The synthesis and characterization of the first example of a C-aryl glucoside-derived renal sodium-dependent glucose cotransporter-2 (SGLT2) inhibitor, dapagliflozin, are described. The clinical candidate dapagliflozin is a potent SGLT2 inhibitor (IC50 = 1 nM) exhibiting 1100-fold selectivity vs SGLT1, as well as high selectivity vs the facilitative transporters GLUT 1 and 4. Its absorption, distribution, metabolism, and excretion profile is favorable: following oral gavage of rats, 84% bioavailability with Cmax achieved in 100 minutes; low clearance rate of 4.8 mL/min/kg; elimination t½ after intravenous administration was 4.6 hours in rats, and 7.4 hours and 3.0 hours in dogs and monkeys, respectively. Oral administration of 0.1 mg/kg of

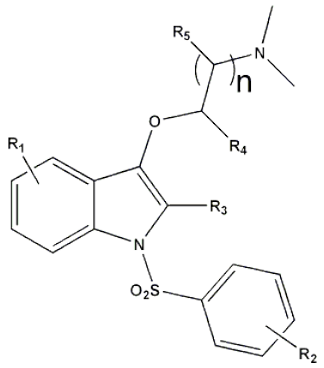
dapagliflozin to normal or diabetic rats produced copious glucosuria unaccompanied by hypoglycemia. Plasma glucose levels of fed streptozotocin-induced diabetic Sprague-Dawley rats were reduced from 500 mg/dL to 200 mg/dL over a 5-hour period following oral administration of 0.1 mg/kg of dapagliflozin.

MEDI 29

3-(Amino)alkoxy indoles: Novel class of centrally acting anti-obesity agents

***Ramakrishna V. S. Nirogi**, Anand V Daulatabad, Narendra Varma Gaddiraju, Parandhama Gudla, Mallesh Junnuri, Srinivasulu Kota, Rama Sastry Kambhampati, and Anil K. Shinde, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, Fax: 91-40-23541152, nvsrk@suven.com*

5-HT6 receptor antagonists from SmithKline Beechame, Roche and recently from Dr. Esteve's lab have reported to reduce body weight and food intake in rats. However, in spite of their demonstrated efficacy in cognition as well as obesity, the lack of desirable pharmacokinetic properties required for these CNS agents is one of the main reasons for full characterization of functional and physiological usefulness of these molecules in human therapy. Part of ongoing programme at Suven for the synthesis of selective 5-HT6 ligands as antiobesity agents, we have designed a series of 3-(Amino)alkoxy indoles derivatives. Unlike the reported known ligands these compounds are conformationally highly flexible molecules. Our effective lead generation coupled with molecular modeling studies gave compounds with Ki in the range of 1 - 5 nM. The synthesis, in-vitro binding data along with SAR and in-vivo efficacy of the lead molecule will be presented.



MEDI 30

Nonpsychotropic biaryl cannabinoid agonists

***Karin Worm**[1], Q. Jean Zhou[1], Gabriel Stabley[2], Robert N. DeHaven[2], Nathalie C. Conway-James[2], Christopher J LaBuda[2], Michael Koblish[2], Patrick J Little[2], and Roland E. Dolle[1]. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, kworm@adolor.com, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341-1127*

Cannabinoid receptor agonists, such as CP55,940 and WIN 55,212-2, produce potent antinociception with equivalent efficacy to morphine in animal models of pain. They also induce a number of unwanted CNS side effects, which are accounted for by the central distribution pattern of CB1 receptors. Catalepsy in mice is indicative of CB1 activation and predictive of cannabinoid psychoactivity. A separation between therapeutic effects and undesirable CNS side effects could be accomplished by preventing the cannabinoid from crossing the blood brain barrier. We report here that it is possible to peripheralize CB ligands, using a unique combination of polar substituents on a cannabinomimetic biaryl core, retaining the binding affinity to the receptors but preventing CNS side effects from occurring as demonstrated by the absence of catalepsy in the ring test at doses up to 100 mg/kg i.p.. Synthesis, SAR and initial biological evaluation in animal models of pain will be presented.

MEDI 31

Synthesis of (-)-Δ^9-tetrahydrocannabinol and (-)-Δ^9-tetrahydrocannabivarin metabolites and their regiospecifically deuterated analogs

Spyros P. Nikas[1]*,* ***Ganesh A. Thakur***[1]*, Damon Parish*[2]*,* ***Shakiru O. Alapafuja***[1]*, Marilyn A Huestis*[3]*, and* ***Alexandros Makriyannis***[1]*. (1) Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, 116 Mugar Life Sciences Building, 360 Huntington Avenue, Boston, MA 02115, spyridonnikas@yahoo.com, gathakur@gmail.com, Alapafuja@yahoo.com, a.makriyannis@neu.edu, (2) Naval Research Laboratory, Washington, DC 20375, (3) Chemistry and Drug Metabolism Section, CPTR Branch, Intramural Research Program, NIDA, NIH, Baltimore, MD*

For centuries marijuana has been a popular recreational drug of abuse because of its psychoactive properties. (-)-Δ^9-Tetrahydrocannabinol [(-)-Δ^9-THC], the major ingredient of marijuana, quickly metabolizes to several cannabinoids-mainly 11-hydroxy-Δ^9-THC, 11-nor-9-carboxy-Δ^9-THC, and 8β, 11-dihydroxy-Δ^9-THC and their glucuronide conjugates. The availability of tetrahydrocannabinols and their metabolites in both their undeuterated and deuterated forms is critical for the analysis of biological and toxicological samples. A recent study tracing the metabolism of marijuana constituents including (-)-Δ^9-THC and (-)-Δ^9-tetrahydrocannabivarin [(-)-Δ^9-THCV] in humans required the synthesis of deuterated analogs as well as their corresponding in vivo metabolites in high isotopic and optical purities. We describe here a concise methodology for the syntheses of (-)-Δ^9-THC and (-)-Δ^9-THCV metabolites. The synthetic sequence involves a minimum number of steps, avoids undesirable oxidative conditions, and incorporates the costly deuterated fragments near the end of the synthetic sequence.

Acknowledgements:This work was supported by grants from the National Institute on Drug Abuse (DA03801, DA07215 and DA09158)

MEDI 32

Deuterated and tritiated enantiomers of CP55,940 as novel probes of cannabinoid receptors

Kejun Cheng[1]*, Klaus Gawrisch*[2]*, and Kenner C. Rice*[1]*. (1) Chemical Biology Research Branch, National Institute on Drug Abuse, National Institutes of Health, Building 8, Rm. B1-22, 8 Center Drive, MSC0815, Bethesda, MD 20892, Fax: 301-402-0589, kejunch@niddk.nih.gov, (2) Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892*

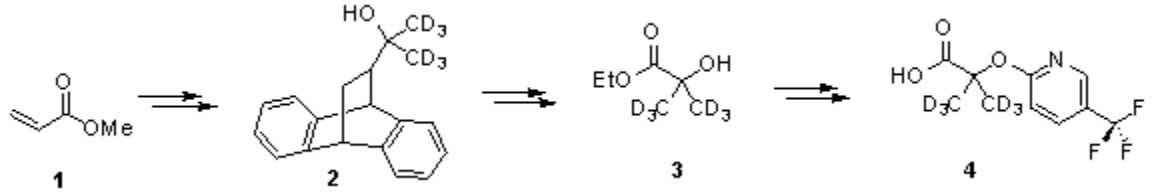
The peripheral type cannabinoid receptor (CB2) is a G-protein coupled receptor that is involved in numerous physiological processes and is therefore a potential target for medication development. Recenty, the functional human CB2 has been expressed in milligram quantities in E. coli, purified to over 80%, and reconstituted in a lipid matrix (artificial membrane) where it retained the expected drug binding properties. This presentation will describe our chemical and biological program to synthesize deuterated and tritiated enantiomers of the cannabinoid ligand CP55,940, and to utilize these probes to further characterize specific interactions of drugs with the CB2 binding pocket. The ligands initially targeted were (a) the tritiated inactive enantiomer (CP56,667) of CP55,940 for determination of nonspecific binding to the lipid matrix and differentiation from specific binding, and (b) CP55,940 containing the fully deuterated (D19) aromatic side chain as a probe to determine structure, location and dynamics of the specifically bound ligand by NMR and other methods.

MEDI 33

Synthesis of isotopically labeled 2-pyridinyloxyisobubanoic acid, a building block for CB-1 inhibitors as drug candidates for obesity treatment

Jonathan Z. Ho *and Matthew P Braun, Department of Drug Metabolism, Merck & Co., Inc, 126 East Lincoln Avenue, Rahway, NJ 07065, Fax: 732-594-6921, jonathan_ho@merck.com*

Synthesis of [2,2-methyl-d_6]-2-(pyridinyloxy)-2,2-dimethylacetic acid from methyl acrylate (**1**) is described. The key step is a Diels-Alder reaction of methyl acrylate with anthracene to protect the double bond followed by reaction with methyl-d_6 Grignard reagent to introduce the deuterium labels as shown in **2**. This approach involved a retro Diels-Alder reaction to regenerate the double bond, which is then converted to an aldehyde through ozonolysis. A one-pot procedure was developed to convert the aldehyde to the ethyl ester **3**, which was then coupled with 2-chloropyridine. Simple hydrolysis under base condition gave the title compound **4**.



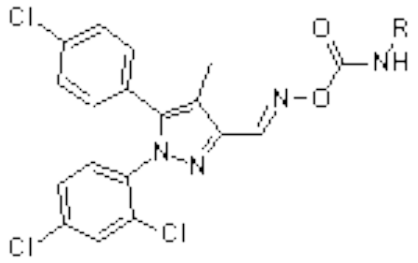
1 2 3 4

MEDI 34

Synthesis and biological evaluations of carbamoyl oxime analogs of the cannabinoid receptor-1 (CB1) anatagonist SR141716

Sung-Hwa Yoon, ***Hee-yeon Kim***, *Hyun-Ji Kim, and Hyo-jae Jung, Department of Molecular Science and Technology, Ajou University, WonchunDong San5, Suwon 443-749, South Korea, Fax: 31-219-2394, shyoon@ajou.ac.kr, hy0122@hanmail.net*

A series of carbamoyl oxime analogues (1) of the biaryl pyrazole N-(piperidinyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-H-pyrazole-3-carboxamide (SR141716) were synthesized to investigate the importance of the hydrazide moiety for an antagonistic CB1 activity. The analogues where the substituted phenylalkyl groups of varying lengths are connected to biaryl pyrazole motif through carbamoyl oxime moiety were synthesized from the corresponding oxime compound with various isocyanates. Among the tested compounds, the compound containing the chlorobenzyl group exhibited high CB1 activity. The synthesis and SAR of this series will be presented.



1

MEDI 35

Synthesis and SAR of Diaryl cyclohexene carboxamides as potent and orally active CB1 antagonists

Charles L. Jayne[1], *Yan Xia*[1], *H. Vaccaro*[1], *Samuel Chackalamannil*[1], *William Greenlee*[1], *George Boykow*[1], *Ruth A. Duffy*[1], *Timothy Kowalski*[2], *and Xiaoming Cui*[1]. *(1) Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, charles.jayne@spcorp.com, (2) Schering-Plough Research Institute, Kenilworth, NJ 07033-0539*

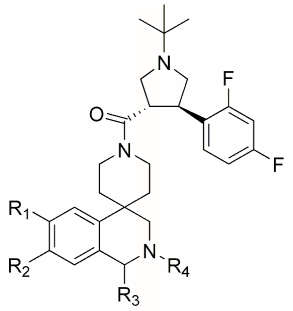
It is believed that the Cannabinoid receptor type 1 (CB1), part of the endocannabinoid system, plays an important role in the regulation of appetite. The increased stimulation of CB1 receptors can lead to weight gain in animals and humans. Development of an antagonist for the CB1 receptor has drawn considerable attention recently as a treatment of obesity as exemplified by rimonabant, a CB1 antagonist currently under FDA review. We synthesized a number of diaryl cyclohexene carboxamides based on the structure of rimonabant. The SAR of their CB1 binding affinity, selectivity over CB2, and *in vivo* efficacy will be described.

MEDI 36

Synthesis and SAR of derivatives from 2, 3-dihydro-1H-spiro [isoquinoline-4, 4'-piperidine] as MC4R agonists for the treatment of obesity

Jian Liu[1]*, Tianying Jian*[1]*, Iyassu K. Sebhat*[1]*, Rui Tang*[2]*, David H. Weinberg*[2]*, Tanya MacNeil*[2]*, Angeles Cabello*[3]*, Airu S. Chen*[2]*, Howard Y. Chen*[2]*, Cherrie A. Shepherd*[4]*, Alison Strack*[4]*, R. Miller*[5]*, Ralph Stearns*[5]*, Zhesheng Chen*[1]*, Tom Holt*[1]*, Tung M. Fong*[6]*, Matthew J. Wyvratt*[1]*, and Ravi P. Nargund*[1]*. (1) Department of Medicinal Chemistry, Merck & Co., Inc, Rahway, NJ 07065, Fax: 732-594-3007, jian_liu@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ 07065, (3) CIBE, Merck & Co., Inc, (4) Department of Pharmacology, Merck & Co., Inc, Rahway, NJ 07065, (5) Department of Drug Metabolism, Merck & Co., Inc, Rahway, NJ 07065, (6) Department of Metabolic Disorders, Merck & Co., Inc, Rahway, NJ 07065*

Abstract The melanocortin-4 receptor (MC4R), widely expressed in the hypothalamus, contributes to the control of feeding and sexual behavior in rodents. Efforts have been invested by various research groups to identify suitable agonists of the MC4 receptor as treatments for obesity and sexual dysfunction. In recent years, a significant number of small molecule MC4R agonists have been reported. This presentation describes a series of potent MC4R selective agonists (1) containing a 2, 3-dihydro-1H-spiro [isoquinoline-4, 4'-piperidine] amide. Extensive SAR studies were carried out with different substitutions on the spiro piperidine ring. This work led to the identification of a compound with excellent binding affinity (IC50 = 11 nM) and agonist functional activity (EC50 = 6 nM, 114% activation). After oral administration, the compound had sufficient exposure in DIO rats (dosed at 3 mpk) and mice (dosed at 10 mpk) to demonstrate efficacy in lowering food intake. The presentation will discuss the synthesis, structure-activity relationship and pharmacology of select compounds from this series.



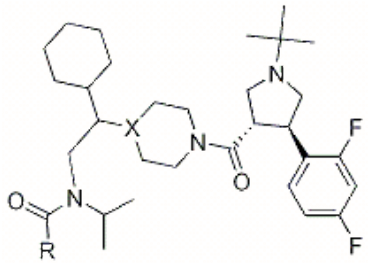
1

MEDI 37

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

Qingmei Hong[1], *Raman K. Bakshi*[1], *James Dellureficio*[1], *Rui Tang*[2], *Rubana N. Kalyani*[2], *Tanya MacNeil*[2], *Aurawan Vongs*[2], *Charles I. Rosenblum*[2], *David H. Weinberg*[2], *Qianping Peng*[3], *Constantin Tamvakopoulos*[3], *Randy R. Miller*[3], *Ralph A. Stearns*[3], *Doreen Cashen*[2], *William J. Martin*[2], *Airu S. Chen*[2], *Joseph M. Metzger*[4], *Howard Y. Chen*[2], *Alison M. Strack*[2], *Tung M. Fong*[2], *D. Euan MacIntyre*[4], *Lex H. T. Van der Ploeg*[2], *Arther A. Patchett*[1], *Matthew J. Wyvratt*[1], *and Ravi P. Nargund*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, 126 E. Lincoln Avenue, P.O.Box 2000, Rahway, NJ 07065, qingmei_hong@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ 07065, (3) Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, (4) Department of Pharmacology, Merck Research Laboratories, Rahway*

The melanocortin receptors are known as a family of five G-protein-coupled receptors and mediate a variety of physiological functions. In particular, the melanocortin-4 receptor subtype has attracted considerable attention from medicinal chemists and biologists because of its potential in the treatment of obesity and sexual dysfunction over the last decade. In this presentation, we report optimization of privileged structures and discovery of novel N-acylated piperazine and piperidine derivatives as MC4R agonists.

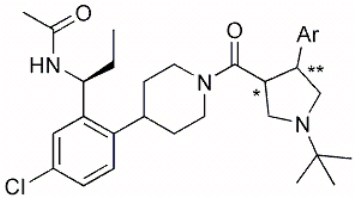


MEDI 38

Potent and orally bioavailable nonpeptidyl melanocortin subtype-4 receptor modulators: Syntheses, SAR and pharmacokinetics

Liangqin Guo[1], *Zhixiong Ye*[1], *Iyassu K. Sebhat*[1], *Feroze Ujjainwalla*[1], *Heather L. Sings*[1], *David H. Weinberg*[2], *Rui Tang*[2], *Tanya MacNeil*[2], *Constantin Tamvakopoulos*[3], *Qianping Peng*[3], *Euan MacIntyre*[4], *Lex H. T. Van der Ploeg*[5], *Mark T. Goulet*[1], *Matthew J. Wyvratt*[1], *and Ravi P. Nargund*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, RY 50G-332, Rahway, NJ 07065, Fax: (732)-594-3007, liangqin_guo@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ 07065, (3) Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, (4) Department of Pharmacology, Merck Research Laboratories, Rahway, NJ 07065, (5) Department of Obesity Research, Merck & Co., Inc, Rahway, NJ 07065*

The melanocortin receptors are known as a family of five seven–transmembrane G-protein-coupled receptors. Of these five subtypes, the melanocortin-4 receptor (MC4R) has been clearly linked to the regulation of energy homeostasis and feeding regulation. Increasing efforts have been attracted to develop potent and selective non-peptide MC4R agonists. In this presentation, the synthesis, SAR and pharmacokinetics of a series of orally bioavailable, non-peptidyl, t-butyl pyrrolidine derived, potent and MC4R selective compounds will be discussed (Figure 1).

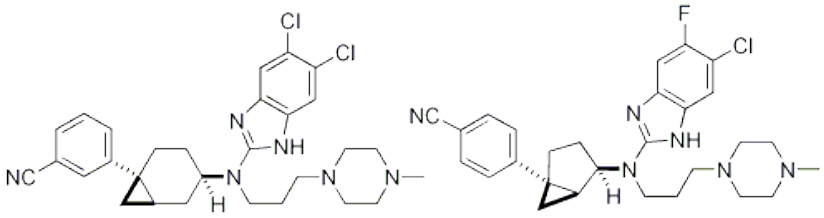


MEDI 39

Aminobenzimidazoles as potent Melanin Concentrating Hormone (MCH)-R1 antagonists

T K Sasikumar[1]*, Li Qiang*[1]*, Duane A Burnett*[1]*, William J Greenlee*[1]*, Brian E Hawes*[2]*, Timothy J Kowalski*[3]*, Kim O'Neill*[2]*, Brian D Spar*[3]*, and Blair Weig*[2]*. (1) Chemical Research CV and CNS, Schering-Plough, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7164, thavalakulamgar.sasikumar@spcorp.com, (2) CNS Biology, Schering-Plough, (3) CNS Pharmacology, Schering-Plough*

Melanin concentrating hormone (MCH) is a 19 membered neuropeptide that is found in the lateral hypothalamus and regulates food intake. There is evidence for involvement of MCH in feeding and obesity. Hypothalamic MCH peptide levels increase during fasting in ob/ob and WT mice. ICV administration of MCH or analogs stimulates feeding in rodents and MCH-/- mice, while otherwise healthy, are hypophagic and leaner than WT mice. MCH receptor knock-out mice are lean, hypophagic, hyperactive, have reduced fat mass, have increased metabolic rate and they are resistant to diet induced obesity (DIO). Evidence from knock-outs suggests an MCH receptor antagonist should be beneficial for treatment of obesity and related disorders. Discovery of a new class of small molecule MCH-R1 antagonists will be discussed.



h-MCH-R1 K_i = 2.2 nM

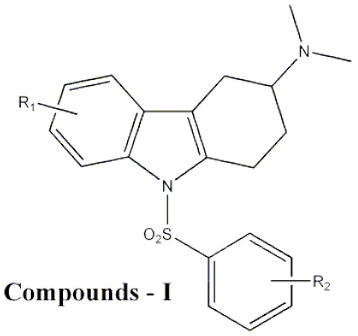
h-MCH-R1 K_i = 4.9 nM

MEDI 40

Tetrahydro carbazoles: Novel, potent and selective 5-HT6 receptor antagonists

Rama Sastry Kambhampati*, Jagadish B. Konda, Prabhakar Kothmirkar, Trinath R. Bandyala, Sivasekhar NK. Yarra, Sobhanadri Arepalli, Anil K. Shinde, and Ramakrishna V. S. Nirogi, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, krsastri@suven.com*

The intriguing distribution of 5-HT6 receptors in the brain together with its role in the higher cognitive processes such as memory and more recently in obesity is well documented. The lack of desirable pharmacokinetic properties required for these CNS agents is one of the main reasons for full characterization of functional and physiological usefulness of these molecules in human therapy. Our continuing efforts towards design and discovery of selective 5-HT6 antagonists have lead to the identification of novel rigidized tryptamine derivatives. The effective lead generation and optimization methods have resulted in a series of potent 5-HT6 receptor ligands with Ki in the range of 1 - 5 nM, when tested by the in-vitro radio-ligand binding techniques. Synthesis, physicochemical properties and in-vitro binding data along with SAR will be discussed.



Compounds - I

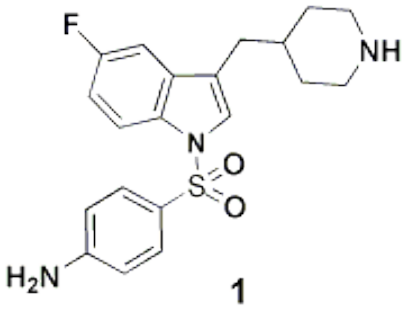
MEDI 41

Novel 1-(arylsulfonyl)-3-(piperidinylmethyl)-1H-indoles as potent and selective 5-HT6 antagonists

Ping Zhou[1]*, Yanfang Li*[1]*, Boyd L. Harrison*[1]*, Guo Ming Zhang*[2]*, Deborah Smith*[2]*, Michael G. Kelly*[1]*, Lee Schechter*[2]*, and Albert J Robichaud*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, Fax: 732-274-4505, zhoup@wyeth.com, (2) Department of Neuroscience, Wyeth Research, Princeton, Princeton, NJ 08543*

The 5-HT6 serotonin receptor subtype is one of the seven major types of serotonin receptors (5-HT1-5-HT7). This receptor is a member of the seven-transmembrane-spanning G-protein-coupled receptor family that is positively coupled to adenylate cyclase. The potential role of selective 5-HT6 receptor ligands in the treatment of various central nervous system disorders such as depression, anxiety, cognition, and feeding disorders has stimulated a surge of interest in this area. A novel class of 1-(arylsulfonyl)-3-(piperidinylmethyl)-1H-indoles was designed and prepared as potent and selective 5-HT6 ligands. Among these, compound 1 showed excellent affinity (Ki = 1 nM) towards the 5-HT6 receptor, and excellent selectivity over

5-HT7 receptor. In addition, compound 1 is a full antagonist in a 5-HT6 functional assay with superior potency (IC50 = 1.3 nM)



1

MEDI 42

SUVN-504: Potent and selective high brain penetrating 5-HT6 receptor antagonist

***Gopinadh Bhyrapuneni**, Nageswararao Muddana, Koteshwara Mudigonda, Vishwottam N. Kandikere, and Ramakrishna V. S. Nirogi, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, gopi@suven.com*

The $5HT_6$ receptor is the latest serotonin receptor identified by molecular cloning. Its mRNA appears to be distributed in the brain, making it an attractive CNS therapeutic target. SUVN-504 is a highly selective $5\text{-}HT_6$ receptor antagonist with high affinity for the human receptor (pKi 3.15 nM) and is orally bioavailable in rats. Effective lead-optimization of critical physico-chemical properties has led to the high brain penetration index. The present study describes the in vivo brain penetration of the SUVN-504 in the male wistar rats. SUVN-504 was administered through femoral vein at a constant infusion rate over 12 hr at target dose rate of 1 mg/kg/hr. Blood samples were collected to confirm steady-state blood concentrations. Blood and brain samples were analyzed by LC-MS/MS. SUVN-504 produced with a brain-blood ratio of 13:1 in rats with high oral bioavailability. Therefore, SUVN-504 is selected for further development.

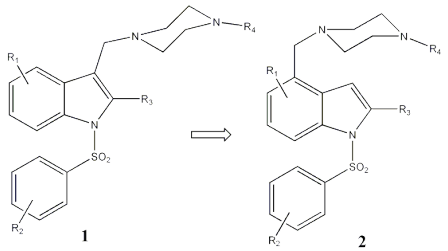
MEDI 43

Aminoalkyl indoles: Novel, potent and highly selective 5-HT6 receptor antagonists

***Anil K. Shinde**, Amol D. Deshpande, Anil K. Chindhe, Rajesh Kumar Badange, Kameswara R. Karuturi, Narasimha Reddy P. Gangadasari, Raja Rajeswari Katta, and Ramakrishna V. S. Nirogi, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, anilshinde@suven.com*

The exclusive expression of 5-HT6 receptor in the brain makes it a target of choice for CNS mediated disorders like Alzheimer's, Parkinson's disease, Dementia and other Neurodegenerative disorders. Some attempts are in progress for the clinical proof of concept for 5-HT6 antagonists as a new therapeutic class. Structure 1 was previously reported by us at Suven as potent, safe, highly selective and orally bioavailable 5-HT6 receptors antagonist. In

order to explore the SAR scope and potentially to improve pharmacokinetic/pharmacodynamic, and CNS penetration properties of the molecules, -CH2-piperazine in structure 1 was moved from C3 of indole to C4 of indole. Structure 2 gave a series of novel and potent 5-HT6 receptor antagonists with Ki in the range of 1-5 nM, when tested by the in-vitro radio-ligand binding assays. Synthesis of these molecules, binding affinity and selectivity as well as some functional data will be presented along with computational analysis.

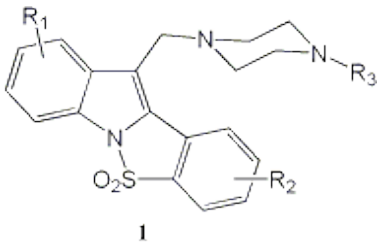


MEDI 44

Conformationally restricted piperazines: Novel class of potent and selective 5-HT6 receptor ligands

Ramakrishna V. S. Nirogi*, Amol D. Deshpande, Adi R. Dwarampudi, Venugopala Rao Bhatta, Laxman Kota, Ravichandra R. V. Vangavarugu, Rama Sastry Kambhampati, and Anil K. Shinde, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, Fax: 91-40-23541152, nvsrk@suven.com*

Modulation of 5-HT receptors has been actively pursued for treatment of numerous disease states. Specifically, 5-HT6 receptor antagonists are being perceived for the treatment of CNS disorders and feeding disorders. Though highly selective and potent in-vitro ligands are available, the full characterization of functional and physiological usefulness of these compounds is limited due to the lack of desired brain penetration and pharmacokinetic properties required for the CNS agent. Keeping these factors in the mind we have designed 5-HT6 ligands on a chemically novel skeleton. The attempts have been made to impart the drug like properties to these molecules by optimizing their physicochemical properties. Our primary hit was found to have the Ki in the micromolar range. Our effective lead optimization strategies have resulted in the molecules with Ki in the range of 5 - 15 nM at the 5-HT6 receptor. Synthesis, physicochemical properties and the in-vitro binding data along with the SAR will be presented.



MEDI 45

Small-molecule Y_2 receptor antagonists: Identification of a novel and potent series using pharmacophore-based virtual screening

***Mark Seierstad**, Computer Aided Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, 3210 Merryfield Row, San Diego, CA 92121, mseierst@prdus.jnj.com*

Drug-like antagonists of the neuropeptide Y Y_2 receptor (which might be useful for the regulation of food intake and bone formation) are rare in the literature. Only a few have been described that have nanomolar potency, with the most potent having an IC_{50} of 100 nM.

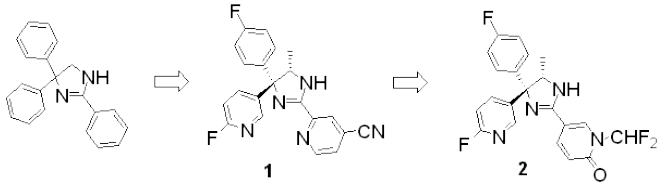
We report the discovery of a novel series of Y_2 receptor antagonists. Pharmacophore models were constructed using a set of known ligands, including small molecules and also a neuropeptide Y analogue. Compounds from our corporate database that fit these models were selected for biological screening. One compound series that emerged from these efforts contained several active antagonists. A medicinal chemistry program has since produced high affinity and low molecular weight Y_2 antagonists.

MEDI 46

Discovery and optimization of imidazoline derivatives, a potent, orally active neuropeptide Y Y5 receptor antagonist

***Makoto Ando**, Nagaaki Sato, Shiho Ishikawa, Makoto Jitsuoka, Keita Nagai, Tsuyoshi Nagase, Hirobumi Takahashi, Aya Sakuraba, Hiroyasu Tsuge, Mioko Hirayama, Junko Ito, Hisashi Iwaasa, Hiroko Matsushita, Akira Gomori, Satoshi Mashiko, Akane Ishihara, Naoko Fujino, Sachiko Tanaka, Tomoyuki Ohe, Kiyoshi Tadano, Takahiro Fukuroda, Yasuyuki Ishii, Akio Kanatani, and Takehiro Fukami, Tsukuba Research Institute, Banyu Pharmaceutical CO., LTD, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan*

Neuropeptide Y is a 36-amino acid peptide with centrally mediated potent orexigenic effects. Five types of NPY receptors (Y1, Y2, Y4, Y5 and y6) have been characterized, and pharmacological data suggest that the NPY Y5 receptor (Y5R), located primarily in the hypothalamus, is involved in feeding regulation. Screening of our chemical collection against the human Y5R resulted in the identification of 2,4,4-triaryl imidazoline with an IC_{50} value of 60 nM at the Y5. Optimization of the triarylimidazoline lead led to potent derivative **1** that is orally active in rodents. However, intravenous administration of **1** showed a significant QT prolongation in anesthetized dogs. The QT issue was overcome by further modification of 2-substituents, and clinical candidate **2** was identified. The enantioselective synthesis, SAR and in vivo data of the imidazoline derivatives will be presented.



MEDI 47

Synthesis and SAR of thiophene acid-mimetics as PTP1B inhibitors

Eva Binnun[1], *Zhao-Kui Wan*[1], *Bruce Follows*[1], *Steven J. Kirincich*[1], *Douglas Wilson*[1], *Wei-Xin Xu*[2], *Diane Joseph-McCarthy*[3], *Junjun Wu*[1], *Michael J. Smith*[1], *Yanling Zhang*[4], *May Tam*[4], *Dave Erbe*[4], *Steve Tam*[1], *Eddine Saiah*[1], *and Jinbo Lee*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, Fax: 617-665-5682, (2) Department of Chemical and Screening Sciences, Wyeth Research, Cambridge, MA 02140, (3) Department of Structural Biology & Computational Chemistry, Wyeth Research, Cambridge, MA 02140, (4) Cardiovascular and Metabolic Disease, Wyeth Research, Cambridge 02140*

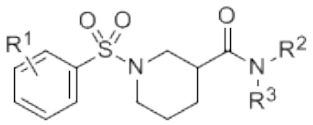
Protein tyrosine phosphatase 1B (PTP1B) plays a critical role in the signal transduction of both insulin and leptin pathways. As a therapeutic target, PTP1B has received considerable attention from the drug industry as a potential treatment for diabetes mellitus. Two independent studies demonstrated that PTP1B knockout mice show greater insulin sensitivity,and maintained lower glucose and insulin levels. Designing phosphate mimetics with desirable drug-like properties has been a significant challenge industry-wide. Most of the reported competitive, reversible PTP1B inhibitors contain a phosphate group. While reasonable potency levels have been achieved in many compounds, cell permeability, in general, has remained poor and continues to represent one of the most significant obstacles to successful small molecule drug design associated with this target. Previously, we have reported at length on our novel thiophene diacid series of inhibitors. While the potency of many of these compounds was excellent, cell permeability remained a considerable challenge. Accordingly, efforts were shifted to the incorporation of an acid mimetic group into the design of our thiophene series. While such moieties would certainly improve cell membrane permeability, avoiding a dramatic decrease in potency would be a significant challenge, and required the careful design of compounds whose acid mimetic group could efficiently capture the key binding interactions in precisely the same manner as the more robust carboxylate. A wide variety of acid mimetic groups were surveyed, and while many substitutions were accompanied by loss of activity, several groups did preserve potency, while showing an improvement in cell permeability. Specifically, both tetrazole and thiazolidinone moieties, proved to be quite promising, providing the most favorable balance between cell permeability and potency that has been observed in the thiophene series to date. En route to these novel series, a comprehensive detailed SAR for monoacid PTP1B inhibitors was developed, and we report these data herein.

MEDI 48

Discovery and synthesis of nipecotic amide as novel, potent and selective 11ß-HSD-1 inhibitors

Jincong Zhuo[1], *Meizhong Xu*[1], *Colin Zhang*[1], *Dingquan Qian*[1], *Yanlong Li*[1], *Reid Huber*[1], *Maryanne Covington*[2], *Cindy Marando*[1], *Brian Metcalf*[1], *and Wenqing Yao*[1]. *(1) Incyte Corporation, Experimental Station - E336/208B, Route 141 & Herry Clay Road, Wilmington, DE 19880, Fax: 302-425-2750, jzhuo@incyte.com, (2) Bristol-Myers Squibb Company*

11ß-HSD-1 (11ß-hydroxysteroid dehydrogenase type I) is an enzyme that belongs to the short-chain dehydrogenase superfamily. It is highly expressed in liver and adipose tissues. 11ß-HSD-1 catalyzes the inter-conversion of inactive cortisone to active cortisol. 11ß-HSD-1 knock out mice show improved lipid profiles and hepatic insulin sensitivity. Therefore, 11ß-HSD-1 inhibitors have been of great interest as a therapeutic intervention for symptoms of metabolic syndrome including visceral adiposity, hyperglycemia. We will discuss the discovery and SAR of a novel series of nipecotic amides as potent and selective 11ß-HSD-1 inhibitors.



MEDI 49

Novel analogs as 11β-HSD1 inhibitors

Unmesh Shah[1]*, Craig D. Boyle*[1]*, Samuel Chackalamannil*[1]*, Hana Baker*[2]*, Timothy Kowalski*[3]*, Lili Zhang*[4]*, and Giuseppe Terracina*[4]*. (1) 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) CV/Metabolic Diseases Research, Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (4) Neurobiology, Schering-Plough Research Institute, Kenilworth, NJ 07033*

11β-Hydroxysteroid dehydrogenase (11βHSD) catalyzes the interconversion of active cortisol and inert cortisone, thereby protecting the mineralocorticoid receptor (MR) from glucocorticoid excess. Excessive glucocorticoid activity is associated with obesity, diabetes, cognitive impairment, depression, and anxiety. Two isozymes of 11βHSD have been isolated, each performing critical biological roles. 11β-HSD2 inactivates cortisol (by converting it to inactive cortisone), protecting key tissues. By contrast, 11β-HSD1 regenerates the active cortisol, resulting in enhanced glucocorticoid effects. Consequently, inhibition of 11β-HSD1 is a potential therapeutic target for both metabolic and glucocorticoid-associated CNS disorders.

Herein, we wish to report the discovery of potent 11β-HSD1 inhibitors for the potential treatment of diabetes and metabolic syndrome. The synthesis and SAR of novel analogs will be discussed. In vivo data of representative compounds will also be presented.

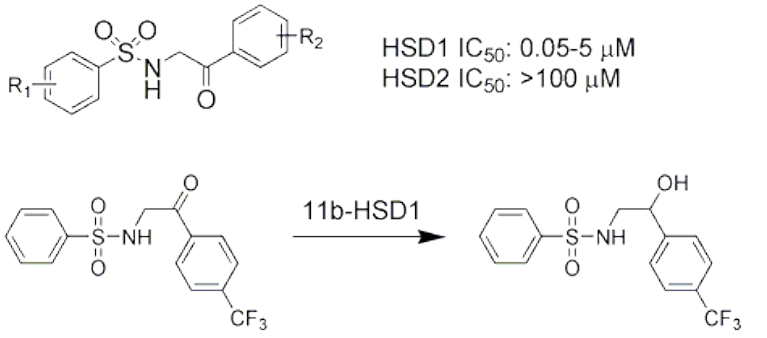
MEDI 50

B-keto sulfonamides as selective inhibitors of the 11b-HSD1

Manus Ipek[1]*, Jason Xiang*[1]*, Lihren Chen*[1]*, Nelson Huang*[1]*, Jim Li*[1]*, Wei Li*[1]*, Tarek Mansour*[1]*, John C McKew*[1]*, Jill Nunez*[1]*, Vipin Suri*[2]*, Tam May*[2]*, Steve Tam*[1]*, James F Tobin*[2]*, Charlie Wu*[1]*, Yuzhe Xing*[2]*, Xin Xu*[3]*, and Yanling Zhang*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 200 CambridgePark Drive, Cambridge, MA 02140, mipek@wyeth.com, (2) Cardiovascular and Metabolic Diseases, Wyeth Research, (3) Drug Safety and Metabolism, Wyeth Research*

Glucocorticoid hormones are important chronic regulators of metabolism. Intracellular reactivation of inactive glucocorticoids has emerged as a key mechanism for regulation and amplification of glucocorticoid action. The reactivation is catalyzed by 11b-Hydroxysteroid Dehydrogenase type 1 (11b-HSD1). Mice over-expressing 11b-HSD1 in adipose or liver display a phenotype very similar to metabolic syndrome, while 11b-HSD1 knock out mice show a marked improvement in insulin sensitivity, lipid and cholesterol profiles. These data indicate that inhibitors of 11b-HSD1 could be novel therapeutics for patients with type 2 diabetes, obesity and metabolic syndrome.

Presented herein is the synthesis and SAR study of the b-keto sulfonamide series. In our screening strategy, a cell-based assay was used as our primary assay to evaluate analogs. The mechanism by which b-keto sulfonamides inhibit 11b-HSD1 activity was investigated.



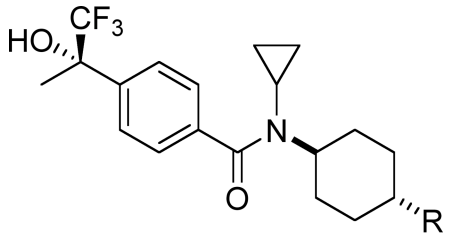
MEDI 51

Discovery and biological evaluation of novel benzamide derivatives as potent 11β-HSD1 inhibitors for the treatment of type II diabetes

Lisa D. Julian[1]*, Tracy Bostick*[2]*, Sebastien Caille*[2]*, Hon Chan*[1]*, Michael Degraffenreid*[1]*, Xiao He*[1]*, Randall W. Hungate*[3]*, Juan Jaen*[4]*, Ben Jiang*[1]*, Jacob Kaizerman*[1]*, Jinsong Liu*[1]*, Dustin McMinn*[1]*, Jay P. Powers*[3]*, Yosup Rew*[1]*, Athena Sudom*[1]*, Daqing Sun*[1]*, Hua Tu*[5]*, Stefania Ursu*[1]*, Zhulun Wang*[1]*, Xuelei Yan*[1]*, and Qiuping Ye*[1]*. (1) Amgen, Inc, 1120 Veterans Blvd, South San Francisco, CA 94080, ljulian@amgen.com, (2) Chemistry Process Research and Development, Amgen, Inc, Thousand Oaks, CA 91320, (3) Department of Chemistry Research & Discovery, Amgen, Inc, Thousand Oaks, CA 91320, (4) Department of Chemistry Research and Discovery, ChemoCentryx, Inc, Mountain View, CA 94043, (5) Department of Biology, Amgen, Inc, South San Francisco, CA 94080*

Glucocorticoids regulate glucose and lipid homeostasis, acting through intracellular glucocorticoid receptors in the liver, muscle, and fat tissues. Elevated levels of glucocorticoids can result in insulin resistance by impairment of insulin dependent glucose uptake, enhanced hepatic gluconeogenesis via induction of PEPCK and G6Pase, increased lipolysis, and the inhibition of insulin secretion from pancreatic β-cells. As a result of sustained glucocorticoid excess, patients can develop dyslipidemia, visceral obesity, and other symptoms of metabolic syndrome. The 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) enzyme catalyzes the conversion of cortisone to the active glucocorticoid hormone cortisol, regulating the local activation of glucocorticosteroid receptors. We report the discovery of potent inhibitors (**1**) of 11β-HSD1, with excellent in vivo pharmacokinetics and oral bioavailability. Additionally, a

monkey ex vivo study of benzamide **1** (R = 3-pyridyl) demonstrated effective tissue inhibition of 11β-HSD1 in the liver and adipose.



1

MEDI 52

Discovery and SAR of novel derivatives as 11β-hydroxysteroid dehydrogenase type 1 inhibitors

Claire M. Lankin[1]*, Craig D. Boyle*[1]*, Samuel Chackalamannil*[1]*, Unmesh Shah*[1]*, Hana Baker*[2]*, Timothy Kowalski*[3]*, Lili Zhang*[4]*, and Giuseppe Terracina*[4]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7164, claire.lankin@spcorp.com, (2) CV/Metabolic Diseases Research, Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (4) Neurobiology, Schering-Plough Research Institute, Kenilworth, NJ 07033*

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that converts inactive cortisone to cortisol in tissues such as liver and fat, increasing the local concentrations of active glucocorticoid. Data suggests that excess local glucocorticoid may be involved in the development of abdominal obesity and metabolic syndrome. Therefore, the inhibition of 11β-HSD1 may represent a potential treatment for diabetes and metabolic syndrome by suppressing the regeneration of active cortisol and regulating glucocorticoid action.

The synthesis, structure activity relationship and biological activity of these derivatives as inhibitors of 11β-HSD1 will be described.

MEDI 53

Synthesis and biologic evaluation of selective inhibitors of 11β-HSD1 as a potential treatment for metabolic disorders

Santhosh F. Neelamkavil[1]*, Craig D. Boyle*[1]*, Samuel Chackalamannil*[1]*, Hana Baker*[2]*, Timothy Kowalski*[3]*, Lili Zhang*[4]*, and Giuseppe Terracina*[4]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, K-15-2-2545, Kenilworth, NJ 07033, Fax: 908-740-7164, santhosh.neelamkavil@spcorp.com, (2) CV/Metabolic Diseases Research, Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033-0539, (4) Neurobiology, Schering-Plough Research Institute, Kenilworth, NJ 07033*

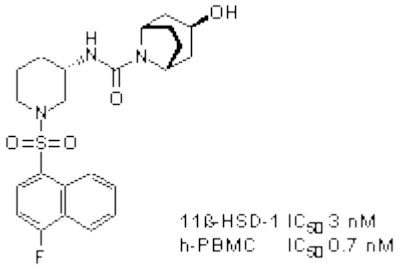
11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that activates the glucocorticoid receptor by converting inactive cortisone to active cortisol. In contrast, 11β-HSD2 catalyzes the inactivation of active glucocorticoid. Genetic deletion of 11β-HSD1 lowers plasma glucose levels in mice fed on high-fat diets and attenuates the activation of enzymes involved in hepatic gluconeogenesis suggesting that inhibitors of this enzyme may be of therapeutic use in various metabolic disorders. This presentation will discuss our discovery of several potent and selective compounds as inhibitors of 11β-HSD1.

MEDI 54

Syntheses and SAR of piperidin-3-yl ureas as potent and selective 11β-HSD-1 inhibitors

Yun-Long Li[1]*, Lori Bostrom*[2]*, Jincong Zhuo*[1]*, Yanlong Li*[1]*, Maryanne Covington*[3]*, Reid Huber*[1]*, Brian Metcalf*[1]*, and Wenqing Yao*[1]*. (1) Incyte Corporation, Experimental Station E336, Route 141 & Henry Clay Road, Wilmington, DE 19880, yunli@incyte.com, (2) Incyte Corporation, Wilmington, DE 19880-0500, (3) Bristol-Myers Squibb Company*

The enzyme 11β-hydroxysteroid dehydrogenase type 1, or 11β-HSD-1, catalyzes the intracellular conversion of functionally inert cortisone to active cortisol. Cortisol elevates blood glucose levels by increasing glucose production in the liver and by inhibiting the uptake and disposal of glucose in muscle and adipose tissue, essentially acting as an antagonist of insulin. 11β-HSD-1 inhibitors may abrogate cortisol's antagonistic actions toward insulin and thus offer a new approach to treating type 2 diabetes and allied conditions such as dyslipidemia, atherosclerosis, and coronary heart disease. Herein we report the design, syntheses and SAR of novel 3-aminopiperidinyl based ureas as potent and selective 11β-HSD-1 inhibitors.

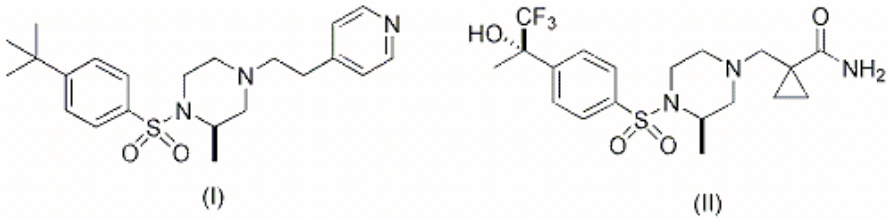


MEDI 55

Discovery and optimization of arysulfonamide as a novel class of 11beta-HSD1 inhibitors

Daqing Sun[1]*, Michael DeGraffenreid*[1]*, Xiao He*[1]*, Juan Jaen*[1]*, Jay P. Powers*[1]*, Xuelei Yan*[1]*, Yongmei Di*[2]*, Hua Tu*[2]*, Stefania Ursu*[2]*, Ji Ma*[3]*, Shichang Miao*[3]*, Liang Tang*[3]*, Qiuping Ye*[3]*, Athena Sudom*[4]*, and Zhulun Wang*[4]*. (1) Department of Chemistry Research & Discovery, Amgen, Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, daqings@amgen.com, (2) Department of Biology, Amgen, Inc, South San Francisco, CA 94080, (3) Department of PKDM, Amgen, Inc, South San Francisco, CA 94080, (4) Department of Structural Biology, Amgen, Inc, South San Francisco, CA 94080*

11 beta-Hydroxysteroid dehydrogenase type 1 (11 beta-HSD1) is a key enzyme that converts the inactive glucocorticoid cortisone to the active form (cortisol) in specific tissue, notably liver, adipose, and brain, and therefore regulates tissue-specific glucocorticoid level. Given its role in tissue-specific glucocorticoid action and the link of the hepatic and adipose glucocorticoid action to insulin resistance and dyslipidemia, 11 beta-HSD1 inhibition is a promising strategy to improve insulin sensitivity and treat type II diabetes. In this presentation, we will disclose the discovery of a series of arysulfonamides (I), a novel class of 11 beta-HSD1 inhibitors that shows potent and selective inhibition of both mouse and human 11 beta-HSD1 in different cells. We will also present our efforts to advance the SAR and improve selectivity by reducing p450 and hERG activities. These efforts resulted in compound (II), which exhibits superior potency, excellent oral bioavailability and efficacy in a cyno ex vivo model.



MEDI 56

Azapaullones: GSK-3 inhibitors activating beta cell protection and proliferation

Hendrik Stukenbrock[1]*, Rainer Mussmann*[2]*, Matthias Austen*[2]*, Marcus Geese*[2]*, Simone Kegel*[2]*, Olivier Lozach*[3]*, Laurent Meijer*[3]*, and Conrad Kunick*[1]*. (1) Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstrasse 55, 38106 Braunschweig, Germany, Fax: +49-(0)531-391-2799, c.kunick@tu-bs.de, (2) DeveloGen AG, Germany, (3) Station Biologique, Centre National de la Recherche Scientifique, 29682 Roscoff, France*

Diabetes is a severe disease with rising relevance, in particular for western industrial nations. Novel therapies are able to complement established treatments and provide additional benefit for the patients. Protecting and regenerating pancreatic beta cells is a promising concept to face the complications which result from diabetes. 1-azakenpaullone, a selective GSK-3β inhibitor, showed the ability to protect INS-1E cells from apoptosis, to induce proliferation of INS-1E cells in a dose dependent manner, and to promote beta cell replication in isolated rat islets. We developed a novel series of azapaullones which were evaluated as possible beta cell regenerating and proliferating agents. In addition to remarkable GSK-3β inhibitory activity some compounds exhibited a strong protective and proliferative effect on INS-1E cells.

MEDI 57

Withdrawn

MEDI 58

Influence of selective fluorination on the biological activity and proteolytic stability of glucagon-like peptide 1

He Meng *and Krishna Kumar, Department of Chemistry, Tufts University, 62 Talbot Ave, Medford, MA 02155, he.meng@tufts.edu*

The development of peptide-based drugs has recently intensified because of the relative simplicity and high specificity of active agents. However, peptide and protein drugs generally require injection and suffer from low metabolic stability. While the introduction of fluorine in the form of trifluoromethyl groups into small molecule therapeutics often improves druggability, it has not been extensively applied to the modification of peptides and proteins. We report here the design and synthesis of fluorinated analogues of the gut hormone peptide GLP-1. These derivatives were further characterized for their binding affinity to the cognate receptor, signal transduction ability, and proteolytic stability. We demonstrate that incorporation of highly fluorinated amino acids led to the enhanced enzymatic stability and preserved biological activity. These results indicate that fluorinated amino acids could be potentially useful for engineering peptide drug candidates.

MEDI 59

Synthesis and biological evaluation of 3-aryl-3-(4-phenoxy)-propionic acid as a novel series of G protein-coupled receptor 40 (GPR40) agonists

Fengbin Song[1]*, Songfeng Lu*[1]*, Joe Gunnet*[2]*, Jun Z. Xu*[1]*, Pam Wines*[1]*, Yin Liang*[1]*, Chris Baumann*[1]*, Jim Lenhard*[1]*, William V. Murray*[1]*, Keith T. Demarest*[1]*, and Gee-Hong Kuo*[1]*. (1) Drug Discovery Division, Johnson and Johnson Pharmaceutical Research and Development, L.L.C, 8 Clarke Dr, Cranbury, NJ 08512, Fax: 609-655-6930, (2) Chromocell Corporation, New Brunswick, NJ 08902*

A high-throughput screening of J&J sub-libraries that contains carboxylic acid functional group resulted in the discovery of a bromophenyl derivative as a moderate potent GPR40 agonist. The chemical elaboration of this bromophenyl led to the discovery of a novel series of GPR40 agonists with submicromolar potency. Some of our compounds behaved as full-agonists when comparing its activities in increasing Ca+2 in HEK-293 cells to the endogenous ligand linoleic acid. Several GPR40 agonists have also been demonstrated to induce glucose-mediated insulin secretion in the mouse MIN6 cells. Our data may support the hypothesis that GPR40 may play an important role in FAs induced glucose-sensitive insulin secretion.

MEDI 60

Dipeptidyl peptidase IV inhibitors incorporating fused azoles as effective amide isosteres

Hong Dong[1], *Wallace T. Ashton*[1], *Rosemary M. Sisco*[1], *Kathryn A. Lyons*[1], *Huaibing He*[1], *Barbara Leiting*[2], *Reshma A. Patel*[2], *Joseph K. Wu*[2], *Xiaoping Zhang*[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, Rahway, NJ 07065*

Therapies based on glucagon-like peptide 1 (GLP-1), an incretin hormone that stimulates glucose-dependent insulin biosynthesis and secretion, have emerged as one of the most promising areas in diabetes research. GLP-1 lacks oral activity and is rapidly degraded by dipeptidyl peptidase IV (DPP-4). Inhibition of DPP-4 promotes sustained elevation of endogenous GLP-1 levels, in a glucose-dependent manner, thus improving glucose tolerance with minimal risk of hypoglycemia. Previous work from these laboratories showed that appropriately substituted γ-aryl-β-aminoacyl derivatives of ring-fused piperazines and piperidines are potent, selective, and orally bioavailable inhibitors of DPP-4. We now report the synthesis and biological evaluation of analogous compounds in which the amide moiety was replaced by a fused triazole or imidazole. The effect of ring size, substitution pattern, and fused ring number was investigated. The potency at DPP-4 and selectivity versus other DASH proteins along with the rat pharmacokinetic properties of key compounds will be presented.

MEDI 61

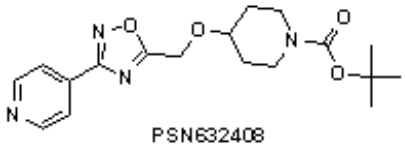
WITHDRAWN

MEDI 62

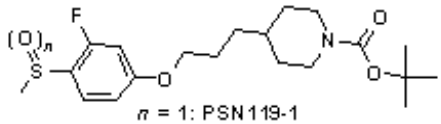
Synthesis, SAR, and in vivo efficacy of novel GPR119 agonists with a 4-[3-(4-methanesulfinylphenoxy)propyl]-1-Boc-piperidine core

Matthew C. T. Fyfe[1], *Adam J. Babbs*[2], *Lisa S. Bertram*[2], *Stuart E. Bradley*[2], *Sheila M. Doel*[2], *Smita Gadher*[2], *William T. Gattrell*[2], *Revathy P. Jeevaratnam*[2], *John F. Keily*[2], *James G. McCormack*[2], *Hilary A. Overton*[2], *Chrystelle M. Rasamison*[2], *Christine Reynet*[2], *Philip J. Rushworth*[2], *Colin P. Sambrook Smith*[2], *Vilas K. Shah*[2], *David F. Stonehouse*[2], *Simon A. Swain*[2], *Jonathan R. White*[2], *Peter S. Widdowson*[2], *Geoffrey M. Williams*[2], *and Martin J. Procter*[2]. *(1) Prosidion Limited, Windrush Court, Watlington Road, Oxford OX4 6LT, United Kingdom, Fax: 01865 871 279, mfyfe@prosidion.com, (2) Prosidion Limited, Oxford OX28 1ES, United Kingdom*

GPR119 is a $G\alpha_s$-coupled class A GPCR expressed predominantly in the pancreas and gastrointestinal tract. Agonists of this receptor could represent a rare opportunity for oral agents to achieve blood glucose control with simultaneous body weight loss, an outcome only possible with injectable therapeutics at present. Here, we describe the optimization of the previously-described pyridine-containing GPR119 agonist PSN632408, utilizing a yeast-based fluorimetric assay, which led to the discovery of the more potent sulfoxide PSN119-1. When administered orally to rats, this compound achieved high plasma concentrations, as did its active sulfone metabolite PSN119-1M. In several rodent models of obesity and type 2 diabetes, PSN119-1 reduced food intake and improved oral glucose tolerance, giving credence to the premise that GPR119 agonists have the makings of effective oral antidiabesic agents.



PSN632408



n = 1: PSN119-1
n = 2: PSN119-1M

MEDI 63

N$^{\varepsilon}$-methanesulfonyl-lysine as a nonhydrolyzable functional surrogate for *N*$^{\varepsilon}$-acetyl-lysine

Nuttara Jamonnak*, David G. Fatkins, Lanlan Wei, and Weiping Zheng, Department of Chemistry, University of Akron, 190 E. Buchtel Commons, Akron, OH 44325*

Protein posttranslational reversible lysine *N*$^{\varepsilon}$-acetylation and deacetylation have been recognized as an emerging intracellular signaling mechanism that plays critical roles in regulating gene transcription, cell-cycle progression, apoptosis, DNA repair, and cytoskeletal organization. Acetyltransferase-catalyzed creation, deacetylase-catalyzed destruction, and bromodomain-mediated specific recognition of *N*$^{\varepsilon}$-acetyl-lysine on proteins define the central events of this signaling mechanism. In our efforts toward developing novel inhibitors of the bromodomain/*N*$^{\varepsilon}$-acetyl-lysine recognition, whose chemical modulating strategies and modulators are still under-developed as compared to other events involved in this signaling mechanism, we developed the first non-hydrolyzable (or intracellular protein deacetylase-

resistant) functional surrogate, i.e. N^{ε}-methanesulfonyl-lysine, for N^{ε}-acetyl-lysine regarding bromodomain binding interaction. In specific, our experimental results suggested that N^{ε}-methanesulfonyl-lysine replacement for N^{ε}-acetyl-lysine i) did not compromise the binding affinity for the bromodomain, ii) conferred resistance to protein deacetylases, and iii) conferred only weak inhibition against protein deacetylases. The availability of this non-hydrolyzable analog will not only promote the inhibitor development, but also facilitate the functional examination of protein posttranslational acetylation due to its capability to provide the constitutive phenotype of protein acetylation.

MEDI 64

Design, synthesis and bioactivity of novel inhibitors of E. coli Aspartate Transcarbamoylase

***Joby Eldo**, Sabrina Heng, and Evan R. Kantrowitz, Department of Chemistry, Boston College, Merkert Chemistry Center, 2609 Beacon Street, Chestnut Hill, MA 02467, Fax: 617-552-2705, eldo@bc.edu*

In mammals aspartate transcarbamoylase (ATCase) is a portion of a multifunctional enzyme (CAD) which is required for de novo pyrimidine nucleotide biosynthesis. The ATCase portion of CAD catalyzes the second step in pyrimidine nucleotide biosynthesis, the reaction between carbamoyl phosphate and L-aspartate to give N-carbamoyl-L-aspartate and inorganic phosphate. ATCase has become a target for the development of anti-proliferative drugs and inhibitors of ATCase are considered as potential anti-tumor agents, since the levels of ATCase have been shown to be elevated in cancer cells. Here we report the synthesis and bioactivity of a series of inhibitors of the ATCase. These inhibitors are analogues of a highly potent inhibitor of this enzyme, N-phosphonacetyl-L-aspartate (PALA). Analogues have been synthesized with modifications at the alpha- and beta-carboxylates as well as at the aspartate moiety. The ability of these compounds to inhibit the enzyme was evaluated. These studies, with functional group modified PALA derivatives, showed that amide groups can be a useful substitute of the carboxylate in order to reduce the charge on the molecule, and indicate that the relative position of the functional group in the beta-position is more critical than the nature of the functional group. Some of the molecules synthesized here are potent inhibitors of the enzyme.

MEDI 65

Thermal stability and activity of fluorinated single-isoleucine mutants of chloramphenicol acetyltransferase

***Natalya Voloshchuk**[1], Man Xia Lee[1], Wan Wen Zhu[1], Ismet Caglar Tanrikulu[2], and Jin K. Montclare[1]. (1) Department of Chemical and Biological Sciences, Polytechnic University, 6 Metrotech Center, Brooklyn, NY 11201, nvoloshc@poly.edu, (2) Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125*

Residue-specific incorporation of 5',5',5'-trifluoroleucine (TFL) into chloramphenicol acetyltransferase (CAT) results in reduction in the thermal stability of the protein. To

deconvolute which TFL residues participate in the loss of thermal stability, a highly sensitive microplate-based cell lysate thermostability and activity screen was developed. Thirteen single-isoleucine mutants were created and screened. From the assay, fluorinated mutants L82I T and L208I T exhibited large losses in thermal stability while the fluorinated mutant L158I T was determined to be more active than the parent CAT T at elevated temperatures. Additional secondary structure characterization of L158I T confirmed the enhanced thermal stability suggesting that TFL at position 158 contributes to some of the loss in thermostability upon fluorination.

MEDI 66

Analogs of orotidine monophosphate (OMP): Their effect on the activity of OMP decarboxylase

Srinath Thirumalairajan *and Stephen L. Bearne, Department of Biochemistry and Molecular Biology, Dalhousie University, 5850 College Street, Sir Charles Tupper Medical Building, Halifax, NS B3H 1X5, Canada, Fax: 902-494-1355, sri@dal.ca*

Orotidine monophosphate decarboxylase (ODCase) catalyzes the decarboxylation of OMP to yield UMP in the pathway for the de novo biosynthesis of pyrimidines. The enzyme effects catalysis with a very high catalytic proficiency and without the aid of any cofactors or metal ions. Structural and electronic analogues of OMP that are modified at the 6-position of the pyrimidine base have been designed and synthesized. The effects of these analogues on the activity of ODCase will be presented.

MEDI 67

Assessing the role of tyrosine 190 in the catalytic mechanism of hamster N-acetyltransferase 2 by site-directed mutagenesis, pre-steady state and steady state kinetic studies

Xin Zhou*, Li Liu, Patrick E. Hanna, and Carston R. Wagner, Department of Medicinal Chemistry, University of Minnesota, 308 Harvard St. SE, Minneapolis, MN 55455, zhoux088@umn.edu*

Arylamine N-acetyl transferases (NATs) are responsible for detoxification of arylamine and arylhydrazine drugs and potentiation of carcinogenic xenobiotics through transferring an acetyl group from acetyl CoA to various substrates. The active site cysteine of hamster NAT2 has been shown to be the highly reactive thiolate-imidazolium ion pair with a pKa of 5.2. The catalytic mechanism for hamster NAT2 and by analogy all NATs proceeds through rapid formation of an acyl-cysteine intermediate, followed by rate limiting acyl transfer, which is dependent on a shift in the catalytic triad histidine pKa from >9 to 5.5. Beyond the obvious contributions of the Asp-122, the parameters governing this remarkable change are not understood. Upon closer inspection of the bacterial NAT structure, the conserved residue, Tyr-190, was found to form a close hydrogen bond with Asp-122. To assess the importance of this residue on the catalytic mechanism of NAT's we prepared a series of mutants at this position to determine the role of the hydroxyl moiety (Tyr-190 to Phe), hydrophobicity (Tyr-190 to

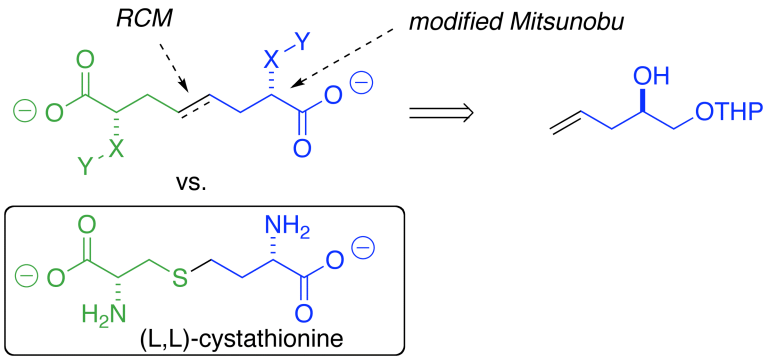
Isoleucine) and side-chain packing (Tyr-190 to Alanine). The Y190F, Y190I, and Y190A mutants exhibited significantly reduced kcat values for transacetylation of p-aminobenzoic acid (PABA) from the acetyl donor p-nitrophenylacetate (PNPA) compared to wild type. For both the Y190I and Y190A mutants, pre-steady state and steady-state kinetic analyses revealed elevated pKa's for the pH vs. rate data (approximately 0.5-1 unit) either in the first step (acetylation of the NAT) or in the second step (transacetylation of the arylamine substrate), resulting in a much less reactive active site cysteine and altered acceptor substrate specificity. Collectively, these results reveal that tyrosine 190 is intimately involved in maintaining the electrostatic potential of the hamster NAT2, and likely human NAT1, catalytic residues.

MEDI 68

Development of C2-symmetric, active site-directed inhibitors for Cystathionine beta-Synthase

***Christopher D. McCune**, Weijun Shen, Woo Jin Chung, and David B. Berkowitz, Department of Chemistry, University of Nebraska, 824 Hamilton Hall, Lincoln, NE 68588-0304, Fax: 402-472-9402, cmccune1@bigred.unl.edu*

This presentation will highlight our efforts to develop new classes of inhibitors for the important human PLP-dependent enzyme, cystathionine beta-synthase (CBS). This enzyme is central to the transsulfuration pathway, whereby reduced sulfur equivalents are converted from dietary methionine into usable redox equivalents in the form of glutathione. CBS itself combines L-serine with L-homocysteine to give (L,L)-cystathionine, with release of a molecule of water. Our inhibitor design exploits the latent C2-symmetry inherent in the (L,L)-cystathionine enzymatic reaction product, as indicated in the figure. Streamlined syntheses have been developed for each inhibitor series, via a sequence that features modified Mitsunobu conditions and Grubbs cross metathesis, as key steps.



MEDI 69

Discrimination of carbonic anhydrase isozymes by the excited-state lifetimes of polymerized liposome incorporated lanthanide ions

Adekunle Elegbede[1]*, Manas Haldar*[1]*, Sumathra Manokaran*[2]*, Sanku Mallik*[1]*, and D. K. Srivastava*[3]*. (1) Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND 58105, Adekunle.Elegbede@ndsu.edu, (2) Department of Chemistry, Biochemistry and Molecular Biology, North Dakota State University, Fargo 58105, (3) Department of Chemistry, Biochemistry and Molecular Biology, North Dakota State University, Fargo, Fargo, ND 58105-5516*

Differentiation of isozymes of an enzyme is important for the diagnosis of various diseases. However, due to the marked similarity of the active sites and homology of primary structures, this differentiation is a challenging task. We prepared polymerized liposomes incorporating an inhibitor and chelated Tb^{3+} and Eu^{3+} ions as lipid headgroups. A polymerizable lipid with chelated Cu^{2+} ions was also included in the liposomal formulations to facilitate the interactions with proteins. We observed that in the presence of recombinant human carbonic anhydrase isozymes, there were significant increases in sensitized emission intensity of the lanthanide ions as well as in the excited state lifetimes. We found that the changes in the luminescence of either of the lanthanide ions are specific for particular isozymes. Combination of the observed parameters for both lanthanide ions provides an accurate and efficient method for differentiation of the isozymes of carbonic anhydrase.

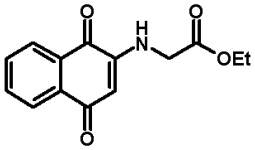
MEDI 70

Design, synthesis and chemical reactivity of 1,4-naphtoquinone derivatives as cysteine protease irreversible inhibitors

Claudia Valente[1]*, Rui Moreira*[1]*, Rita C. Guedes*[1]*, Jim Iley*[2]*, Mohammed Jaffar*[3]*, and Kenneth T. Douglas*[3]*. (1) CECF, Faculty of Pharmacy, University of Lisbon, Avenida das Forças Armadas, 1600-083 Lisboa, Portugal, cvalente2@sapo.pt, (2) Chemistry Department, The Open University, UK, MK7 6AA Milton Keynes, United Kingdom, (3) School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK, M13 9PL Manchester, United Kingdom*

Quinones are a unique class of compounds that can function (i) as redox cyclers and as (ii) electrophiles via Michael-type addition leading to covalent modification of thiols of vital components. Atovaquone, a hydroxy-1,4-naphtoquinone, used as antiprotoazoal drug is a clear evidence that the potentially high reactivity of this scaffold can be modulated. Papain-like cysteine proteases play crucial roles in diseases such as osteoporosis, rheumathoid arthritis, cancer, and in a wide variety of parasitic infections. In this work, a series of 1,4-naphthoquinone derivatives were found to inhibit papain and bovine spleen cathepsin B in an

irreversible manner. The chemical reactivity of the compounds towards cysteine as a model thiol is dependent on the naphthoquinone LUMO energy, whereas papain inactivation is not.



K_I= 9.57 μM and k_2= 35.4 $M^{-1}s^{-1}$ (papain)

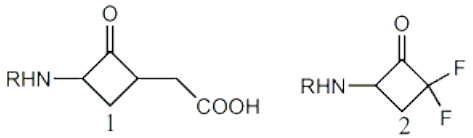
K_I= 14.0 μM and k_2= 8.03 $M^{-1}s^{-1}$ (bovine cathepsin B)

MEDI 71

Synthetic approaches to amino acid cyclobutanone derivatives

Preeti Kataria[1]*, Nick Armoush*[1]*, and Daniel P. Becker*[2]*. (1) Department Of Chemistry, Loyola University Chicago, 1068 W. Sheridan Road, Chicago, IL 60626, pkatari@luc.edu, (2) Department of Chemistry, Loyola University, Chicago, IL 60626*

Proteases are important in many physiological processes but may also have an adverse effect in propagating diseases like cancer, osteoporosis, and arthritis. The latter characteristic of proteases surfaces the role of protease inhibitors. Current research efforts are centered on the synthesis and elaboration of 2-amino-4-carboxy cyclobutanone 1, a novel amino acid, which may be elaborated in both the P and P' directions, and toward the synthesis and functionalization of 2-amino-4,4-difluorocyclobutanone 2, which is structurally related to trifluoromethyl ketones that have been successfully employed as serine and cysteine protease inhibitors.



MEDI 72

Phosphonosulfonates are potent inhibitors of dehydrosqualene synthase and staphyloxanthin biosynthesis in Staphylococcus aureus

Yongcheng Song[1]*, George Liu*[2]*, Fenglin Yin*[3]*, Victor Nizet*[4]*, and Eric Oldfield*[1]*. (1) Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, IL 61801, (2) Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA 90048, (3) Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, Urbana, IL 61801, (4) Division of Pediatrics, Pharmacology & Drug Discovery, UCSD School of Medicine and Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA 92093*

Staphylococcus aureus is the major cause of nosocomial as well as community-acquired staph infections. One of the components of the defense mechanisms of S. aureus is the virulence factor staphyloxanthin, a golden carotenoid pigment, whose numerous double bonds can react with reactive oxygen species (ROS) generated by macrophages and neutrophils, thereby

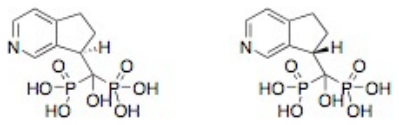
making S. aureus resistant to ROS-mediated killing. The first committed step in staphyloxanthin biosynthesis is the head-to-head condensation of two farnesyldiphosphate (FPP) molecules to form dehydrosqualene, catalyzed by dehydrosqualene synthase (dSQS; CrtM gene). We now found that a phosphonosulfonate compound, a human squalene synthase inhibitor developed by Bristol-Myers-Squibb as a cholesterol lowering drug, is able to potently inhibit the staphyloxanthin biosynthesis in Staphylococcus aureus with IC50 value of ~ 1 μM. We report the synthesis and the structure activity relationships (SAR) of 36 phosphonosulfonate compounds, in an effort to find a better inhibitor of staphyloxanthin biosynthesis.

MEDI 73

Modeling, synthetic, crystallographic, and activity studies of novel bisphosphonates as inhibitors of farnesyl pyrophosphate synthase

James M. Hogan[1]*, Sylvine Deprele*[1]*, Boris A. Kashemirov*[1]*, BL Barnett*[2]*, Artem Evdokimov*[3]*, Jim Dunford*[4]*, R. Graham G. Russell*[4]*, Frank H. Ebetino*[3]*, and Charles E. McKenna*[1]*. (1) Department of Chemistry, University of Southern California, 810 Downey Way, University of Southern California, Los Angeles, CA 90089, Fax: 213-740-0930, jameshogan@gmail.com, (2) The Chemistry Dept, University of Cincinnati, Cincinnati, OH, (3) Procter & Gamble Pharmaceuticals, Mason, OH 45040, (4) Nuffield Department of Orthopaedic Surgery, University of Oxford, Oxford OX3 7LD, United Kingdom*

Two factors determining the mechanism of in vivo bone antiresorptive activity by nitrogen-containing bisphosphonates (N-BPs) are their ability to target bone mineral (bone affinity) and subsequently, a specific biochemical target within the osteoclast. Thus, once delivered to the bone surface, the N-BPs are taken up by osteoclasts, where they inhibit the enzyme human farnesyl pyrophosphate synthase (hFPPS), disrupting normal cell function. From recently available crystal structures of hFPPS complexed with N-BPs, it has become clear that differences in inhibitor activity at the enzyme level derive from interactions within the geranyl pyrophosphate (GPP) binding site. In particular, the protonated nitrogen in N-BPs forms hydrogen bonds with THR-201 and the carbonyl backbone oxygen of LYS-200. Using AutoDock 3, we modeled enantiomers of a conformationally restricted N-BP, NE-10501 in the GPP site, and found that only the R isomer is competent for the THR-201 and LYS-200 interactions. NE-10501 was synthesized and the crystal structure of its complex with hFPPS was determined, confirming the prediction that the R enantiomer should be stabilized preferentially. Based on this finding, and other considerations, a series of N-BP analogs were designed and docked into the active site of hFPPS. Selected analogs were then synthesized for crystallographic structural studies and bioassay evaluations of hFPPS inhibition. The results indicate that docking studies based on the hFPPS active site structure are usefully predictive in the design of novel N-BP inhibitors for this enzyme.



(*R*) NE-10501 (*S*)

MEDI 74

Structure-based design of reversible peptides inhibitors of Factor VII-a

***Cristina C. Clement**, Chemistry Department, Lehman College, City University of New York (CUNY), 250 Bedford Park BLVD West, Bronx, New York City, NY 10468, cclement_us@yahoo.com, Lisa Gingold, Department of Chemistry, Lehman College, CUNY, New Yorrk City, NY 10468, and Manfred Philipp, Chemistry Department, Lehman College, City University of New York, New York City, NY 10468*

We used the structure-based design approach to generate in silico libraries of peptides with potential inhibitory activity against Factor VII-a. The 1qfk.pdb was used as template in docking experiments which were performed using the software “SCULPT” from MDL. We first generated a set of peptides with different chain length and different sequence space and assessed the free energy of interaction between the protein target and the ligands using the MMFF94 (force-field) built-in the software SCULPT. Both the van der Waals and the electrostatic interactions were used to generate the free energy of interaction between Factor VII-a and the peptides ligands during rigid docking experiments. The peptide Gly-Ser-Ala-D-Phe-Phe-Arg-CONH2 was discovered as a lead compound in the original series of peptides and was synthesized using F-moc solid phase peptide chemistry approach. In vitro kinetics of Factor VII-a inhibition showed that this reversible peptide inhibitor has an IC-50 of 20 uM. Ki (inhibitory constant) was estimated to be 2 nM and is the first peptide reported in the field to be a powerful inhibitor of Factor VII-a, supporting the structure-based design as a reliable approach to generate new lead compounds and also to optimize the leads by using powerful docking experiments and reliable scoring functions.

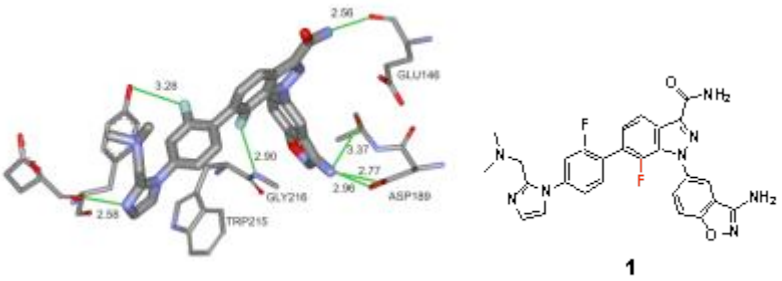
MEDI 75

7-Fluoroindazoles as potent and selective factor Xa inhibitors

***Yu-Kai Lee**, Tianbao Lu, Daniel J. Parks, Tho V. Thieu, Thomas Markotan, Wenxi Pan, David F. McComsey, Karen L. Milkiewicz, Carl Crysler, Nisha Ninan, Marta C. Abad, Edward C. Giardino, Bruce E. Maryanoff, Bruce P. Damiano, and Mark R. Player, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development LLC, 665 Stockton Drive, Exton, PA 19341*

We have developed a novel series of potent and selective factor Xa inhibitors that employ a key 7-fluoroindazolyl moiety. The 7-fluoro group on the indazole scaffold replaces the carbonyl group of an amide that is found in previously reported factor Xa inhibitors. The role of the 7-fluoro group in binding with human factor Xa was established unequivocally through x-ray crystallography. For example, the structure of a co-crystal containing 7-fluoroindazole **1** showed the 7-fluoro group hydrogen bonding with the N–H of Gly216 (3.0 Å) in the peptide backbone (see figure). The structure-activity relationship for this series was consistent with this finding, as the factor Xa inhibitory potencies were about 60-fold greater for the 7-

fluoroindazoles versus the corresponding indazoles. Highly convergent synthesis of fXa inhibitors will also be described.



1

MEDI 76

Discovery of N-{(1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride (DT-831j): A novel, potent and orally active direct inhibitor of factor Xa

Tsutomu Nagata[1]*, Toshiharu Yoshino*[1]*, Noriyasu Haginoya*[1]*, Kenji Yoshikawa*[1]*, Masatoshi Nagamochi*[1]*, Shozo Kobayashi*[1]*, Satoshi Komoriya*[1]*, Aki Yokomizo*[1]*, Ryo Muto*[1]*, Mitsuhiro Yamaguchi*[1]*, Ken Osanai*[1]*, Makoto Suzuki*[2]*, and Hideyuki Kanno*[1]*. (1) Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd, 1-16-13, Kita-Kasai, Edogawa-ku, Tokyo 134-8630, Japan, nagatso1@daiichipharm.co.jp, (2) Drug Discovery Research Laboratory, Daiichi Pharmaceutical Co., Ltd, Edogawa-ku, Tokyo 134-8630, Japan*

The extrinsic and intrinsic coagulation systems converge at the activation of factor X to Xa. Activated factor X (fXa) has an important role in conversion of prothrombin to thrombin, which produces blood clots. Thus, fXa is a key enzyme in the coagulation cascade and also an attractive target enzyme for the therapy of thrombosis and related diseases. We investigated fXa inhibitors and found cycloalkanediamine derivatives having a potent fXa inhibition. In this presentation, we would like to report on the SAR of cycloalkanediamine derivatives, and the discovery of DT-831j, a hightly potent and orally active, direct fXa inhibitor.

MEDI 77

Induced polarization in drug-receptor binding: Contribution to the binding affinity of a meta-chlorobenzyl side chain in the S1 pocket of thrombin

Menshawy Mohamed[1]*, Bernhard Baum*[2]*, Marek Freindorf*[3]*, Gerhard Klebe*[2]*, and David G. Hangauer*[1]*. (1) Department of Chemistry, University at Buffalo, Natural Sciences Complex, Box 603000, Buffalo, NY 14260-3000, mm323@buffalo.edu, (2) Institute of Pharmaceutical Chemistry, Philipps-University Marburg, Marburg 35032, Germany, (3) Center for Computational Research, University at Buffalo, The State University of New York, Buffalo, NY 14260*

Induced polarization of the electronic density in ligands by their protein receptors is a largely unexplored contributor to the drug-receptor binding processes. Other researchers have reported the surprisingly strong binding affinity of a meta-chlorobenzyl side chain in the anionic S1 pocket of thrombin and ascribed this to hydrophobic binding. We have designed and evaluated a series of meta-chlorobenzyl side chain analogs, and our data suggests that hydrophobic binding is not the reason for the surprisingly strong binding affinity of this side chain. The binding affinity of these analogs was evaluated by x-ray crystallography, ITC, quantum mechanical (QM) and combined quantum mechanical – molecular mechanical (QM/MM) calculations. The results of our study suggest that the unique polarization of the meta-chlorobenzyl side chain in the S1 pocket of the protein is a major contributor to its enhanced binding affinity.

MEDI 78

Drug target validation using transcription profiling and reverse-engineered gene networks

Melissa M. Dominguez[1]*, Elissa Cosgrove*[2]*, Yingchun Zhou*[3]*, Eric D. Kolaczyk*[3]*, Scott E. Schaus*[1]*, and Timothy S. Gardner*[2]*. (1) Department of Chemistry, Boston University, 24 Cummington Street, Boston, MA 02215, (2) Department of Biomedical Engineering, Boston University, Boston, MA 02215, (3) Department of Mathematics and Statistics, Boston University, Boston, MA 02215*

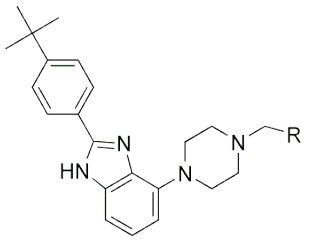
Drug target validation is critical for drug development and a rapid and thorough method of validation will greatly aid the process. Transcription profiling is a valuable tool for investigating the mode of action for drugs and other types of perturbations and the current microarray format can provide expression data for thousands of genes. These profiles are difficult to analyze since the majority of genes are not directly affected by the initial perturbation. Our goal is to develop a network based algorithm that predicts the molecular target of a biologically active compound from the transcription profile. Here we present research focused on developing this method and using it to identify the targets of compounds whose targets are unknown.

MEDI 79

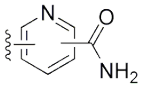
Imidazole-acetamide substituted piperazinylbenzimidazole antagonists of the Gonadotropin Releasing Hormone receptor

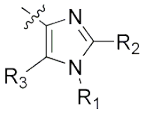
Joseph T. Lundquist IV[1]*, John F. Mehlmann*[1]*, Lloyd Garrick*[1]*, Jeffrey C. Pelletier*[1]*, Jay Wrobel*[2]*, Joshua E. Cottom*[3]*, Linda Shanno*[3]*, Murty V. Chengalvala*[3]*, Christine Huselton*[4]*, and Irene B. Feingold*[5]*. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, lundquj@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426, (3) Department of Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (4) Biotransfomation Division, Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (5) Department of Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426*

Gonadotropin-Releasing Hormone (GnRH) Receptor antagonists are utilized as a means to control sex-hormone dependant disorders such as endometriosis, breast cancer, prostate cancer and precocious puberty in children. To identify promising antagonists in our laboratory, potential candidates were analyzed using a panel of in vitro assays. These include binding inhibition assays with human and rat GnRH receptors and functional assays (human inositol phosphate release inhibition and rat GnRH release inhibition). We previously identified several active 4-(1-piperazinyl)benzimidazole antagonists of GnRH with a pendant pyridine substituted with an amide (e.g. 1). In addition, various imidazoles 2 have shown activity. To further explore the structure-activity relationships of these compounds (SAR), we combined structural features of 1 and 2 by preparing imidazoles functionalized with acetamides (e.g. 3). Some of these compounds 3 possessed greater in vitro potency, compared to 1 and 2. Potency was reduced with compounds such as 4. Chemistry, in vitro pharmacology and pharmacokinetics will be discussed.



R =

(**1**) 



R_2, R_3 = H or alkyl
(**2**) R_1 = H
(**3**) R_1 = $CH_2CONR_4R_5$
(**4**) R_1 = $CH_2CH_2NHCOR_6$

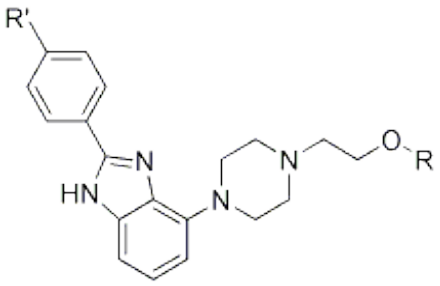
MEDI 80

Simultaneous biological optimization and structural simplification of a pendant heterocyclic thiobenzimidazolone on a series of 2-phenyl-4-(piperazin-1-yl)benzimidazole antagonists of the Gonadotropin Releasing Hormone Receptor

Jeffrey C. Pelletier[1]*, Murty V. Chengalvala*[2]*, Joshua E. Cottom*[2]*, Lloyd Garrick*[1]*, James Jetter*[3]*, Wenling Kao*[3]*, Linda Shanno*[2]*, and Jay Wrobel*[4]*. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, (2) Department of Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (3) Department of Chemical & Screening Sciences, Wyeth Research, Collegeville, PA 19426, (4) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426*

We recently described the preparation of a series of 2-phenyl-4-(piperazin-1-yl)benzimidazoles as small molecule, orally available antagonists of the Gonadotropin Releasing Hormone Receptor. Excellent biological activity requires that the (1-piperazinyl)-4-benzimidazole template have pendant cyclic functionality connected via a methylene or an ethoxy linker. The lead series contains a thiobenzimidazolone as the pendant heterocycle (R = thiobenzimidazolone). Our efforts were directed at simplifying the pendant heterocyclic structure to remove the thiocarbonyl and optimize biological activity. Most compounds were

prepared using parallel synthesis techniques. Chemistry, receptor binding and functional, cell-based biology in human and rat species will be discussed.



R was optimized using parallel synthesis

MEDI 81

Design, synthesis and SAR of uracil diamines as potent GnRH receptor antagonists

Charles Huang[1]*, Warren Wade*[1]*, Yun-Fei Zhu*[1]*, Chen Chen*[1]*, Zack Guo*[1]*, Yongsheng Chen*[1]*, Scott Struthers*[2]*, Martin W. Rowbottom*[1]*, Jamie Rueter*[1]*, Duncan Wu*[1]*, Joann Xie*[2]*, and John Saunders*[1]*. (1) Department of Medicinal Chemistry, Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130, Fax: 858-617-7925, chuang@neurocrine.com, (2) Department of Endocrinology, Neurocrine Biosciences Inc, San Diego, CA 92130*

Gonadotropin-releasing hormone (GnRH), or luteinizing hormone-releasing hormone (LHRH) is believed to play a very important role in modulating reproductive functions. Non-peptide GnRH antagonists have been extensively studied due to their potential therapeutic benefit in treating endometriosis, uterine fibroids, and prostate and breast cancers. A series of uracil diamines were discovered as novel and potent GnRH receptor antagonists. Chemical synthesis and structure-activity relationship (SAR) of this series will be presented.

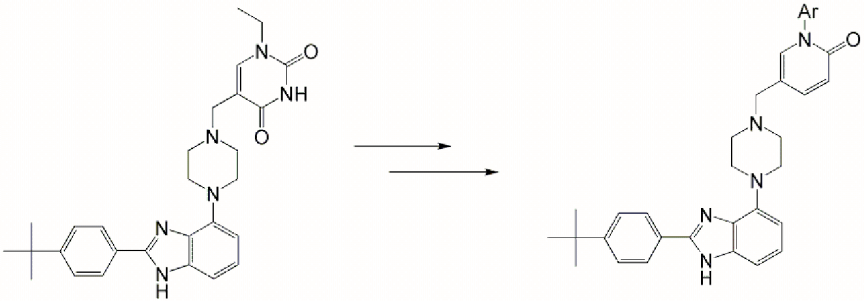
MEDI 82

Parallel synthesis of substituted pyridones for use as Gonadotropin Releasing Hormone (GnRH) antagonists

Daniel Green[1]*, Jeffrey C. Pelletier*[2]*, Murty V. Chengalvala*[3]*, Joshua E. Cottom*[3]*, and Linda Shanno*[3]*. (1) Department of Chemical & Screening Sciences, Wyeth Research, 500 Arcola Rd., Collegeville, PA 19426, greend@wyeth.com, (2) Department of Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426, (3) Department of Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Gonadotropin Releasing Hormone antagonists are useful in the treatment of sex-hormone dependant disorders such as endometriosis, breast and prostate cancer, and precocious puberty in children. Currently approved therapy is limited to peptide antagonists and superagonists, which are delivered via parenteral routes. Our goal was to develop a small molecule orally available antagonist for the treatment of these diseases. Working off an advanced lead compound, parallel synthesis was employed to rapidly explore the potential

biological activity of substituted pyridones against GnRH. In vitro potency, functional activity, metabolism, and pharmaceutical properties will be discussed.



MEDI 83

Substituted 5-oxopyrazoles as HCV polymerase inhibitors

Tong Wang[1]*, Dansu Li*[1]*, Gerald W. Shipps Jr.*[2]*, Kristin E. Rosner*[2]*, Patrick Curran*[1]*, Yongqi Deng*[1]*, Janeta Popovici-Muller*[1]*, Alan B Cooper*[3]*, and Viyyoor Girijavallabhan*[4]*. (1) Schering-Plough Research Institute, 320 Bent street, Cambridge, MA 02141, (2) Schering-Plough Research Institute, Cambridge, MA 02139, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033, (4) Schering Plough Research Institute, Kenilworth, NJ 07033*

Greater than 2 % of the world population is chronically infected with hepatitis C virus (HCV) and significant percentage of them will progress to cirrhosis and hepatocellular carcinoma. As the HCV polymerase (NS5B) is essential for viral replication and growth, it represents an ideal target for drug discovery and treatment of HCV infections. In this presentation, we discuss our effort to optimize a substituted 5-oxopyrazole hit compound. Using an efficient parallel scheme, we have identified novel and potent HCV polymerase inhibitors.

MEDI 84

HCV NS3 serine protease inhibitors: Discovery of carbamate derived new P4 capping moieties with improved profile

A. Arasappan[1]*, A. I. Padilla*[1]*, F. Bennett*[1]*, S. L. Bogen*[1]*, Kevin X Chen*[1]*, S. Hendrata*[1]*, Y. Huang*[1]*, Edwin Jao*[1]*, W. Pan*[1]*, R. E. Pike*[1]*, S. Ruan*[1]*, M. Sannigrahi*[2]*, S. Venkatraman*[1]*, B. Vibulbhan*[1]*, Wanli Wu*[1]*, W. Yang*[1]*, A. K. Saksena*[1]*, V. Girijavallabhan*[1]*, Xiao Tong*[3]*, K-C. Cheng*[4]*, N-Y. Shih*[1]*, and F. G. Njoroge*[1]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, K-15-3-3545, Kenilworth, NJ 07033, ashok.arasappan@spcorp.com, (2) Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, (3) Virology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (4) Drug Metabolism, Schering-Plough Research Institute*

Hepatitis C virus (HCV) infection is a global health crisis leading to liver cirrhosis, hepatocellular carcinoma and liver failure in humans. An estimated 3% of the human population is infected with HCV. The major goal of our research program was to develop new, specifically-targeted, orally active, NS3 serine protease inhibitors that could be developed as

effective anti-HCV drug candidate to improve the virologic response. Proof of concept studies in humans with HCV NS3 serine protease inhibitors has validated this hypothesis. Our recent efforts in this area were directed towards improving the overall profile of the inhibitors. In this poster we will elaborate on our studies leading to the discovery of carbamate-derived new P4 moieties that resulted in inhibitors with enhanced potency and improved rat oral bioavailability.

MEDI 85

Molecular docking and 3-D-QSAR studies on benzimidazole series of Hepatitis C virus NS5B polymerase inhibitors

Pallav D Patel *and Tanaji T Talele, Department of Pharmaceutical Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, pallav.patel06@stjohns.edu*

To understand the binding modes of benzimidazole series of compounds as well as to get a deeper insight into the structure-activity relationship, we performed docking studies, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). All the compounds were docked in the allosteric binding site of a recently developed crystal structure of HCV NS5B polymerase (PDB ID: 2dxs). Furthermore, docking experiments suggested the importance of hydrogen bonding interaction between the carboxamide and the carboxyl carbonyl oxygen atoms of the inhibitors and the guanidine group of Arg503. By exporting the docked conformations to Sybyl, 3D-QSAR models with cross-validated r2cv values of 0.622 and 0.759 for CoMFA and CoMSIA, respectively, were built. Validation of the models with an external set of compounds yielded satisfactory predictive r2 values of 0.766 and 0.835 for CoMFA and CoMSIA, respectively. The best CoMSIA model indicated that electrostatic and H-bond acceptor interactions (~80%) contribute more towards biological activity than the steric interactions. These statistically significant models can serve as guides for the rational design of potent inhibitors of HCV NS5B polymerase. A detail discussion of the 3D-QSAR and the structure-based computational results of these compounds will be provided.

MEDI 86

Discovery of new P4 (esters, acids, ketones) extended ketoamide inhibitors of the HCV NS3 serine protease with improved potency and PK profile

Stephane L Bogen[1]*, Weidong Pan*[1]*, S. Ruan*[1]*, Ashok Arasappan*[1]*, Frank Bennett*[1]*, Kevin Chen*[2]*, S. Hendrata*[1]*, Y. Huang*[1]*, Edwin Jao*[1]*, Y-T. Liu*[1]*, R. Lovey*[1]*, Latha Nair*[1]*, A. I. Padilla*[1]*, R. Pike*[1]*, Patrick Pinto*[1]*, M. Sannigrahi*[3]*, Francisco Velazquez*[1]*, S. Venkatraman*[1]*, B. Vibulbhan*[1]*, Wanli Wu*[1]*, W. Yang*[1]*, A. K. Saksena*[1]*, Viyyoor Girijavallabhan*[4]*, Xiao Tong*[5]*, K-C. Cheng*[6]*, N-Y. Shih*[1]*, and F. George Njoroge*[7]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, K-15-3545, Kenilworth, NJ 07033, stephane.bogen@spcorp.com, (2) Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, (4) Schering Plough Research Institute, Kenilworth, NJ 07033, (5) Virology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (6) Schering-Plough Research Institute, Kenilworth, NJ 07033-0359, (7) Chemical Research Department, Schering Plough Research Institute, Kenilworth, NJ 07033*

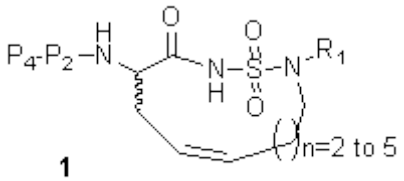
Hepatitis C is the most prevalent liver disease. Viral hepatitis C (HCV), a small (+)-RNA virus, infects chronically an estimated 300 million people worldwide. HCV displays genetic heterogeneity with the genotype 1 being most common in the US, Europe and Japan, and the most challenging to eradicate. The NS3 serine protease, a pivotal enzyme required for maturation of Hepatitis C virons, assists in processing of the HCV polyprotein by cleaving four downstream sites. Because of its central role in viral replication, inhibition of HCV NS3 serine protease has been actively pursued as target for antiviral therapy. Proof of concept studies in humans with HCV NS3 serine protease inhibitors has been established. Today, we report that extension of our earlier inhibitor to the P4 pocket using esters, acids or ketones moieties and optimization of the P1' capping led to the discovery of new ketoamide inhibitors of the HCV NS3 serine protease with improved in vitro potency. In addition of being potent inhibitor of HCV subgenomic RNA replication, some new P4 inhibitors were also found to have improved PK profile.

MEDI 87

Novel HCV protease inhibitors: Using acyl-sulfamides to form P1-P1′ macrocycles

Jason P Shanley[1]*, Hui-Ju Chen*[1]*, Charles W Hutchins*[2]*, Dale J. Kempf*[1]*, Larry L. Klein*[1]*, Kevin Kurtz*[1]*, Alex Konstantinidis*[1]*, and Keith F. McDaniel*[1]*. (1) Anti-Viral Research, Abbott Laboratories, Dept. 47D Bldg. AP52, 200 Abbott Park Rd, Abbott Park, IL 60064-3537, jason.shanley@abbott.com, (2) Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6098*

Recent efforts in the field of Hepatitis C research have focused on attempts to discover new small molecule drug combinations to compliment or replace Pegylated Interferon/Ribavirin, the current standard of care. This treatment is effective for less than 50% of patients with Genotype 1 virus, and many debilitating side effects often result in the discontinuation of therapy. During the course of our research in peptidomimetic HCV Protease inhibitors, we became interested in the optimization of inhibitor-enzyme interactions in the S1` pocket. This poster examines the incorporation of macrocyclic P1-P1' acylsulfamides (**1**) as well as acyclic acyl-sulfamides into known HCV protease P2-P4 cores to explore the S1` pocket. Molecular modeling was utilized throughout the design process. The solution to synthetic challenges and IC_{50} values for these inhibitors, with some having single digit to sub-mmol activity against genotype1 HCV protease, are reported.



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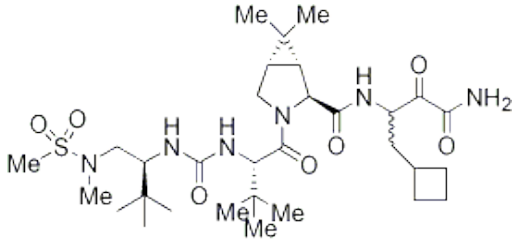
MEDI 88

Discovery of Novel P4 capped sulfonamide derived inhibitors of HCV NS3 protease

Srikanth Venkatraman[1], *Wanli Wu*[2], *Melissa Blackman*[3], *Ashok Arasappan*[2], *Frank Bennett*[2], *Stephane L Bogen*[2], *Kevin X Chen*[2], *Siska Hendrata*[1], *Yuhua Huang*[2], *Edwin Jao*[2], *Latha Nair*[2], *A. I. Padilla*[2], *Weidong Pan*[2], *R. Pike*[2], *Patrick Pinto*[2], *S. Ruan*[2], *Mousumi Sannigrahi*[2], *Francisco Velazquez*[2], *Bancha Vibulbhan*[2], *Weiying Yang*[2], *Anil Saksena*[2], *Viyyoor Girijvallabhan*[3], *Xiao Tong*[4], *K-C. Cheng*[5], *Neng-Yang Shih*[2], *and F. George Njoroge*[2]. *(1) Chemical Research, Schering Plough Research Institute, 2015 Galloping Hill Road, A-301, MS 3545, Kenilworth, NJ 07033, Fax: 908-740-7152, Srikanth.Venkatraman@spcorp.com, (2) Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Chemical Research Department, Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, (4) Virology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (5) Drug Metabolism, Schering-Plough Research Institute*

Hepatitis C Virus (HCV) infection is the major cause of chronic liver disease, leading to cirrhosis and hepatocellular carcinoma, which affects more than 200 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 genotype 1 and relapse patients is moderate at best, with only about 40% of the patients showing sustained virological response. Lack of effective methods to treat chronic HCV infections, and patients relapsing from interferon therapy necessitates discovery of new drugs. Significant efforts are now directed towards development of therapies that target key enzymes vital to HCV replication and maturation. In this presentation we discuss, the identification of novel P3 sulfonamide capped ketoamide inhibitors that exhibit excellent binding in NS3 enzyme assay and replicon cellular assay.



K_i* = 5.00 nM

EC_{90} (rep) = 50 nM

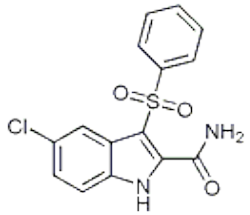
MEDI 89

Synthesis and anti-HIV-RT activity of a series of indole alkyl sulfones

Xufang Zhang[1], *Vandna Munshi*[2], *Dan diStefano*[3], *Linda Ecto*[3], *Peter J. Felock*[2], *Meizhen Feng*[2], *Jessica A. Flynn*[3], *MingTain Lai*[2], *Yuexia Liang*[4], *Meiquing Lu*[2], *Mike Miller*[2], *Greg Moyer*[2], *Rebecca A. Poehnelt*[5], *Sridhar Prasad*[6], *Rosa I. Sanchez*[4], *William Schleif*[6], *Maricel Torrent*[5], *Sinoeun Touch*[3], *BangLin Wan*[1], *and Theresa M. Williams*[1]. *(1) Medicinal Chemistry Department, Merck and Co. Inc, 770 Sumneytown Pike, PO Box 4 West Point, PA 19486-*

0004, Fax: 215-652-3971, xufang_zhang@merck.com, (2) Antiviral Research, Merck and Co. Inc, PO Box 4 West Point, PA 19486-0004, (3) Vaccine and Biologics Research, Merck and Co. Inc, PO Box 4 West Point, PA 19486-0004, (4) Drug Metabolism, Merck and Co. Inc, PO Box 4 West Point, PA 19486-0004, (5) Molecular Systems, Merck and Co. Inc, PO Box 4 West Point, PA 19486-0004, (6) N/A

Highly active anti-retroviral therapy (HAART) combination regimens have dramatically decreased the morbidity and mortality among patients with HIV infections. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have become the key components in the combination regimens. Three NNRTIs, efavirenz, nevirapine, and delavirdine, have been approved by FDA for the treatment of the HIV infection. Unfortunately, emergence of resistant strains of human immunodeficiency virus type 1 (HIV-1) requires new anti-HIV agents that are effective against these resistant mutants. The indole aryl sulfone (IAS) L-737,126 (1) is an NNRTI discovered at Merck that potently inhibits the growth of HIV-1 expressing wide type RT. However, it loses significant activity vs clinically resistant strains expressing the K103N or Y181C mutation. Research showed that substituents on the IAS common pharmacophore improved activity vs key clinical resistance mutations. Our research efforts focused on replacing the aryl sulfone, and we designed, synthesized and evaluated the activity of novel indole alkyl sulfones. These compounds were tested for their ability to inhibit both WT and mutant RTs in a polymerase assay and in a cell based viral replication assay. The best indole alkyl sulfones were potent inhibitors of WT RT, and in contrast to L-737,126, showed good activity in the presence of the Y181C mutation. However, the K103N mutant retained resistance. The chemistry to prepare a key intermediate, ethyl 5-chloro-3-thioindole-2-carboxylate (2) will be presented, along with its reaction with a variety of electrophiles to give the desired alkylation products. The NNRTI and in vitro antiviral activity of this series of compounds will be discussed.



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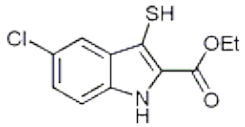


2

MEDI 90

Design and synthesis of HIV-1 protease inhibitors incorporating oxazolidinones as P2/P2' ligands in pseudosymmetric dipeptide isosteres

G. S. Kiran Kumar Reddy[1]*, Akbar Ali*[1]*, Madhavi N. L. Nalam*[2]*, Saima Ghafoor Anjum*[1]*, Hong Cao*[1]*, Robin S. Nathan*[1]*, Celia A. Schiffer*[2]*, and Tariq M. Rana*[1]*. (1) Chemical Biology Program, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, 364 Plantation Street, Worcester, MA 01605, Fax: 508-856-6696, (2) Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA*

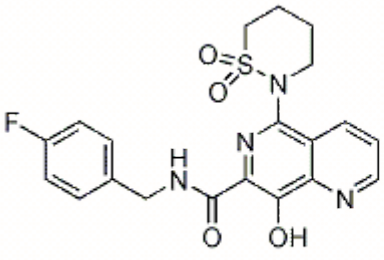
The design, synthesis, and biological evaluation of novel HIV-1 protease inhibitors based on hydroxyethylene and (hydroxyethyl)hydrazine dipeptide isosteres incorporating N-phenyloxazolidinone-5-carboxamides as P2 and P2' ligands are described. In addition to their inhibitory activities against wild-type protease, selected compounds were further evaluated for their activities against a panel of multidrug-resistant (MDR) protease variants and for their antiviral potencies in MT-4 cells. The crystal structures of lopinavir (LPV) and two new inhibitors containing phenyloxazolidinone-based ligands in complex with wild-type HIV-1 protease are also presented.

MEDI 91

Potent HIV integrase inhibitor with excellent pharmacokinetics

Melissa Egbertson[1]*, Michelle Kuo*[1]*, Debra Perlow*[1]*, Marie Langford*[1]*, Jeffrey Melamed*[1]*, John Wai*[1]*, Joseph Vacca*[1]*, Audrey Wallace*[1]*, Yvonne Leonard*[1]*, Daria J. Hazuda*[2]*, Peter J. Felock*[2]*, Kara Stillmock*[2]*, William Schleif*[3]*, Lori J. Gabryelski*[3]*, Gregory Moyer*[3]*, Joan Ellis*[4]*, Lixia Jin*[4]*, and Steven D. Young*[1]*. (1) Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3, PO Box 4, West Point, PA 19486, Fax: 215-652-3971, melissa_egbertson@merck.com, (2) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) Department of Viral Vaccine Research, Merck Research Laboratories, West Point, PA 19486, (4) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

HIV-1 integrase catalyzes the insertion of proviral DNA into the host genome. L-000870810, an 8-hydroxy-1,6-naphthyridine, inhibits HIV-1 replication in cell culture (Hazuda et al. *PNAS*, 2004, *101,* 11233) and significantly decreased viral load and increased CD4 cell count in patients infected with HIV (Little et al. CROI, 2005). Efforts directed at improving compound physical properties in the 1,6-naphthyridine series led to the discovery of the compound A, a equipotent antiviral agent with excellent pharmacokinetic properties.



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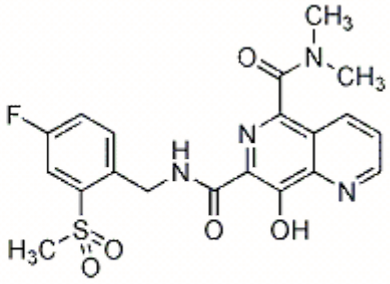


Compound A

MEDI 92

Molecular modeling, synthesis, and in vitro/in vivo evaluation of 1,4-dihydropyridine, pyrrole, and benzopyran analogs as HIV-1 RT inhibitors

Tanaji T Talele[1], *Dinesh Manvar*[2], *Kena Raval*[2], *Virendra N Pandey*[3], *and Anamik Shah*[2]. *(1) Department of Pharmaceutical Sciences, College of Pharmacy & Allied Health Professions, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, Fax: 718-990-1877, talelet@stjohns.edu, (2) Department of Chemistry, Saurashtra University, Rajkot 360005, India, (3) Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, Newark, NJ 07103*

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) is a major target of current antiretroviral drug therapy for the treatment of AIDS. Non-nucleoside RT inhibitors (NNRTIs) interact with a specific pocket of HIV-1 RT (the nonnucleoside inhibitor binding pocket, NNIBP) that is close to, but distinct from, the nucleoside RT inhibitor (NRTI) binding pocket. Molecular modeling studies based on the X-ray structure of a complex of HIV-1 RT with nevirapine (PDB ID: 1VRT), suggested the synthesis of novel 1,4-dihydropyridine, pyrrole, and benzopyran analogues whose HIV-1 RT inhibitory activity was assessed using in vitro and in vivo assays. The new analogues exhibited Ki value in the range of 1.4 μM to 2.3 μM. These analogues were found to be less toxic than efavirenz and nevirapine in CEM cells as judged by their CC50 values. The synthesis, biological activity, cytotoxicity, and induced-fit docking results will be discussed in detail.

MEDI 93

Phthalimide-containing hydrazides and amides as diketo acid-class HIV-1 integrase inhibitors

Xue Zhi Zhao[1], *Elena A. Semenova*[2], *B. Christie Vu*[3], *Chenzhong Liao*[1], *Marc C Nicklaus*[1], *Stephen H. Hughes*[3], *Yves Pommier*[2], *and Terrence R. Burke Jr.*[1]. *(1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, Frederick, MD 21702, (2) Laboratory of Molecular Pharmacology, CCR, NCI, NIH, Bethesda, MD 20892, (3) HIV Drug Resistance Program, NCI, NIH, Frederick, MD 21702*

Integrase (IN) is a crucial enzyme in the life cycle of human immunodeficiency virus type 1 (HIV-1) that has recently been validated as an antiviral target after promising clinical trials of IN inhibitors. Diketo acids (2,4-dioxobutanoic acids, DKAs) were originally reported as a promising class of IN inhibitors that exhibit good antiviral activity. DKAs are often characterized by preferential inhibition of one of the two catalytic functions of IN, strand transfer. Inhibition is thought to involve chelating divalent Mg2+ or Mn2+ ions that are held in the IN active site by a conserved triad of acidic residues D64, D116, E152, termed the “DDE motif”. With the DKAs as a starting point, several generations of highly potent non-acid-containing IN inhibitors have been reported and these are thought to function in similar fashion by chelating the active site divalent metal ions. In the current report we present phthalimide-containing hydrazides and amides that are structurally related to the DKA-class. These compounds inhibit purified IN in vitro; some of the compounds are also active against HIV-1 derived vectors in cell-based assays.

MEDI 94

Design, synthesis, and biological evaluation of HIV-1 protease inhibitors incorporating phenyloxazolidines as novel P2 ligands

Akbar Ali[1]*, G. S. Kiran Kumar Reddy*[1]*, Hong Cao*[1]*, Saima Ghafoor Anjum*[1]*, Madhavi N. L. Nalam*[2]*, Celia A. Schiffer*[2]*, and Tariq M. Rana*[1]*. (1) Chemical Biology Program, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, 364 Plantation Street, Worcester, MA 01605, Fax: 508-856-6696, (2) Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA*

The design, synthesis and biological evaluation of novel HIV-1 protease inhibitors incorporating N-phenyloxazolidines into the (hydroxyethylamino)sulfonamide scaffold as P2 ligands is described. Series of inhibitors with variations at P2, P2', and P1' were synthesized. Compounds with (S)-enantiomer of substituted phenyloxazolidines at P2 show highly potent inhibitory activities against wild-type HIV-1 protease. Selected inhibitors were evaluated against a panel of multi-drug resistant (MDR) mutant proteases as well as for their anti-viral potencies in cellular assays. Crystal structure analysis of the two most potent inhibitors in complex with wild-type HIV-1 protease provided valuable information on the interactions between the inhibitor and the protease enzyme.

MEDI 95

Discovery of novel HIV-1 integrase inhibitors by pharmacophore search

Iwona E Weidlich[1]*, Christophe Marchand*[2]*, Yves Pommier*[2]*, and Marc C. Nicklaus*[1]*. (1) Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute, NIH, DHHS, Frederick, MD 21702, (2) Laboratory of Molecular Pharmacology, National Cancer Institute, NIH, Bethesda, MD 20892*

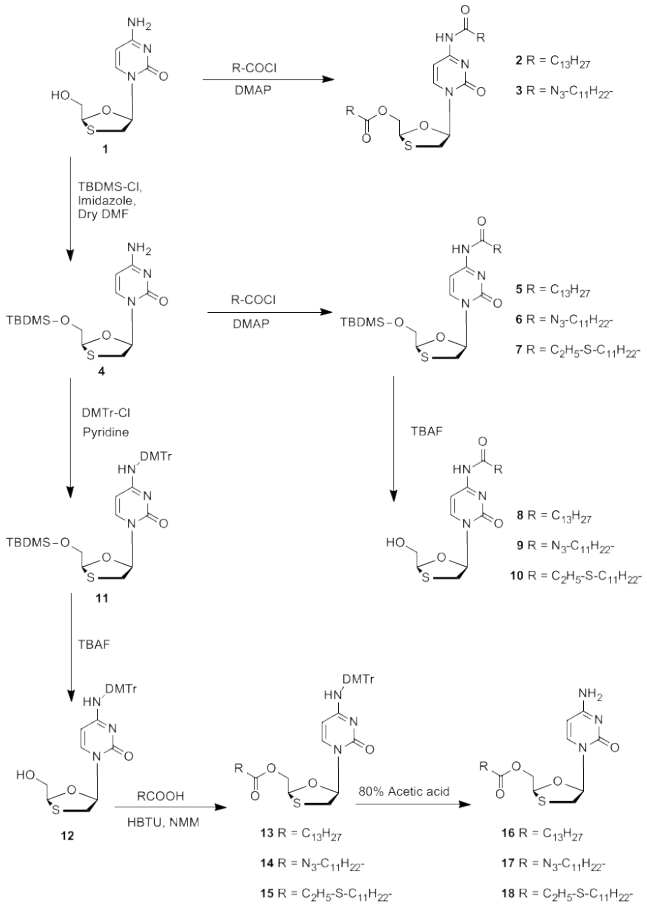
HIV-1 integrase (IN), one of the three viral-encoded enzymes required for the replication of the virus, is still an attractive though difficult target for the development of efficient anti-HIV drugs. Though a few promising clinical candidates exist, at present no anti-HIV drugs based on IN inhibition have been approved by the FDA. One of the reasons for the difficulties is the absence of crystal structures of the full-length enzyme and/or of the enzyme complexed with viral DNA. To address this, we had previously constructed models of full-length HIV-1 integrase complexed with models of viral and human DNA. We report here the results of virtual screening methods applied to one of these models. They yielded several ìM level inhibitors of the strand transfer reaction catalyzed by wild-type HIV-1 integrase, representing novel chemical structures. Additionally, we describe ligand-based development of HIV-1 integrase inhibitors, especially of strand transfer (ST) inhibitors based on known ST inhibitors with confirmed efficacy in patients. Based on the unique chemical features of these compounds as well as on features they have in common with the wider class of diketo acids IN inhibitors, two series of, in total, fourteen pharmacophores were developed, using the program Catalyst 4.11. We used these pharmacophores to search the ChemNavigator iResearch Library, an aggregated database of currently about 25 million purchasable screening samples, to select samples for purchase and subsequent assaying. We report on the status of these efforts.

MEDI 96

Synthesis and anti-HIV activities of fatty acyl derivatives of 2',3'-dideoxy-3'-thiacytidine

Hitesh Kumar Agarwal[1]*, Michael Hanley*[1]*, Gustavo F. Doncel*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5787, hkag@rediffmail.com, (2) CONRAD laboratory, Eastern Virginia Medical School, Norfolk, VA 23507*

To enhance anti-HIV efficacy, duration of action, and uptake into infected cells, and resistance profile of 3'-thia-2',3'-dideoxycytidine (**1**, 3TC, lamivudine), a number of fatty acyl derivatives of 3TC were synthesized and evaluated. Two disubstituted, three 4-amino monosubstituted, and three 5'-*O*-ester derivatives of 3TC were synthesized. 5'-Hydroxyl group of 3TC was protected in the presence of *tert*-butyldimethylsilyl chloride to afford **4** that was converted to 4-amino monosubstituted derivatives (**8-10**). Furthermore, the protection of N4-amino group in **4** in the presence of DMTr-Cl, the deprotection of 5'-*O*-TBDMS in the presence of TBAF, esterification of 5'-hydroxyl group in the presence of fatty acids, HBTU and NMM, followed by the cleavage of N4-DMTr group with acetic acid afforded 5'-*O*-fatty acyl derivatives of 3TC (**16-18**). 3TC was also reacted with fatty acids to give disubstituted derivatives (**2** and **3**). The N_4 or 5'-OH monosubstituted derivatives possessed comparable and, in some cases, better potency than 3TC.

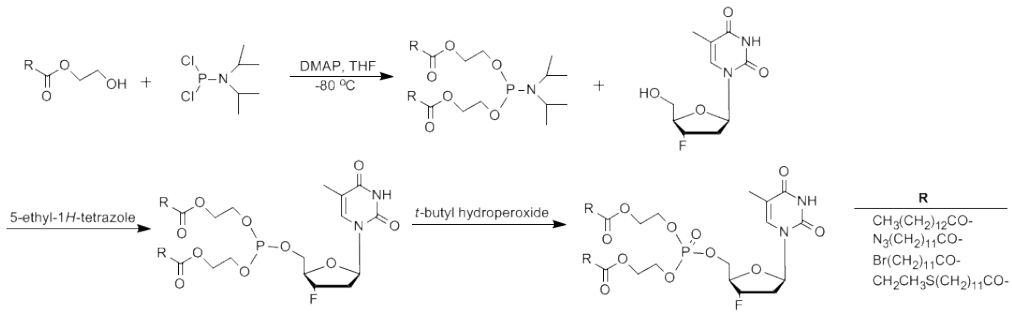


MEDI 97

Synthesis and evaluation of bis(fatty acyl-glycol)phosphate triester derivatives of 3'-fluoro-2',3'-dideoxythymidine

Hitesh Kumar Agarwal[1]*, Gustavo F. Doncel*[2]*, and Keykavous Parang*[1]*. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5787, hkag@rediffmail.com, (2) CONRAD laboratory, Eastern Virginia Medical School, Norfolk, VA 23507*

Nucleoside reverse transcriptase inhibitors often face two challenges that limit their anti-HIV activity: limited cellular uptake because of their hydrophilic nature and the rate-limiting monophosphorylation step. Herein, we designed bis(fatty acyl-glycol) phosphate triester derivatives of 3'-fluoro-2',3'-dideoxythymidine (FLT) to circumvent these problems. 5'-Hydroxyl group of FLT was linked to two fatty acyl groups through a phosphate triester linker to enhance the lipophilicity. Furthermore, it was expected that the prodrugs release the FLT-monophosphate intracellularly upon cellular uptake. Fatty acyl-glycol ester conjugates were reacted with diisopropylphosphoramidous dichloride to afford diisopropylphosphoramidous bis(fatty acyl-glycol) conjugates. Replacement of diisopropylamino group with FLT in presence of 5-ethyl-1*H*-tetrazole followed by oxidation with *t*-butyl hydroperoxide produced the final products. The anti-HIV activities of the products were significantly lower (12.5 to >100 µg/mL) than that of FLT (0.2-0.3 µg/mL) against lymphocytotropic and monocytotropic HIV strains (R5 virus). This suggests that the compounds had very limited cellular uptake, possibly due to extracellular hydrolysis to FLT-monophosphate.



MEDI 98

Water-soluble prodrugs of lopinavir, ritonavir and new investigational HIV PIs

David A. DeGoey*, William J. Flosi, David J. Grampovnik, Kennan C. Marsh, Larry L. Klein, Michelle A. Long, and Dale J. Kempf, Global Pharmaceutical Research and Development, Abbott Laboratories, Department R4CQ, Building AP52, 200 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-938-2756, david.degoey@abbott.com*

HIV protease inhibitors (PIs) are relatively lipophilic molecules, and are poorly soluble in water. Some PIs are not absorbed efficiently from the solid state, and require formulations to solubilize the drug. Consequently, PIs have been associated with high pill counts and large

capsules. Water-soluble prodrugs could reduce the pill count for these important therapies. We studied the synthesis, cleavage rates, and oral administration of prodrugs of lopinavir/ritonavir (Kaletra™), and some new HIV PIs. We concluded that phosphate and carboxylic acid esters attached directly to the central hydroxy group of these PI cores had slow cleavage rates. We developed a two-step synthesis to introduce a linker that improved the rate of cleavage, and oxymethylphosphate (OMP) and oxyethylphosphate (OEP) prodrugs provided high levels of aqueous solubility and oral bioavailability. The novel OEP prodrugs released acetaldehyde upon cleavage, instead of formaldehyde, and the new synthetic method may be applicable to other drug classes.

MEDI 99

Non-hydrolysable glycosylated porphyrins and chlorins: Potential new photodynamic therapy agents and applications in vivo imaging

Sebastian A. Thompson[1]*, Diana Samaroo*[2]*, Mikki Vinodu*[2]*, and Charles Michael Drain*[3]*. (1) Department of Chemistry & Biochemistry, Hunter College and Graduate Center of the City University of New York, 695 Park Ave., New York, NY 10021, Fax: 212-772-5332, sthompson@gc.cuny.edu, (2) Department of Chemistry, Hunter College of CUNY, New York, NY 10021, (3) Department of Chemistry, Hunter College & Graduate Center of the City University of New York, New York, NY 10021*

A non hydrolysable tetra-S-glycosylated porphyrin (PGlu-4) is presented as a potential new photodynamic therapeutic (PDT). PGlu-4 does not hydrolyze under physiological condition, is selective taken up by a variety of cancer cells, and is mainly found to be bound to or in the mitochondria. Apoptosis or necroses are activated depending on the concentration of the macrocycle and the irradiation power. The components of the cell culture media (e.g. albumin, glucose) strongly effect uptake and degree of PGlu-4 aggregation. Interaction of PGlu-4 with proteins effect distribution and degree of aggregation inside the cell as well. Chlorin derivatives were made to increase the absorption in the red region of the spectra, but we find that these have ca. 5-fold increase fluorescence quantum yields, therefore these may serve as good fluorescence imaging agents. We observe chlorin fluorescence located at the mitochondria when cell are treated as little as 10 nM compound.

MEDI 100

Gd(III)-based bile acid conjugates for dual magnetic resonance and fluorescence imaging

Sooyoun Lim*, Xiang Ma, and Hyun-Soon Chong, Chemistry Division, Biological, Chemical, and Physical Sciences Department, Illinois Institute of Technology, 3101 S. Dearborn St, LS 182, Chicago, IL 60616, chong@iit.edu*

Magnetic resonance imaging (MRI), a non-invasive and high resolution imaging technique has become a powerful tool in diagnostic medicine. The development of the adequate synthetic bifunctional chelates that can hold contrast enhancing metal while being conjugated to a targeting moiety is a critical step for disease-specific MRI. The bifunctional versions of the

promising Gd(IIII) chelate, NETA, C-NETA and C-NE3TA have been synthesized and conjugated to a liver targeting moiety, bile acid. The bile acid-ligand conjugates after being complexed with gadolinium(III) have been evaluated for their T1 relaxivities, cellular uptakes, MRI, and fluorescence imaging. The synthesis and in vitro evaluation of Gd(III) based bile acid conjugates as dual MR and flurorescence imaging agents will be reported.

MEDI 101

pH-Sensitive cyanine dyes for optical imaging of acidic environments

Scott A. Hilderbrand *and Ralph Weissleder, Center for Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School, 149 13th St. Rm 5404, Charlestown, MA 02129, Scott_Hilderbrand@hms.harvard.edu*

There is intense interest in the design of fluorogenic near infrared (NIR) probes for imaging applications. These environment responsive sensors, when coupled to nanoparticle scaffolds, benefit from increased in vivo retention times and enhanced signal via delivery of multiple fluorophores to the desired target. In this report development of nano-scale NIR fluorescence-based particles for pH imaging is reported. Abnormal tissue pH is commonly associated with pathophysiological disorders such as cancer, atherosclerosis, cysitic fibrosis and various renal conditions. Imaging probes for interrogation of these environments may ultimately allow for earlier disease diagnosis. For effective visualization of acidified tissues in vivo, careful design of a bright, water-soluble pH-sensitive fluorochrome is critical. To meet these requirements, new highly soluble pH-responsive cyanine dyes were developed in which the dye pKa can be tuned to match the acidic environment of interest. Ratiometric probes can be prepared by conjugation of the pH-sensitive reporters and pH-insensitive reference fluorophores to a suitable nano-scaffold. The functionality of these probes is demonstrated by visualization acidic intracellular compartments and by fluorescence reflectance imaging in mouse models.

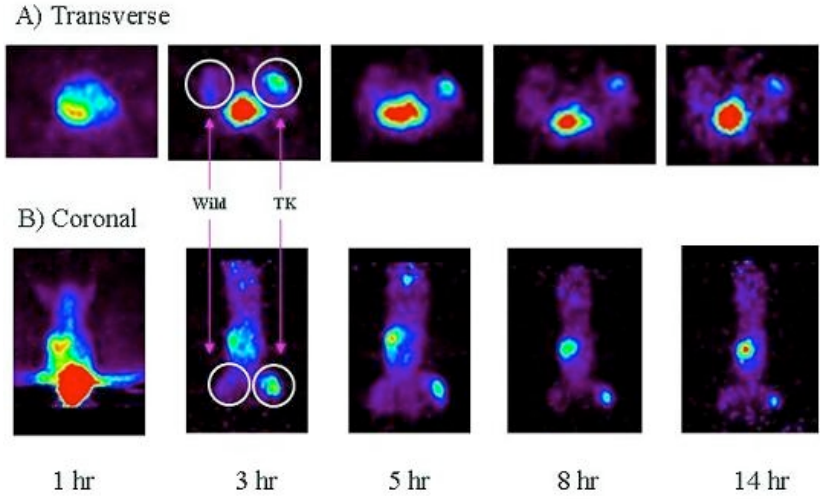
MEDI 102

The preparation of the stable substrate for imaging HSV1-TK expression and its biological study

gwangil An[1], kyochul Lee[1], Taehyun Choi[2], ***Hakjune Rhee****[3], Hyunseok Ahn[1], Kwonsoo Chun[1], gijeong Cheon[2], sangmoo Lim[2], and Byungseok Moon[1]. (1) Radiopharmaceuticals Laboratory, Korea Institute of Radiological & Medical Sciences, 215-4, Seoul 139-706, South Korea, Fax: 82-2-970-2409, gwangil@kcch.re.kr, (2) Nuclear Medicine Laboratory, Korea Institute of Radiological & Medical Sciences, Seoul 139-706, South Korea, (3) Department of Chemistry, Hanyang University, Ansan, South Korea, hrhee@hanyang.ac.kr*

The study for a number of 5-iododeoxyuridine analogues has been exclusively since the potential antiviral and antitumor therapeutic agents. The major goal of those studies was to prepare the more suitable radioiodine-labeled nucleoside analogues are effective and stable in vivo biodistribution as well as in vitro test. In this study, we wish to report an efficient synthesis of carbocyclic radioiododeoxyuridine analogue and biological evaluation for monitoring of HSV1-TK (herpes simplex virus type 1 thymidine kinase) gene transduced MCA hepatoma

cells and wild-type MCA cells. The synthetic route for tin precursor employed cyclopentadiene as a starting material and proceed in good yield through 8 steps which contain Pd(0)-catalyzed coupling reaction and radioiodination as key reactions. The precursor was radioiodinated with I-125 (for SPECT study) and I-124 (for PET study) to produce radiopharmaceuticals. Iodination was performed using no carrier added Na 124I wherein Na 124I was produced from MC-50 cyclotron in KIRAMS.



MEDI 103

Synthesis of novel technetium-99m-PIB complex as SPECT imaging agent for CNS disease

Kuanqiang Gao[1]*, Chunying Wu*[2]*, and Yanming Wang*[2]*. (1) Center for Pharmaceutical Biotechnology, University of Illinois at Chicago, 900 S. Ashland Avenue, Chicago, IL 60607, Fax: 312-413-9303, kgao2@uic.edu, (2) Case Center for Imaging Research, Case Western University, Cleveland, OH 44106*

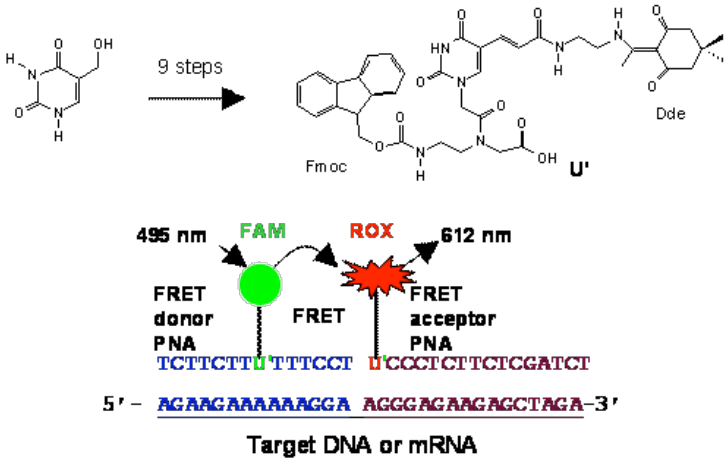
The synthesis of a novel Technetium-99m labeled PIB (2-(4-(methylamino)phenyl)-6-hydroxybenzothiaz ole) derivative has been described and the structural characterization and in vitro binding studies were conducted using the corresponding rhenium surrogate. The spectroscopic studies confirmed that the revealed that the complexation reaction gave exclusively the syn isomer. In vitro binding studies indicated that this complex has a high affinity to beta-amyloid than PIB.

MEDI 104

Peptide nucleic acid (PNA) FRET agents for imaging gene expression

Bereket Y. Oquare*, Huafeng Fang, and John-Stephen Taylor, Department of Chemistry, Washington University in Saint Louis, One Brookings Drive, cb # 1134, St. Louis, MO 63130, Fax: 314-935-4481, byoquare@wustl.edu*

Nucleic acid based agents for imaging gene expression in vivo would be attractive biochemical tools. Successful agents should be specific for the target gene, be stable in side the cell, and have low background signal. Antisense peptide nucleic acids (PNAs) are attractive nucleic acid analogs for detecting expressed mRNAs since they are resistant to degradation, do not activate degradation of the target mRNA by RNaseH and can invade regions of secondary structure and possibly sites where proteins are bound. We describe the design and synthesis of a peptide nucleic acid (PNA)-based fluorescent resonance energy transfer (FRET) system for detecting mRNA. Donor and acceptor PNAs were constructed utilizing an orthogonally protected Fmoc PNA building block (U') that we recently developed and were derivatized with FAM and ROX (Fig.1). These PNAs showed complementary DNA and RNA dependent FRET. (This material is based upon work supported by the National Heart Lung and Blood Institute of the National Institutes of Health as a Program of Excellence in Nanotechnology (HL080729)).



MEDI 105

Decaprenyl diphosphate synthase inhibitors activate gamma delta T cells

Fenglin Yin[1], *Yonghui Zhang*[2], *Rong Cao*[3], *Craig T Morita*[4], *and Eric Oldfield*[2]. *(1) Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, 600 S. Mathews Avenue, Urbana, IL 61801, fyin@uiuc.edu, (2) Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (3) Center for biophysics and computational biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (4) Department of Internal Medicine and the Interdisciplinary Group in Immunology, University of Iowa, Iowa City, IA 52242*

Gamma delta T cells play an important role in innate immunity since they represent a first of line defense against various pathogens, as well as being involved in tumor cell killing. Bisphosphonates show moderate activity in gamma delta T cell activation, due to inhibition of the enzyme farnesyl diphosphate synthase (FPPS), resulting in accumulation of isopentenyl diphosphate (IPP), a major diphosphate “phosphoantigen”. A much larger effect might be expected if other enzymes, which utilize larger amounts of IPP, are inhibited. The enzyme decaprenyl pyrophosphate synthase (DPPS) makes a C50 prenyl diphosphate precursor for ubiquinone biosynthesis by condensing seven IPP molecules to FPP. We synthesized a series of novel bisphophonates and tested them against the human DPPS enzyme. The

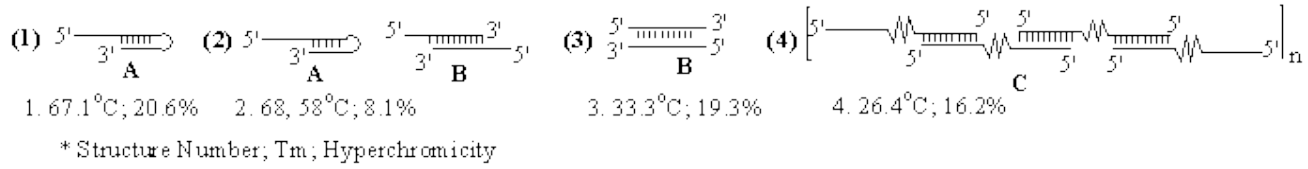
bisphosphonates having potent activity against DPPS were found to be exceptionally active in T cell activation, indicating a new drug target for use in immunotherapy.

MEDI 106

Impact of secondary structure of agonists of Toll-like receptor 9 on immune stimulatory activity

***Dong Yu**, Mallikarjuna R Putta, Lakshmi Bhagat, Daqing Wang, Meiru Dai, Jimmy X. Tang, Ekambar R. Kandimalla, and Sudhir Agrawal, Idera Pharmaceuticals, Inc, 345 Vassar Street, Cambridge, MA 02139, Fax: 617-679-5582, dyu@iderapharma.com*

Oligodeoxynucleotides (ODN) containing natural CpG or synthetic stimulatory motifs and form secondary structures act as agonistsofTLR9 and induce high levels of IFN-alpha in human cell-based assays. Our previous studies showed that synthetic agonists of TLR9 with palindromic sequences (4) and hairpin ODN sequences (1) form secondary structures and induce potent immune responses in mouse and human cell-based assays. ODN with palindromic sequences that allow formation of overlapping duplex or hairpin structures have been reported by others as class C CpG ODN [5'-TCGTCGTTTTCGGCGCGCGCCG-3'(2), 5'-TCGTCGAACGTTCGAGATGAT-3' (3)]. In the present study we have examined the ability of the four types of sequences (1-4) to form intra- and inter-molecular secondary structures by thermal melting studies and correlated their immune responses in cell-based assays and in vivo in mice. Both intra- (A) and inter-molecular (B and C) secondary structure forming ODN induced potent immune responses in mouse and human cell-based assays. Surprisingly ODN which form intra-molecular structures (A) did not induce cytokines in vivo in mice. ODN that form inter-molecular structures B and C induced cytokine secretion in mice. These results suggest that ODNs which form intra-molecular structures (A), such as 1 and 2, may not be appropriate candidates for TLR9 mediated immune responses.



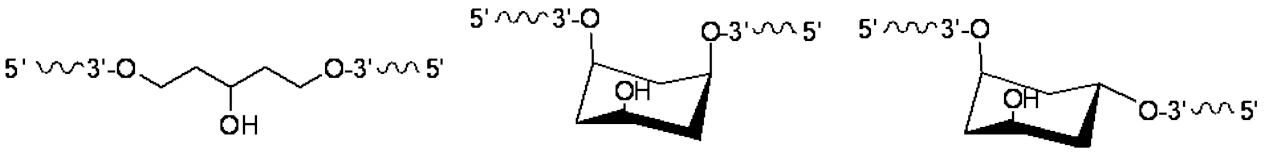
MEDI 107

Synthetic agonists of Toll-like receptor 9: Impact of linkers

***Mallikarjuna R. Putta**, Dong Yu, Daqing Wang, Lakshmi Bhagat, Meiru Dai, Jimmy X. Tang, Ekambar R. Kandimalla, and Sudhir Agrawal, Idera Pharmaceuticals, Inc, 345 Vassar Street, Cambridge, MA 02139, Fax: 617-679-5582, mputta@iderapharma.com*

Oligodeoxynucleotide (ODN)-based agonists of TLR9 with two 5'-ends have shown potent immune stimulatory activity compared with agonists that have single 5'-end in mouse and human cell-based assays and in vivo in mice and non-human primates. In the present study, we have designed and synthesized novel linear (C5), and cyclic (C6) linkers (Fig). These novel

linkers allowed us to synthesize synthetic agonists of TLR9 with different spatial orientations of the two 5'-ends to understand ODN-receptor interactions and subsequent immune stimulatory profiles. The agonists of TLR9 with new linker modifications maintained immune stimulatory activity in HEK293 cells expressing TLR9, and mouse and human cell-based assays. Additionally, TLR9 agonists with novel linkers induced IL-12 secretion in vivo in mice. These in vitro and in vivo results suggest that TLR9 recognizes synthetic agonists containing new linkers and induces potent immune responses.



Figure

MEDI 108

Synthetic oligoribonucleotides containing secondary structures activate Toll-like receptor 8 and induce immune responses

***Tao Lan**, Lakshmi Bhagat, Meiru Dai, Jimmy X. Tang, Ekambar R. Kandimalla, and Sudhir Agrawal, Idera Pharmaceuticals, Inc, 345 Vassar Street, Cambridge, MA 02139, Fax: 617-679-5582, tlan@iderapharma.com*

Single-stranded viral RNAs have been shown as ligands for Toll-like receptor (TLR) 7 and/or TLR8. Previously we have designed novel structures of single-stranded oligoribonucleotides (ORN) containing two 5'-ends. These novel ORN, referred to as Stabilized Immune Modulatory RNA (SIMRA), are stable against nucleases and acted as agonists of TLR8 and 7. In the present study, we have designed and synthesized several ORN sequences with the ability to form intermolecular duplexes. Such novel ORN are more stable against nucleases because of the secondary structure. The new ORN that form secondary structures activated HEK293 cells expressing human TLR8, but not human TLR3 that is receptor for double-stranded RNA. The new ORN showed potent induction of cytokines and chemokines in human cell-based assays. The ORN that can form secondary structures are a novel class of TLR8 ligands.

MEDI 109

Synthesis and biological evaluation of NETA and NETA analogs as iron depletion agents

***Xiang Ma** and Hyun-Soon Chong, Chemistry Division, Biological, Chemical, and Physical Sciences Department, Illinois Institute of Technology, 3101 S. Dearborn St, LS 182, Chicago, IL 60616, ma@iit.edu*

Iron depletion using iron chelators is known as one of the most efficient strategies for the treatment of excess iron-caused diseases. The structurally novel ligand, NETA possessing both a macrocyclic cavity and an acyclic pendant metal binding group has been designed for therapeutic and diagnostic applications. We previously reported that NETA possesses great

potential for antibody targeted radiation cancer therapy and MRI. We have screened NETA and NETA along with other potential iron depletion agents for iron depletion in Hela cells. NETA was found to be effective in depleting iron in Hela cells displaying significantly enhanced inhibition compared to DFO which is clinically available for treatment of iron overloading diseases. Synthesis and biological evaluation of NETA and NETA analogues as an iron depletion agent in various cell lines will be reported.

MEDI 110

Synthesis of a reactive linker for the construction of antibody-drug hybrid molecules

Joshua D. Thomas[1]*, Thomas Hofer*[2]*, Christoph Rader*[2]*, and Terrence R. Burke Jr.*[1]*. (1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, Bldg. 376 Boyles St., CCR, NCI-Frederick, NIH, Frederick, MD 21702, Fax: 301-846-6033, josthom@ncifcrf.gov, (2) Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda, MD 20892*

Although small synthetic molecules and monoclonal antibodies are valuable therapeutic agents in their own right, superior selectivity and pharmacokinetics may result from a merging of these two technologies. Previous applications of such an approach have involved the covalent attachment of a chemotherapeutic drug to a specific monoclonal antibody. In order to broaden the utility of this technique, we have developed methodology by which an antibody or antibody fragment can be selectively conjugated through a C-terminal selenocysteine to various small synthetic molecules. In the present work, we describe the synthesis of a reactive linker through which a high-affinity alpha4beta1 integrin binding ligand is selectively conjugated to an antibody fragment (Fc protein). The resulting bioconjugate is able to bind to primary human peripheral blood mononuclear cells by virtue of the Fc protein and selectively target cells expressing human integrin alpha4beta1.

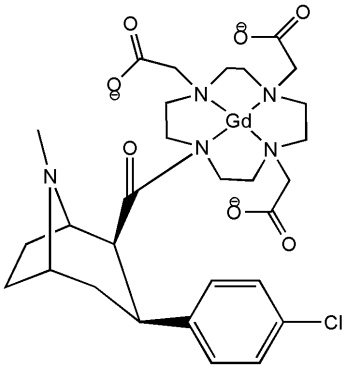
MEDI 111

Synthesis and use of cocaine-based MRI contrasting agents to detect the concentration of DAT

Gregory R Naumiec *and Brenton DeBoef, Department of Chemistry, University of Rhode Island, 50 Lower College Rd, Kingston, RI 02881, gnaumiec@chm.uri.edu*

Magnetic resonance imaging is a non-radioactive and higher special resolution alternative to other diagnostic techniques such as SPECT or PET. Paramagnetic complexes are used as MRI contrasting agents because their unpaired electrons decrease relaxation times of the

nearby water molecules, thus increasing the signal. Our research involves the synthesis and use of cocaine-based contrasting agents in order to measure the concentration of dopamine transporter (DAT). Knowing the concentration of DAT in the brain can help diagnosis conditions such as drug addiction, depression, and Parkinson's disease.

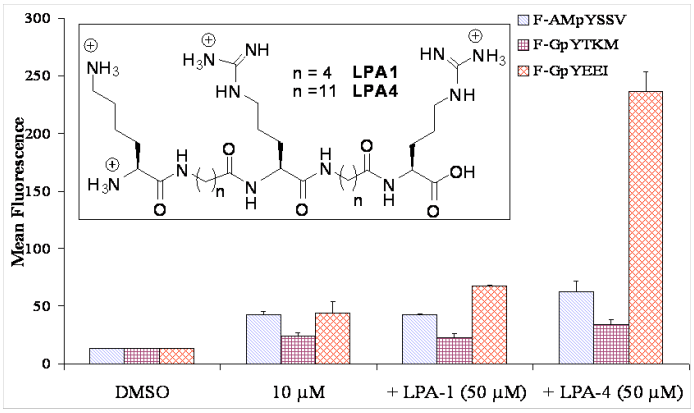


MEDI 112

Noncovalent cellular delivery of phosphopeptides by amphipathic peptides

***Guofeng Ye**, Nguyen H. Nam, Anil Kumar, and Keykavous Parang, Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5787, guofengye@mail.uri.edu*

A number of amphipathic peptides containing two arginine and one lysine residues were synthesized and evaluated for non-covalent cellular delivery of phosphopeptides. Fluorescence polarization assay showed that peptides containing long hydrophobic linkers, such as LPA4, can form a complex with the fluorescein-labeled GpYEEI (F-GpYEEI). LPA4 was further evaluated for potential application in cellular delivery of phosphopeptides to BT-20 live cells. Confocal microscopy and fluorescent flow cytometry studies with the mixture of LPA4 (50 μM) and F-GpYEEI (10 μM) in BT-20 cells showed dramatic increase in the fluorescence intensity in cytosol of cells after 30 minutes, suggesting that LPA4 can function as a delivery tool of F-GpYEEI. LPA1 was used as a negative control. LPA4 was not able to deliver other control peptides, F-AMpYSSV and F-GpYTKM, into the cells. These studies suggest that positively-charged amphipathic peptides can be used for non-covalent cellular delivery of specific phosphopeptides, and confirm our earlier results in the fixed cells.



MEDI 113

Bisphosphonates targeting geranylgeranyl diphosphate synthase: A QSAR investigation

Rong Cao[1]*, Yonghui Zhang*[2]*, Fenglin Yin*[3]*, Michael P. Hudock*[4]*, and Eric Oldfield*[2]*. (1) Center for biophysics and computational biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, rongcao@chad.scs.uiuc.edu, (2) Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (3) Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, Urbana, IL 61801, (4) Center for Biophysics and Computational Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801*

Protein prenylation, including farnesylation and geranylgeranylation, is an important posttranslational modification that either anchors proteins to membranes or facilitates protein-protein binding. Blocking protein prenylation has been shown to represent a potentially useful therapeutic approach for cancer therapy. We thus synthesized and tested a series of bisphosphonates targeting human geranylgeranyl diphosphate synthase (GGPPS). The most active compound has an IC50 of 300 nM against the enzyme and possesses low micro-molar activity against tumor cell lines. A QSAR analysis of GGPPS inhibitors indicates the importance of hydrophobic and steric interactions but not positive charge character required in farnesyl diphosphate synthase (FPPS) inhibition. The results suggest a different inhibitor binding mode in GGPPS.

MEDI 114

Study of solvent interactions in solvolytic reactions of several common pharmaceutical intermediates

Malcolm J. D'Souza[1]*, Zoon H. Ryu*[2]*, Dennis N. Kevill*[3]*, and Byoung-Chun Park*[3]*. (1) Department of Chemistry, Wesley College, 120 N State Street, Dover, DE 19901, Fax: 302-736-2301, dsouzama@wesley.edu, (2) Department of Chemistry, Dong-Eui University, Busan, South Korea, (3) Department of Chemistry & Biochemistry, Northern Illinois University, DeKalb, IL 60115*

Background: There has been significant interest in the hydrolysis, alcoholysis, and aminolysis processes of acyl halides, as such reactions are useful models for enzymatic mechanisms. A recent study (*Tetrahedron Letters,* 42, **2001,** 7747-7750), proposed a concerted (S_N2) process for the methanolysis of paclitaxel-related derivatives having a chloroacetyl substituent on the C2' oxygen. **Methods:** The effects of solvent variation of the available specific rates of solvolysis of acetyl, chloroacetyl, trimethylacetyl, phenylacetyl, diphenylacetyl, and α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides, are analyzed using the extended Grunwald-Winstein equation utilizing the N_T scale based on S-methyldibenzothiophenium ion solvolysis combined with a Y_{Cl} scale based on 1-adamantyl chloride solvolysis. **Conclusions:** The results obtained are consistent with our earlier suggestion that acid chlorides of monoesters of carbonic acid and of carboxylic acids tend to solvolyze with competing addition-elimination (with rate-determining addition) and ionization S_N1 (assisted by nucleophilic solvation) pathways. [Grant support: NIH grant 2 P20 RR016472-06 from the NCRR]

MEDI 115

Drug-receptor binding affinity: The strength of hydrophobic binding can be increased by adding hydrogen bonds

Laveena Muley[1], *Michael Smolinski*[1], *Bernhard Baum*[2], *Christof Gerlach*[2], *Marek Freindorf*[3], *Gerhard Klebe*[2], *and David G. Hangauer*[1]. *(1) Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, NY 14260, lmuley@buffalo.edu, (2) Institute of Pharmaceutical Chemistry, Philipps-University Marburg, Marburg 35032, Germany, (3) Center for Computational Research, University at Buffalo, The State University of New York, Buffalo, NY 14260*

The characterization of weak, non covalent interactions involved in the complex process of molecular recognition is of fundamental interest. The interplay between these non-covalent interactions is often ignored when attempting to predict the binding affinity of ligands to their receptors. The objective of the current study was to demonstrate the interplay between hydrophobic binding and hydrogen bonding using a series of systematically varied thrombin inhibitors. Binding affinities, binding orientations, molecular dynamics, and the thermodynamics of binding were evaluated. The data shows that the improvement in the free energy of binding, per square angstrom of added hydrophobic contact surface area, is significantly higher in the presence of an additional hydrogen bond than in its absence. This information needs to be incorporated into ligand binding affinity prediction algorithms in order to improve their accuracy.

MEDI 116

Hemostatic effects of liposomes carrying fibrinogen gamma-chain dodecapeptide and encapsulating adenosine 5'-diphosphate as a platelet substitute

Yosuke Okamura[1], *Ippei Maekawa*[2], *Makoto Handa*[3], *Yasuo Ikeda*[3], *and Shinji Takeoka*[1]. *(1) Department of Life Science and Medical Bioscience, Graduate School of Advanced Science and Engineering, Waseda University, 3-4-1, Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan, Fax: 813-5286-3217, y.okamura@ruri.waseda.jp, (2) Department of Life-Science and Medical-Bio Science, Graduate School of Advanced Science and Engineering, Waseda University, Tokyo 169-8555, Japan, (3) Department of Internal Medicine, School of Medicine, Keio University, Tokyo 169-8582*

We studied platelet substitutes for treatment of bleeding and focused on a dodecapeptide; HHLGGAKQAGDV (H12), which is a fibrinogen ã-chain carboxy-terminal sequence. In this study, we conjugated H12 to the surface of a liposome which encapsulated an adenosine 5'-diphosphate (ADP), and evaluated their in vitro and in vivo hemostatic effects. The H12(ADP)liposomes was significantly enhanced the collagen-induced platelet aggregation in comparison with the H12-liposomes (non-encapsulation), indicating that ADP release from the H12(ADP)liposome was triggered when they were incorporated in the platelet aggregates. The bleeding times of the normal ([platelet] = $8.1\pm0.9\times10^5$ /iL) and thrombocytopenic rats ([platelet]=$2.0\pm0.3\times10^5$ /iL) were 178±56 and 682±198 s, respectively. The H12(ADP)liposomes at a dose of 10 mg/kg shortened the tail bleeding time to 349±49 s, whereas, the H12-liposomes at the same dose did not shorten the bleeding time (572±127 s).

These results indicate that the H12(ADP)liposomes would be a suitable candidate for an alternative to human platelet concentrates.

MEDI 117

From SAMs to drugs: Application of the Pharmacomer Technology Platform to small molecule drug discovery

Bridget M Cole[1]*, Paul Sweetnam*[2]*, Enoch Kim*[3]*, David Duffy*[4]*, James Ellis*[5]*, Dominick Casalena*[4]*, Alessandra Bartolozzi*[1]*, Yingfei Yang*[1]*, Hope Foudoulakis*[1]*, Brian Kirk*[1]*, Elsa Mak*[5]*, Eric Wong*[5]*, Sharon McGonigle*[5]*, Stewart Campbell*[6]*, Olivier Schueller*[7]*, John Ferkany*[7]*, and William Prince*[8]*. (1) Department of Chemistry, Surface Logix Inc, 50 Soldiers Field Place, Brighton, MA 02135, Fax: 617-783-8877, bcole@surfacelogix.com, (2) CSO, Surface Logix Inc, Brighton, MA 02135, (3) Department of Exploratory Research, Surface Logix Inc, Brighton, MA 02135, (4) Platform Technology, Surface Logix Inc, Brighton, MA 02135, (5) Department of Biology, Surface Logix Inc, Brighton, MA 02135, (6) Department of Chemistry, Ancora Pharmaceuticals Inc, Medford, MA 02155, (7) Clinical Development, Surface Logix Inc, Brighton, MA 02135, (8) Chief Development Officer, Surface Logix Inc, Brighton, MA 02135*

Surface Logix has rapidly built a strong pipeline of clinical candidates using the Pharmacomer Technology Platform to drive drug design. This proprietary technology, based on research pioneered by Professor George Whitesides, uses self-assembled monolayers (SAMs) to model small molecule-protein interactions and to measure interfacial properties that determine PK and PD characteristics. The Pharmacomer Platform has been successfully employed to minimize interactions with tissue proteins to develop PDE5 inhibitor SLx 2101, a promising phase II clinical candidate for the treatment of hypertension. Using the platform to fine-tune interfacial free energy delivered SLx 4090, an entercoyte-specific Microsomal Triglyceride Transfer Protein antagonist that is currently in phase II studies for the treatment of hypertriglyceridemia. Overall, the Pharmacomer platform provides a powerful approach to small molecule drug design via its ability to predictably modulate properties of small molecules.

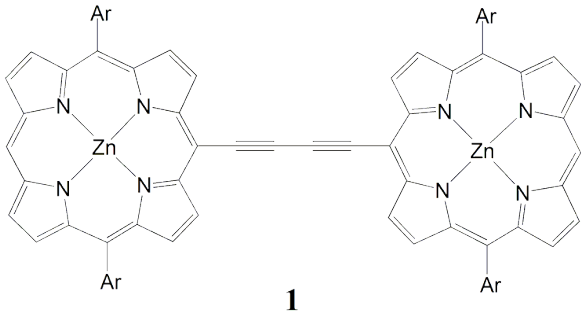
MEDI 118

Conjugated porphyrin dimers with large two-photon absorption cross section for photodynamic therapy

Milan Balaz[1]*, Hazel A. Collins*[1]*, Marina K. Kuimova*[2]*, Emma Dahlstedt*[1]*, Klaus Suhling*[3]*, David Phillips*[2]*, and Harry L. Anderson*[1]*. (1) Department of Chemistry, University of Oxford, Mansfield Road, OX1 3TA Oxford, United Kingdom, milan.balaz@chem.ox.ac.uk, (2) Department of Chemistry, Imperial College, London, United Kingdom, (3) Department of Physics, Kings' College, London, United Kingdom*

Two-photon excited photodynamic therapy (TPE-PDT) is the use of a chromophore with a high TPE cross section as a photosensitizer in PDT. The main advantage of two-photon excitation is that it allows the generation of singlet oxygen to be pin-pointed to a small volume reducing collateral damage. In addition, near-infrared light of twice the wavelength of the absorption band can be used to produce the excited state of the sensitizer increasing biological tissue

penetration. Recently we have discovered that porphyrin dimer such as 1 has an exceptionally high two-photon absorption cross-section of ca 6,000 GM at 780 nm and high singlet oxygen yields. The main challenge is the functionalization of large porphyrin dimers in order to achieve good cellular uptake and low dark toxicity. The synthesis of hydrophilic positively and negatively charged porphyrin dimers, their singlet oxygen yields, and in vitro one–photon PDT results will be presented.



1

MEDI 119

Review of various classes of organic compounds for optimal purification on RediSep Rf Diol media

Veronica D. Thomason*, Chromatography Department, Teledyne - Isco, 4700 Superior Street, Lincoln, NE 68504, Fax: 402-465-3089, vthomason@teledyne.com*

Silica gel is typically used for normal phase purification by flash chromatography. Often the highly polar and acidic silanol groups on bare silica cause separation time to be lengthy and difficult. Teledyne Isco offers RediSep Rf Diol columns as an versatile alternative to silica gel for the purification of peptides, carbohydrates and polar compounds.

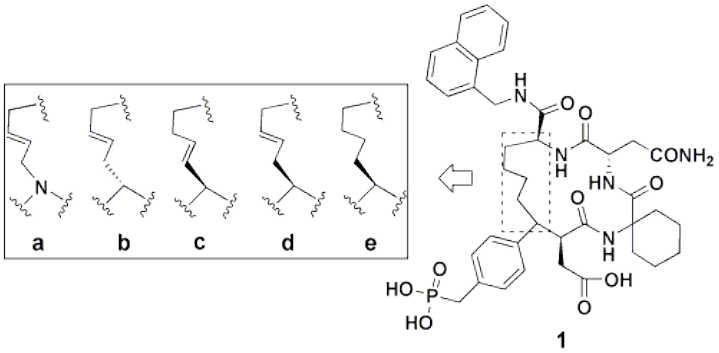
MEDI 120

Examination of secondary conformational constraint in the design of macrocyclic Grb2-SH2 domain-binding ligands

Fa Liu*[1], Karen M. Worthy[2], Lakshman Bindu[2], Robert J Fisher[2], 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) Protein Chemistry Laboratory, SAIC-Frederick, Frederick, MD 21702*

Global conformational constraint has been successfully applied in the development of macrocyclic Grb2-SH2 domain-binding ligands. However, our recent studies have shown that the chirality of certain stereogenic centers in the backbones of ring-closing metathesis (RCM)-derived macrocycles is not crucial for high binding affinity. Accordingly, a series of compounds were designed and synthesized to systematically examine the role of secondary conformational constraint in these macrocylces. First, a nitrogen was introduced in place of the phosphotyrosine (pTyr) mimetic beta-methylene in order to alter the orientation of both the

pTyr benzyl ring and the macrocycle conformation (1a). Second, the stereochemistry at the beta-methylene of the pTyr mimetic was reversed (1b). Third, the double bond resulting from RCM-derived macrocyclization was shifted (1c and 1d) or reduced (1e) in order to alter the local conformation and provide increased flexibility. The effects of these changes on binding were determined by surface plasma resonance studies measuring the direct interaction of ligand with surface-bound Grb2-SH2 domain protein.



1

MEDI 121

Synthetic efforts toward the development of Shc SH2 domain-binding peptides

Won Jun Choi[1]*, Andrew G. Stephen*[2]*, Robert J Fisher*[2]*, and Terrence R. Burke Jr.*[1]*. (1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, Frederick, MD 21702, (2) Protein Chemistry Laboratory, SAIC-Frederick, Frederick, MD 21702*

Shc is a non-catalytic SH2 domain-containing adapter protein that is involved with Ras activation through several growth factor receptor tyrosine kinases. The importance of Shc in the proliferative signal transduction of certain cancers has made antagonists of Shc signaling potentially attractive as therapeutic targets. Accordingly, we have undertaken efforts to develop Shc SH2 domain binding inhibitors. Modeling studies for binding to Shc SH2 domains have indicated that a hexamer phosphotyrosine-containing peptide should be capable of high affinity binding. Based on a lead peptide, we designed and synthesized a variety of analogues that employed fluorescein isothiocyanate (FITC) labeling at either the N or C terminus with variation of spacer length and configuration for joining the FITC group to the peptide. We also examined N-substituted glycine-containing peptides (peptoids) as an approach toward enhancement of binding affinity. A fluorescence anisotropy assay was used for convenient and efficient evaluation of Shc SH2 domain binding affinity. The design, synthesis and evaluation of these analogues will be reported.

MEDI 122

Multimodal nanoagent for the diagnosis and treatment of atherosclerosis

Jason R. McCarthy*, Ethan Korngold, Farouc Jaffer, and Ralph Weissleder, Center for Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School, 149 13th St. Rm 5404, Charlestown, MA 02129, jason_mccarthy@hms.harvard.edu*

Atherosclerosis remains the most common cause of mortality in the developed world and new methods to efficiently treat macrophage-rich atherosclerotic lesions are needed. Based upon the hypothesis that nanoparticles can be targeted to atheromata, we have designed a multimodal nanoagent capable of the imaging and therapy of inflamed plaques. Crosslinked iron-oxide nanoparticles (CLIO) serve as a nanoscaffold capable of acting as a magnetic resonance imaging contrast agent. To this particle is conjugated AlexaFluor 750 for fluorescence imaging, and a conjugatable derivative of meso-tetrahydroxyphenylchlorin, a potent photodynamic therapy (PDT) agent. Previous evidence has shown that PDT has the potential to stabilize vulnerable atherosclerotic lesions. In vitro, this nanoagent exhibits exquisite phototoxicity to RAW 264.7 murine macrophages. As compared to the commonly used chlorin e6, the PDT nanoagent is approximately 6-fold more phototoxic, on a chlorin-to-chlorin basis, and 70-fold more potent on a molecular basis. In order to determine in vivo efficacy, 24 week old apolipoprotein E deficient (apoE-/-) mice on a high cholesterol diet were injected with the agent and imaged 24 hours later using intravital fluorescence microscopy (IVM). The particles were found to localize within atheromata, as evidenced by the signal in the 750 nm fluorescence channel. The atherosclerotic lesions were then irradiated with a 650 nm laser to induce phototoxicity. After one week, the mice were reinjected with the agent and imaged. IVM revealed reduced nanoagent uptake by the lesion, indicating local ablation of macrophages, which was further supported by correlative histology. The plaque stabilizing potential of this nanoagent is still under investigation.

MEDI 123

WITHDRAWN

MEDI 124

Anodized nanotubular titanium as novel drug eluting orthopedic implants

***Chang Yao**, Division of Engineering, Brown University, 182 Hope St, Providence, RI 02912, chang_yao@brown.edu, and Thomas J. Webster, Division of Engineering and Orthopedics, Brown University, Providence, RI 02912*

Titanium-based materials are widely used for orthopedic implants, such as hip and knee replacements. The weakness in these implants is that their surfaces are not bioactive enough to support adequate new bone bonding with the implants. For this reason, an electrochemical method known as anodization was used to modify the titanium surface properties. Basically, by using fluorine-containing electrolyte, nanotubular structures were obtained all over the titanium surface instead of plain micro-rough surfaces before anodization. In vitro studies revealed enhanced osteoblast adhesion and long term functions on such anodized titanium compared to unanodized titanium. For drug loading purposes, anodized titanium was further chemically modified to possess varied surface wettability. Then, antibiotic and anti-inflammatory drugs were loaded into the titanium nanotube structures by physical soaking and electro-deposition. In this way, a controlled drug release was achieved and will be beneficial for new bone growth after implantation.

MEDI 125

A structure- and NMR-based approach for the discovery of novel agents against Influenza A virus

William H. Bisson *and Maurizio Pellecchia, Apoptosis/Infectious Diseases, The Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, CA 92037, wbisson@burnham.org*

In the face of the persistent threat of human influenza A virus (H1N1) and the new mutated strains (H3N2), in addition to the recent outbreaks of avian influenza (H5N1) in Southeast Asia, there is an impending need for novel and effective supplies of anti-influenza virus agents. By using Nuclear Magnetic Resonance (NMR) spectroscopy we have studied a 25-residue peptide which is composed by the trans-membrane sequence amino acids of the viral M2 protein, an essential proton channel for viral maturation. Here we propose a combined approach utilizing in silico screening followed by NMR measurements for ligand binding studies and characterization. By using this approach, novel and specific agents against different strains of influenza A virus by directly targeting both wild-type and mutant M2 variants could be obtained. The combination of these data with a range of biochemical activities will provide a framework onto which to develop potentially novel anti-influenza therapies.

MEDI 126

Inhibition of inducible nitric oxide synthase expression by structural analogs of pterostilbene

Cassia S Mizuno*, Agricultural Research Service, U.S Department of Agriculture, University Ave, University, MS 38677, Fax: 662-915-1035, cmizuno@olemiss.edu, Shiby Paul, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, Nanjoo Suh, Rutgers, The State University of New Jersey, Susan Lehman Cullman Laboratory for Cancer Research, Piscataway, NJ 08854, and Agnes M. Rimando, Agricultural Research Service, US Department of Agriculture, University, MS 38677*

Increased expression of inflammatory genes such as inducible nitric oxide synthase (iNOS) has been observed in azoxymethane (AOM)-induced colon cancer model. In our earlier studies, pterostilbene was demonstrated to inhibit iNOS expression, and also significantly suppressed the total aberrant crypt foci (ACF) induced by azoxymethane (AOM) as well as AOM-induced colonic cell proliferation. These results triggered our investigation of analogs of pterostilbene. Over 20 natural and synthetic derivatives of pterostilbene were synthesized. Of the stilbenoids tested (Z)-4-(3,5-dimethoxystyryl)aniline was shown to strongly inhibit iNOS expression at 10 μM, in in vitro assays, as well as the growth of HT-29 human colon cancer cell line. All analogs moderately inhibited the expression of inducible cyclooxygenase 2 (COX-2) at 30 μM concentration. These results suggest that RTE may be an effective colon cancer preventive agent, possibly by inhibiting iNOS and COX-2.

MEDI 127

Design and synthesis of novel cyclic oxyguanidines as potential iNOS inhibitors

Guo-Hua Chu[1]*, Minghua Gu*[1]*, Bertrand Le Bourdonnec*[1]*, Christopher W. Ajello*[1]*, Lara K. Leister*[1]*, Joel A. Cassel*[2]*, Robert N. DeHaven*[2]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, Fax: 484-595-1551, ghchu@adolor.com, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341*

Nitric oxide is produced by the oxidation of the terminal guanidine group of L-arginine by three distinct isoforms of nitric oxide synthase (NOS): the constitutively expressed neuronal NOS (nNOS) and endothelial NOS (eNOS), and the induced isoform - iNOS. Overexpression of iNOS has been implicated in the pathology of a large number of inflammatory diseases. In recent years there has been significant interest in the role of iNOS in the pathophysiology of inflammatory and neuropathic pain. Recent studies indicated that GW274150, a potent and highly selective iNOS inhibitor, exhibits analgesic effects in rat models of inflammatory and neuropathic pain. Selective inhibitors of iNOS may therefore be a useful therapy for the treatment of these diseases. We report the design and synthesis of novel cyclic oxyguanidines as potential iNOS inhibitors. These agents combine the structural features of the iminopiperidine and iminohomopiperidine iNOS inhibitors, and L-canavanine, the naturally occurring oxyguanidine containing iNOS inhibitor.

MEDI 128

Design and synthesis of novel imidazolepyrimidines as potent iNOS dimerization inhibitors - Part I

Guo-Hua Chu[1]*, Bertrand Le Bourdonnec*[1]*, Minghua Gu*[1]*, Christopher W. Ajello*[1]*, Lara K. Leister*[1]*, Paul A. Tuthill*[1]*, Ian Sellitto*[1]*, Heather O'Hare*[1]*, Joel A. Cassel*[2]*, Robert N. DeHaven*[2]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, Fax: 484-595-1551, ghchu@adolor.com, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341*

The three isoenzymes of NO synthase (NOS) catalyze the conversion of L-arginine to nitric oxide (NO) and citrulline: the constitutively expressed neuronal NOS (nNOS) and endothelial NOS (eNOS), and the induced isoform - iNOS. There is considerable experimental evidence that the excessive NO production following induction of iNOS plays an important role in the pathology of a large number of inflammatory diseases. Recent studies revealed that GW274150, a potent and highly selective iNOS inhibitor, displays analgesic effects in rat models of inflammatory and neuropathic pain. Selective inhibitors of iNOS would therefore be a useful approach to the treatment of inflammatory diseases and pain. As a part of our research program in this area, a series of novel imidazolepyrimidines was designed and synthesized as potent inhibitors of iNOS dimer formation, a key prerequisite for proper functioning of the enzyme. The details of the synthesis and the biological activity of these novel iNOS dimerization inhibitors will be presented.

MEDI 129

Releasing of nitric oxide from elastic electrospun nanofibers

Piyaporn Kampeerapappun[1], *Marcos Lopez*[2], *Patricio Lopez-Jaramillo*[3], *and Daniel J. Smith*[1]. *(1) Department of Chemistry, The University of Akron, 190 Buchtel Commons, Akron, OH 44325, pk12@uakron.edu, (2) Free Radical Research Center and Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI 53226, (3) VILANO Group, Cardiovascular Foundation of Colombia, Floridablanca, Colombia*

In general, nitric oxide is known to exert beneficial results related to an adequate healing due to its antibiotic and vasodilatory effects. For this purpose, we have developed a multilayer transdermal electrospun wound dressing which allows the controlled release of nitric oxide from a NO2-/ascorbic acid system encapsulated in polymer nanofibers. Using this approach, a wound dressing capable of delivering micromolar NO/cm2 for 6 h and 24 h at 37 C has been successfully produced and it can maintain its activity after sterilization procedures. Double-blind clinical trials were performed to determine the efficacy of the nitric oxide releasing patch (NOP) in treating diabetic foot ulcers (DFU). Results confirm that with daily application, a complete re-epithelization, development of fibrous tissue and recovery of sensitivity in the affected area is obtained within months.

MEDI 130

Design and synthesis of novel imidazolepyrimidines as potent iNOS dimerization inhibitors

Ian F Sellitto[1], *Betrand LeBourdennec*[1], *Guo-Hua Chu*[1], *Minghua Gu*[1], *Christopher W. Ajello*[1], *Lara K. Leister*[1], *Paul A. Tuthill*[1], *Heather O'Hare*[1], *Joel A. Cassel*[2], *Robert N. DeHaven*[2], *and Ronald E. Dolle*[1]. *(1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, Fax: 484-595-1551, isellitto@adolor.com, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341*

Nitric oxide (NO) is a small reactive molecule with an important role in various physiological processes, including modulation of inflammatory responses and regulation of vascular tone. Nitric oxide synthase (NOS) catalyzes the formation of NO and L-citrulline from L-arginine (Arg) and oxygen. The NOS family consists of three known mammalian isoforms. Neuronal NOS (nNOS) and endothelial NOS (eNOS) are constitutively expressed under noninflammatory conditions, and their activity is tightly regulated by Ca^{2+} calmodulin. Inducible NOS (iNOS) is a key mediator of inflammation and host defense systems. Expression of iNOS is induced at a transcriptional level by inflammatory stimuli, including interferon (IFN), interleukin (IL)-1, tumor necrosis factor (TNF), and bacterial lipopolysaccharide (LPS). Production of excess NO and prolonged induction of iNOS have been observed in various inflammatory and autoimmune diseases, including septic shock, hemorrhagic shock, systemic lupus erythematosus, Sjögren's syndrome, vasculitis, rheumatoid arthritis (RA) and osteoarthritis (OA). Selective inhibitors of iNOS would therefore be a useful approach to the treatment of inflammatory diseases and pain. As a part of our discovery research program in this area, a series of novel imidazolepyrimidines was designed and synthesized as potent

inhibitors of iNOS dimer formation, a key prerequisite for proper functioning of the enzyme. The details of the synthesis and the biological activity of these novel iNOS dimerization inhibitors will be presented.

MEDI 131

Potential applications of fendiline NONa in coronary health

Melinda K. Carnahan[1]*, Wilmarie Flores*[1]*, and Daniel J. Smith*[2]*. (1) Department of Chemistry, University of Akron, Knight Chemical Laboratory, Akron, OH 44325-3601, (2) Department of Chemistry, The University of Akron, Akron, OH 44325-3601*

The medicinal benefits of the nitric oxide (NO) donor compounds termed diazeniumdiolates are well established and include antithrombolitic, cytostatic, and vasorelaxant activities. Additionally, fendiline, a coronary vasodilator, increases intracellular NO concentrations via interaction with the Ca2+ cascade. Modification of fendiline with NO generates a new, lipophilic member of the diazeniumdiolate family, fendiline diazeniumdiolate (FDL-NONa), which has increased potential as a pharmaceutical NO donor and multiple applications in the coronary health market. This bifunctional vasodilator, when dissolved using methanol in buffer solution, releases NO to generate a half-life of 1.6 hours at 37 C and pH 7.41. Extension of this half-life can be achieved by varying the water insoluble particulate size of the donor in PBS. Furthermore, excellent binding of FDL-NONa to both glass and metal surfaces provides a direct correlation between coating thickness and NO release profile and decomposition of this compound in vivo generates species which pose no health concern.

MEDI 132

Synthesis, pharmacological and toxicological studies of nitric oxide releasing analog of acetaminophen

Tilak Raj Bhardwaj[1]*, Manoj Kumar*[2]*, Neeraj Mehta*[3]*, and Neelima Dhingra*[3]*. (1) Medicinal Chemistry Division, Professor of Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences, Centre of Advanced Studies in Pharmaceutical Sciences, Panjab University, Chandigarh- 160 014, India, bhardwajrajtilak@yahoo.co.in, (2) Medicinal Chemistry Division, Reader in Pharmaceutical Chemistry, Chandigarh- 160 014, India, (3) Medicinal Chemistry Division, Senior Research Fellow, Chandigarh- 160 014, India*

Acetaminophen (paracetamol) is a widely used drug which possesses analgesic and antipyretic activity, devoid of anti-inflammatory activity and is hepatotoxic. In recent approach, nitric oxide releasing non-steroidal anti-inflammatory drugs (NO-NSAIDs) have been synthesised to counteract the gastric and liver toxicity caused by conventional NSAIDs. We have synthesized a NO-releasing derivative of acetaminophen and evaluated it for analgesic activity (acetic acid induced writhings), anti-inflammatory activity (carrageenan-induced hindpaw oedema),liver toxicity (liver function tests i.e. LFTs in serum; and histopathology) and serum nitrate/nitrite release (using ELISA). The NO-releasing derivative has been found to have better peripheral analgesic activity and significant anti-inflammatory activity as compared

to the parent drug. The derivative was found to release NO in vivo and is devoid of liver toxicity as indicated by serum LFTs and histopathological studies.

MEDI 133

Preclinical pharmacokinetic study of Zaltoprofen in rats

***Nageswararao Muddana**, Gopinadh Bhyrapuneni, Koteshwara Mudigonda, Vishwottam N. Kandikere, and Ramakrishna V. S. Nirogi, Discovery Research, Suven Life Sciences Ltd, Serene Chambers, Road No 7, Banjara Hills, Hyderabad 500034, India, Fax: 914023541152, nageshwara@suven.com*

Zaltoprofen, chemically, 2-(10,11-dihydro-10-oxodibenzo [b, f] thiepin-2-yl) propionic acid is a potent non-steroidal anti-inflammatory drug (NSAID). Zaltoprofen is a unique compound that inhibits cyclooxygenase and exhibits anti-bradykinin activity. The objective of the present investigation is to study the pharmacokinetics of zaltoprofen in rats after a single intravenous dose or oral administration. In the current investigation, zaltoprofen was administered intravenously (0.3 mg/kg) and orally (1 mg/kg) to male Wistar rats as a solution. At predetermined time points, plasma was collected from rats and analyzed for zaltoprofen by HPLC. Data were analyzed using noncompartmental analysis model. Zaltoprofen was well tolerated during the course of study. After intravenous dosing, the plasma concentration of zaltoprofen declined monoexponentially with a terminal half-life of 2.82 h and was absorbed rapidly after oral dosing with 84% bioavailability.

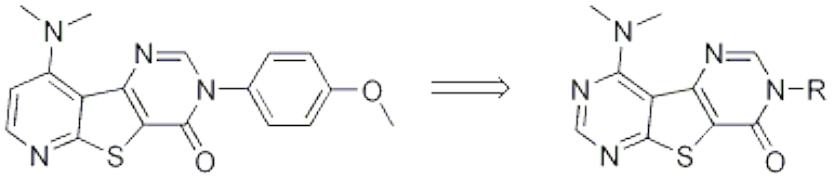
MEDI 134

Discovery of orally active mGluR1 receptor antagonists for the treatment of chronic pain

***Stephanie Cooke**[1], Peter Korakas[1], Lisa S. Silverman[1], Julius Matasi[1], Deen Tulshian[2], Duane Burnett[1], William J Greenlee[2], A. Reggiani[3], A. Veltri[3], R. Bertorelli[3], P Downey[3], S. Fredduzzi[3], M. Grilli[3], E. Nicolussi[3], G. Lozza[3], G Forlani[3], R Petrò[3], V Liporati[3], G. Tarozzo[3], S Contib[3], and C. Foglia[3]. (1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, MS 2545, Kenilworth, NJ 07033, stephanie.cooke@spcorp.com, (2) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Department of Neurobiological Research, Schering-Plough Research Institute, Milan, Italy*

The screening of Schering-Plough file compounds identified the pyriodothienopyrimidinone 1 as having a high affinity (IC_{50}= 9.5 nM) for the metabotropic glutamate receptor 1 (mGluR1). Glutamate is the principal excitatory neurotransmitter in mammalian brains. Two subtypes of these receptors are known, and they are ionotropic and metabotropic. Metabotropic receptors are responsible for the binding of glutamate which causes an intracellular biochemical cascade mediated via an integral seven-transmembrane spanning the domain linked to a G-protein (GPCR region). There are eight metabtropic glutamate receptors linked into three groups (I, II, III). mGluR1 is included in group I with mGluR5. mGluR1 is located in the CNS region and is involved in pain perception. The mGluR1 receptor knock out mice have been shown to have

lower pain sensitivity. Optimization of lead compound 1 led to discovery of several orally active potent mGluR1 antagonists with very good selectivity. The SAR of this effort will be presented.



1

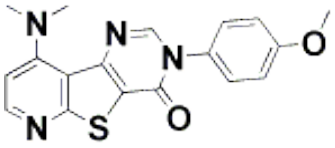
hmGluR1 IC_{50} = 9.5 nM
hmGluR2 & hmGluR5 IC_{50} = inactive at 10μM
RR AUC @ 10 mpk 679 ngh/mL

MEDI 135

The SAR and discovery of tricyclic mGluR1 antagonists for the treatment of chronic pain

Julius Matasi[1], *Stephanie Cooke*[1], *Peter Korakas*[1], *Lisa S. Silverman*[1], *Deen Tulshian*[2], *Duane A. Burnett*[1], *William J Greenlee*[2], *A. Reggiani*[3], *A. Veltri*[3], *R. Bertorelli*[3], *P Downey*[3], *S. Fredduzzi*[3], *M. Grilli*[3], *E. Nicolussi*[3], *G. Lozza*[3], *A Forlani*[3], *R Petrò*[3], *V Liporati*[3], *G. Tarozzo*[3], *S. Conti*[3], *and C. Foglia*[3]. *(1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, MS 2545, Kenilworth, NJ 07033, Fax: 908-740-7152, julius.matasi@spcorp.com, (2) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Department of Neurobiological Research, Schering-Plough Research Institute, Milan, Italy*

Metabotropic glutamate receptors (mGluRs) belong to G-protein coupled super-family receptors and are clustered into three groups (I, II and III) based on their sequence homology. Group I member, mGluR1, play a key role in central sensitization of pain. The high throughput screening of Schering-Plough file compounds identified compound 1 as a high affinity mGluR1 antagonist. A program was initiated to develop SAR using this lead. During the course of this study, several highly potent and selective mGluR1 antagonists were identified. Many of these compounds exhibited oral activity in rat SNL (spinal nerve ligation) model. Synthesis and SAR of these compounds will be presented.



1

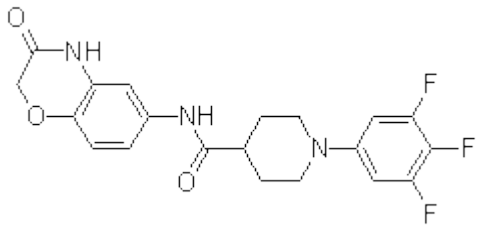
hmGLUR1 IC_{50} = 9.5 nM
hmGLUR2 & 5 = inactive

MEDI 136

Discovery of piperidine carboxamide TRPV1 antagonists

***Raul R. Calvo**, Wing S Cheung, Sui Po Zhang, Tasha Hutchinson, and Mark R. Player, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development LLC, 665 Stockton Drive, Exton, PA 19341, rcalvo1@prdus.jnj.com*

A series of piperidine carboxamides were developed as potent antagonists of the transient receptor potential receptor vanilloid 1 (TRPV1), an emerging target for the treatment of pain. A focused library of polar head groups led to the identification of a benzoxazinone amide that afforded good potency in cell-based assays. Synthesis and structure-activity relationships will be described.



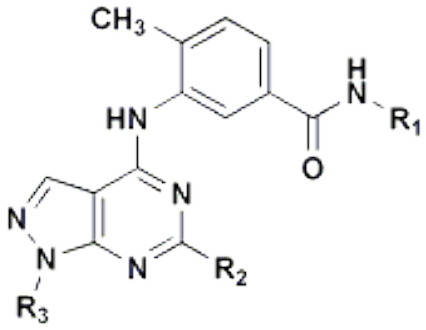
MEDI 137

Pyrazolo-pyrimidines as selective and potent p38 inhibitors

***Robert V. Moquin**[1], Jagabandhu Das[1], Gary Schieven[2], Sidney Pitt[3], Rosemary Zhang[3], Ding Ren Shen[3], Kim W McIntyre[3], Kathleen M Gillooly[3], Jack Sack[4], Arthur Doweyko[5], Hongjian Zhang[6], Susan E. Kiefer[4], Kevin Kish[7], Joel Barrish[8], John H. Dodd[9], and Katerina Leftheris[9]. (1) Lawrenceville Discovery Chemistry, Bristol-Myers Squibb PRI, Provinceline Rd and Route 206, P.O. Box 4000, Princeton, NJ 08543-4000, robert.moquin@bms.com, (2) Discovery Biology, Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ 08543-4000, (3) Department of Immunology, Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ 08543-4000, (4) Macro-Molecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, (5) CADD, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (6) Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, (7) Computer Aided Drug Design, Department of Macromolecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, (8) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, (9) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ 08543-4000*

p38 kinase is a key enzyme involved in regulating the production and action of pro-inflammatory cytokines such as tumor necrosis factor (TNF). Inhibitors of p38 kinase therefore may have utility in the treatment of multiple inflammatory diseases such as rheumatoid arthritis (RA). We have recently discovered a novel series of pyrazolo-pyrimidines as highly potent, and selective p38 inhibitors. The lead compound from this series possesses activity in an in vivo

preclinical model of acute inflammation. Synthesis, SAR studies and an X-ray co-crystal structure of a prototypical analog bound to the enzyme will be presented.

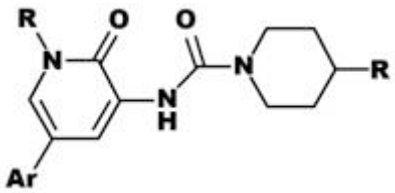


MEDI 138

Calcitonin gene-related peptide (CGRP) receptor antagonists: Development of the pyridinone series

Diem N. Nguyen[1]*, Anthony W. Shaw*[1]*, Daniel V. Paone*[1]*, Christopher S. Burgey*[1]*, Samuel L. Graham*[1]*, Scott D. Mosser*[2]*, Christopher A Salvatore*[2]*, Yvonne M Leonard*[3]*, Cynthia Miller-Stein*[4]*, Stefanie A. Kane*[2]*, Kenneth S. Koblan*[2]*, Theresa M. Williams*[1]*, and Joseph P Vacca*[1]*. (1) Department of Medicinal Chemistry, Merck Research Laboratories, Sumneytown Pike, West Point, PA 19486, diem_nguyen@merck.com, (2) Pain Research, Merck & Co. Inc, PO Box 4 West Point, PA 19486-0004, (3) Merck Research Laboratory, (4) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

It has been hypothesized that activation of trigeminal sensory nerves and calcitonin gene-related peptide (CGRP) release play a central role in the pathophysiology of migraine. Furthermore, it has been shown that the iv-administered CGRP antagonist BIBN4096BS (olcegepant) gave similar clinical efficacy to triptans for the acute treatment of migraine. In our effort to find potent, orally bioavailable CGRP receptor antagonists for the treatment of migraine, a novel series based on a pyridinone template was investigated. After optimizing the privileged structure and the placement of the attached phenyl ring, systematic SAR was carried out on both the *N*-alkyl and C-5 aryl substituents. Several analogs with good potency and promising pharmacokinetic profiles were identified.



MEDI 139

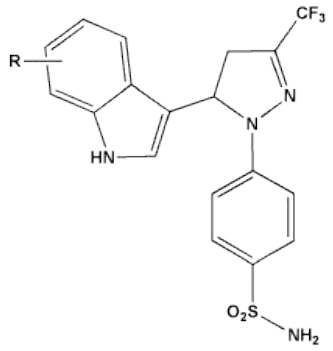
Synthesis and biological evaluation of novel 5-(3-indolyl)-1-(4-sulfamylphenyl)-3-trifluoromethyl pyrazolines as dual inhibitors of COX/LOXs

*Vinaykumar Billa[1], **Venkat R Pallela**[1], Rengasamy Boominathan[1], Muralidhar R Mallireddigari[1], Balaiah Akula[1], Revathi Patti[2], Stanley C Bell[2], E. Premkumar Reddy[1], and MV. Ramana Reddy[1]. (1) Fels Institute for Cancer Research, Temple University School of Medicine, 3307 North Broad Street, Philadelphia, PA 19140-5101, vbilla@temple.edu, pallela@temple.edu, (2) Department of Medicinal Chemistry, Onconova Therapeutics Inc, Lawrenceville, NJ 08648*

Cyclooxygenases (COXs) are key enzymes in the synthesis of prostaglandin H2, a precursor for the biosynthesis of prostaglandins, thromboxanes and prostacyclins. Since COX-2 is involved in inflammation and pain, molecules that inhibit its enzymatic activity would be of therapeutic value. Many non-steroidal anti-inflammatory drugs (NSAIDs) were found to interact with these enzymes and inhibit their enzymatic activity non-specifically. Several new inhibitors developed recently, celecoxib, rofecoxib and valdecoxib, selectively inhibit COX-2 enzyme without interfering with COX-1 enzymatic activity.

Lipoxygenases (Lox's) belong to a class of non-heme iron-containing enzymes which catalyzes hydroperoxidation reaction of fatty acids to peroxides. LOX‘s have been shown to involve in the production of leucotrienes which are known to contribute to the progression of osteoarthritis, asthma and inflammation. Lipoxygenases has also been implicated in the oxidation low-density lipoprotein (LDL), which ultimately causes atherosclerosis. It clearly shows that a dual inhibitor of the COX/LOX enzymatic pathways offers a better alternate approach in designing a new drug with excellent safety profile and least side effects.

Herein we report the synthesis of a series of novel 5-(3-indolyl)-1-(4-sulfamylphenyl)-3-trifluoromethyl pyrazolines and their activity against cyclooxygenases and lipoxygenases. We will discuss the activities of the single enantiomers resolved from the racemate mixture, aromatization of the pyrazoline ring to pyrazole and finally the molecular modeling studies.

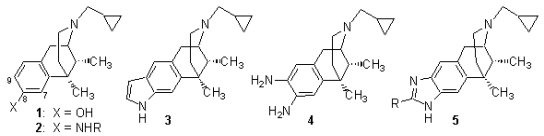


MEDI 140

Syntheses and opioid receptor binding affinities of conformationally restricted analogs of Cyclazocine

Rakesh R Ganorkar[1]*, Qun Lu*[1]*, Mark P. Wentland*[1]*, and Jean M. Bidlack*[2]*. (1) Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Cogswell Lab, 110 8th Street, Troy, NY 12180, Fax: 518-276-4887, ganorr@rpi.edu, (2) Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, NY 14642*

As a part of our goal to identify orally-active analogues of cyclazocine (1) having potent kappa agonist and mu antagonist binding properties, we previously reported that when its prototypic 8-OH substituent was replaced by secondary amino groups (2), high affinities towards opioid receptors was observed. Also, the conformationally restricted analogue, 3, an 8,9-fused indole derivative showed good binding affinity. In order to further probe into the SAR with regard to these conformationally restricted derivatives, herein we report the synthesis of novel cyclazocine analogues bearing an 8,9- fused imidazole ring (5). The 9-position of cyclazocine was functionalized by its nitration. Triflate formation, followed by addition-elimination (with benzylamine) and catalytic reduction afforded 8,9- diamino cyclazocine- derived intermediate, 4. Various differentially substituted 5-membered rings were constructed from this diamino intermediate. These novel analogues were then assessed for their affinities towards opioid receptors.



MEDI 141

Design, synthesis of a new chiral sigma-1 receptor ligand and validation as a potential anticocaine agent

Marion Toussaint[1]*, Brice Delair*[2]*, Catherine Foulon*[3]*, Alexandre Lebeau*[1]*, Nadège Lempereur*[2]*, Claude Vaccher*[3]*, Tangui Maurice*[2]*, and* ***Patricia Melnyk***[1]*. (1) Team 3, UMR8161 CNRS, Lille1 University, Lille2 University, Pasteur Institute of Lille, 1, Rue du Pr Calmette, BP447, 59021*

Lille, France, Fax: 33 3 20 87 12 33, marion.toussaint@ibl.fr, patricia.melnyk@ibl.fr, (2) INSERM U 710, EPHE, Montpellier II University, 34095 Montpellier, France, (3) EA4034, Pharmacy Faculty, Lille2 University, 59006 Lille, France

Substituted hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications. Our strategy was to design a new series of more constrained derivatives. Indeed, the privileged structure tetrahydroisoquinoleine Tic was selected as a pharmacophoric moiety and mixed compounds showed nanomolar affinity for σ1 receptor. Activation of this receptor has been shown to be involved in the psychostimulant and appetitive effects of cocaine. As previous results of our lab showed the importance of the stereochemistry of the Tic core and amino side chain, enantiomerically pure compound 1 was designed and synthesized. The effects of 1 were tested on: (i) the cocaine-induced lomocotor stimulation and sensitization; and (ii) acquisition and reactivation of cocaine-induced conditioned place preference (CPP), in mice. The compound presents a typical σ1 receptor agonist profile, facilitating cocaine-induced behavioral effects and generalizing with the drug-induced state. It may be developed as a potent new agonist therapy.

MEDI 142

Tricyclic mluR1 antagonists for the treatment of chronic pain

Chad Knutson[1]*, Chad Bennett*[1]*, Peter Korakas*[1]*, Duane A. Burnett*[1]*, Deen Tulshian*[2]*, William J Greenlee*[2]*, A. Reggiani*[3]*, Rosalia Bertorreli*[3]*, M. Grilli*[3]*, C. Foglia*[3]*, S. Fredduzzi*[3]*, G. Lozza*[3]*, and G. Tarozzo*[3]*. (1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, MS 2800, Kenilworth, NJ 07033, chad.knutson@spcorp.com, (2) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Department of Neurobiological Research, Schering-Plough Research Institute, Milan, Italy*

Abstract: Pain is among the most common reason patients seek medical care. Chronic pain, particularly that caused by nerve injury or disease related neuropathy is currently a poorly treated condition. This is largely due to the fact that pain signaling mechanisms are not fully understood. The glutamate system, regulated by glutamic acid, the most abundant neurotransmitter found in the brain, has been implicated as an important player in pain signaling. Specifically, mGluR1 knockout mice exhibit reduced sensitivity to a variety of painful stimuli including that due to nerve injury, suggesting an mGLuR1 antagonist may be useful in treating pain. To this end we examined a series of tricyclic noncompetitive mGluR1 receptor antagonists. The tricyclic pyridine and pyridizinone antagonists were potent at mGLuR1 and selective over the other members of the mGluR family. The in vitro and in vivo SAR for the series will be presented.

MEDI 143

Novel biaryl pyrazinone amides as hNav1.7 blockers for the treatment of neuropathic pain

***Feng Ye**, Medicinal Chemistry Department, Merck Research Labs, 126 E Scott Ave., Rahway, NJ 07065, and Pengcheng Shao, Department of Medicinal Chemistry, Merck Research Labs, Rahway, NJ 07023*

Sodium channels are a family of nine proteins that control the flow of sodium ions across cell membranes and are involved in all levels of nerve conduction and propagation, and in the determination of neuronal excitability. It has been long hypothesized that a sodium channel blocker could be effective in treatment of neuropathic pain. More recently, human genetic studies have strongly implicated that hNav1.7 plays a key role in pain signaling.

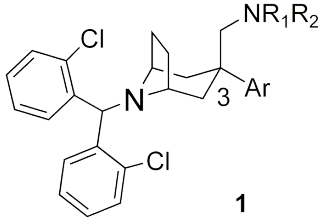
In order to search for novel sodium channel blockers, a series of biaryl pyrazinone amide compounds were synthesized and evaluated for Nav1.7 blocking activity. SAR showed that various substitutions were tolerated at N-1 position. This allowed us to finely tune the molecule for optimal physical and biological properties. 1,2-Propanediol was identified as one of the substitutions gave improved in vivo efficacy and reduced off target activities.

MEDI 144

Synthesis and structure-activity relationships of 3-substituted 8-benzhydryl-nortropane analogs as nociceptin receptor ligands

***Shu-Wei Yang**[1], Deen Tulshian[1], Ginny D Ho[1], William J Greenlee[1], Stephen Eckel[2], and John Anthes[2]. (1) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, 2015 Galloping Hill Rd., Kenilworth, NJ 07033, Fax: 908-740-7164, shu-wei.yang@spcorp.com, (2) Allergy and Immunology, Schering-Plough Research Institute*

Nociceptin receptor (NOP, ORL-1), an orphan opioid receptor found in 1994, has high sequence homology to the opioid receptor family (μ, κ, and δ), however NOP does not bind classical endogenous opioid receptor ligands. Nociceptin, NOP endogenous ligand, has been reported to mediate various physiological processes, for instance, pain, cough, anxiety, and cognition. Selective NOP agonists might have clinical potential for the treatment of related diseases without the adverse effects associated with other opioid receptors. In our NOP program, we have synthesized potent NOP agonists based upon 8-benzhydryl-nortropane (8-[bis(phenyl)methyl]-8-azabicyclo[3.2.1]octane) scaffold. In this poster, we will present synthesis and structure activity relationships of a series of analogs represented by structure **1**.



Ar = Ph, Bn, Heterocycles

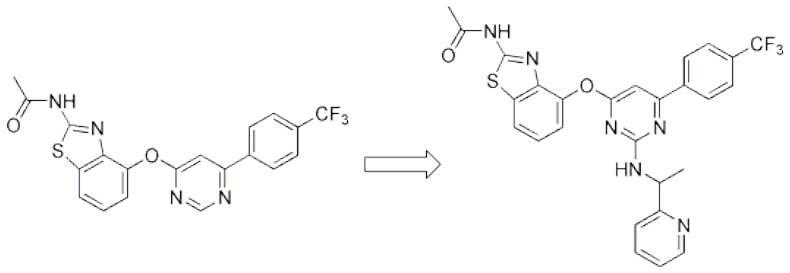
1

MEDI 145

Design of trisubstituted pyrimidines as vanilloid receptor 1 (TRPV1) antagonists with improved solubility

Xianghong Wang[1], *Partha Chakrabarti*[1], *Narender Gavva*[2], *Vassil I. Ognyanov*[1], *Liping H. Pettus*[1], *Rami Tamir*[2], *Helming Tan*[1], *Phi Tang*[1], *James JS. Treanor*[2], *and Mark H. Norman*[1]. *(1) Department of Chemistry Research and Discovery, Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, qwang@amgen.com, (2) Department of Neuroscience, Amgen Inc*

Vanilloid receptor-1 (TRPV1) is a non-selective ion channel that is activated by multiple noxious stimuli (capsaicin, protons, and heat) and contributes to the transmission of pain signals in nociceptors. Our first TRPV1 clinical candidate (1; AMG 517, Figure 1) had low solubility which presented challenges in its development. A series of trisubstituted pyrimidines were synthesized to improve aqueous solubility of compound 1, while maintaining potency against TRPV1. We describe herein the structure-activity and structure-solubility relationship studies that led to the identification of compound 2. The aqueous solubility of 2 (≥ 200 µg/mL, 0.01 HCl; 6.7 µg/mL, PBS; 145.5 µg/mL SIF) was significantly improved over 1. In addition, compound 2 was found to have TRPV1 antagonist activity (CAP IC50 = 1.5 nM) comparable to that of 1.



1
(AMG 517)

2

Figure 1

MEDI 146

Synthesis of carbon-11 labeled benzoxazole derivatives as new potential PET radioligands for imaging of 5-HT_3 receptor

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

Serotonin (5-hydroxytryptamine, 5-HT) type 3 (5-HT_3) receptor is an attractive target for the development of therapeutic agents for various diseases, since 5-HT_3 is associated with a variety of biological pathways in central and peripheral nervous systems, and selective 5-HT_3 receptor antagonists effectively prevent the nausea and vomiting that commonly occur during

cytotoxic cancer chemotherapy and/or radiation therapy. A series of benzoxazoles have been recently developed by Sato group as novel 5-HT_3 receptor partial agonists. To translate therapeutic agents for diagnostic use, we have designed and synthesized carbon-11 labeled benzoxazole derivatives as new potential radioligands for use in biomedical imaging technique positron emission tomography (PET) to map 5-HT_3 receptor. The target radioligands, 5-chloro-7-methyl-2-(4-[^{11}C]methyl-1-piperazinyl)benzoxazole, 5,7-dimethyl-2-(4-[^{11}C]methyl-1-piperazinyl)benzoxazole, 5-chloro-7-methyl-2-(4-[^{11}C]methyl-1-homopiperazinyl)benzoxazole and 5,7-dimethyl-2-(4-[^{11}C]methyl-1-homopiperazinyl)benzoxazole, were prepared by *N*-[^{11}C]methylation of their corresponding precursors, 5-chloro-7-methyl-2-(1-piperazinyl)benzoxazole, 5,7-dimethyl-2-(1-piperazinyl)benzoxazole, 5-chloro-7-methyl-2-(1-homopiperazinyl)benzoxazole and 5,7-dimethyl-2-(1-homopiperazinyl)benzoxazole, using [^{11}C]CH_3OTf and isolated by HPLC purification procedure in 30-45% radiochemical yields based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB), 20-25 min overall synthesis time from EOB, > 98% radiochemical purity, and 4.0-6.0 Ci/µmol specific activity at EOB.

MEDI 147

Synthesis of (S)-[18F]-fluoro-Exaprolol, via [18F]-1-fluoro-2-propanamine, for imaging cerebral beta-adrenergic receptors with PET

Karin A. Stephenson[1]*, Erik M. van Oosten*[2]*, Alan A. Wilson*[1]*, Andrei K. Yudin*[2]*, Jeffrey H. Meyer*[1]*, Sylvain Houle*[1]*, and Neil Vasdev*[1]*. (1) PET Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON M5T 1R8, Canada, karin.stephenson@camhpet.ca, (2) Department of Chemistry, University of Toronto, Toronto, ON M5S 3H6, Canada*

Cerebral ß-adrenergic receptors (ß-ARs) are of interest in several illnesses, in particular, major depressive disorder. Imaging cerebral ß-AR levels could be accomplished with positron emission tomography (PET), however, there is no radiotracer available to achieve this in humans. Herein, we report the synthesis of a novel fluorine-18 (^{18}F, half-life = 109.7 min) labelled analog of a known ß-AR antagonist, [^{18}F]-(S)-fluoro-Exaprolol. (S)-1-(2-cyclohexylphenoxy)-2,3-epoxypropane was prepared as the labelling precursor (60% yield) via the (S)-glycidyl nosylate. Radiolabelling was accomplished by reacting the (S)-epoxide with 1-[^{18}F]fluoro-2-propanamine. To generate 1-[^{18}F]fluoro-2-propanamine we applied a novel ring-opening reaction of benzyloxycarbonyl (CBz)-protected 2-methylaziridine with [^{18}F]potassium cryptand fluoride. The CBz-group was quantitatively removed by H_2/Pd-C in MeOH and the resulting amine was heated with the (S)-epoxide for 30 min in a sealed vessel. (S)-[^{18}F]-fluoro-Exaprolol was prepared with 12% conversion of radioactivity from the amine with an end of synthesis time of 2 hours. Ex vivo biodistribution studies in rodents will also be presented.

MEDI 148

Synthesis of carbon-11 labeled 7-aroyl-aminoindoline-1-sulfonamides as new potential PET agents for imaging cancer tubulin polymerization

***Min Wang**, Mingzhang Gao, and Qi-Huang Zheng, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-202, Indianapolis, IN 46202, Fax: 317-278-9711, wang1@iupui.edu*

The tubuline polymerization is an attractive target for anticancer therapy and in the development of cancer imaging agents for use in biomedical imaging technique positron emission tomography (PET). A novel series of 7-aroyl-aminoindoline-1-sulfonamides have been recently developed by Liou group as potent antitublin agents. We present here the synthesis of carbon-11 labeled 7-aroyl-aminoindoline-1-sulfonamides, *N*-[1-(4-[^{11}C]methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-acetamide, furan-2-carboxylic acid [1-(4-[^{11}C]methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-amide, 4-fluoro-*N*-[1-(4-[^{11}C]methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-benzamide and *N*-[1-(4-[^{11}C]methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-isonicotinamide as new potential PET radioligands for imaging cancer tubuline polymerization. The target tracers were prepared by *O*-[^{11}C]methylation of their corresponding precursors, *N*-[1-(4-hydroxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-acetamide, furan-2-carboxylic acid [1-(4-hydroxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-amide, 4-fluoro-*N*-[1-(4-hydroxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-benzamide and *N*-[1-(4-hydroxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-isonicotinamide, using [^{11}C]CH_3OTf and isolated by a simplified solid-phase extraction (SPE) purification procedure using either a Sep-Pak Plus C18 cartridge or a semi-prep C18 guard cartridge column in 40-55% radiochemical yields based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB), 15-20 min overall synthesis time from EOB, > 98% radiochemical purity, and 4.0-6.0 Ci/μmol specific activity at EOB.

MEDI 149

Synthesis of radiolabeled 2-oxoquinoline derivatives as new potential PET agents for imaging of CB2 receptor

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

G-protein-coupled receptors cannabinoid receptors, including subtypes CB1 and CB2, are associated with various diseases such as central nervous system (CNS), cardiovascular and cancer diseases. Recent attention has turned to CB2 receptors, since they are expressed on many immune cells like natural killer cells, T cells and B cells. CB2 receptor provides an attractive target for the development of therapeutic agents. 2-Oxoquinoline derivatives have been recently developed by Raitio group as novel CB2 receptor inverse agonists. To translate therapeutic agents for diagnostic use, we have designed and synthesized a carbon-11 labeled 2-oxoquinoline derivative as a new potential radioligand for use in biomedical imaging technique positron emission tomography (PET) to map CB2 receptor. The target compound 7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxylic acid [2-(4-[^{11}C]methoxyphenyl)ethyl]amide was prepared by *O*-[^{11}C]methylation of its corresponding precursor 7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxylic acid [2-(4-hydroxyphenyl)ethyl]amide using [^{11}C]CH_3OTf and isolated by solid-phase extraction (SPE) purification procedure in 40-50% radiochemical yields based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB), 15-20 min overall synthesis time from EOB, > 98%

radiochemical purity, and 4.0-6.0 Ci/μmol specific activity at EOB. 2-Oxoquinoline derivatives 7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxylic acid [2-(4-nitrophenyl)ethyl]amide and 7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxylic acid [2-(4-fluoroxyphenyl)ethyl]amide were also synthesized from isovanillin in multiple steps with moderate to excellent chemical yields. Both compounds could be used as nitro-precursor and fluoro-standard for fluorine-18 radiolabeling.

MEDI 150

Discovery and biological evaluation of novel 2-acetamido-indoles as potent and selective openers of Kv7/KCNQ potassium channels

Thomas E Christos[1], *Grant McNaughton-Smith*[1], *Robert N. Atkinson*[1], *Matthew E. Secrest*[1], *Aaron C. Gerlach*[2], *Scott D. Conary*[2], *Brett M. Antonio*[2], *Sally J. Stoehr*[2], *and Rosemarie Roeloffs*[3]. *(1) Department of Chemistry, Icagen, Inc, 4222 Emperor Blvd., Durham, NC 27703, Fax: 919-941-0813, tchristos@icagen.com, (2) Department of Biology, Icagen, Inc, Durham, NC 27703, (3) Department of Pharmacology, Icagen, Inc, Durham, NC 27703*

The molecular correlates of M-channels are Kv7.2 – Kv7.5, also known as KCNQ2 – KCNQ5 channels. They are expressed throughout the central and peripheral nervous system and opening of these channels reduces neuronal excitability. Thus, small molecule modulation of these channels may provide an effective strategy to treat conditions of excessive neuronal excitability such as epilepsy and neuropathic pain. Anti-epileptic proof of principle has been established in a recent Phase IIb clinical study using retigabine, a micromolar opener of M-channels, where retigabine produced a dose-dependent reduction in partial-onset seizures. However, retigabine can enhance GABAergic transmission and produces some CNS side effects. Thus, a need exists for more potent and selective Kv7.x channel openers to maximize therapeutic index. Herein, we describe the synthesis, selectivity and structure-activity relationships of a novel series of 2-acetamido-indoles (1) derived through screening of our proprietary compound library. In the SHSY5Y human neuroblastoma cell line, these compounds potently hyperpolarized the cell membrane potential through the opening of endogenously expressed M-channels. Select compounds were orally active in an animal model of epilepsy.

MEDI 151

Classifcation QSAR modeling of the imbalanced dataset of hERG K+ channel blockers and openers

Kun Wang[1], *Alexander Golbraikh*[2], *Bryan R. Roth*[3], *and Alexander Tropsha*[2]. *(1) Medicinal Chemistry, University of North Carolina at Chapel Hill, School of Pharmacy, CB# 7360, Beard Hall Rm 301, Chapel Hill, NC 27599, Fax: 919-966-0204, kunwang@email.unc.edu, (2) Laboratory for Molecular Modeling, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7360, (3) National Institute of Mental Health Psychoactive Drug Screening Program and Department of Biochemistry, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599*

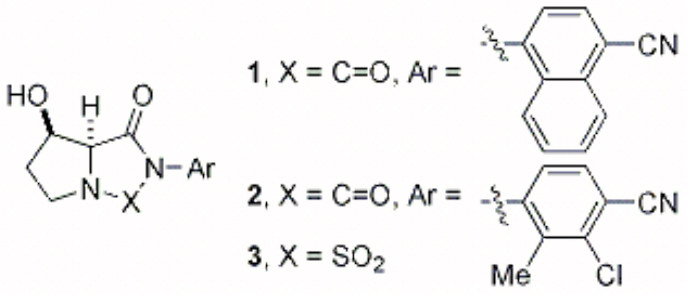
The hERG K+ channel has elicited intense scientific interest due to its association with arrhythmia and sudden death. Drug induced hERG K+ channel blockade can cause QT prolongation and fatal arrhythmia, which has raised big concern of pharmaceutical industry and regulatory agencies. For a diverse imbalanced dataset of 54 blockers and 193 openers we report the results of kNN QSAR, decision tree and random forest approaches. Model performance metrics such as prediction accuracy, false positive and false negative rate were computed. The results show the improved prediction accuracy for minority class—blockers as compared to published models for the same dataset.

MEDI 152

Synthesis and SAR of thiadiazolone dioxides as selective androgen receptor modulators

Mark Manfredi[1]*, Yingzhi Bi*[2]*, Alexandra Nirschl*[1]*, James Sutton*[1]*, Ramakrishna Seethala*[1]*, Rajasree Golla*[1]*, Blake Beehler*[1]*, Paul Sleph*[1]*, Gary Grover*[3]*, Jacek Ostrowski*[1]*, and Lawrence Hamann*[4]*. (1) Metabolic Diseases Drug Discovery, Bristol-Myers Squibb Company, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3450, mark.manfredi@bms.com, (2) Lexicon Pharmaceuticals Incorporated, Princeton, NJ 08543, (3) Department of Physiology and Biophysics, Robert Wood Johnson Medical School, Piscataway, NJ 08854-5635, (4) Virology Chemistry, Bristol-Myers Squibb Company, Wallingford, CT 06492*

Potent, selective androgen receptor modulators (SARMs) are of interest as potential treatments for sarcopenia (slow, progressive loss of muscle mass) - an ever increasing health risk facing the elderly. Previous efforts from our labs had identified compounds 1 and 2 to be highly potent and muscle selective agonists. Herein we report the effects of replacing the 3-oxo group of 2 with a sulfonyl group (e.g. 3) . These tetrahydropyrrlo[1,2-b][1,2,5]thiadiazol-2(3H)-one 1,1-dioxide analogues were found to be potent SARMs. Binding affinity for the most active analogue 3 was ~5 times greater than that of 2; however, functional activity was ~5 fold lower. Synthesis, binding and functional assay SAR, as well as in vivo characterization of selected analogs in a standard rodent model will be presented.



MEDI 153

Design of potent and selective LXR agonists from a series of indazole aniline core compounds

Stephen Marc Bowen[1], *Robert J. Steffan*[1], *Edward Matelan*[2], *Raymond Unwalla*[1], *Ponnal Nambi*[3], *Elaine Quinet*[3], *Anita Halpern*[3], *Dawn Savio*[3], *Anna Wilhelmsson*[4], *Annika Goos Nilsson*[4], *Crina Ursu*[4], *Erik Arnelof*[4], *Johnny Sandberg*[4], *Christopher Enroth*[4], *Tomas Bonn*[4], *Mathias Farnegardh*[4], *and Jay Wrobel*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, bowens@wyeth.com, (2) Chemical & Screening Sciences, Wyeth Research, Collegeville, PA 19426, (3) Department of Cardiovascular and Metabolic Diseases, Wyeth Research, Collegeville, PA 19426, (4) Karo Bio AB, Huddinge, Sweden*

The leading cause of death in developed countries is atherosclerosis, a condition in which plaque forms on the arterial walls. This plaque formation occurs when macrophages take up cholesterol esters resulting in the formation of foam cells. Recently the LXR signaling pathway has been targeted for the potential treatment of atherosclerosis. LXR is a nuclear receptor transcription factor with two isoforms of the LXRa and LXRb. Oxy sterols are natural ligands for LXR. Binding of these ligands causes formation of a heterodimer with RXR. Transcription is initiated by the heterodimer, which results in up regulation of the LXR target genes ABCA1 (ATP binding cassette transporter A1) and SREBP1-c (sterol regulatory element binding protein 1-c). Reverse cholesterol transport (RCT), an efflux of cholesterol from macrophages in plaque, is controlled by ABCA1. This results in reduction in lesion development and plaque formation. SREBP1-c upregulation in liver causes lipogenesis, which leads to an increase in the levels of triglycerides (TG), an undesired effect. SAR for a series of indazole anilines will be presented. These compounds were prepared to exploit additional binding contacts in the ligand binding domain (LBD) of LXR, specifically with Arg 319, Ser 238, and Leu 330. These indole anilines all showed good affinity for hLXR and had no cross-reactivity with the PPAR's.

MEDI 154

Quinoline biarylethers as high affinity, potent LXR agonists

Ronald C. Bernotas[1], *Robert R. Singhaus Jr.*[1], *David Kaufman*[1], *John W. Ullrich*[1], *Robert L. Morris*[1], *Horace Fletcher III*[1], *Li Di*[2], *Ray J Unwalla*[1], *Ponnal Nambi*[3], *Elaine Quinet*[3], *Dawn Savio*[3], *Anita Halpern*[3], *Irene B. Feingold*[4], *Anna Wihelmsson*[5], *Annika Goos Nilsson*[5], *Crina Ursu*[5], *Erik Arnelof*[5], *Johnny Sandberg*[5], *Christopher Enroth*[5], *and Jay Wrobel*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, bernotr@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ 08543, (3) Department of Cardiovascular and Metabolic Diseases, Wyeth Research, Collegeville, PA 19426, (4) Department of Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (5) Karo Bio AB, Huddinge, Sweden*

Liver X receptors (LXRs) are nuclear receptors that control cholesterol-lipid metabolism. Upon dimerization with retinoid X receptors (RXRs), activation of either receptor increases the expression of proteins involved in cholesterol efflux from cells, notably ABCA1 and ABCG1. The endogenous ligands for LXRs are oxysterols. LXR agonists may have the potential to

lower cholesterol levels without increasing triglycerides. As part of a program focused on LXR agonists, we have identified a series of 4-(biarylether)-quinolines with excellent LXR affinity and functional activity. The synthesis, biological activity, and SAR of these quinolines will be described.

MEDI 155

Quinoline biarylether amides as liver X receptor modulators

David Kaufman[1], *Ronald C. Bernotas*[1], *Robert R. Singhaus Jr.*[1], *Michael Collini*[1], *John W. Ullrich*[1], *Ray J Unwalla*[1], *Li Di*[2], *Ponnal Nambi*[3], *Elaine Quinet*[3], *Anita Halpern*[3], *Dawn Savio*[3], *Irene Feingold*[4], *Anna Wihelmsson*[5], *Annika Goos Nilsson*[5], *Crina Ursu*[5], *Erik Arnelof*[5], *Johnny Sandberg*[5], *Christopher Enroth*[5], *and Jay Wrobel*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ 08543, (3) Department of Cardiovascular and Metabolic Diseases, Wyeth Research, Collegeville, PA 19426, (4) Department of Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (5) Karo Bio AB, Huddinge, Sweden*

The liver X receptor is an oxysterol-activated nuclear receptor which helps regulate the transcription of genes involved in the coordinate regulation of cholesterol and lipid metabolism. The LXR nuclear receptor family is comprised of two isoforms, LXRα and LXRβ, which are encoded by independent genes. LXRβ is involved in the upregulation of the ABCA1 and ABCG1 genes. This helps regulate cholesterol accumulation in the body both by stimulating reverse cholesterol transport in macrophages and by inhibiting intestinal cholesterol absorption. Our goal is to identify LXR agonists that increase cholesterol efflux without increasing triglycerides levels, with the ultimate target of reducing atherosclerotic lesions. The design, synthesis and LXR activity of quinoline biarylether amides will be presented.

MEDI 156

Discovery and structure-activity relationship studies of indole derivatives as Liver X receptor (LXR) agonists

Madhavi Pannala[1], *Farid Bakir*[1], *Sunil Kher*[1], *Norma Wilson*[1], *Trang Nguyen*[1], *Ila Sircar*[1], *Kei Takedomi*[1], *Chiaki Fukushima*[1], *James Zapf*[1], *Kui Xu*[2], *Shao-Hui Zhang*[2], *Juping Liu*[2], *Morera Lisa*[2], *Lisa Schneider*[2], *Naoki Sakurai*[2], *Rick Jack*[2], *and Jie-Fei Cheng*[1]. *(1) Department of Chemistry, Tanabe Reseach Laboratories, 4540, Towne Centre Court, San Diego, CA 92121, Fax: 858-558-0650, mpannala@trlusa.com, (2) Department of Biology, Tanabe Reseach Laboratories, San Diego, CA 92121*

Liver X receptors (LXR alpha and LXR beta) belong to the type 2 family of the nuclear hormone receptor superfamily that function as transcription factors. LXRs function as heterodimers with the retinoid X receptors (RXR) and regulate the expression of a number of genes involved in cholesterol and fatty acid metabolism.Upon agonist binding, the DNA binding domain (DBD) of LXR interacts with LXR response elements on target genes to initiate transcription. One LXR target gene is the ATP-binding cassette transporter ABCA1, which is

involved in reverse cholesterol transport (RCT) from macrophages in the atherosclerotic plaques to high-density lipoproteins (HDL) in the plasma. As such, increasing RCT by LXR agonism is a potential therapeutic approach for a number of pathophysiological states including dyslipidemia, atherosclerosis, and diabetes. As a part of our research program aimed at disocvery of potent LXR agonists, We have identified novel liver X receptor (LXR) agonists. Structure-activity relationship studies on these indole based LXR agonists will be presented.

MEDI 157

Synthesis, hypolipidemic activity and computational studies of phenoxyacetic acid derivatives related to α-asarone and clofibrate

*Nancy Argüelles[1], **José Luis Medina-Franco**[2], Aaron Mendieta[3], Fabiola Jiménez[1], Leticia Garduño[4], Maria del Carmen Cruz[3], Germán Chamorro[4], and Joaquín Tamariz[1]. (1) Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, IPN, Prol. Carpio y Plan de Ayala, Ciudad de México 11340, Mexico, (2) Bio5 Institute, University of Arizona, 1657 E. Helen Street, Tucson, AZ 85719, medina@pharmacy.arizona.edu, (3) Centro de Investigación en Biotecnología Aplicada, IPN, Tlaxcala 90700, Mexico, (4) Laboratorio de Toxicología, Escuela Nacional de Ciencias Biológicas, IPN, Ciudad de México 11340, Mexico*

In a continued effort to develop potent hypolipidemic agents, several phenoxyacetic acid derivatives related to α-asarone and clofibrate have been designed in our group.[1-3] The significant amount of structure-activity relationship data has lead to several compounds with high activity. Furthermore, molecular docking studies of α-asarone with 3-hydroxy-3-methylglutaryl-coenzyme A reductase [4] suggest structural modifications that could enhance its binding affinity with this enzyme. In this work, the design, synthesis and in vivo hypolipidemic profile of novel phenoxyacetic acid derivatives is presented. Docking-based models that help to explain the high activity of synthesized compounds at the molecular level are also discussed. [1] Labarrios, F, et al. J. Pharm. Pharmacol. 1999, 51, 1. [2] Cruz, M. C. et al. Drug Dev. Res. 2003, 60, 186. [3] Zúñiga, C. et al. Drug Dev. Res. 2005, 64, 28. [4] Medina-Franco, J. L. et al. Bioorg. Med. Chem. Lett. 2005, 15, 989.

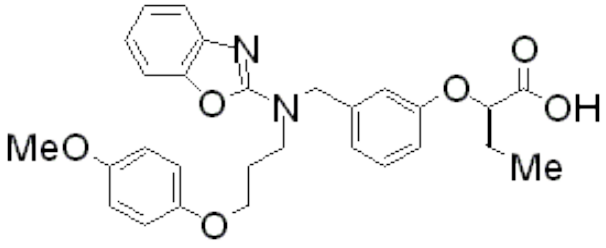
MEDI 158

Identification of highly potent and subtype-selective PPARalpha agonists: Synthesis, SAR and in vivo efficacy

***Yukiyoshi Yamazaki**[1], Kazutoyo Abe[1], Tsutomu Tohma[1], Masahiro Nishikawa[1], Hidefumi Ozawa[1], Ayumu Okuda[1], Takaaki Araki[1], Soichi Oda[1], Keisuke Inoue[1], Kimiyuki Shibuya[1], Bart Staels[2], and Jean-Charles Fruchart[2]. (1) TOKYO NEW DRUG RESEARCH LABOLATORIES 1, KOWA CO. LTD, 2-17-43, NOGUCHICHO, 189-0022 Higashimurayama, Japan, Fax: +81-(0)42-395-0312, y-yamazk@kowa.co.jp, (2) Department d'Atherosclerose, Institut Pasteur de Lille, 59019 Lille, France*

The fibrates have been widely used for the clinical treatment of dyslipidemia by lowering serum triglycerides and raising HDL cholesterol. However, fibrates only show weak human PPARalpha agonistic activity and low subtype selectivity in cell-based assays. Since we have

postulated that more potent and subtype-selective PPARalpha agonists would be expected to provide a superior therapeutic effect in patients with dyslipidemia than currently available fibrates. Here we report a novel PPARalpha agonist composed of a well-combination of benzoxazole, phenoxyalkyl side-chain, and phenoxybutyric acids moieties exhibits a high potency (EC50 = 1 nM) and subtype-selectivity (>1000-fold) for human PPARalpha transactivation assays. The synthesis, structure-activity relationships and in vivo studies of a novel series of phenoxybutyric acids-based PPARalpha agonists will be presented.

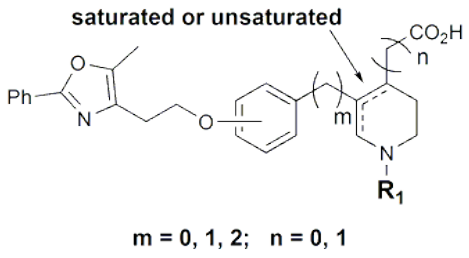


MEDI 159

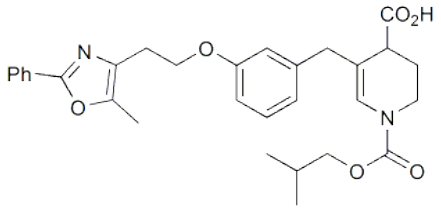
Design, synthesis and structure-activity relationships of piperidine and dehydropiperidine carboxylic acids as novel, potent PPARalpha/gamma dual activators

Xiang-Yang Ye[1]*, Yi-Xin Li*[2]*, Shung Wu*[1]*, Arthur Doweyko*[3]*, Dennis Farrelly*[4]*, Neil Flynn*[4]*, Liqun Gu*[4]*, Kenneth T. Locke*[5]*, Jonathan Lippy*[5]*, Kevin O'Malley*[5]*, Celeste Twamley*[5]*, Litao Zhang*[5]*, Denis E. Ryono*[1]*, Narayanan Hariharan*[4]*, Robert Zahler*[1]*, and Peter T. W. Cheng*[1]*. (1) Metabolic Diseases Chemistry, Bristol-Myers Squibb Co, P.O. BOX 5400, Princeton, NJ 08543-5400, Fax: 609-818-3460, xiang-yang.ye@bms.com, (2) Discovery Analytical Sciences, Bristol-Myers Squibb Co, Princeton, NJ 08543-5400, (3) CADD, Bristol-Myers Squibb Co, Princeton, NJ 08543-4000, (4) Metabolic Diseases Biology, Bristol-Myers Squibb Co, Princeton, NJ 08543-5400, (5) Lead Evaluation, Bristol-Myers Squibb Co, Princeton, NJ 08543-5400*

Modulation of PPARα and PPARγ activities represents an attractive approach for the treatment of diabetes and its associated cardiovascular complications. Several series of substituted dehydropiperidine and piperidine-4-carboxylic acid analogs (Structure A) were designed and synthesized as novel, potent PPARα/γ dual activators. The SAR of these series of analogs is discussed. An unusual migration of the carbon-carbon double bond occurred during the basic hydrolysis of the α,β-unsaturated dehydropiperidine esters, and the structures of the migration products (e.g. B) were determined through a series of 2D NMR experiments.



A



B

MEDI 160

Discovery and structure-activity relationships of BMS-711939, a potent and highly selective PPARalpha activator

Yan Shi[1], *Jun Li*[2], *Lawrence J. Kennedy*[2], *Hiwei Tao*[3], *Xiang-Yang Ye*[3], *Stephanine Chen*[3], *Hao Zhang*[4], *Andres Hernandez*[3], *Sean Chen*[3], *Zhi Lai*[3], *Wei Wang*[3], *Pratik Devasthale*[3], *Rebecca Smirk*[5], *Shung Wu*[6], *Scott A. Bolton*[3], *Denis Ryono*[3], *Ying Wang*[3], *Kenneth T Locke*[7], *Kevin M. O'Malley*[7], *Litao Zhang*[8], *Raiajit Srivastava*[3], *Bowman Miao*[3], *Daniel Meyers*[3], *Hossain Monshizadegan*[3], *Debra Search*[3], *Denise Grimm*[3], *Rongan Zhang*[3], *Thomas Harrity*[9], *Lori Kunselman*[9], *Henry Wong*[3], *Juliang Zhu*[3], *Ashok Trehan*[3], *Ngiap-Kie Lim*[3], *Huiping Zhang*[3], *Bang-Chi Chen*[3], *Michael Cap*[9], *Jodi Muckelbauer*[3], *Chiehying Chang*[10], *Stanley Krystek*[10], *Yi-Xin Li*[3], *Vinayak Hosagrahara*[11], *Lisa Zhang*[11], *Pathanjali Kadiyala*[3], *Carrie Xu*[3], *Michael Blanar*[3], *Robert Zahler*[12], *Ranjan Mukherjee*[3], *Peter T. Cheng*[3], *and Joseph A. Tino*[3]. *(1) Bristol-Myers Squibb, P. O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3450, yan.shi@bms.com, (2) Discovery Chemistry, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (3) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (4) Hopewell Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (5) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton NJ 08543-540, (6) Metabolic Disease Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (7) Lead Evaluation, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (8) Lead Evaluation, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (9) Metabolic Diseases Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (10) Bristol-Myers Squibb Pharmaceutical Research Institute, NJ, (11) PCO, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (12) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton*

Elevated circulating levels of triglycerides (TG) and low circulating levels of high-density lipoprotein cholesterol (HDLc) are independent risk factors for coronary artery disease (CAD). The peroxisome proliferators activated receptors PPAR&alpha, PPAR&gamma, and PPAR&delta are ligand-activated transcription factors that play a key role in lipid homeostasis. The fibrate class of PPAR&alpha activators (e.g. gemfibrozil and fenofibrate) raise HDLc and lower TGs; however, their efficacy may be limited by their low potency at PPAR&alpha. More potent and selective PPAR&alpha activators may offer enhanced efficacy and an improved side effect profile. Herein, we present a series of potent and highly selective PPAR&alpha activators derived from the oxybenzylglycine PPAR&alpha/&gamma dual activator muraglitazar. Multiple structural changes from muraglitazar, including: 1) regioisomeric switch from the 1,4-oxybenzyl glycine to a 1,3-oxybenzyl glycine, 2) replacement of the aryl carbamate by alkyl carbamates and 3) additional substituents on the central phenyl core were found to affect PPAR&alpha/&gamma selectivity dramatically. Details of the SAR studies of this series resulted in the discovery of a potent and highly selective (> 1000-fold) PPAR&alpha activator BMS-711939. The in vitro and in vivo profile of BMS-711939 will be presented.

MEDI 161

Novel zwitterionic phenoxyacetic acid derivatives as potent PPAR agonist

Mitsuhiro Yamaguchi*, Yoshihiro Shibata, Masahiro Ohta, Katsuji Kagechika, Hiroyuki Usui, and Toshiharu Ohta, Medicinal Chemistry Research Laboratories I, Daiichi Sankyo Co.,LTD, 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan, Fax: 81-3-5436-8578, yamag20l@daiichipharm.co.jp*

Peroxisome poliferator-activated receptors (PPAR) are ligand-activated transcription factors and have been of interest as important pharmaceutical targets. Thiazolidindiones, PPAR gamma agonists, are efficacious as insulin sensitizing agent in the treatment of type 2 diabetes. But these agents cause undesirable side effects including weight gain. On the other hand, PPAR alpha agonists are known to decrease serum triglyceride level, increase HDL cholesterol level and reduce weight gain. Therefore adding PPAR alpha activity to PPAR gamma agonists may be superior for treating type 2 diabetes and metabolic syndrome. We found a series of zwitterionic phenoxyacetic acid derivatives that have potent activity on both PPAR alpha and gamma subtypes. They showed significant serum glucose and lipid lowering effects in db/db mice without weight gain.

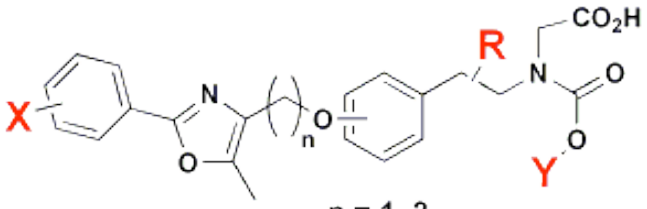
MEDI 162

Structure activity relationship studies of phenethylglycine PPARa/g dual activators for the treatment of metabolic diseases

Shung Wu[1]*, Rebecca Smirk*[2]*, Hao Zhang*[3]*, Sean Chen*[4]*, Dennis Farrelly*[5]*, Liqun Gu*[5]*, Andrew Peters*[5]*, Thomas Harrity*[5]*, Michael Cap*[5]*, C Chu*[5]*, Lori Kunselman*[5]*, Nathan Morgan*[5]*, Randolph Ponticiello*[5]*, Rachel Zebo*[5]*, Litao Zhang*[6]*, Kenneth T Locke*[7]*, Jonathan Lippy*[6]*, Kevin M. O'Malley*[7]*, Vinayak Hosagrahara*[8]*, Lisa Zhang*[8]*, Pathanjali Kadiyala*[4]*, Carrie Xu*[4]*, Arthur Doweyko*[9]*, Jodi Muckelbauer*[4]*, Robert Zahler*[10]*, Narayanan Hariharan*[5]*, and Peter T. Cheng*[4]*. (1) Metabolic Disease Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3460, shung.wu@bms.com, (2) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton NJ 08543-540, (3) Hopewell Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (4) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (5) Metabolic Diseases Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (6) Lead Evaluation, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (7) Lead Evaluation, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (8) PCO, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, (9) Department of Macromolecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, (10) Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton*

In our efforts to further elucidate the structure activity relationships of the previously reported oxybenzylglycine PPARa/g dual activator muraglitazar, we have systematically examined the effects of various structural variations of the oxybenzylglycine skeleton, including variation of: 1) the glycine moiety, e.g. the effects of homologation and substituents (R), 2) the linker to the phenyloxazole group, 3) the substituents (X) of the phenyloxazole moiety and 4) the

carbamate group (Y). The approach has led to the discovery of a novel oxyphenethyl glycine series 1. The analogs in this series generally exhibit good in vitro binding and functional activity at both PPARa and PPARg. In addition, a number of analogs have demonstrated good in vivo efficacy in the diabetic db/db mouse model. The SAR leading to the discovery and the optimization of this series as well as the in vivo efficacy will be described.



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MEDI 163

Discovery of para-alkylthiophenoxyacetic acids as a novel series of potent and selective PPAR delta agonists

***Rui Zhang**, Aihua Wang, Alan DeAngelis, Patricia Pelton, Jun Xu, Peifang Zhu, Lubing Zhou, Keith Demarest, William V Murray, and Gee-Hong Kuo, Drug Discovery Division, Johnson and Johnson Pharmaceutical Research and Development, 8 Clarke Drive, Cranbury, NJ 08512, rzhang4@prdus.jnj.com*

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors acting as metabolic sensors regulating the expression of genes involved in glucose and lipid homeostasis. It has been demonstrated that selective PPAR delta agonists may have clinical utility in the treatment of dyslipidemia, obesity and diabetes and may complement the actions of existing therapies such as the widely used statins.

This paper describes the identification of highly potent and highly selective novel PPAR delta agonists. The general synthesis and detailed SAR study have also been discussed.

MEDI 164

Novel bisphosphonates targeting prenyltransferases

***Yonghui Zhang**[1], Fenglin Yin[2], Rong Cao[3], Michael P Hudock[4], Kilannin Krysiak[1], Annette Leon[5], Craig T Morita[6], and Eric Oldfield[1]. (1) Department of Chemistry, University of Illinois at Urbana-Champaign, 600S. Mathews Ave., Urbana, IL 61801, yhzhang@uiuc.edu, (2) Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, Urbana, IL 61801, (3) Center for biophysics and computational biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (4) Department of Chemistry, University of Illinois, Urbana, IL 61801, (5) Center for Biophysics and Computational Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (6) Department of Internal Medicine and the Interdisciplinary Group in Immunology, University of Iowa, Iowa City, IA 52242*

The enzyme farnesyl diphosphate synthase (FPPS, EC 2.5.1.10) has been implicated as the main target of bisphosphonates like Fosamax, Boniva and Zometa. Herein, we showed that some novel bisphosphonates, based on rational design, could also inhibit several other enzymes, including geranylgeranyl disphosphate synthase (GGPPS), and decaprenyl disphosphate synthase (DPPS) involved in the mevalonate pathway. Some of these novel bisphosphonates have direct activity against tumor cells and also activate gamma delta T cells of the innate immune system to kill tumor cells, with the most potent species having activities 100 – 1000 times greater than current bisphosphonates in T cell activation and tumor cell killing. We also show it is possible to make more active and selective inhibitors, including ones might have less activity for bone, of potential use in immunotherapy and as anti-infectives.

MEDI 165

Design, synthesis, and biological evaluation of 17-thiazole-4-azasteroids as tissue-selective androgen receptor modulators

Mildred L. Kaufman[1]*, Helen J. Mitchell*[2]*, George D. Hartman*[2]*, Thomayant Prueksaritanont*[3]*, Azriel Schmidt*[3]*, Chang Bai*[3]*, Fang Chen*[3]*, Donald B. Kimmel*[3]*, Mark E. Duggan*[1]*, and Robert S. Meissner*[2]*. (1) Department of Medicinal Chemistry, Merck Research Laboratories, P. O. Box 4, WP 14-2, West Point, PA 19486, mildred_kaufman@merck.com, (2) Department of Medicinal Chemistry, Merck Research Labs, West Point, PA 19486, (3) Department of Molecular Endocrinology, and Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

The androgen receptor is a member of the nuclear receptor superfamily and is responsible for mediating the physiological action of endogenous androgen ligands such as dihydrotestosterone (DHT) and testosterone. A selective androgen receptor modulator (SARM) that is osteoanabolic and has little or no undesirable side effects is desirable for the treatment of osteoporosis. The 17-thiazole-4-azasteroids are a novel class of compounds which have been identified as selective androgen receptor modulators (SARMs). The synthesis and biological data on this class of compounds will be evaluated.

MEDI 166

Synthesis, structure-activity relationship, in vitro/in vivo profiles and molecular modeling of novel oxa-steroids as potent and selective progesterone receptor antagonists

Fu-An Kang*, Jihua Guan, Nareshkumar Jain, George Allan, Olivia Linton, Pamela Tannenbaum, Jun Xu, Peifang Zhu, Joseph W Gunnet, Xin Chen, Keith Demarest, Scott Lundeen, and Zhihua Sui, Johnson & Johnson Pharmaceutical Research and Development, LLC, 665 Stockton Drive, Exton, PA 19341, Fax: 610-458-8249, fkang@prdus.jnj.com*

The progesterone receptor (PR) is a member of the nuclear receptor superfamily of transcription factors. PR modulators have great potential for a wide spectrum of clinical uses. The discovery of the first PR antagonist, mifepristone (RU-486), has stimulated an intensive search for more potent and selective antiprogestins. However, current PR antagonists are

compromised as clinically useful agents due to overt glucocorticoid receptor antagonism. We will present the synthesis, structure-activity relationship, in vitro/in vivo profiles, and molecular modeling of a novel series of 7-oxa-steroids as potent and selective PR antagonists. Our study has demonstrated that the unnatural 7-oxa-steroids not only excellently mimic the natural steroids in terms of shape and activity, but also exhibit significant selectivity versus other steroid receptors and remarkable in vivo efficacy.

MEDI 167

Preparation of diverse array of imidazoles for general screening

David J. Malwitz *and Pawel Nowak, Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd., 222/ lab 2083, Pearl River, NY 10965, Fax: 845-602-5561, malwitd@wyeth.com*

The ability of pharmaceutical industry to screen large numbers of compounds quickly using HTS technologies continues to stimulate the demand for preparation of novel arrays of small molecules. An increased access to chemical diversity is needed to target all of biological space and to increase the number of “drugable” targets. Literature precedents indicate that a number of drug-like heterocyclic libraries based on at least eight scaffolds can be prepared form symmetrical and/or unsymmetrical 1,2-diketones. The construction of a diverse library of trisubstituted imidazoles, potential inhibitors of p38 MAP kinase from 1,2-diketones will be presented.

MEDI 168

Rapid SAR against functional Cardiac Ion Channels using an automated patch clamp system

Nathan J Lautermilch*, Adam Bishop, Teddy Lin, Shimin Wang, and James Baumgartner, Department of Pharmacology, MDS PS, 22011 30th Dr SE, Bothell, WA 98021, Fax: 425-487-3787, Nathan.Lautermilch@mdsinc.com*

The withdrawal of drugs from the marketplace due to arrhythmias underscores the need for effective cardiac safety screening, and necessitates identification of potential liabilities earlier in the drug discovery process. This information can assist in decision-making strategies to identify compounds more likely to fail in later, more expensive phases of drug development. We have developed three different ion channel assays using the PatchXpress automated patch clamp platform to test compounds for adverse effects on the major ion channels responsible for the cardiac action potential.

Sodium, calcium, and potassium comprise the major currents of the cardiac action potential. Compounds that interact with these channels, either individually or together can dramatically alter the cardiac action potential. Patch clamp is the gold standard to identify potential drug liabilities and accurately assess potential risks. Automated patch-clamping greatly reduces cost and increases throughput to provide rapid turnaround testing coincident with medicinal chemistry development cycles.

MEDI 169

Selection of compounds in discovery stage based on the novel HTS solubility measurement and parallel artificial membrane permeability assay

Katsuya Akimoto[1]*, Kyosuke Suzuki*[1]*, Shinsaku Tsukamoto*[1]*, Kenichi Sudo*[2]*, and Osamu Okazaki*[1]*. (1) Drug Metabolism & Pharmacokinetics Research Laboratories, DAIICHI SANKYO CO., LTD, 16-13, Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan, akimom34@daiichipharm.co.jp, (2) DAIICHI SANKYO CO., LTD, Tokyo 134-8630, Japan*

To evaluate the oral absorbability of compounds in high throughput mode, we examined the in-house guiding principle based on solubility in artificial intestinal juice and PAMPA results. Dimethylsulfoxide (DMSO) is widely used as a solvent for mother solutions and greatly influences measurement results. A unique method incorporating the DMSO freeze-drying process was established for measuring solubility. By our method, solubility to ca. 1 mg/mL can be measured sufficiently accurately by a 10 mM mother solution in DMSO. PAMPA permeability was assessed by the double-sink protocol. The donor solutions were adjusted to pH 5.0 and 7.4. By categorizing compounds on their solubility in artificial intestinal juice and PAMPA permeability similarly as in the biopharmaceutical classification system, we can grasp the oral absorbability profile for compounds of each project at an early stage, obtaining excellent candidate compounds in the short term.

MEDI 170

Design and synthesis of site-selective fluorescent naphthalimide probes for microscopy

Leah L. Groess, Ashley M. Dreis, Kyle M. Kopidlansky, and ***David E. Lewis****, Department of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, WI 54702, Fax: 715-836-4979, groessll@uwec.edu, lewisd@uwec.edu*

The 4-amino-1,8-naphthalimide fluorophore provides an excellent base onto which to build site-selective binding motifs for the synthesis of highly fluorescent probes for microscopy. We have successfully completed the synthesis of probes high-cholesterol microdomains, but many of these hydrophobic probes readily cross the plasma membrane to enter intracellular membranes. In many cases, this results in unacceptably high background fluorescence when imaging the plasma membrane. We have been developing a series of new naphthalimides with attached hydrophilic moieties to limit the rate of diffusion of the dye across the plasma membrane. To this end, we have attached both localized ionic and carbohydrate groups to the parent fluorophore. The synthesis of these dyes will be discussed.

MEDI 171

Microarray screening of antithrombin interactions on the high affinity heparin glycan chips

***Tae-Joon Park**, Departments of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Biotech Center 4005,110 8th Street, Troy, NY 12180, parkt@rpi.edu, Moo-Yeal Lee, Solidus Biosciences Inc, Troy, NY 12180, Moon Il Kim, Department of Chemical & Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY 12180, Jeffrey G. Martin, Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, NY 12180, Jonathan S. Dordick, Department of Chemical Engineering, Rensselaer Polytechnic Intitute, Troy, NY 12180, and Robert J. Linhardt, Department of Chemistry, Chemical & Biological Engineering, Biology, Rensselaer Polytechnic Institute, Troy, NY*

The emergence of combinatorial methods for new compound synthesis and drug discovery has led to a dramatic increase in the number of drug candidates for in vitro and ultimately in vivo testing. Despite these developments, the clinical progression of new chemical entities to pharmaceuticals particularly once having complex structures such as carbohydrate-based agents is slow since there are multiple factors complicate carbohydrate microarray research. In initial experiments we searched various heparin library spots on glycan chips by probing with various amounts of AT III and detected AT III-binding based on the intrinsic fluorescence of AT III. Several GAGs including natural and modified heparin were evaluated for heparin-AT III interaction using AT III-Sepharose chromatography. Unfractionated, pharmaceutical heparin (with one-third of the chains containing antithrombin III binding sites), high affinity heparin (all chains with antithrombin III binding sites) and low affinity heparin (with no antithrombin III binding sites) were prepared and evaluated.

MEDI 172

Studies on the ligand selectivity and economics of metal scavenging polymers

***Paul A Boguszewski**[1], Andrew F Coffey[2], Aubrey J Mendonca[3], John W Davies[1], and Frank P Warner[2]. (1) Polymer Laboratories Ltd, Now a part of Varian, Inc, Essex Road, Church Stretton, Shropshire SY6 6AX, United Kingdom, Fax: (+44) 01694 722171, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd, Now a part of Varian, Inc, Church Stretton, Shropshire SY6 6AX, England, (3) Polymer Laboratories, Varian, Inc, Amherst, MA 01002*

The innovation of novel-metal mediated reactions and the development of scalability of such processes to bulk scale has led to an explosion in new technologies aimed at the removal of residual metal contamination. The removal of active metal reagents or residues is essential to provide clean and safe compounds for screening. We have developed a range of polymeric materials suitable for metal sequestration and have proven their efficacy for a range of commonly used metals. Two key factors that govern the use of such materials in medicinal chemistry are the selectivity of metal removal products and the economics of using them. Herein, we will describe studies showing the efficacy of a range of metal scavenging products when used in the presence of competing ligands and drug like molecules. Studies showing the effect of metal sequestration when in the presence of other metal species will also be discussed along with novel technology for making metal removal processes more economically viable in bulk and process applications

MEDI 173

New techniques for salt and polymorph screening of new drug candidates

***Carl H Behrens**, Wilmington PharmaTech, One Innovation Way, Suite 302, Newark, DE 19711, Fax: 302-261-7000, carl.behrens@WilmingtonPharmaTech.com, and Hui-Yin Harry Li, Wilmington PharmaTech Company, Newark, DE 19711*

Different salt and polymorphic forms can have major effects on the developability of new drug candidates. Currently, it is required by FDA to provide preparation, identification, and characterization of different crystal forms of new drug development candidates in New Drug Applications. XRPD has been used widely for polymorph characterization, but often having difficulty for new crystal forms due to preferred orientation and other artificial effects. We have found that a combination of SEM, TEM with XRPD is a powerful technique for characterization of new salt and polymorphic forms. Details on further application of this technology and other crystallization techniques will be presented.

MEDI 174

Open access mass-directed purification: Adaptation to diverse loading scales and compound polarities

***Leonard O Hargiss** and Weiqun Wang, Medicinal Chemistry, Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540, Fax: 609-466-3562, Lhargiss@lexpharma.com*

Mass directed reverse-phase preparative HPLC is a powerful tool for automated purification of medicinal chemistry compounds. However, for different phases of the drug discovery process, widely differing synthetic scales must be accommodated. Optimization of chromatographic systems for 100 mg scale purification introduces compromises which reduce yield and/or selectivity when purifying compounds at less than 10 mg scale. We have configured a commercial preparative HPLC-MS system to deliver good chromatography and purification yield over a wide range of sample loads. Small (10 mm ID) and large (30 mm ID) preparative columns each use a dedicated splitter. The splitters share a common make-up pump which delivers a small proportion of column effluent to the detectors. Such a configuration improves utility of the system which may be used for both automated library purification at night, and for walk-up purification during the workday. Improved peak shape at the collector for small scale separations will be demonstrated, as well as selected applications.

MEDI 175

NCI60 screening data: A versatile tool for in silico models predicting substrate properties for ABC-transporter

***Gerhard F Ecker**[1], Barbara Zdrazil[1], and Chakguy Prakasvudhisarn[2]. (1) Department of Medicinal Chemistry, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria, Fax: 431-4277-9551, gerhard.f.ecker@univie.ac.at, (2) Sirindhorn International Institute of Technology, Thammasat University, Pathumthani 12121, Thailand*

ABC-transporter have manifold physiological and pathophysiological functions. Due to its role as multidrug efflux transporter, ABCB1 (P-glycoprotein) is increasingly recognised as antitarget. Interaction with this ATP-driven transport pump influences toxicity to tumour cells, bioavailability, and brain uptake. Thus, models which are able to predict substrate properties are of general interest in the drug development process. We used the NCI60 screening data set published by Szarkas et al. in order to establish a training set for ABCB1 substrates and non-substrates. The data set is based on the correlation of the toxicity of the compounds in the 60 tumour cell lines with the expression rates of ABCB1. Substrates are characterised by a negative correlation coefficient. Using a set of 114 substrates and 145 non-substrates and 32 VSA-descriptors calculated from MOE, binary QSAR runs gave models with overall prediction-accuracies in the range of 59.6% - 80.8%. Generally, non-substrates showed higher prediction accuracies than substrates. In comparison to BQSAR, support vector machines gave more robust models with values in the range of 69.2% - 78.8%.

MEDI 176

Virtual screening of the inhibitors into Tyrosyl-DNA Phoshodiesterase (Tdp1) active sites

Iwona E Weidlich[1]*, Thomas Dexheimer*[2]*, Yves Pommier*[2]*, Christophe Merchand*[2]*, and Marc C Nicklaus*[1]*. (1) Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute, NIH, DHHS, Frederick, MD 21702, (2) Laboratory of Molecular Pharmacology, CCR, NCI, NIH, Bethesda, MD 20892*

Tdp1 inhibitors have become a major area of drug research and structure-based design. We found pharmacophore models of 14 inhibitors that had shown activity against Tdp1 (IC50 ~1-3 uM) and 8 inactive compounds, using the HipHop method for pharmacophore generation in the program Catalyst. We then used 6 such pharmacophore models as queries to search the Maybridge and ChemNavigator databases. The resulting hits were processed with Pipeline Pilot 5.0, applying an organic filter, Lipinski filter, and HTS filter, and removing duplicate molecules. Physico-chemical and ADME-TOX properties were calculated using the programs QikProp 2.5 (Schrodinger) and ADMET Predictor (Simulation Plus). Docking was performed with the program Glide (Schrodinger) in Extra Precision mode. We first docked the known inhibitors into the active site of a crystal structure (PDB code 1NOP) of Tdp1, and subsequently all 88,246 hits obtained in the previous steps. Our results indicated the binding correlation with the inhibitors activity.

MEDI 177

Molecular docking and 3-D-QSAR studies on a series of 6,7-dimethoxy-4-pyrrolidylquinazoline as PDE10A inhibitors

Shridhar Kulkarni *and Tanaji T Talele, Department of Pharmaceutical Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, kshridhar_3@yahoo.co.in*

Docking studies, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) were carried out on a series of 6,7-dimethoxy-4-

pyrrolidylquinazoline derivatives possessing PDE10A inhibitory action to gain an understanding of their binding modes and of the possible structure-activity relationships. For this purpose, all the compounds were docked in the binding site of a recently developed crystal structure of PDE10A (PDB ID: 2O8H). The docking experiments revealed the importance of a hydrogen bonding interaction between the methoxy group of the inhibitors and the amide group in the side chain of Gln716. 3D-QSAR models with cross-validated r2 values of 0.511 and 0.627 for CoMFA and CoMSIA, respectively, were built. Validation of the models with an external set of compounds yielded satisfactory predictive r2 values of 0.650 and 0.577 for CoMFA and CoMSIA, respectively. The CoMFA model indicated that steric properties contribute to an extent of about 80% towards the observed variations in biological activity. These statistically significant models can serve as guides for the rational design of potent inhibitors of PDE10A. A detailed discussion of the 3D-QSAR and the structure-based computational results for these inhibitors will be provided.

MEDI 178

Predicting modifications to the inhibitor of InhA, the M.tb enoyl reductase enzyme to stabilize inhibitor-active site loop interactions using computational chemistry tools

Salma Banu Rafi[1]*, Peter J. Tonge*[2]*, and Carlos L. Simmerling*[2]*. (1) Biochemistry and Structural Biology Graduate Program, Center for Structural Biology, Stony Brook University, Stony Brook, NY 11794, (2) Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400*

No new anti-tuberculosis drug has been introduced in 30 years and resistance to the frontline drug isoniazid is growing. Isoniazid's proposed target is InhA, an enoyl reductase enzyme in FAS-II pathway. We investigated a series of diphenyl-ether compounds as possible drug candidates. We hypothesize that high affinity inhibition of InhA is coupled to ordering of the active site loop. The loop of InhA or its E.coli homolog FabI is ordered in crystal structures when high affinity inhibitors like isoniazid (InhA) or triclosan (FabI) are bound. The loop is flexible in InhA with triclosan which only weakly inhibits this enzyme. To date, the exact mechanism of loop ordering is not known. Based on a feasible loop conformation generated from MD simulations, we have designed inhibitors that interact better with the InhA active site loop and also increase the solubility of the inhibitor. We also show that our calculated binding energies for inhibitors match experimental trends.

MEDI 179

Chemical modifications to improve pharmacokinetic properties of siRNA: Probing the tolerance of phosphorothioate modifications on siRNA activity

Thazha P. Prakash[1]*, Garth A. Kinberger*[1]*, Charles R. Allerson*[1]*, Andrew T. Watt*[2]*, Andreas Berdeja*[1]*, Hans J. Gaus*[1]*, Eric G. Marcusson*[3]*, Eric E. Swayze*[1]*, and Balkrishen Bhat*[1]*. (1) Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc, 1891 Rutherford Road, Carlsbad, CA 92008, Fax: 760-603-4654, tprakash@isisph.com, (2) Antisense Lead Identification, Isis Pharmaceuticals, Inc, Carlsbad, CA 92008, (3) Molecular Pharmacology, Isis Pharmaceuticals, Inc, Carlsbad, CA 92008*

The observation that small synthetic RNAs can inhibit gene expression in cultured mammalian cells has created enormous interest in RNAi based therapeutic approach for creating novel drugs for treatment of disease. Efficacious in vivo silencing of disease genes by local administration or formulated siRNAs have been reported. The non formulated siRNA are unsuitable for systemic use as they get degraded and are cleared fast. One way to overcome this problem is to use phosphorothioate backbone modification, in addition to chemical modifications, to improve metabolic stability and pharmacokinetic properties which will be valuable for systemic application of siRNAs therapeutic. We, therefore, evaluated the tolerance of phosphorothioate modifications in passenger and the guide strands of unmodified and 2'-modified siRNAs. Our data indicated that there is a strong correlation between phosphorothioate number and placement and biological activity. The phosphorothioate modification significantly improved serum stability and plasma protein binding. Details from this study will be presented.

MEDI 180

Polyconjugates: A new synthetic vehicle for in vivo delivery of siRNA to hepatocytes

Darren H. Wakefield[1]*, David Rozema*[1]*, So C. Wong*[1]*, Jason J. Klein*[1]*, Dave L. Lewis*[1]*, Stepanie Bertin*[1]*, Tom Reppen*[1]*, Paula L. Roesch*[1]*, James E. Hagstrom*[1]*, and Jon A. Wolff*[2]*. (1) Mirusbio Corporation, 505 S Rosa Road Suit 104, Madison, WI 53719, Fax: 608-441-2847, darren.wakefield@mirusbio.com, (2) Department of Pediatrics and Medical Genetics, Univerisity of Wisconsin-Madison*

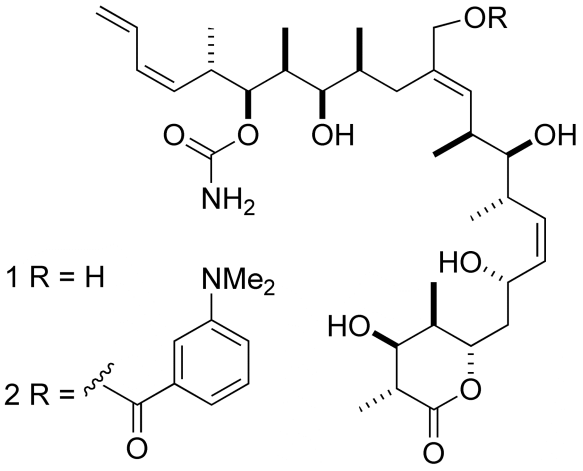
In vivo delivery of siRNA to the appropriate target cell is a major challenge for realizing the full potential of siRNA. Hepatocytes, the key parenchymal cells of the liver, are a particularly attractive target cell for siRNA delivery given their central role in several infectious and metabolic disorders We have developed a new technology for the delivery siRNA to hepatocytes both in vitro and in vivo. Key features of this technology include: a new class of membrane lytic polymers, the ability to reversibly mask the positive charges of these polymers until they reach the acidic environment of endosomes, and the ability to target these masked membrane lytic polymers and their siRNA cargo specifically to hepatocytes in vivo after low pressure intravenous injection. The polymer-siRNA conjugates are targeted by reversible attachment of N-acetylgalactoseamine. Using this delivery system we demonstrate effective knock-down of two endogenous genes in mouse liver: 75% knock-down of apolipoprotein B (apoB) and 65% knock-down of peroxisome proliferator-activated receptor-alpha (PPARα). Knockdown of apoB resulted in phenotypic changes that included a 30% reduction in serum cholesterol and fat accumulation in the liver. The knockdown of apoB mRNA was still measurable 15 days after injection (ca 15%), but serum cholesterol levels returned to normal more rapidly, after 10 days. Significant liver toxicity was not observed on the basis of serum liver enzyme analyses, cytokine assays, and liver histology. These polyconjugates represent a new platform for targetable, in vivo delivery of siRNA.

MEDI 181

Studies toward the synthesis of fluorescent and isotopically labeled discodermolide analogs

Chao Yang[1]*, Abhijit Banerjee*[2]*, Susan Bane*[2]*, and David G. I. Kingston*[1]*. (1) Department of Chemistry, Virginia Polytechnic Institute and State University, Hahn Hall, M/C 0212, Blacksburg, VA 24061, chaoyang@vt.edu, (2) Department of Chemistry, State University of New York at Binghamton, Binghamton, NY 13902*

Discodermolide, a natural product originally isolated from the marine sponge *Discodermia dissoluta*, has potent activity as a mitotic spindle poison. It has good *in vivo* anticancer activity against drug-resistant tumors in animal models, and it entered clinical trials before being dropped because of some unexpected toxicity. It remains of interest as a target for analog synthesis, and a number of synthetic approaches have been disclosed. Discodermolide has a similar mechanism of action to paclitaxel, binding to microtubules and stabilizing them to dissociation to tubulin. It is a highly flexible molecule, and its binding conformation is unknown. As a part of a comprehensive approach to determining the tubulin-binding conformation of discodermolide and to design analogs with improved tubulin-polymerization properties, we have designed the fluorescently labeled discodermolide analog **2**. The synthesis of **2** and related compounds will be described, and preliminary studies of its interaction with tubulin will be presented.



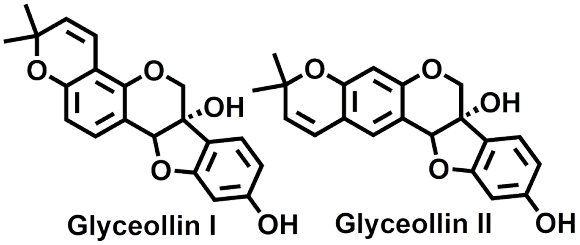
MEDI 182

Stereoselective total synthesis of soybean flavonoids Glyceollin I, II

Rahul S Khupse *and Paul W Erhardt, Department of MedicinalChemistry, Center for Drug Design and Developement, 2801 W Bancroft St, Toledo, OH 43606, Fax: 4195301994, rkhupse@utnet.utoledo.edu*

The glyceollins are selective anti-estrogenic soy flavanoids with the potential for breast cancer treatment. The first total synthesis of the glyceollins I and II and their precursor glycinol was achieved via two routes, one being biomimetic and the other a non-biomimetic. In the

biomimetic route, oxidative rearrangement of the chalcone with thallium salt gave an isoflavone. The reduction of this isoflavone followed by acid catalyzed dehydration provided isoflav-3-ene. However, this route was low yielding and it included use of a highly toxic thallium salt for the key rearrangement reaction. The alternative non-biomimetic route involves synthesis of isoflav-3-ene by using an intramolecular Wittig's olefination. The intermediate isoflav-3-ene was converted into the diol using osmium tetroxide mediated asymmetric dihydroxylation. The diol was transformed into glycinol via quinone methide intermediate which served as a common precursor for both glyceollins I and II. Thus, the total synthesis of all cis enantiomers of glyceollins I and II was achieved in 15 steps.

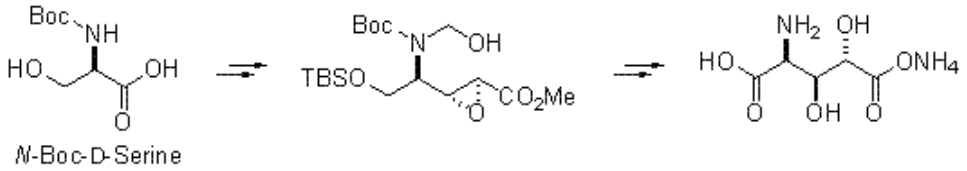


MEDI 183

Stereoselective synthesis of (2S,3S,4S)-3,4-dihydroxy-L-glutamic acid via intramolecular nucleophilic epoxidation

*Young Gyu Kim, **Hyeonjeong Kim**, Dongwon Yoo, Myeong Hak Kim, and Suk-Koo Hong, Department of Chemical and Biological Engineering, Seoul National University, Shinlim-dong 56-1, Kwanak-Goo, Seoul 151-744, South Korea, Fax: 82-2-885-6989, ygkim@snu.ac.kr, dew83123@nate.com*

L-Glutamic acid acts as an excitatory neurotransmitter in the mammalian central nervous system with selective binding to specific ionotropic or metabotropic glutamate receptors. Excessive activation of glutamate receptors is known as a pathogenesis of Huntington's, Alzheimer's and Parkinson's diseases, epilepsy and ischaemia. Each subtype-selective ligand is an important therapeutic target for the treatment of such diseases. Lately the intermolecular affinities and selectivities for a particular GluR subclass of hydroxylated L-glutamic acids have stimulated much interest in the efficient synthesis of them. In particular, (2S,3S,4S)-3,4-dihydroxy-L-glutamic acid (DHGA) is known to be an agonist of mGluR1 and a weak antagonist of mGluR4 but have no discernible activity with respect to mGluR2. In this presentation, an efficient and stereoselective synthesis of (2S,3S,4S)-DHGA will be reported from configurationally stable N-Boc-D-serinal. The key steps involve a noble intrameolcular nucleophilic epoxidation followed by a regio- and stereoselective epoxide opening with the neighboring N-Boc group.

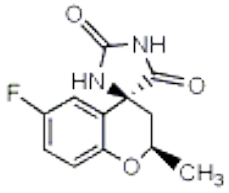


MEDI 184

Improved asymmetric synthesis of the alose reductase inhibitor 2-methyl sorbinil

***Hongxia Jin**, James M. Randazzo, and Peter F. Kador, Department of Pharmacetical Sciences, College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE 68198-6025, Fax: 402-559-9543, hjin@unmc.edu*

2-Methyl Sorbinil (6-fluoro-2,3-dihydro-2-methyl-(2R,4S)-spiro[4H-1-benzopyran- 4,4'-imidazolidine]-2',5'-dione, 2-MS) has been shown in animal models to prevent the formation of diabetic complications that include neuropathy, nephropathy, diabetic corneal lesions, cataract and retinopathy. Currently it is being assessed for the veterinary market for its ability to arrest ocular diabetic complications in the dog. This compound has previously been synthesized in 10 steps according to Dirlam et al. (J. Org. Chem, 1987, 52, 3587-3591). However, resolution with chymotrypsin in the eighth step significantly reduces the overall yield. We have previously modified this synthesis by replacing the chymotrypsin resolution with a selective crystallization to obtain a slight improvement in the overall yield. To facilitate the synthesis of this compound, we have now developed a new, 8-step synthesis utilizing the catalytic enantioselective Strecker reaction as reported by Kato et al (Tetrahedron Lett., 2004, 45, 3147-3151) to construct the second stereoselective center. This significantly increases the overall yield of 2-MS. Details of the synthesis and the evaluation of this compound on canine sugar cataract will be discussed.



2-MS

MEDI 185

Study for total synthesis of antibiotic pestalone and its analog

*Yudao Ma[1], **Yong Dai**[2], Zhijun Sun[1], Xi Fang[1], Changqin Ma[1], and Chun Song[3]. (1) Chemistry Department, Shandong University, Shanda SouthRoad #27, Jinan, Shandong, 250100, P. R. China, Jinan, Shandong, 250100 P.R. China, Jina, China, ydma@sdu.edu.cn, (2) Qilu hospital, Shandong University, Shanda SouthRoad #27, Jinan, Shandong, 250100, P. R. China, Jinan, Shandong, 250100 P.R. China, jinan, China, yong_dai@163.com, (3) Chemistry College, Shandong University, Jinan 250100, China*

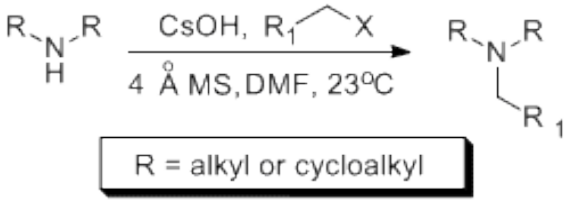
Pestalone(1) was found to exhibit moderate in vitro cytotoxicity in human tumor cell line with GI50 equals 6.0 uM. Important data showed potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MIC = 37 ng/mL) and vancomycin-resistant Enterococcus faecium (MIC = 78 ng/mL). These data suggest Pestalone keeping potential activity for treatment of infectious disease. After total synthesis this natural product by using novel passway, we make its analogue (2) and evaluate their biological activity.

MEDI 186

An efficient and operationally convenient general synthesis of tertiary amines by direct N-alkylation of secondary amines and heterocycles with alkyl halides in the presence of CsOH

Ralph Nicholas Salvatore *and Jason Hovland, Department of Chemistry, Lehman College-City University of New York, Davis Hall 318, 250 Bedford Pk. Blvd. W, Bronx, NY 10468, Fax: 718-960-8150, ralph.salvatore@lehman.cuny.edu*

Amines, Polyamines, and Heterocycles are common functional groups of naturally occurring biologically active compounds and are widely used throughout the chemical industry as basic intermediates to prepare fine chemicals, pharmaceuticals, natural products, bioactive molecules, toxins, and agrochemicals. Due to their unique biological properties, amines have played an important role in chemotherapeutic approaches to a variety of diseases. As a result, the development of new synthetic routes to these compounds has stimulated constant interest and has been the focus of many research groups over the years. From a methodological standpoint, the direct alkylation of secondary amines with alkyl halides is the most straight-forward method for the synthesis of tertiary amines. However, this method on a practical basis has been somewhat limited since direct N-alkylation of secondary amines often results in the formation of the quaternary ammonium salts and a mixture of the desired tertiary amine and the starting secondary amine. In an attempt to address some of these issues, other methods were investigated encompassing direct N-alkylation, N-alkylation of secondary amines via their metal amides with alkyl halides and the use of excess organic bases via the same process. However, each exhibited drawbacks and limitations primarily due to reisolation of the unreacted secondary amine. To mitigate these problems, several alternative methods to direct alkylation have also been reported. Among these methods is the use of solid phase supports and other reactions. These methods, while useful suffer from specific limitations and functional group tolerance. A general method for the direct formation of tertiary amines via direct N-alkylation of secondary amines by alkyl halides in DMF in the presence of CsOH is reported. Biological and Medicinal Chemistry Aspects will be addressed.



MEDI 187

Synthesis of fluorine-containing heterocycles for medicinal chemistry

Mark J. Penny*, School of Biological and Chemical Sciences, Queen Mary, University of London, Walter Besant Building, Mile End Road, London E1 4NS, United Kingdom, Fax: 442078827427, m.j.penny@qmul.ac.uk, Adrian P Dobbs, Department of Chemistry, Queen Mary University of London, London E1 4NS, United Kingdom, Levan Pivnevi, Department of*

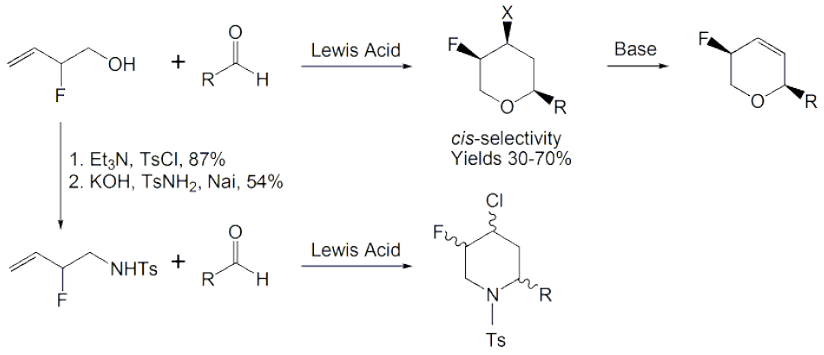
Chemistry, The Open University, Milton Keynes MK7 6AA, and Peter Jones, Discovery Chemistry, Pfizer Global R&D, Sandwich, Kent CT13 9NJ, United Kingdom

Fluorine containing molecules are of great importance to the pharmaceutical industry and many pharmaceutically active molecules contain fluorine, often as a replacement for the hydroxyl group.

A related area of interest is the synthesis of fluorinated sugars, where the CHF or CF2 moiety is introduced as a replacement for the OH moiety, at any of the hydroxyl-bearing positions of the sugar.

Herein is described the synthesis of a variety of fluorine-containing tetrahydropyrans, as intermediates towards fluorinated sugars, via the Prins methodology from the commercially available aldehydes and the fluorinated homoallylic alcohols. The Lewis acid counter-ion, frequently chloride or triflate, may also be incorporated by this method. Basic elimination of the triflate group afforded the more desired dihydropyran, which enables further functionalisation.

This work was further expanded into fluorinated piperidine systems using the same Prins methodology. The fluorinated amine was synthesised by tosylation of the fluorinated alcohol followed by an SN2 displacement with an appropriate amine. These cyclised to give fluorinated piperidines.



MEDI 188

Synthesis of novel fluorinated carbohydrate and pipecolic acid analogs and C-aryl glycosides via a common methodology

***Adrian P Dobbs**, Department of Chemistry, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom, A.Dobbs@qmul.ac.uk, Diluar Khan, School of Biological and Chemical Sciences, Queen Mary, University of London, London E1 4NS, and Robert J Parker, School of Biosciences, University of Exeter, Exeter EX4 4QD, United Kingdom*

Novel methods for the synthesis for carbohydrate analogues, for use in medicinal chemistry, are a constant challenge. A novel organosilicon method has been developed for the preparation of three important, but different classes of biologically active molecule: a-CF3 substituted heterocycles (pyrans and piperidines), pipecolic acids (and their fluorinated

analogues) and C-aryl glycosides. All three classes of compound are of tremendous use in medicinal chemistry and of wide application in the preparation of more complex analogues.

MEDI 189

Applications of polymeric reagents and SPE in the synthesis and purification of reductive amination reactions

Paul A Boguszewski[1]*, Andrew F Coffey*[2]*, John W Davies*[1]*, Aubrey J Mendonca*[3]*, and Frank P Warner*[2]*. (1) Polymer Laboratories Ltd, Now a part of Varian, Inc, Essex Road, Church Stretton, Shropshire SY6 6AX, United Kingdom, Fax: (+44) 01694 722171, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd, Now a part of Varian, Inc, Church Stretton, Shropshire SY6 6AX, England, (3) Polymer Laboratories, Varian, Inc, Amherst, MA 01002*

Reductive amination is a very attractive and commonly employed chemical method in modern drug discovery. It allows the synthesis of structurally diverse amines using readily available starting substrates under mild conditions. A plethora of immobilized reagents and scavengers have been developed to increase reaction throughput and to eliminate post reaction purification issues. Herein we will describe a comparative study, showing the efficacy of a range of polymer supported reducing reagents and scavengers for a broad rage of substrates and reaction conditions. We will also describe novel SPE products that are highly effective in the work-up of reductive amination reactions, which remove excess acetic acid and allow the isolation of final amine product as a freebase species. Recent work in our group looking at the optimization of methods for reductive amination on to aldehyde based solid supports will also be shown.

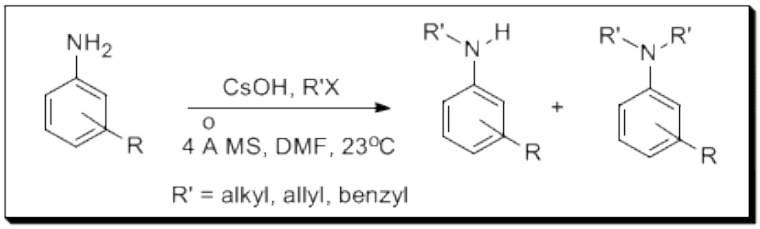
MEDI 190

Selective N-alkylation of aromatic amines

Ralph N. Salvatore*, Department of Chemistry, Lehman College - The City University of New York, Davis Hall 317, 250 Bedford Park Boulevard, Bronx, NY 10468, Fax: 718-960-8750, and Jason Hovland, Department of Chemistry, Lehman College-City University of New York, Bronx, NY*

The selective alkylation of primary amines to secondary amines represents an important class of chemical transformations that have found extensive use in the construction of a vast range of natural products, bioactive molecules, and industrial materials. In particular, aromatic amines, in particular heterocyclic aromatic amines (HAAs), formed during the cooking of foods, are known to induce tumors in rodent bioassays and are known contribute to human cancer risk. Moreover,(HAAs), breast cancer risk has been hypothesized to increase with exposure. Therefore, such aromatic amines require enzymatic activation to bind to DNA and initiate carcinogenesis. This broad utility has made secondary amines important synthetic targets, and traditional routes.In these cases, the use of toxic and corrosive alkylating reagents or carbonyls frequent generation of wasteful salts as byproducts are undesirable in view of environmental concerns. Besides, the difficult to separate. To prevent overalkylation,

troublesome and expensive multistep methods have been devised such as partial protection of primary amines and reduction of mono-N-substituted amides. However, the reaction conditions are often drastic or reagents are not readily available. To overcome these difficulties, highly selective, environmentally benign, and convenient mono-N-alkylation of primary amines is an important synthetic goal. We report a simple and entirely new method for the preparation of N-monoalkyl substituted anilines employing cesium hydroxide as the base of choice in DMF. The reactions have been performed employing several diverse alkyl halides. In addition, different substituted anilines as substrates and alkyl, allyl and benzyl halides as alkylating agents in order to establish the factors that affect the reactivity and chemoselectivity of the N-alkylation process. Biological and Medicinal Aspects will be addressed.



MEDI 191

Synthesis of N-9-substituted 2,8-diaminopurines

Gulzar Ahmed[1]*, Andrew G. Cole*[1]*, Marc-Raleigh Brescia*[1]*, Ian Henderson*[1]*, Lan-Ying Qin*[1]*, Axel Metzger*[1]*, James Wen*[1]*, Ray J. Chan*[1]*, and Linda O'Brien*[2]*. (1) Department of Chemistry, Pharmacopeia Drug Discovery, Inc, PO Box 5350, Princeton, NJ 08543, gahmed@pcop.com, (2) Department of Analytical Chemistry, Pharmacopeia Drug Discovery Inc, Princeton, NJ 08543*

A general and efficient solid-phase synthesis of pharmacologically important N-9-substituted 2,8-diaminopurines from 5-nitrouracil is described. The key synthetic transformation employs a carbodiimide-mediated cyclization of a thiourea. Thiourea formation on solid phase is performed using both thermal and microwave reaction conditions. Regiospecific solution-phase synthesis of key building blocks allows the incorporation of desired substituents at N-9 of the purine nucleus.

MEDI 192

From a polymer crosslinker to soluble epoxide hydrolase (sEH) inhibitors: The quest for lower cost drug intermediates

James R. Sanborn*, Christophe Morisseau, Paul D. Jones, Hsing-Ju Tsai, Sung Hee Hwang, and Bruce D. Hammock, Department of Entomology, University of California, Davis, One Shields Ave, Davis, CA 95616, jrsanborn@ucdavis.edu*

We found that reaction of adamantyl isocyanate (AdNCO) with primary or secondary amines yields 1,3-disubstituted ureas that are potent *in vitro* and *in vivo* inhibitors of sEH, an enzyme that has a pivotal role in hypertension and vascular inflammatory disease in humans. During

the development of novel, efficacious pharmaceuticals, the cost of preparation can influence the decision process. Since adamantyl isocyanate costs approximately $4,700/lb, a search was carried out for alternative isocyanates that might provide ureas of comparable potency to those derived from AdNCO. The polymer cross linker, isopropenyl-α,α-dimethylbenzyl isocyanate (Me_2BzNCO) is 70-fold (~$66/lb) less expensive than AdNCO. Treatment (Me_2BzNCO) with a variety of amines yielded a series of novel ureas which were moderately active (I_{50} ~10-100 nM) sEH inhibitors. *In vitro* activity on sEH and some pharmacokinetic data in canines to define whether novel ureas from (Me_2BzNCO) have comparable activity to those derived from AdNCO will be presented.

MEDI 193

Production of different structural analogs of sophorolipids through modification of fermentation medium

Vishal Shah *and Dan Badia, Department of Biology, Dowling College, Oakdale, NY 11769, ShahV@dowling.edu*

Sophorolipids are extracellular glycolipids produced by the yeast Candida bombicola. These molecules have shown to be effective microbicidal spermicides showing high antibacterial, antifungal, anti-HIV activities. However, their cytotoxicity is equivalent to currently used spermicides. Research to chemically modify the compounds have failed to generate a clinically viable molecule.

Through the research to be presented, we would show that by simple modification of fermentation medium, new structural analogs of Sophorolipids can be generated. These structural analogs have higher antibacterial activities compared to one synthesized using classical fermentation medium. Indeed, with higher antibacterial activities on their own, these molecules provide an ideal backbone for doing chemistry that have been reported in the literature for developing next generation microbicidal spermicides.

MEDI 194

Versatile photosensitizers based on photon upconverting nanoparticles for photodynamic therapy

Peng Zhang[1]*, Wim Steelant*[2]*, Manoj Kumar*[1]*, and Matthew Scholfield*[1]*. (1) Department of Chemistry & Laboratory of Nanomaterials Science, New Mexico Tech, Socorro, NM 87801, pzhang@nmt.edu, (2) Laboratory of Biochemical & Biomedical Research, Department of Chemistry, New Mexico Tech, Socorro, NM 87801*

Photodynamic therapy (PDT) is an emerging technique for cancer treatment that has been gaining acceptance in recent years. One of the key components in effective and efficient PDT is the photosensitizers, also called PDT drugs. We report the design of a type of versatile photosensitizers, which could potentially become the next generation PDT drugs, based on photon upconverting nanoparticles. These nanoparticles-based photosensitizers are excitable with infrared irradiation, which has several times larger tissue penetration depth than the

currently available ones. They are brought close to the target cancer cells through antigen-antibody interaction with good specificity and versatility. The design is also flexible in that various photosensitive molecules can be potentially adopted into the design. Results from in vitro experiments demonstrate their promise of becoming the next generation photodynamic therapy drugs.

MEDI 195

Allosteric modulation of mGluR1 and mGluR5

Tanja Weil[1]*, Gisbert Schneider*[2]*, Steffen Renner*[1]*, Swetlana Derksen*[2]*, Mirko Hechenberger*[3]*, and Christopher G. Parsons*[3]*. (1) Department Chemical R&D, Merz Pharmaceuticals, Altenhöferallee 3, Frankfurt am Main D-60438, Germany, Tanja.Weil@merz.de, (2) Institute of Organic Chemistry & Chemical Biology, Johann Wolfgang Goethe-University, D-60323 Frankfurt, Germany, (3) Department In vitro Pharmacology, Merz Pharmaceuticals, Frankfurt 60318, Germany*

A virtual screening approach for non-competitive mGluR1 antagonists was developed that facilitated the discovery of moderately active mGluR1 antagonists. One scaffold was selected for the design of a focused library. Since both mGluR1 and mGluR5 allosteric modulators share a common binding pocket, a focused library around this scaffold was synthesized, which lead to the discovery of both mGluR1 and mGluR5 allosteric modulators. Via this strategy, we were able to identify potent mGluR1 antagonists as well as positive and negative mGluR5 modulators. In addition, their binding modes inside the receptor were established based on homology models. The mode of action of positive and negative modulation as well as the binding site of these novel compounds was further analyzed via a mutation analysis within the transmembrane domain. In addition, these results are compared with the mechanism of action of positive and negative modulation of other GPCRs.

MEDI 196

Benzamide inhibitors of soluble epoxide hydrolase

Steven J Taylor*, Stéphane DeLombaert, Anne Eldrup, Neil Farrow, Ingo Mugge, and Fariba Soleymanzadeh, Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Rd./P.O. Box 368, Ridgefield, CT 06488, Fax: 203-798-5297, staylor@rdg.boehringer-ingelheim.com*

Soluble epoxide hydrolase (sEH) is responsible for hydrolyzing regioisomeric epoxides of arachidonic acids (EET's) generating the corresponding vicinal diols. EETs function as chemical autocrine and paracrine mediators in the cardiovascular and renal systems, thus inhibition of sEH is hypothesized to alter the local concentration of EET's thus attenuating the cardiovascular system. Following a high-throughput screen, a benzhydryl benzamide small molecule was discovered as a potent selective sEH inhibitor. Optimization of this initial lead focused on improving the metabolic stability of the molecule while retaining the potency observed in the initial lead structure. A compound from this class was eventually identified to

display an appropriate in vitro profile as well as having desirable in vivo physiochemical properties.

MEDI 197

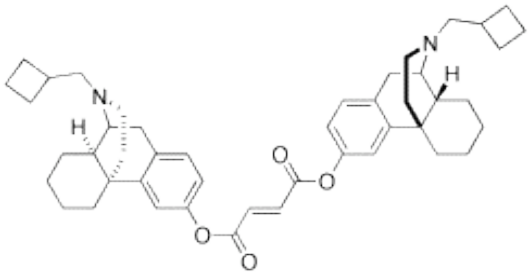
WITHDRAWN

MEDI 198

In vitro metabolic studies of a bivalent KOR agonist, MOR mixed agonist

Brian S. Fulton[1]*, Jennifer L. Mathews*[2]*, Jean M. Bidlack*[2]*, and John L. Neumeyer*[1]*. (1) Alcohol and Drug Abuse Research Center, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478, bfulton@mclean.harvard.edu, (2) Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, Rochester, NY*

Activation of the KOR has been shown to attenuate actions promoted by MOR agonists such as morphine. A novel bivalent ligand, MCL-145 (J. Med. Chem. 2000, 43, 114 – 122; J. Pharm. Exp. Ther. 2005, 315: 821 – 827) a MOR agonist/antagonist, KOR agonist, has been shown to attenuate acute morphine antinociceptive tolerance in ICR mice via a KOR-mediated mechanism. To further examine the biological properties of this ligand the chemical and biological stability of MCL-145 was studied. This ligand consists of two butorphan (J. Med. Chem. 2000, 43, 114 – 122) monomers connected by a fumarate linker. The stability of this ester bivalent ligand was examined under different in-vitro physiological conditions, e.g. neutral pH, monkey plasma, and rat brain homogenates. The stability of the compound, the stability of congeners of MCL-145, and the relevance to their in-vitro and in-vivo physiological activities will be reported.



MCL-145

MEDI 199

Withdrawn

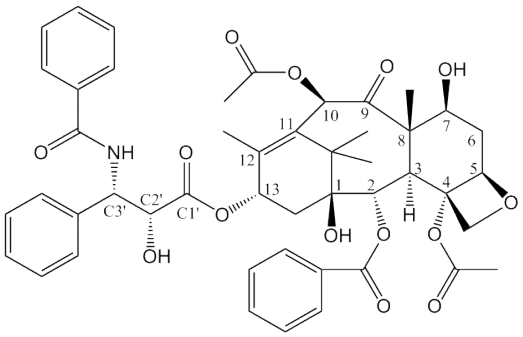
MEDI 200

Paclitaxel (Taxol®) binding to human serum albumin: Insights from computational studies

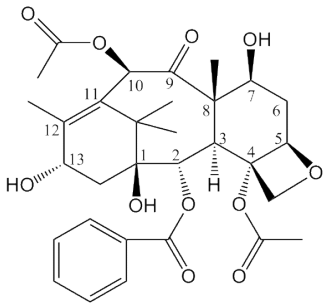
***Krisztina Paal**, Aliaksei Shkarupin, and Laura Beckford, Faculty of Science, University of Ontario Institute of Technology, 2000 Simcoe Street North, Oshawa, ON L1H 7K4, Canada, Fax: 905-721-3304, krisztina.paal@uoit.ca*

Paclitaxel is a very potent antitumor agent widely used in cancer chemotherapy. The hydrophobic nature of the drug renders its formulation difficult and also leads to extensive binding to plasma proteins such as human serum albumin (HSA).

HSA binds and transports a variety of drugs and endogenous ligands including long-chain fatty acids (LCFAs). Conformational changes caused by LCFA binding are known to affect the drug binding properties of albumin. Thus, we performed automated docking studies with two different 3D structures of HSA (fatty acid-free and fatty acid-induced conformations) to explore how paclitaxel binding is affected. The baccatin core and the C13 side chain of the drug were also studied as stand-alone ligands in order to gain insight into the binding mechanism. We found that fatty acid-induced conformational changes of HSA reduce paclitaxel affinity and alter the relative contributions of the two structural elements of the drug to the binding energy.



Paclitaxel



Baccatin III

MEDI 201

WITHDRAWN

MEDI 202

Structural dynamics of the cooperative binding of organic molecules in the human Cytochrome P450 3A4 (CYP3A4)

Dan Fishelovitch, *Department of Human Genetics, Tel-Aviv university, Ramat-Aviv Haim Levanon st, Tel-Aviv 61390, Israel, danfishl@post.tau.ac.il, Carina Hazan, Institute of Chemistry and the Lise-Meitner-Minerva Center for Computational Quantum Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel, Sason Shaik, the department of organic chemistry and the lise meitner-minerva center of computational chemistry, Hebrew University, Jerusalem 91904, Israel, Haim Wolfson, Computer Science, Tel Aviv University, Tel Aviv, Israel, and Ruth Nussinov, Basic Research Program - Macromolecular Structure, SAIC Frederick, Inc. NCI, Frederick, MD 21702*

Cytochrome P450 3A4 is a key enzyme responsible for the metabolism of 50% of all orally administered drugs which exhibit an intriguing kinetic behavior typified by sigmoidal dependence of reaction velocity vs. substrate concentration. The mechanism of cooperative binding is yet unclear. In order to better understand the mechanism of cooperative binding we carried out molecular dynamics simulations for two enzymatic conformers and examined the differences between the substrate-free and the bound enzymes, with one and two substrates. Our results indicate that the effector substrate interacts both with the active substrate and with the enzyme, and this interaction results in side chain reorientation with relatively minor long-range effects. In accord with experiment, we find that F304, in the interface between the active and effector binding sites is a key residue in the mechanism of cooperative binding. When R212 strongly interacts with F304, it counteracts the effector's impact on the enzyme.

MEDI 203

High affinity InhA inhibitors with activity against drug-resistant strains of Mycobacterium tuberculosis

Todd J. Sullivan[1], *Christopher am Ende*[1], *James J. Truglio*[2], *Francis Johnson*[3], *Ann Lenaerts*[4], *Richard A. Slayden*[4], *Caroline Kisker*[5], *and Peter J Tonge*[6]. *(1) Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400, Fax: 631-632-7960, (2) Department of Pharmacological Sciences, Center for Structural Biology, Stony Brook University, Stony Brook 11794-5115, (3) Departments of Pharmacological Sciences and Chemistry, Stony Brook University, Stony Brook, NY 11794-3400, (4) Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523, (5) Rudolf Virchow Center for Experimental Biomedicine, Institute for Structural Biology, University of Würzburg, Würzburg, Germany, (6) Institute of Chemical Biology & Drug Discovery and Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400*

Novel chemotherapeutics for treating multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (MTB) are required to combat the spread of tuberculosis, a disease that kills more than 2 million people annually. InhA, the enoyl reductase enzyme from *Mycobacterium tuberculosis* (MTB), catalyzes the last step in the fatty acid biosynthesis pathway (FAS II). Frontline anti-tuberculosis drugs such as isoniazid (INH) target this enzyme. Drug resistance to INH results primarily from mutations in KatG, the enzyme that activates INH. Consequently, InhA inhibitors that don't require activation by KatG are attractive candidates for drug discovery. One such inhibitor is triclosan, our lead compound for Structure Activity Relationship (SAR) studies, which is a common antibacterial additive in personal care products. Triclosan is a μM inhibitor of InhA and a pM inhibitor of the enoyl reductase from *E. coli* (FabI). Using structural and mechanistic data, we have developed a series of aliphatic-substituted triclosan analogs that have nM affinity for InhA and sub-μM MIC_{99} values for H37Rv MTB. The most potent compound has a K_i value of 1 nM for InhA. It also has MIC_{99} values of 2–3 μg mL^{-1} (6–10 μM) for both drug-sensitive and drug-resistant strains of MTB. (These compounds are active against five clinical strains of *Mycobacterium tuberculosis* with differing drug resistance profiles.) Second generation analogues are now being developed to investigate and address their bioavailability, solubility and cell membrane permeability. These compounds are now being evaluated in a second animal model. Of additional note, these compounds are also active (sub μM MIC's) against *Francisella tularensis*, which is one of the most infectious pathogenic bacteria known to exist and is designated a Class A agent by the U.S. government, due to its high virulence and ease of spread by aerosol. Preliminary data suggests that our compounds are active in an animal model of *F. tularensis*.

MEDI 204

Structure-based design, synthesis, and biological evaluation of novel inhibitors of Mycobacterium tuberculosis malate synthase

Justin P. Roberts[1], Inna Kriger[2], Qingan Sun[2], Eric McKee[3], Thomas R. Ioerger[3], ***Joel S. Freundlich****[1], and James C. Sacchettini[2]. (1) Department of Chemistry, Princeton University, Frick Chemical Laboratory, Princeton, NJ 08544, Fax: 609-258-1980, jprobert@Princeton.EDU, joelf@princeton.edu, (2) Department of Biochemistry and Biophysics, Texas A&M University, College Station, TX 77843-2128, (3) Department of Computer Science, Texas A&M University, College Station, TX 77843-3112*

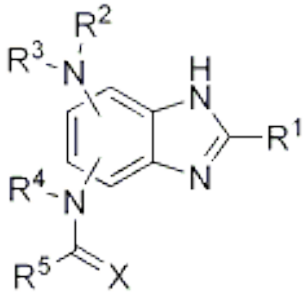
Tuberculosis is responsible for approximately two million mortalities annually. To combat this prolific disease, especially in light of the emergence of multi drug-resistant and extensively drug-resistant strains of the causative agent *Mycobacterium tuberculosis*, significant research efforts are focused on developing novel anti-tuberculars. Currently approved therapeutics are not effective against the persistent phase of this disease where, among other pathways, the glyoxylate shunt is upregulated. Malate synthase, one of the two pertinent enzymes in this bypass, has been a focus of recent efforts in our laboratories. A structure-based investigation of inhibitors of malate synthase has been undertaken in conjunction with high-throughput screening of commercially available libraries. The results of these studies are drug-like molecules with demonstrated inhibition of malate synthase and mycobacterial growth *in vitro*. These studies have the potential for seeding the discovery of a novel class of anti-tubercular agents capable of attacking the persistent phase of tuberculosis.

MEDI 205

Synthesis and optimization of a library of novel benzimidazole leads for antituberculosis drug discovery

Kunal Kumar[1]*, Seung-Yub Lee*[2]*, Ilaria Zanardi*[2]*, Richard A. Slayden*[3]*, and Iwao Ojima*[4]*. (1) Department of Chemistry, State University of New York, Stony Brook, NY 11790-3400, kukumar@ic.sunysb.edu, (2) Institute of Chemical Biology and Drug Discovery, State University of New York, Stony Brook, NY 11790-3400, (3) Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins 80523-1682, (4) Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

The development of antituberculosis drugs which are active against both drug sensitive and drug resistant M. Tuberculosis (Mtb) stains is in urgent need. Inhibition of FtsZ, a tubulin homologue, results in the absence of septation which is essential for bacterial cell division. Recently, we have found that treatment of bacteria with thiobendazole and albendazole resulted in induced filamentation, indicative of FtsZ inhibition. Accordingly we designed and synthesized a library of novel benzimidazoles through rational and systematic design. Methods for the synthesis of trisubstituted benzimidazole compounds have not been explored much, hence novel polymer-assisted solution phase methods were developed for the synthesis of a library of the first-generation trisubstituted benzimidazoles. A number of these compounds exhibited < 4 ìg/mL MIC99 activity in the preliminary screening against Mtb H37RV cells. Polymerization assay confirmed that these compounds inhibited FtsZ polymerization. We will present the synthesis, SAR studies and biological evaluations of these compounds.

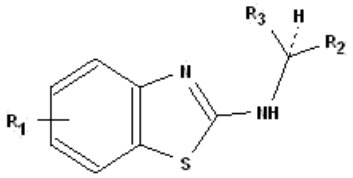


MEDI 206

Synthesis of novel optically active 2-aminobenzothiazole derivatives as antitubercular agents

Bhoomendra A. Bhongade[1]*, Malleshappa N. Noolvi*[2]*, Andanappa K. Gadad*[3]*, and Gurdial Singh*[1]*. (1) Department of Chemistry, The University of the West Indies, Watts Street, St. Augustine, Trinidad and Tobago, Fax: 868-645-3771, BBhongade@fsa.uwi.tt, (2) Department of Medicinal Chemistry, College of Pharmacy, Hubli, India, (3) School of Pharmacy, Faculty of Medical Sciences, The University of The West Indies, Mount Hope, Trinidad and Tobago*

With the emergence of the multi-drug resistance tuberculosis (MDR-TB) strains and its association with various infections particularly in AIDS patients has rendered the existing drugs ineffective thus posing new problems new challenges in the control of disease as well as the development of new drugs. Several new classes of drugs are being explored to overcome this problem. In view of this and the biological potentials of benzothiazoles, here with we report synthesis and anti-TB activity of novel optically active 2-aminobenzothiazoles of general structure I obtained from appropriate aryl amines in three steps. The title compounds were purified by column chromatography and the structures were confirmed from the spectral data (IR, 1H, 13C-NMR). Some of the synthesized compounds exhibited promising anti-TB activity in micro molar range.



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MEDI 207

Addiction and brain mechanisms

***Barry Hoffer**, National Institute for Drug Abuse, National Institutes of Health, 5500 Nathan Shock Drive, Baltimore, MD 21224, BHOFFER@intra.nida.nih.gov*

A major unfilled need in the medical community is effective medication for treatment of drug addiction. This talk will initially briefly review our understanding of the brain mechanisms involved in drug addiction from neurochemical, genetic and brain imaging perspectives. Afterwards, a review of animal models useful for testing potential medications will be presented together with data showing efficacy of various classes of agents in preclinical tests: long acting DAT blockers, D3 receptor antagonists, CB1 cannabinoid receptor antagonists, and GABA receptor agonists. Finally, details of the relapse/reinstatement model will be presented together with potential medications effective in this model.

MEDI 208

Serendipity rediscovered — an oxymoron or rational drug design: Studies on subtype selective BzR/GABAergic ligands

James M. Cook[1], *Harry June*[2], *Elise Weerts*[3], *Micheal L. Van Linn*[1], *Donna Platt*[4], *Tim DeLorey*[5], *Miroslav Savic*[6], *and Terry Clayton*[1]. *(1) Department of Chemistry and Biochemistry, University of Wisconsin Milwaukee Wisconsin, Milwaukee, WI 53211, capncook@uwm.edu, (2) School of Medicine, University of Maryland, (3) Behavioral Biology Research Center, John Hopkins Bayview Medical Center, (4) Behavioral Biology, Harvard Medical School, (5) Molecular Research Institute, Moltech Corporation, (6) Department of Pharmacology, University of Belgrade*

Recently we have developed a series of subtype selective ligands for BzR/GABAergic receptors. In this series of agents, 3-PβC•HCl and βCCt have been shown to decrease alcohol self-administration in alcohol preferring rats (June, et. al.) and more recently in baboons (Weerts, et. al.) and rhesus monkeys (Platt, et. al.), respectively. In a different study, α5 subtype selective ligands have been developed which bind with potent affinity only at α5 BzR subtypes and enhance cognition in animal models. Moreover, these ligands exhibit weak inverse agonist activity at α5 subtypes and very weak agonist activity at α2 subtypes. The lead compound was able to reverse the scopolamine-induced deficits in cognition in the trace fear conditioning paradigm in contextual memory but not in audio cued memory (DeLorey et. al.). Recent results in these areas will be presented.

MEDI 209

Ligand based structural biology of the endocannabinoid system

Alexandros Makriyannis*, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115, a.makriyannis@neu.edu*

The proteins comprising the endocannabinoid system which include two GPCRs (CB1 and CB2), a number of metabolizing and biosynthetic enzymes and a putative transporter system are suitable targets for drug development. Structural information on the catalytic sites of these proteins allows us to design novel ligands with improved pharmacological properties. We have developed a method for obtaining direct information on the binding motif of ligands with the CB1 and CB2 receptors as well as other endocannabinoid proteins using high affinity covalent ligands. Our approach combines chemical and biochemical methods aimed at identifying the site of covalent attachment of the ligand. This is accomplished through the use of suitable receptor mutants, receptor expression, followed by purification and analysis of the digests using mass spectroscopic methods. The information is used to develop models for ligand-receptor interactions. Supported by R37-DA03801 and P01-DA-09158.

MEDI 210

Development of potential drug abuse medications derived from the hallucinogenic natural product salvinorin A

***Thomas E. Prisinzano**, Division of Medicinal & Natural Products Chemistry, University of Iowa, S327 PHAR, MNPC, 115 S. Grand Avenue, Iowa City, IA 52242, Fax: 319-335-8766, thomas-prisinzano@uiowa.edu*

Drug abuse is a major public health problem in the United States. A large body of evidence indicates that κ opioid receptors (κORs) are involved in the abuse related effects of drugs subject to abuse and may offer a pharmacological target to treat drug abuse and its attendant pathology. κORs have also been implicated in the actions of *Salvia divinorum*, a hallucinogenic mint plant that is currently unscheduled and readily available to the public over the internet. The active component of *S. divinorum*, the neoclerodane diterpene salvinorin A, has been identified as a potent and selective κOR ligand. As part of our program to develop novel compounds to treat drug dependence, we have begun to investigate the structure-activity relationships of the salvinorin A at opioid receptors. Here, we report that structural modification of salvinorin A has resulted in the identification of novel neoclerodane diterpenes with opioid receptor affinity and activity.

MEDI 211

Medicinal chemistry in drug abuse research

***Kenner C. Rice**, Chemical Biology Research Branch, National Institute on Drug Abuse, National Institutes of Health, Building 8, Rm. B1-22, 8 Center Drive, MSC0815, Bethesda, MD 20892, Fax: 301-402-0589, kr21f@nih.gov*

The annual economic cost of the abuse of legal and illegal drugs to the U.S. is estimated at more than $500 billion and the worldwide human cost to drug abusers and their families is enormous. Recent research has shown that chronic drug abuse alters multiple brain centers and their function, and that genes, stress and various environmental factors play a central role in such behavior. Our group has taken an organic and medicinal chemical approach to the study of drugs of abuse by the design and synthesis of novel ligands as (a) probes for study of their mechanism of action and (b) agents for the treatment and prevention of drug abuse. This presentation will include some of our studies on imaging agents, potential stimulant abuse medications, agents for study of the stress system, and the development of the NIH Opiate Total Synthesis as a practical route to either enantiomer of morphine alkaloids and their derivatives as research tools and drugs.

MEDI 212

Captopril: A look back

***Edward W. Petrillo**, Discovery Performance Strategies, 5 Walking Purchase Drive, Pennington, NJ 08534, Fax: 609-737-1054, edward.petrillo@gmail.com*

When Miguel Ondetti and David Cushman invented captopril, the first orally active angiotensin-converting enzyme (ACE) inhibitor, they demonstrated the power of understanding the detailed interaction of drugs with molecular targets. Their design hypothesis, developed without the benefit of protein sequence and three-dimensional structure that are routinely available today,

guided the design of every subsequent ACE inhibitor and heralded the onset of the most productive era in the history of medicinal chemistry. The clinical introduction of ACE inhibitors transformed cardiovascular medicine and eased the suffering of millions. These events can now be reviewed in light of newly-available structural information on ACE and deeper insight into the role of the renin-angiotensin system.

MEDI 213

The birth of Risperdal®

***Ludo E. J. Kennis**, Johnson & Johnson Pharmaceutical R&D LLC, Turnhoutseweg 30, 2340 Beerse, Belgium, ludo.kennis@pandora.de*

The success of Haldol (Haloperidol) was a strong stimulant to look for a successor and stay in the market of psychiatry. The profile of the successor had to be " better " than Haldol. Chemical modification of existing antipsychotic structures has led to several candidates like milenperone and setoperone. The project also resulted in interesting candidates in other applications like domperidone, oxatomide, ketanserin and ritanserin. Finally it took 11 years in the chemical discovery for the birth of risperidone and ocaperidone. Although the positive symptoms can be controlled today, the search for an antipsychotic therapy which can also control the negative and cognitive aspects in psychiatry is still going on.

MEDI 214

Discovery of Singulair® and its impact on treatment of asthma in children and adults

***Robert N. Young**, Department of Chemistry, Merck Frosst Canada Inc. and Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada, Fax: 604-291-3765, robert_young@sfu.ca*

In the late 1970's the cysteinyl leukotrienes (CysLTs) were identified as novel peptidolipid mediators that were the active principles in "Slow Reacting Substance of Anaphylaxis (SRS-A)" and their role in the etiology of asthma was postulated. In 1979 a project was initiated at Merck Frosst first to synthesize leukotrienes, and then to discover potent and orally active inhibitors of leukotriene biosynthesis or antagonists of CysLT1, (the receptor for leukotriene D4, the most potent of the CysLTs). Sustained and intensive efforts over almost 20 years identified a number of development candidates, which reached clinical trials but were not deemed acceptable, before the discovery and development of the CysLT1 receptor antagonist, SINGULAIR (montelukast, MK-0476). SINGULAIR was approved by the FDA in 1998 as a well-tolerated and effective therapy for the treatment of chronic asthma, and is now approved also for allergic rhinitis. The success of SINGULAIR is due to its efficacy with rapid onset, excellent safety profile, simple once-daily oral dosing (including formulations optimized for children) and lack of significant drug or food interactions. SINGULAIR is one of the few drugs approved at initial launch for use by adults and by children (initially as young as 6 years) and is now approved for marketing in at least 109 countries and for use in infants as young as age 6 months. As the only well-tolerated oral agent that is effective both for asthma and for allergic rhinitis, SINGULAIR has changed the management of respiratory disease all around the world.

MEDI 215

The discovery and development of imatinib, a new paradigm for small molecule targeted cancer therapy

***Ulrike B. Pfaar**, Oncology, Novartis Pharma AG, WKL-4.90.1.32, Klybeckstr. 141, Basel CH-4056, Switzerland, Fax: +41 61 6962299, ulrike.pfaar@novartis.com*

Imatinib (Gleevec™) is used as first-line treatment of chronic myeloid leukemia (CML) and for Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Abl tyrosine kinase activity of Bcr-Abl in vitro and in vivo. The discovery of imatinib, however, also provided insight into principal mechanisms of resistance occurring in accelerated or blast-crisis CML patients. This stimulated the tailored drug development of nilotinib and dasatinib for treatment of CML in imatinib-resistant patients. In addition, imatinib is a potent inhibitor of the receptor kinase for stem cell factor, c-Kit and of the platelet-derived growth factor receptor kinase (PDGF-R). As a consequence of these activities, Imatinib is also indicated for other indications such as the treatment of gastrointestinal stromal tumors GISTs driven by deregulated c-Kit signaling, and hypereosinophilic syndrome driven by deregulated PDGF-R signaling.

MEDI 216

Discovery and development of Zetia®: Serendipity and design in the discovery of ezetimibe

***Duane A. Burnett**, CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, MS 2800, Kenilworth, NJ 07033, duane.burnett@spcorp.com*

Lowering atherogenic LDL cholesterol in man has been shown to lower the incidence of heart disease and extend lives. While HMG-CoA reductase inhibitors have been particularly effective in this endeavor, they primarily treat endogenously synthesized cholesterol and have little impact on dietary or intestinally derived cholesterol. In our efforts to affect this second source of cholesterol, we discovered a novel class of β-lactam cholesterol absorption inhibitors that operated via an unknown mechanism. Optimization of the in vivo SAR lead to the discovery of our first clinical candidate, SCH 48461. A close examination of the metabolism of this compound revealed an important oxidative metabolite with greatly improved potency. Incorporation of this “positive metabolism” and blocking additional sites led to the discovery of ezetimibe. Ezetimibe is the first molecular entity approved for use as a cholesterol absorption inhibitor alone or in combination with statins to treat hypercholesterolemia.

MEDI 217

Migraine: An overview beyond triptans

***Charles M. Conway**, Neuroscience Biology, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492*

Over 300 million people worldwide are migraineurs and nearly 20 million migraine attacks occur every day, according to recent estimates by the World Health Organization and others (Ref). Before the 1990's, migraine was treated mainly using NSAIDs and ergotamines, usually with limited success. With the introduction of the 5-HT1B/1D receptor agonist Imitrex® (sumatriptan), response rates significantly improved. A broad range of triptan options are now available including Amerge® (naratriptan), Axert® (almotriptan), Frova® (frovatriptan), Maxalt® (rizatriptan), Relpax® (elatriptan), and Zomig® (zolmitriptan). However, the triptans, are not without side-effects and, due to their active vasoconstrictive properties, include labeling that limits their broad utility (e.g., contraindicated in patients with ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, or uncontrolled hypertension). The need clearly exists for novel approaches beyond the triptans for treating migraine, and new mechanisms are being explored. In addition, migraine sufferers would benefit from modes of drug delivery that provide faster onset of relief than is usually obtained with traditional oral pills, especially given the nausea and gastric stasis that can accompany the disorder.

MEDI 218

Selective iGluR5 antagonists for the treatment of migraine

***Paul L. Ornstein**, Sandra A. Filla, Kevin J. Hudziak, Smriti Iyengar, David Bleakman, Ken H. Ho, Donna K. Dieckman, Amy C. Smith, and Kirk W. Johnson, Discovery Research, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, ornsteinpl@lilly.com*

The discovery of sumatriptan and related compounds has revolutionized the treatment of migraine. However, there still remains a need to identify novel therapies with distinct mechanisms of action to enhance the arsenal available to physicians to treat this condition. Our identification of novel, selective antagonists for iGluR5 kainate receptors allowed us to generate pharmacological evidence in support of these agents as novel migraine therapy. Through structure activity studies on a series of 6-substituted decahydroisoquinolines, we've discovered novel, potent, subtype selective iGluR5 antagonists. In this talk we will present aspects of these SAR studies as well as data that show the potential for these compounds to treat migraine.

MEDI 219

Calcitonin gene-related peptide receptor antagonists for the treatment of migraine

***Theresa M. Williams**[1], Christopher S. Burgey[1], Daniel V. Paone[1], Anthony W. Shaw[1], Ian M. Bell[1], James Z. Deng[1], Jane deSolms[2], Steven N. Gallicchio[1], Diem N. Nguyen[1], Craig M. Potteiger[1], Craig A. Stump[1], Amy G. Quigley[1], Cory R. Theberge[1], Bang-Lin Wan[1], C. Blair Zartman[1], Xu-Fang Zhang[1], Priya Kunapuli[3], Stefanie A. Kane[4], Ken S. Koblan[4], Rodney A. Bednar[4], Victor K. Johnston[4], John J. Mallee[4], Scott D. Mosser[4], Ruth Z. Rutledge[4], Christopher Salvatore[4], Daniel R. McMasters[5], James C. Hershey[6], Halea Corcoran[6], Betsy Lyle[6], Bradley Wong[2], Shane Roller[2], Cynthia M. Miller-Stein[7], Janice F. Rowe[7], Sean Yu[7], Samuel L. Graham[1], and Joseph P. Vacca[1]. (1) Medicinal Chemistry Department, Merck & Co. Inc, 770 Sumneytown Pike, PO Box 4 West Point, PA 19486-0004, Fax: 215-6523971, theresa_williams@merck.com, (2) (3) Automated Biotechnology NW-1, Merck & Co. Inc, PO*

Box 4, PA 19486-0004, (4) Pain Research, Merck & Co. Inc, PO Box 4 West Point, PA 19486-0004, (5) Molecular Systems, Merck & Co. Inc, PO Box 4 West Point, PA 19486-0004, (6) Molecular Endocrinology, Merck & Co. Inc, PO Box 4 West Point, PA 19486-0004, (7) Drug Metabolism, Merck & Co. Inc, PO Box 4 West Point, PA 19486-0004

Antagonists of the Calcitonin Gene-Related Peptide (CGRP) receptor represent a promising new approach for the treatment of migraine headache. CGRP is a vasodilator and neuropeptide involved in the pathogenesis of migraine headache. In a Phase II clinical study, intravenous infusion of the Boehringer-Ingelheim CGRP antagonist BIBN4096BS effectively relieved migraine pain and was well-tolerated. No cardiovascular or cerebrovascular effects were observed. Since CGRP receptor antagonists lack direct vasoconstrictor activity, this approach may offer advantages over current 5–$HT_{1B/1D}$ receptor agonists, where cardiovascular liabilities are a major perceived risk Ideally a CGRP receptor antagonist would be given orally. High throughput screening at Merck focused on discovering compounds with the potential to be developed into orally active CGRP receptor antagonists. A non-peptide lead structure with micromolar affinity for the CGRP receptor was identified. Although its high molecular weight and weak receptor affinity were disadvantages, several features of the molecule were attractive from the standpoint of lead optimization. The compound had a modular structure that linked a benzodiazepine core to a novel tetralin spirohydantoin. Structure activity studies identified key areas of the lead that contributed to receptor affinity, and optimization produced significant enhancements in potency. Pharmacokinetic studies focused on achieving oral bioavailability. Promising compounds were profiled in a novel pharmacodynamic model based on capsaicin-induced CGRP release in rhesus monkeys. Elements of design and optimization leading to MK-0974, an orally bioavailable CGRP receptor antagonist currently in clinical trials, will be discussed.

MEDI 220

Design and synthesis of potent cgrp antagonists for migraine

Prasad Chaturvedula[1]*, Gene M. Dubowchik*[1]*, Andrew P Degan*[1]*, Xiaojun Han*[1]*, Charles M. Conway*[2]*, Deborah Cook*[2]*, Carl Davis*[3]*, Rex Denton*[4]*, Robert Macci*[5]*, Neil R Mathias*[6]*, Sokhom Pin*[2]*, Laura Signor*[2]*, George Thalody*[2]*, Richard Schartman*[5]*, Kimberly A Widmann*[7]*, Cen Xu*[2]*, and John E. Macor*[1]*. (1) Neuroscience Chemistry, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492, (2) Neuroscience Biology, Bristol-Myers Squibb, Wallingford, CT 06492, (3) Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Wallingford, CT 06492, (4) Discovery Toxicology, Bristol-Myers Squibb, Wallingford, CT 06492, (5) Pharmaceutics, Bristol-Myers Squibb, Wallingford, CT 06492, (6) Pharmaceutical Development, Bristol-Myers Squibb, New Brunswick, NJ 08903, (7) Bioanalytical Research, Bristol-Myers Squibb, Wallingford, CT 06492*

Calcitonin Gene Related Peptide (CGRP), a naturally occurring 37 amino-acid peptide, has been implicated in the pathogenesis of migraine. Multiple lines of clinical evidence point to a role for CGRP in migraine. Treatment with a CGRP receptor antagonist would alleviate migraine by returning dilated intracranial arteries to normal without the liabilities of active vasoconstriction associated with triptans. Our medicinal chemistry effort has focused on the identification of potent CGRP antagonists with systemic bioavailability and potential for rapid onset of action. We will describe the design and synthesis of novel amino acids and GPCR

privileged structures leading to potent CGRP antagonists with excellent aqueous solubility. The compounds display good systemic bioavailability and show dose-dependent activity in a validated in vivo marmoset migraine model.

MEDI 221

Thermally-generated aerosol prochlorperazine as a fast-acting treatment for migraine

***James V. Cassella**, Alexza Pharmaceuticals, 1020 East Meadow Circle, Palo Alto, CA 94303*

Fast relief of the pain and associated symptoms of migraine is compromised in the most commonly used prescription therapies by the relatively slow onset inherent in traditional oral delivery. The Staccato™ system is designed to administer drugs as thermally-generated condensation aerosols to the deep lung. This handheld portable device allows for a non-invasive, inhaled administration of prochlorperazine (PCZ), resulting in rapid systemic absorption. This presentation describes the Staccato™ system as well as results of Phase I and IIa clinical testing with Staccato PCZ (AZ-001). Phase I: Eight healthy volunteers initially received 0.625 mg AZ-001 and 0.5 mg IV PCZ over 5 sec in a randomized crossover design. Tmax for AZ-001 was 1.8±0.6 min. All PK parameters were equivalent to the IV dosing. In the dose escalation follow on, 40 volunteers in parallel blinded cohorts of eight AZ-001 (doses: 1.25, 2.5, 5 or 10 mg) + 2 placebo were dosed. IV-like kinetics and dose proportionality were demonstrated across the five dose groups. Phase IIa: A multi-center, randomized, double-blind, placebo-controlled trial enrolled male and female patients with migraine headache. Subjects with a pain rating of moderate or severe were randomized to receive either 5 or 10 mg AZ-001 or placebo. A total of 73 patients completed the in-clinic 2 hr evaluation. Survival difference was statistically significant for the 10 mg dose group vs placebo for patients in the intent to treat analysis. An analysis based on treatment-received showed that pain-free scores were statistically significant compared to placebo for the 10 mg dose group at the 30, 45, 60 and 120 minute time points. There were no serious adverse events and AZ-001 was generally well tolerated.

MEDI 222

Evaluation of reactive metabolites in pharmaceutical discovery and development

***Sidney D. Nelson**, Department of Medicinal Chemistry, University of Washington, Seattle, WA 98195, Fax: 206 685 9297, sidnels@u.washington.edu*

Some drugs either have been removed from the market, or have been labeled with "black box" warnings because they have caused life-threatening toxic effects. Most of these toxicities are idiosyncratic, and evidence suggests that most are caused by reactive metabolites. Over the past 25 years, knowledge has accumulated concerning chemical substructures that form reactive metabolites, which will be one focus of this presentation. A second focus will be a discussion of two general approaches that some pharmaceutical companies are using in their discovery and development programs to help make benefit/risk decisions concerning drug candidates. One approach uses methodologies (e.g. covalent binding) that can be said to rapidly, but crudely, assess reactive metabolite interactions with cellular proteins. Other

approaches utilize "omic" technologies to assess possible effects of reactive metabolites on dysregulation of various cellular regulatory pathways. Examples of each approach will be highlighted with examples. Finally, there will be some discussion of the advantages and disadvantages of each approach, and how some improvements to each might yield information that is more revealing concerning mechanisms of toxicity.

MEDI 223

Bioactivation and drug design: Challenges in predicting the occurrence of idiosyncratic adverse drug reactions in early discovery

***Amit S Kalgutkar**, Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, Fax: 860-686-1059, amit_kalgutkar@pfizer.com*

The issue of chemically reactive drug metabolites is one of growing concern in the pharmaceutical industry inasmuch as some, but not all, reactive intermediates are believed to play a role as mediators of drug-induced toxicities. Reactive metabolites, if not detoxified, can covalently modify essential cellular targets. The identity of the susceptible biomacromolecule(s), and the physiological consequence of its covalent modification, will dictate the resulting toxicological response. While it is now relatively straightforward to identify these short-lived electrophilic species through appropriate in vitro "trapping" experiments, our current understanding of mechanistic aspects of drug-induced toxicities is such that we cannot predict which reactive intermediates are likely to cause a toxic insult and which will be benign. As a result, several companies have adopted approaches to minimize the potential for bioactivation of drug candidates at the discovery/lead optimization phase as a default strategy. Literature and in-house examples, which highlight all of the attributes described above, will be presented.

MEDI 224

Predicting the toxicological consequences of drug-derived reactive metabolites: Nitric oxide synthase as a model

***Yoichi Osawa**, Department of Pharmacology, University of Michigan, Ann Arbor, MI 48103, Fax: 734 763 4450, osawa@umich.edu*

Nitric oxide synthases (NOS) are cytochrome P450-like hemoprotein enzymes that catalyze the conversion of L-arginine to citrulline and NO. NO is a gaseous signaling molecule that is involved in a variety of physiological processes, including neurotransmission and penile erection. NOS was used as model to probe how drug-derived reactive metabolites cause NOS dysfunction and toxicity. We found that certain guanidine-based drugs are metabolized by NOS to reactive intermediates that cause the inactivation, covalent alteration, and enhanced proteasomal degradation of NOS. Moreover, the hsp90- and hsp70- based chaperones were found to play a critical role in directing the selective culling or repair of the inactivated NOS. We present a model that describes how chaperones recognize covalently altered proteins and direct NOS protein quality control. These studies indicate that drug-mediated stabilization and

destabilization of proteins is an important consideration in the pharmacological and toxicological aspects of drug development. Supported in part by NIH GM77430 and DA22354

MEDI 225

Modeling and informatics support for safety and metabolism studies in early drug discovery projects

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

Access to metabolism and toxicology data is critical to effective decision making in early drug discovery projects, but simply providing unstructured metabolism- and safety-related information on targets and chemical series to project teams trying to make decisions is not adequate due to the varied nature and quality of metabolism and toxicology data. This presentation includes project examples of how relevant data can be structured, mined and in some cases modelled to enhance decision-making. Brief descriptions of the varying data types and their usage in project decision making will be presented along with some strategies for hypothesis generation around adverse events using a combined approach of molecular modelling/virtual screening and text mining. Together, these tools, built to be appropriate to the various data types, represent a basic toolkit for the toxicologist and drug metabolism scientist needing to make meaningful contributions to the myriad decisions made in early drug discovery projects.

MEDI 226

Comparative performance of folate-targeted transfection complexes derived from a family of bisvinyl ether cationic lipids

*Jeroen Van den Bossche and **David H. Thompson**, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, Fax: 765-496-2592, jvandenb@purdue.edu, davethom@purdue.edu*

The development of non-viral vectors for gene delivery that can rival the efficiency of viral vectors is an unmet challenge in the development of safe artificial gene delivery vehicles. Of the many known barriers to efficient transfection, control over intracellular trafficking and release from acidic endosomal compartments are among the most poorly understood steps in this multistep process. We report the synthesis, complexation behavior, intracellular uptake and expression levels of a family of acid-labile vinyl ether cationic lipids with diethylenetriamine headgroups. Folate-bearing lipoplexes formed by these lipids have been designed to target acidic endosomes via receptor-mediated endocytosis using folic acid conjugates as the targeting agent. Once inside acidic endosomes, the lipoplexes undergo degradation and endosomal escape, presumably by permeabilization of the endosomal membrane via detergent action of the lipid hydrolysis products as reported for a related compound, BCAT, developed in our laboratory (Pharm. Res. 2002 19, 1292).

MEDI 227

Folate receptor-targeted therapies for inflammatory and autoimmune diseases

***Philip S. Low**, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, Fax: 765-494-5272, Chrystal M Paulos, Surgery Branch, National Cancer Institute/National Institute of Health, Bethesda, MD 20892, and Bindu Varghese, Chemistry, Purdue University, West Lafayette, IN 47907*

Activated (but not quiescent) macrophages release multiple mediators of inflammation including TNF-alpha, IL-1, IL-6, prostaglandins, reactive oxygen species, and numerous degradative enzymes. Activated macrophages (but not quiescent macrophages or most other normal cells) also express elevated numbers of folate receptors (FR) that allow selective targeting of folate-linked drugs/imaging agents to the same cells. Because many inflammatory and autoimmune diseases, including rheumatoid arthritis, atherosclerosis, stroke, psoriasis, Crohn's disease, osteoarthritis, ischemia/reperfusion injury, glomerulonephritis, lupus, and sarcoidosis are characterized by significant activated macrophage involvement, these same diseases can be imaged and treated by folate-conjugated imaging and therapeutic agents. This seminar will summarize preclinical and clinical progress aimed at exploiting FR targeting to diagnose and treat the aforementioned inflammatory diseases. Because FR targeted drugs avoid uptake by most nonpathologic tissues, toxicity associated with nontargeted anti-inflammatory drugs appears to be largely avoided by folate targeting.

MEDI 228

Intraliposomal stabilization of anticancer drugs

***Daryl C. Drummond**, Hermes Biosciences, 61 Airport Blvd., Suite D, South San Francisco, CA 94080, Fax: 650-873-2501, drummond@hermesbio.com*

Controlling the rate of drug release from liposomal carriers is essential for optimum drug delivery. We have developed a novel nanoliposome construct encapsulating a variety of difficult to entrap anticancer drugs, including irinotecan, vincristine, topotecan, vinorelbine, and the histone deacetylase inhibitor LAQ824 with a high degree of drug loading efficiency and in vivo retention. Using a modified gradient loading method featuring a sterically hindered amine with highly charged, multivalent anionic trapping agents, including both polymeric (polyphosphate) or non-polymeric (sucrose octasulfate or inositol hexaphosphate) agents, liposomes were capable of entrapping drugs at exceptionally high drug-to-lipid ratios (> 1000 g CPT-11/mol phospholipid) and retaining encapsulated drug in vivo with a half-life of drug release significantly improved compared to formulations prepared using more standard loading technologies (t1/2 for nanoliposomal CPT11, vinorelbine, and LAQ824 was 56.8, 27.2, and 26.1 h, respectively). The acute toxicity of various liposomal formulations was affected differently, with the MTD of the liposomal formulation increasing considerably for CPT11 compared to the free drug (>320 vs 60 mg/kg), remaining similar for others (VNB), and decreasing for others (TPT and LAQ824). However, the observed therapeutic index was improved for all the drugs studied following stable liposome encapsulation.

Nanoliposomal CPT-11 demonstrated markedly superior efficacy when compared to free CPT-11 in human breast (BT474) and colon (HT29) cancer xenograft models, while nanoliposomal vinorelbine displayed improved activity in a wide range of lung, colon, and breast cancer xenograft models. LAQ824 displayed improved efficacy and also demonstrated improved histone acetylation levels and ErbB2 receptor downregulation over extended periods when encapsulated. These studies shows that intraliposomal stabilization of many anticancer drugs using a polymeric or highly charged, non-polymeric polyanionic trapping agent results in stable and long circulating nanocarrier formulations of important drugs and strikingly active antitumor agents.

MEDI 229

Mechanism of the translocation of guanidium-rich peptides into cells

Jonathan Rothbard[1]*, Paul A. Wender*[2]*, and Tad Jessop*[1]*. (1) Department of Chemistry, Stanford University, Stanford, CA 94305, rothbardj@gmail.com, (2) Department of Chemistry, Department of Molecular Pharmacology, Stanford University, Stanford, CA 94305*

A series of experiments will be presented that provide a mechanistic hypothesis for how short oligomers of arginine can migrate across the plasma membrane of a cell. The water soluble, positively charged guanidinium headgroups of the transporter form bidentate hydrogen bonds with H-bond acceptor functionality on the cell surface, with ion exchange of its counterions. The resultant ion pair complexes partition into the lipid bilayer and migrate across at a rate related to the membrane potential. The complex dissociates on the inner leaf of the membrane and the transporter enters the cytosol. This mechanism is consistent with the apparent lack of stereospecificity in the process, because the key feature is the formation of the bidentate hydrogen bonds with the guanidine head groups, and not the stereochemistry of the backbone. Similar logic explains why there is neither a structural requirement for a unique spacing of the guanidines extending from the backbone, nor along the backbone and even can rationalize why dendrimers and oligosaccharides decorated with sufficient number of guanidines are transported effectively. The requirement for a minimum number of guanidines required for transport is explained because peptides with greater guanidine content will form more hydrogen bonds and bind to the surface with greater affinity, thus increasing the local concentration. This hypothesis does not preclude competing uptake by other mechanisms including endocytosis, which is likely to dominate with large cargos.

MEDI 230

Synthetic mimics of mammalian cell surface receptors: New tools for drug delivery

Blake R. Peterson*, Department of Chemistry, The Pennsylvania State University, 104 Chemistry Bldg, University Park, PA 16802, Fax: 814-863-5319, brpeters@chem.psu.edu*

Receptors on the surface of mammalian cells promote the cellular uptake of proteins and other nutrients through the mechanism of receptor-mediated endocytosis. To mimic this process, we are synthesizing artificial receptors that function as prosthetic molecules on the cell surface; they insert into cellular plasma membranes, project ligand-binding motifs into the extracellular

environment, and enable cells to actively internalize cell-impermeable compounds. These synthetic receptors comprise the plasma membrane anchor N-alkyl-3beta-cholesterylamine linked to motifs that bind proteins and cell-impermeable drugs. When added to living mammalian cells, these prosthetic molecules rapidly cycle between plasma membranes and intracellular endosomes, promoting the delivery of ligands into intracellular compartments. Because of their ability to define new pathways across biological membrane barriers, synthetic cell surface receptors represent promising tools for drug delivery.

MEDI 231

KXO1: The first non-ATP competitive Src inhibitor for clinical development in oncology applications-1

David G Hangauer[1]*, Irwin Gelman*[2]*, Lyn Dyster*[1]*, Allen Barnett*[1]*, Michael Smolinski*[1]*, Taher Hegab*[1]*, and Lingqiu Gao*[2]*. (1) Kinex Pharmaceuticals, New York State Center of Excellence in Bioinformatics & Life Sciences, 701 Ellicott St., Buffalo, NY 14203, dhangauer@kinexpharma.com, (2) Roswell Park Cancer Institute, Buffalo, NY 14263*

Utilizing Kinex Pharmaceuticals platform technology, MimeticaTM, KXO1 was discovered as a novel small molecule Src tyrosine kinase inhibitor. KXO1 targets the peptide substrate binding site rather than the ATP site wherein most tyrosine kinase inhibitors bind. This unique binding site provides much higher selectivity than is obtained with ATP competitive Src inhibitors. KXO1 inhibits Src kinase activity in whole cells with low nM potency and is >1,000-fold less active against other tyrosine kinases such as EGFRTK, PDGFRTK, JAK1, JAK2, ZAP70 and Lck. KXO1 is also a low nM potency inhibitor of cancer cell growth for a broad range of solid tumor and leukemia cancer cell types in vitro, and is orally effective in animal tumor models. KXO1 has successfully completed preclinical development for oncology applications and will be the first non-ATP competitive Src inhibitor to enter clinical trials.

MEDI 232

KXO1: The first non-ATP competitive Src inhibitor for clinical development in oncology applications-2

David G Hangauer[1]*, Irwin Gelman*[2]*, Lyn Dyster*[1]*, Allen Barnett*[1]*, Michael Smolinski*[1]*, Taher Hegab*[1]*, and Lingqiu Gao*[2]*. (1) Kinex Pharmaceuticals, New York State Center of Excellence in Bioinformatics & Life Sciences, 701 Ellicott St., Buffalo, NY 14203, dhangauer@kinexpharma.com, (2) Roswell Park Cancer Institute, Buffalo, NY 14263*

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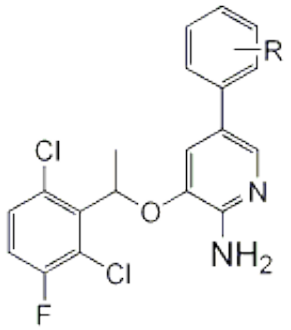
KXO1 has successfully completed preclinical development for oncology applications and will be the first non-ATP competitive Src inhibitor to enter clinical trials.

MEDI 233

Discovery and chiral synthesis of potent c-Met (HGFR) aminopyridine inhibitors

***Pei-Pei Kung**, Department of Medicinal Chemistry, Pfizer, PGRD, 10770 Science Center Drive, San Diego, CA 92121, Fax: 858-526-4447, peipei.kung@pfizer.com*

The discovery of potent and selective c-Met (HGFR) 2-aminopyridine-4-phenyl inhibitors is presented. Optimization of the kinase inhibitory potency (Ki=210 nM) and the cell potency of the initial lead (IC50=1 microM) is described. This optimization effort involved synthesizing 30 compounds and led to the discovery of a lead compound with improved potency (Ki=20 nM; IC50=40 nM), metabolic stability (t1/2=260 min) and physical properties (solubility>200 microM) relative to the initial lead. The development of a chiral synthetic route to this improved molecule utilizing biotransformation is also described along with PK/PD and TGI experiments.



MEDI 234

New perspectives on the medicinal chemistry of the somatostatin receptor agonist SOM230

***Ian Lewis**, Rainer Albert, Janos Pless, Rainer Kneuer, Herbert A. Schmid, Antonio P. Silva, Daniel Hoyer, Gisbert Weckbecker, and Christian Bruns, Global Discovery Chemistry, Novartis Institutes of Biomedical Research, S-507.3.03, CH-4002 Basel, Switzerland, Fax: +41 61 324 7821, ian.lewis@novartis.com*

The somatostatin (SRIF, somatotropin release inhibiting factor) field has been a success story in terms of medicinal chemistry and drug discovery offering a variety of therapeutic opportunities, e.g. acromegaly, gastrointestinal neuroendocrine tumors, whole body imaging and radiotherapy. Indeed, a rational medicinal chemistry approach capitalising on structure activity relationships led to the discovery of SOM230, stable cyclohexapeptide somatostatin analogue which exhibits unique binding to human SRIF receptors (sst1-5). This approach, based on transposing functional groups, in the form of unnatural amino acids, from SRIF-14 into the stable, reduced size cyclohexapeptide template. Further, the hydroxyproline urethane extension of SOM230 has been functionalized with the chelators DTPA and DOTA, which is a

necessary prerequisite for the possible development of ligands which could be used for whole body imaging. Uniquely, SOM230 exhibits binding with a 30 to 40 times higher affinity than Sandostatin® to the sst1 and sst5 receptors and exhibits higher efficacy in preclinical models in lowering Growth Hormone, Insulin-Like Growth Factor-1, ACTH and corticosterone than Sandostatin®. Phase III clinical studies are underway to establish the therapeutic potential of SOM230 including novel treatment of Cushing's disease.

MEDI 235

Modulation of peripheral serotonin levels by enzyme inhibitors for the potential treatment of irritable bowel syndrome (IBS)

Zhi-Cai Shi[1]*, Raj Devasagayaraj*[1]*, Kunjian Gu*[1]*, Haihong Jin*[1]*, S David Kimball*[1]*, Brett Marinelli*[1]*, Lakshman Samala*[1]*, Sheldon Scott*[1]*, Ashok Tunoori*[1]*, Ying Wang*[1]*, Yi Zang*[1]*, Chengmin Zhang*[1]*, Terry Stouch*[1]*, Jim Liu*[2]*, Dave Powell*[3]*, Weimei Sun*[2]*, Melissa Yang*[3]*, Amr Nouraldeen*[4]*, Alan Wilson*[4]*, and Xiang-Qing Yu*[4]*. (1) Department of Medicinal Chemistry, Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540, Fax: 609-466-6079, zshi@lexpharma.com, (2) Department of Pharmaceutical Discovery, Lexicon Genetics, The Woodlands, TX 77381, (3) Department of Pharmaceutical Biology, Lexicon Genetics, The Woodlands 77381, (4) Department of Drug Metabolism and Pharmacokinetics, Lexicon Genetics*

Using mouse knockout technology, Lexicon has identified an enzyme found predominantly in the gastrointestinal (GI) tract that regulates peripheral serotonin levels. Inhibitors of this enzyme dose-dependently reduce the concentration of serotonin in the GI tract in multiple species, without affecting serotonin levels in the brain. By lowering serotonin concentrations and reducing activation of serotonergic receptors in peripheral tissues, these inhibitors should be useful in the treatment of irritable bowel syndrome (IBS). IBS is a common gastrointestinal disorder characterized by pain, discomfort and motility problems that affects between 10-20% of adults in the United States. The discovery and SAR of a series of compounds that inhibit this target will be discussed.

MEDI 236

Substituted-pyridine 2-amino-3,5-dihydro-4H-imidazol-4-ones as highly potent, and selective BACE1 inhibitors

Michael S. Malamas[1]*, Keith Barnes*[2]*, Yu Hui*[3]*, Ping Zhou*[1]*, Albert J Robichaud*[1]*, Jonathan Bard*[4]*, Jim Turner*[4]*, Yun Hu*[5]*, Kristi Y. Fan*[1]*, Rajiv Chopra*[6]*, and Matthew Johnson*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, malamam@wyeth.com, (2) Albany Molecular Research, Albany, (3) Albany Molecular Research, Albany, NY, (4) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08852, (5) Discovery Neuroscience, Wyeth Research, Princeton, NJ, Princeton, NJ 08543-8000, (6) Novartis, MA*

Alzheimer's Disease (AD) is a progressive, degenerative disease of the brain and most common form of dementia. Increasing evidence implicates the amyloid b-peptide (Ab, 39–43

residues) in the neurodegenerative pathogenesis. The Ab peptide is neurotoxic and the principal component of the neuritic plaque found in the brains of AD patients. Inhibition of secretases responsible for Ab formation may stop or slow AD progression by preventing its production. The design and synthesis of highly potent, and selective inhibitors of b-secretase (BACE1) was based on the initial hit 2-amino-3-methyl-5,5-diphenyl-3,5-dihydro-4H-imidazol-4-one (IC50 = 3 uM). Our SAR design strategy supported by molecular modeling studies and X-ray structures of BACE1 co-crystallized with various ligands. This approach enabled us to identify distinct areas within the various sub-sites of the rather large ligand-binding pocket of BACE1 and design pyridine containing 2-amino-3,5-dihydro-4H-imidazol-4-ones as highly potent (IC50 ~10 nM) and selective (>300x vs BACE2; >1000x vs Cathepsin D) BACE1 inhibitors. Key residue/size differences at the S2' sub-site between the BACE1 and BACE2 & Cathepsin D were recognized and have contributed to the selectivity of the compounds. We were able to direct substitutions toward the FLAP region of the binding pocket, as well as deep into S2' region and markedly improve the selectivity of the compounds. Several compounds have demonstrated high potency in ELISA cell-based assays as well. These potent and selective BACE1 inhibitors will contribute toward the understanding of APP processing, as well as the development of disease-modifying AD therapeutics.

MEDI 237

8,8-Disubstituted-2,3,4,8-tetrahydroimidazo[1,5-a]pyrimidin-6-amines as highly potent, selective and orally active BACE1 inhibitors

Michael S. Malamas[1]*, Keith Barnes*[2]*, Yu Hui*[3]*, Jim Erdei*[1]*, Iwan Gunawan*[1]*, Nowak Pawel*[1]*, Albert J Robichaud*[1]*, Jonathan Bard*[4]*, Jim Turner*[4]*, Yun Hu*[5]*, Eric Wagner*[4]*, Suzan Aschmies*[5]*, Kristi Fan*[1]*, Rajiv Chopra*[6]*, and Matthew Johnson*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, malamam@wyeth.com, (2) Albany Molecular Research, Albany, (3) Albany Molecular Research, Albany, NY, (4) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08852, (5) Discovery Neuroscience, Wyeth Research, Princeton, NJ, Princeton, NJ 08543-8000, (6) Novartis, MA*

Alzheimer's Disease (AD) is a progressive, degenerative disease of the human brain and inflicts mainly older people. The initial symptoms include memory loss, impaired judgment, and disorientation. The progression of AD leads to impairment of the brain and eventually death. Although the cause of AD is still unclear, increasing evidence implicates the amyloid b-peptide (Ab, 39–43 residues) in the neurodegenerative pathogenesis. Ab is formed by the sequential cleavage of the cell membrane anchored b-amyloid precursor protein (APP) by two proteases, known as b- and g-secretases. The Ab peptide is neurotoxic and the principal component of the neuritic plaque found in the brains of AD patients. Inhibition of secretases responsible for Ab formation may stop or slow AD progression by preventing its production. The design and synthesis of highly potent, selective and orally active inhibitors of b-secretase (BACE1) was based on the HTS hit WY-24454 (IC50 = 40 uM). Our SAR design strategy supported by X-ray structures of BACE1 co-crystallized with various ligands, and molecular modeling studies. This approach enabled us to rapidly explore the rather large ligand-binding pocket of BACE1 and identify key protein/ligand interactions that produced structurally diverse, and highly potent (IC50 ~10 nM) BACE1 inhibitors. Key ligand-protein interactions were recognized to produce highly selective compounds against other aspartyl protease proteins, such as BACE2, and Cathepsin D. Several compounds have demonstrated high potency in cell-based assays, and

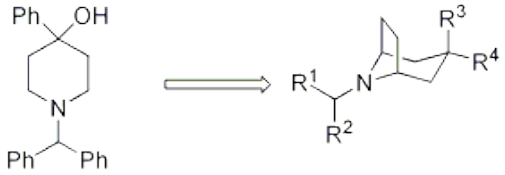
were also orally efficacious in vivo, near normalizing plasma Ab levels. These orally active and selective BACE1 inhibitors will contribute toward the understanding of APP processing, as well as the development of disease-modifying AD therapeutics.

MEDI 238

Synthesis and discovery of tropane derivatives as nociceptin receptor agonists for the management of cough

Ginny D Ho[1]*, Ana Bercovici*[1]*, Ahmad Fawzi*[2]*, Xiomara Fernandez*[2]*, William Greenlee*[3]*, Eugenia Y. Kiselgof*[1]*, Robbie L. McLeod*[2]*, Fay Ng*[1]*, April Smith Torhan*[2]*, Zheng Tan*[1]*, Deen Tulshian*[1]*, Shu-Wei Yang*[1]*, and Hongtao Zhang*[4]*. (1) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, 2015 Galloping Hill Rd., Kenilworth, NJ 07033, Fax: 908-740-7152, ginny.ho@spcorp.com, (2) Department of Neurobiology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Schering-Plough Research Institute, Kenilworth, NJ 07033, (4) CV/CNS Biology, Schering-Plough Research Institute, Kenilworth, NJ 07033*

The nociceptin receptor, NOP, is a G protein-coupled receptor that was cloned in 1994. It bears high homology to the classic opioid receptors, but has little cross reactivity with their native ligands. Nociceptin, the endogeneous ligand to NOP, was discovered in 1995 and shown to be a peptide ligand that activates the NOP receptor, but not the classic opioid receptors. Intensive pharmacological studies with the nociceptin receptor and its peptide ligand and analogs over the past several years have resulted in significant advances in understanding the interaction of nociceptin with biological systems. In our in-house studies, either central (ICV) or peripheral (IV) administration of nociceptin in conscious guinea pigs produces inhibition of capsaicin induced cough. In this presentation, we will disclose part of our studies in the nociceptin receptor area as an effort to identify a small molecule nociceptin receptor agonist for the management of cough. The synthesis, SAR development of 1, PK and in vivo activity of selected compounds will be presented.



1 2

NOP K_i= 13 nM

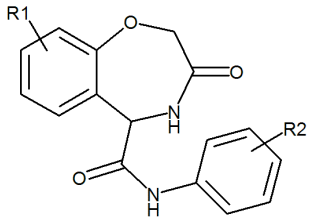
MEDI 239

Benzoxazepinones: The discovery of a novel SARM template

Stephen Rafferty[1]*, Robert Gampe*[1]*, Bajin Han*[1]*, Sab A. Randhawa*[2]*, Eugene L. Stewart*[3]*, and Christopher M. Yates*[1]*. (1) Molecular Discovery Research-Discovery Medicinal Chemistry, GlaxoSmithKline, Five Moore Dr, P.O. Box 13398, Research Triangle Park, NC 27709, swr78127@gsk.com, (2) Medicinal Chemistry, GlaxoSmithKline, Research Triangle Park, NC*

27709, (3) Computational, Analytical, and Structural Sciences, GlaxoSmithKline, Research Triangle Park, NC 27709

Nuclear receptors (NRs) are a class of structurally related proteins that modulate gene expression by acting as ligand-dependent transcription factors. The steroid receptors, for example, the androgen receptor (AR), represent a subclass of the nuclear receptor superfamily. The terms Selective Androgen Receptor Modulator (SARM) refers to an AR ligand which functions as an agonist in some tissues (e.g. muscle), while having no effect or even an antagonist effect in other tissues (e.g. prostate). An ideal SARM has all the beneficial effects of endogenous androgens, while sparing sexual accessory organs, specifically the prostate. It is this avenue on which our group chose to focus in the search for non-steroidal SARMs. The synthetic design, SAR, and in vivo studies for the benzoxazepinone series (shown below) will be presented, with the in vivo data categorizing this series as a true AR modulator: anabolic effect (muscle growth) without prostate stimulation.



MEDI 240

Peptide cyclodimerization by the Cu(I)-mediated azide-alkyne cycloaddition reaction

Reshma Jagasia[1]*, Justin M. Holub*[2]*, Markus Bollinger*[3]*, Kent Kirshenbaum*[2]*, and MG. Finn*[1]*. (1) Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, reshma@scripps.edu, (2) Department of Chemistry, New York University, New York, NY 10003, (3) Institut fur Organische Chemie und Biochemie, Technische Universitat Munchen, Munchen, Germany*

Cyclic peptides and related structures are of longstanding interest as biologically-active compounds, in general because of their ability to display protein-like epitopes with restricted conformational flexibility. We recently reported the cyclization of peptides containing both azide and alkyne functionalities by the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. On-resin reaction gave high yields of head-to-tail cyclic dimers rather than the expected cyclic monomers, even for sequences of substantial length and no obvious conformational, steric, or torsional constraints. Results of studies designed to explore the scope and robustness of this cyclodimerization phenomenon will be described here, as well as the use of the process in the development of a peptide-based inhibitor for the p2/NC cleavage site of HIV-1 protease.

MEDI 241

Session introduction: Abeta production inhibitors

***Charlie F. Albright**, Research and Development, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492-7660*

The progress in the design of inhibitors of Abeta formation and their potential impact on the treatment of Alzheimer's disease will be reviewed

MEDI 242

Pharmacodynamics of highly potent BACE-1 inhibitors in both Pgp-deficient and normal mice

***Lorin A. Thompson III**, Lawrence R. Marcin, Jianliang Shi, Mendi A. Higgins, Richard E. Olson, Andrew C. Good, Catherine R. Burton, Donna M. Barten, Jodi K. Muckelbauer, Jeremy H. Toyn, Kimberley A. Lentz, James E. Grace, John J Herbst, Anthony M. Marino, Jere E. Meredith, Charlie F. Albright, and John E. Macor, Research and Development, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492-7660, lorin.thompson@bms.com*

Alzheimer's disease pathology includes the accumulation in the brain of extracellular amyloid plaques composed largely of the beta-amyloid peptide, and genetic evidence obtained from familial forms of AD suggests that increased production of the 42 amino acid form of beta-amyloid has a primary role in the disease. As a result, both enzymes involved in beta-amyloid production, BACE1 and gamma secretase, have been investigated as possible targets for therapeutic intervention in this important disease. BACE1 inhibitors with high potency in cellular assays have been described in the literature, however central efficacy in animal models has been difficult to demonstrate. This is primarily a result of poor blood-brain barrier penetration as a result of both poor intrinsic permeability and active efflux by P-gp. This presentation will describe a novel series of BACE inhibitors with subnanomolar potency in cellular assays and present an analysis of the factors influencing brain penetration including the P-gp effect at the BBB by comparing central efficacy in both Pgp-deficient and wild-type mice.

MEDI 243

Discovery of high affinity beta-secretase inhibitors using fragment-based lead generation and structure-based design

***Jeffrey S. Albert**, CNS Discovery Research, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437, jeffrey.albert@astrazeneca.com*

Beta-secretase is a leading target for the development of therapies to treat Alzheimer's disease. Despite intense research over the past decade, only recently have high-affinity drug-like inhibitors of beta-secretase emerged. Fragment based approaches to lead generation rely on identifying drug fragments that contain minimal functionality for binding to the target of

interest. Using NMR methods, we screened a library of low molecular weight compounds to identify hits that bound to the active site of beta-secretase with affinities (IC50) of 1-5 mM. X-ray crystallography facilitated the rapid evolution of these weak hits into high affinity (IC50 <100 nM) drug leads.

MEDI 244

BACE (Beta-Amyloid site Cleaving Enzyme; ß-Secretase) inhibitors for the treatment of Alzheimer's disease

Ellen W. Baxter[1]*, Richard S. Alexander*[2]*, Scott A. Ballentine*[2]*, Francois P. Bischoff*[3]*, Robert E. Boyd*[2]*, Mirielle Braeken*[3]*, Douglas E. Brenneman*[2]*, Steven J. Coats*[2]*, Kelly A. Conway*[2]*, Andrew L. Darrow*[2]*, Hans De Winter*[3]*, Yifang Huang*[2]*, Sergey E. Ilyin*[2]*, Alfonzo D. Jordan*[2]*, Ludo E. J. Kennis*[3]*, Chi Luo*[2]*, Marc H. Mercken*[3]*, Serge M. A. Pieters*[3]*, Junya Qu*[2]*, Jennifer A. Piesvaux*[2]*, Charles H. Reynolds*[2]*, Mark J. Schulz*[2]*, Malcolm K. Scott*[2]*, Christopher A. Teleha*[2]*, Brett A. Tounge*[2]*, and Allen B. Reitz*[2]*. (1) Johnson & Johnson Pharmaceutical R&D, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477-0776, Fax: 215-628-4985, ebaxter@prdus.jnj.com, (2) Johnson & Johnson Pharmaceutical R&D LLC, Spring House, PA 19477-0776, (3) Johnson & Johnson Pharmaceutical R&D LLC, 2340 Beerse, Belgium*

Alzheimer's Disease (AD) currently affects four million Americans and is a growing medical concern with the increasing percentage of elderly in the population. The amyloid hypothesis has been proposed to explain the etiology of AD; ß-secretase (BACE) and γ-secretase cleave the amyloid precursor protein (APP) at the N- and C-terminus, respectively, to provide ß-amyloid peptides, Aß1-40 and Aß1-42, which aggregate into neurotoxic oligomers and fibrils. As a disease-modifying approach to AD, we initiated a program to discover and design novel BACE inhibitors. After a high throughput screen of the Johnson & Johnson PRD compound collection, several low micromolar inhibitors of BACE were identified. The most promising hit had Ki = 1 uM, and was crystallized in the active site of BACE. The X-ray structure of this compound in BACE was used to guide the design of more potent inhibitors, and the best have Kis in the single digit nanomolar range.

MEDI 245

Optimization of the in vivo activity of potent, Notch-sparing gamma secretase inhibitors

Anthony Kreft[1]*, Boyd L. Harrison*[1]*, Magid Abou-Gharbia*[1]*, Jay Afragola*[2]*, Asaf Alimardinov*[2]*, Madelene Antane*[1]*, Suzan Aschmies*[3]*, Kevin Atchison*[3]*, Thomas Caggiano*[1]*, Michael Chlenov*[1]*, Derek Cole*[2]*, Thomas Comery*[3]*, George Diamantidis*[1]*, John Ellingboe*[2]*, Kristi Fan*[1]*, Cathleen Gonzalez*[3]*, Diane Hauze*[4]*, Molly Hoke*[1]*, Yun Hu*[3]*, Xinyi Huang*[4]*, Donna Huryn*[1]*, Uday Jain*[1]*, Mei Jin*[3]*, Gulnaz Khafizova*[2]*, Dennis Kubrak*[1]*, Kristina Kutterer*[5]*, Melissa Lin*[2]*, Peimin Lu*[3]*, Joseph Lundquist*[4]*, Ronald L. Magolda*[1]*, Charles Mann*[1]*, Robert Martone*[3]*, Michael May*[2]*, Scott Mayer*[1]*, John Mehlmann*[4]*, William J. Moore*[6]*, Koi Morris*[1]*, Aram Oganesian*[7]*, Menelas Pangalos*[3]*, Alex Porte*[1]*, Peter Reinhart*[3]*, Lynn Resnick*[1]*, David R. Riddell*[3]*, Jean Schmid*[2]*, June Sonnenberg-Reines*[3]*, Joseph Stock*[2]*, Roy Sun*[3]*, Erik Wagner*[3]*, Zheng Wang*[1]*, Kevin Woller*[6]*, Zheng Xu*[3]*, Margaret M Zaleska*[3]*, Minsheng Zhang*[1]*, Hua Zhou*[3]*, and J. Steven Jacobsen*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543,*

krefta@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY, Pearl River, NY 10965, (3) Discovery Neuroscience, Wyeth Research, Princeton, NJ, Princeton, NJ 08543-8000, (4) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA, Collegeville, PA 19426, (5) Chemical & Screening Sciences, Wyeth Research, Pearl River, NY, Pearl River, NY 10965, (6) Division of Chemical Technologies, ArQule, Inc, Woburn, MA, Woburn, MA 01801, (7) Drug Safety & Metabolism, Wyeth Research, Collegeville, PA, Collegeville, PA 19426

Alzheimer's disease (AD) is the most devastating human disease for which there is still no highly effective treatment. Currently available AD therapies only provide symptomatic treatment. The proposed causative role for Abeta40 and Abeta42 in the pathophysiology of AD has provided a rational strategy for the design of disease-modifying anti-AD drugs (DMAADs). By blocking the synthesis of these putative pathogenic peptides, it is hoped that the progression of AD will be slowed or prevented. We have focused our efforts on inhibition of gamma secretase, the final enzyme in the biosynthesis of Abeta40 and Abeta42 from APP. A caveat with this approach is that selectivity of gamma secretase inhibition of APP processing is required due to the importance of other gamma secretase substrates such as Notch in important physiological processes such as G.I. cell renewal. We have previously reported on the discovery of the Notch-sparing gamma secretase inhibitor (GSI) 5-chloro-N-[(1S)-2-ethyl-1-(hydroxymethyl)butyl]-2-thiophenesulfonamide (EC50Abeta40 and Abeta42 = 25 nM and 27 nM, respectively, EC50Notch= 246 nM) by optimization of an HTS lead. However, this compound shows limited oral activity in Tg2576 mice due to rapid in vivo metabolism. By identifying and blocking the sites of metabolism of this lead and related analogs we have designed and synthesized novel GSIs with potent, oral in vivo activity that also retain Notch-sparing selectivity. The evolution of this series of compounds will be discussed.

MEDI 246

The pathobiology of asthma and COPD: Targeting new pathways for treatment

***William M. Abraham**, Department of Research, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, FL 33140-2894, Fax: 305-674-2198, abraham@msmc.com*

Asthma and chronic obstructive pulmonary disease (COPD) are diseases characterized by airway inflammation. Although there is overlap in symptoms between the two disease entities, the inflammatory processes as defined by the cells, mediators, pulmonary targets, and therapeutic responses suggest that they are distinct. Mast cells, eosinophils, macrophages and Th2 lymphocytes and mediators including histamine, prostaglandin D2, tryptase, cysteinyl leukotrienes (LT), interleukin (IL)-5 and IL-13 characterize asthma pathobiology, whereas neutrophils, macrophages and cytotoxic T lymphocytes and mediators including IL-8, LTB4, elastase and tumor necrosis factor -α are associated with COPD. The difference in the inflammatory components of the two diseases is reflected in the response to therapy. Thus, glucocorticosteroids are effective anti-inflammatory agents in asthmatic patients, but not individuals with COPD. In this presentation, we will describe the inflammatory pathways that contribute to these two airway diseases and identify therapeutic targets that may be potentially useful for prevention and/or treatment.

MEDI 247

Protease inhibitors for treating pulmonary inflammatory disorders: Focus on chymase and cathepsin G

***Bruce E. Maryanoff**, M. N. Greco, M. J. Hawkins, E. T. Powell, L. De Garavilla, and H. R. Almond Jr., Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-4985, bmaryano@prdus.jnj.com*

Asthma involves airway inflammation that includes the recruitment of neutrophils, eosinophils, and mast cells to sites of injury. Neutrophils are also important in chronic obstructive pulmonary disease (COPD), for which there is a large unmet medical need. Leukocyte serine proteases such as cathepsin G (Cat G) and chymase can degrade extracellular matrix and trigger the release of pro-inflammatory mediators. Neutrophil Cat G degrades matrix proteins, damages airway epithelial cells, and stimulates vascular permeability; mast cell chymase plays an important role in the pathogenesis of asthma. With the aid of structure-based drug design, we discovered a nonpeptide, dual inhibitor of Cat G and chymase (JNJ-10311795) and a selective, nonpeptide chymase inhibitor, both possessing novel chemotypes. These compounds were advanced into preclinical development. JNJ-10311795 markedly reduced neutrophil counts in a rat peritonitis model (iv) and was efficacious in the sheep model of asthma (it). The chymase inhibitor was orally efficacious in a hamster model of cutaneous inflammation and the sheep asthma model.

MEDI 248

Discovery of AMG 009: A CRTH2 and DP dual-antagonist

***Julio C. Medina**[1], Jiwen Liu[1], Zice Fu[1], Michael Schmitt[2], Yingcai Wang[1], Marshall C. Derek[1], H. Lucy Tang[3], Timothy Sullivan[3], George Tonn[1], and Tassie Collins[1]. (1) Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, Fax: (650)244-2015, (2) Amgen Inc, South San Francisco, CA, (3) Amgen Inc, South San Francisco*

CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) and DP (D prostanoid) are G protein coupled receptors that share the same ligand, prostaglandin D2 (PGD2). However, these receptors are expressed in different cell types and may play complimentary roles. CRTH2 is expressed on eosinophils, basophils, and T helper 2 (Th2) lymphocytes and activation by PGD2 induces chemotaxis and eosinophil degranulation. DP is expressed on airway epithelium, smooth muscle and platelets and upon stimulation increases the level of cAMP and mediates flushing, sneezing, mucosal plasma exudation, and nasal blockage. Since PGD2 is released by mast cells in large amounts during asthmatic responses, it has been postulated that blocking CRTH2 and DP could be therapeutically valuable to asthma and other allergic diseases. In this presentation, we will disclose the optimization and evaluation in in vivo asthma models of a series of phenylacetic acid derivatives with potent activity against the CRTH2 and DP receptors that led to the selection of AMG 009 as a preclinical development compound.

MEDI 249

Structure activity relationships of a series of thiazolopyrimidine based CXCR2 antagonists with additional CCR2b activity

Iain A. S. Walters*, Department of Medicinal Chemistry, AstraZeneca, Bakewell Road, Loughborough, United Kingdom, Iain.Walters@astrazeneca.com*

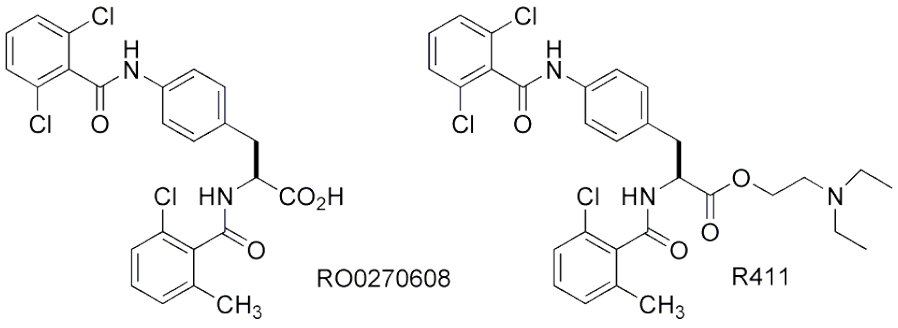
An overview will be given of a full preclinical research programme investigating a series of thiazolopyrimidine based CXCR2 antagonists with additional CCR2b activity for the prospective oral treatment of inflammatory disorders such as rheumatoid arthritis, chronic obstructive pulmonary disease, asthma and psoriasis. The presentation will begin with the discovery of the initial lead compounds from high throughput screening, followed by a survey of the key structure activity relationships used to optimise potency and pharmacokinetic properties. The talk will conclude with the profile of optimal compounds suitable for in vivo pharmacological studies.

MEDI 250

Discovery of R411: A VCAM/VLA-4 antagonist for the treatment of asthma

Jefferson W. Tilley*[1], Achyutharao Sidduri[1], Li Chen[1], Jiang Ping Lou[1], Gerald Kaplan[1], Gary Cavallo[2], Nadine Tare[2], Lou Renzetti[2], Horst Welker[3], and Alexis Rames[3]. (1) Discovery Chemistry, Roche Research Center, 340 Kingsland Street, Nutley, NJ 07110, jefferson.tilley@roche.com, (2) Repiratory, Inflammation and Autoimmune Disease, Roche Research Center, (3) Clinical Research, Roche Basle Research Center*

Alpha4 integrins are expressed on leukocytes with the exception of neutrophils and are involved in the trafficking of these cells to sites of inflammation. We describe work leading to the discovery of the potent alpha4 integrin antagonist RO0270608 and its pharmacology in animal models of asthma. Since RO0270608 is poorly absorbed after oral administration, a pro-drug form, R411, was developed for testing in humans. Oral administration of R411 to human volunteers gave good, dose proportional blood levels of RO0270608 and was well tolerated. Preliminary results from a 13 week, phase 2 clinical trial of R411 in moderately severe asthma showed improvements in FEV1 and exacerbations relative to controls.

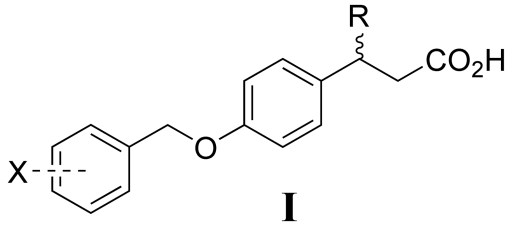


MEDI 251

Beta-substituted carboxylic acids as potent, orally bioavailable agonists of GPR40

Jonathan Houze[1]*, Wei Qiu*[1]*, Alex Zhang*[1]*, Rajiv Sharma*[1]*, Liusheng Zhu*[1]*, Ying Sun*[1]*, Michelle Akerman*[2]*, Michael Schmitt*[3]*, Yingcai Wang*[1]*, Jiwen Liu*[1]*, Jinqian Liu*[1]*, Julio Medina*[1]*, Jeffrey Reagan*[1]*, Jian Luo*[1]*, George Tonn*[1]*, Jane Zhang*[1]*, Jenny Lu*[1]*, Michael Chen*[1]*, Edwin Lopez*[1]*, Kathy Nguyen*[1]*, Li Yang*[1]*, Liang Tang*[1]*, Hui Tian*[1]*, Stephen Shuttleworth*[1]*, and Daniel Lin*[1]*. (1) Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, Fax: 650-837-9369, jhouze@amgen.com, (2) Amgen Inc, S. San Francisco, CA 94080, (3) Amgen Inc, South San Francisco, CA*

The therapeutic utility of insulin secretagogues in aiding type II diabetics to maintain glucose homeostasis is well established. However, hypoglycemia is a common side effect with many current insulin secretagogues. Fatty acids have been shown to be promoters of *glucose stimulated* insulin secretion (GSIS), and a therapeutic agent working through the same pathway potentially could avoid undesirable hypoglycemia. The identification of fatty acids as the ligands for the previously orphaned receptor GPR40 has sparked interest in GPR40 modulators as potential therapeutically useful potentiators of GSIS. We identified certain β-substituted carboxylic acids as moderately potent GPR40 agonists. Modification of the substituents on the carboxylic acid β-position and the benzyl ether resulted in compounds displaying improved potency and pharmacokinetic profile. The synthesis, optimization, and evaluation of the effects on GSIS in rodents by β-substituted carboxylic acids will be described.



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MEDI 252

Endogenous kinase conformational switching pockets: A new general strategy for small molecule kinase inhibition

Daniel L. Flynn[1]*, Peter A. Petillo*[1]*, Mike Kaufman*[1]*, Wei-Ping Lu*[1]*, Scott C. Wise*[1]*, Michael Clare*[1]*, Lance Stewart*[2]*, Robin Clark*[2]*, Mic Feese*[2]*, and Lawrence Chun*[2]*. (1) Deciphera Pharmaceuticals LLC, 4950 Research Park Way, Lawrence, KS 66047, dflynn@deciphera.com, (2) deCODE biostructures, Bainbridge Island, WA 98110*

Currently, ATP mimetics are the mainstream platform for developing kinase inhibitors, wherein small molecules target the ATP pocket. In searching for a general approach to kinase modulation that not does utilize the ATP pocket, we have targeted the endogenous conformational switch pockets that exist in kinases. The cognate ligands for these switch pockets are embedded within the kinase structures. Switch pockets interact with their cognate ligands to regulate kinase shape and catalytic activity in vivo. This presentation will highlight

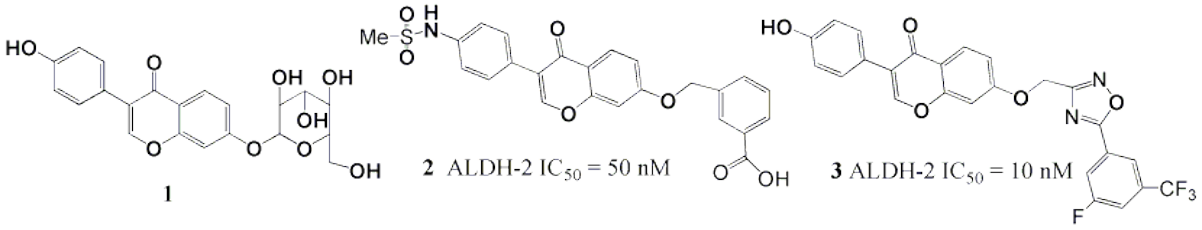
the attributes of targeting kinase switch pockets by demonstrating its application to B-raf kinase, bcr-abl kinase, and other kinases. The bcr-Abl program has afforded potent development candidates that inhibit bcr-Abl kinase and various mutants including the T315I mutant that is resistant to Gleevec and dasatinib. The B-Raf program has afforded sub-nanomolar inhibitors of V600E B-Raf kinase. In vitro, whole cell, and in vivo data will be highlighted for both programs.

MEDI 253

Novel aldehyde dehydrogenase-2 inhibitors as a potential treatment of alcohol addiction

Jeff Zablocki[1]*, Matthew Abelman*[1]*, Michael G. Organ*[2]*, Yaroslav Bilokin*[2]*, Guan Cao*[2]*, Debasis Malik*[2]*, Wing Ming Keung*[3]*, Guoxin Tao*[3]*, David Overstreet*[4]*, Daniel Soohoo*[5]*, Nancy Chu*[5]*, Jia Hao*[5]*, Kwan Leung*[5]*, Hugh Genin*[6]*, Maria Pia Arolfo*[7]*, Lina Yao*[7]*, Peidong Fan*[7]*, and Ivan Diamond*[7]*. (1) Department of Bioorganic Chemistry, CV Therapeutics, 3172 Porter Drive, Palo Alto, CA 94304, (2) Department of Chemistry, Toronto Total Synthesis, Burlington, ON L7T1A6, Canada, (3) Harvard Medical School, Boston, MA 02115, (4) Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, (5) Department of Pre-Clinical Development, CV Therapeutics, Inc, (6) Accelrys Inc, San Diego, CA 92121, (7) Department of Neuroscience, CV Therapeutics, Inc*

Daidzin 1, inhibits aldehyde Dehydrogenase-2 (ALDH-2, IC50 = 40 nM) and is the active principle of an ancient Chinese herbal medicine “kudzu root” that has been used to treat alcohol addiction for over a 1000 years. Although “kudzu root” has some effect in humans, the low oral bioavailability and short half-life of the principle daidzin (F < 1% and t1/2 = 0.18 h, rat) has led us to optimize its pharmaceutical properties. In particular, we found replacements for the polar glucose group that led to two distinct series of molecules illustrated by the meta-benzyl acid derivative 2 and the 5-phenyloxadiazolyl compound 3 that retained similar inhibition of the ALDH-2 enzyme and resulted in an increased oral bioavailability and half-life. Both 2 and 3 inhibit alcohol consumption in rodent models in a dose-dependent manner at doses well below those for acamprosate and comparable to those for naltrexone, approved agents for alcohol addiction. The docking poses for 2 and 3 will be presented based on an X-ray of daidzin-ALDH-2 complex.



MEDI 254

Small molecule inhibitors of macrophage inhibitory factor (MIF)

***Thais Sielecki**, Department of Research, Cytokine PharmaSciences, 150 South Warner Road, Suite 420, King of Prussia, PA 19406, tsielecki@cytokinepharmasciences.com*

Elevated levels of Macrophage Migration Inhibitory Factor (MIF) have been implicated in a number of inflammatory disease states, including arthritis, multiple sclerosis, Crohn's disease, and cancer. MIF activity can be inhibited through direct binding of MIF or through binding of the MIF receptor. Antibodies to MIF have been shown to treat a variety of diseases via the reduction of MIF activity. Cyokine PharmaSciences has designed small molecules that inhibit MIF activity in vitro, and subsequently demonstrated that they have anti-MIF activity in vivo in several systemic, chronic animal disease models. In contrast to antibodies, these small molecules are orally bioavailable. This seminar will introduce the target, review antibody approaches to MIF inhibition and discuss preclinical data for Cytokine PharmaSciences Inc.'s MIF small molecule series.

MEDI 255

Sodium and calcium channels as drug targets for neuropathic pain

***Andreas Termin**, Department of Chemistry, Vertex Pharmaceuticals, 11010 Torreyana Road, San Diego, CA 92121, andreas_termin@sd.vrtx.com*

Neuropathic pain is a chronic pain state, where the nerve-fibers are damaged or injured. This leads to misfiring of the neurons and eventually to a change in the function of the nerve in the injured area. Neuropathic pain or neuralgia can have multiple causes, and is most often suffered by patients with diabetes (diabetic neuropathy), HIV (HIV-related neuropathic pain), and herpes (post-herpetic neuralgia).

Patients who have neuropathic pain describe it as a burning sensation or an electric shock, and have compared it to sitting on needles and pins. The most commonly used drugs are anti-epileptic agents, anti-depressants, local anesthetics, and narcotics. Unfortunately, the current therapies are efficacious in only a fraction of the patient population and leave physicians with limited treatment options.

Most molecules in use to date are active against multiple targets. With the exception of the narcotics, their most common denominator is activity on sodium or calcium channels.

We believe that a rational, channel specific approach will lead to better therapeutics for this area of drug discovery. Therefore, we have developed a comprehensive platform that combines high throughput screening for ion channels, medicinal chemistry, and in vivo neuropathic pain pharmacology. This offers us the opportunity to rapidly identify and develop new profiles with molecules specifically designed for the treatment of neuropathic pain, and potentially for other nervous system diseases where ion channels play a critical role.

In this presentation, we will discuss our screening technology (E-VIPR), which allowed us to evaluate our corporate collection as well as known drugs for their sodium and calcium channel activity. We will show data for molecules that compare favorably with known drugs. We will also discuss animal models for neuropathic pain and the effect of subtype specific NaV blockers in these models.

MEDI 256

Design and synthesis of potent 5-HT6 ligands for cognitive impairment

Hassan Elokdah[1]*, Kevin Liu*[2]*, Derek Cole*[2]*, Ronald C Bernotas*[1]*, Ronald L Magolda*[2]*, Lee E. Schechter*[3]*, Guo Ming Zhang*[3]*, Deborah Smith*[3]*, and Albert J Robichaud*[2]*. (1) Chemical & Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, elokdah@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, (3) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543*

We have earlier reported on the identification of novel ligands for the 5-HT6 receptor within our research group. Potent and selective 5-HT6 receptor ligands are useful in the treatment of CNS disorders such as schizophrenia, depression, and Alzheimer's disease (AD). Our recent efforts focused on the discovery of 5-HT6 receptor antagonists for the treatment of learning and memory deficits in neurodegenerative diseases such as AD. 5-HT6 receptor antagonists are reported to alleviate the cognitive deficits associated with AD through multiple pathways, including the enhancement of the levels of the neurotransmitters acetylcholine and glutamate. Optimization of the binding and functional afinities as well as the pharmaceutical properties of an early series led to the discovery of a series of arylsulfonyl derivatives with high selectivity, excellent binding affinity and potent functional activity. The SAR, in vivo activity as well as changes in neurotransmitter release following oral administration of key derivatives will be presented.

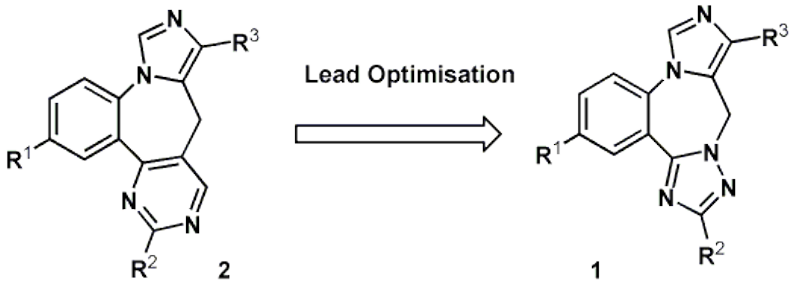
MEDI 257

Novel potent and selective inverse agonists at the GABAA a5 receptor sub-type

A W Thomas[1]*, T M Ballard*[2]*, F Blasco*[2]*, T Buttelmann*[1]*, H Fischer*[2]*, M-C Hernandez*[2]*, F Knoflach*[2]*, H Knust*[2]*, R Moog*[2]*, H Stadler*[2]*, G Trube*[2]*, P Waldmeier*[2]*, and M Wooley*[2]*. (1) Pharmaceutical Research Basel, Discovery Chemistry, Hoffmann-La Roche, PRBD-CM, 092/6.56, Basel, Switzerland, Fax: +41 61 68 88714, andrew.thomas@roche.com, (2) F. Hoffmann-La Roche, Switzerland*

Extensive detailed pharmacological evidence exists in both rodents and humans suggesting non-selective inverse agonists at the benzodiazepine site of the GABAA receptor (BZR) enhance cognitive functions. However, non-selective inverse agonists induce anxiogenic and pro-convulsive effects. Through the greater understanding of the complex pharmacology of the GABA A receptor sub-types it is now strongly believed that the cognitive effects are mediated through inverse agonism of the GABA A alpha5 receptor sub-type which has been supported by recent results in the clinic. Within our research program we have identified several novel

series' of potent and selective GABAA alpha5 receptor inverse agonists. The poster will describe the discovery of an imidazotriazolobenzodiazepine chemical class, by lead optimisation of an imidazopyrimidinobenzazepine lead series, and culminate in the full profile of key compounds.



MEDI 258

Design, synthesis, and SAR of azabicyclic aryl amides as a7 nicotinic acetylcholine receptor agonists for the treatment of cognitive deficits in schizophrenia and Alzheimer's disease: Discovery of PHA-543,613

***Donn G Wishka**, Neurosciences, Pfizer Global R&D, Eastern Point Rd, Groton, CT 06340, donn.g.wishka@pfizer.com*

Nicotinic acetylcholine receptors (nAChRs) are found throughout the central and peripheral nervous systems, as well as in the neuromuscular junction. Numerous studies have established the importance of nAChRs within the CNS, in particular their link to higher processes such as memory, cognition, reward, and sensory processing.

A novel set of azabicyclic aryl amides has produced potent and selective agonists of the a7 nicotinic acetylcholine receptor (a7 nAChR). PHA-543613 (N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide), a novel agonist of the a7 nAChR, has been identified as a potential treatment for the cognitive deficits associated with schizophrenia and Alzheimer's disease. PHA-543613 is a potent and selective agonist of the a7 nAChR with excellent in vitro and in vivo profiles. This compound is characterized by rapid brain penetration, high oral bioavailability in rat, and demonstrates in vivo efficacy in both the auditory sensory gating and novel object recognition models. Herein, we describe the synthesis and structure-activity relationship studies leading to the discovery of PHA-543613, as well as the biological data predictive of its utility in the treatment of cognitive deficits.

MEDI 259

5-HT$_{1A}$ Antagonists as cognitive enhancers: The discovery of lecozotan

***Wayne E. Childers Jr.** and Boyd L. Harrison, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, childew@wyeth.com*

Alzheimer's Disease (AD) and other forms of dementia affect nearly 28 billion victims worldwide at an annual cost that approaches $248 billion for direct and indirect care. The causes of AD remain unknown but evidence suggests that damage to the brain occurs years before symptoms began to appear. There are no approved treatments for AD that modify the disease process. Currently available symptomatic agents such as cholinesterase inhibitors and the noncompetitive NMDA antagonist memantine are characterized by a modest response rate and, in the case of cholinesterase inhibitors, a relatively short period during which the drugs induce an improvement in symptoms. In 1994, Bowden et al. hypothesized that a serotonin 5-HT_{1A} antagonist might function as a superior cognitive enhancer by simultaneously modulating several of the neurotransmitter systems known to be altered in AD. However, the identification of full 5-HT_{1A} antagonists has been difficult owing to the high degree of pre-synaptic 5-HT_{1A} receptor reserve in the dorsal raphe which amplifies very small degrees of intrinsic activity. This presentation will describe our efforts to discover “silent” 5-HT_{1A} antagonists, culminating in the identification of lecozotan which is currently in advanced clinical trials.

MEDI 260

Histamine H3 receptor antagonists: Potential to address CNS deficits of memory, cognition, and attention

***Marlon D. Cowart**, Neuroscience Research, R4MN, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, marlon.d.cowart@abbott.com*

The histamine H3 receptor is expressed in neurons where it plays an important role in negatively modulating the release of neurotransmitters, including histamine, acetylcholine, and dopamine. Antagonists of the receptor induce release of these transmitters, and importantly, are especially potent and effective in overcoming deficits in preclinical models assessing components memory, cognition, and attention. Results will be presented depicting the potency and in vivo efficacy of new series and standard compounds. In vitro SAR for the target (H3) and off-target sites (e.g. hERG, H1-4 receptors) will be analyzed, and profiles presented of specific example compounds, assessing for example general their CNS effects, PK properties, and overall drug-likeness.

MEDI 261

Overview of the biology of the PDE family

***Eric Karran**, Neurodegenerative Diseases Drug Hunting Team, Lilly UK, Erl Wood Manor, Windlesham, Surrey, United Kingdom, Fax: +44 1276 583525, karrane@lilly.com*

Cyclic nucleotides are key intracellular signalling molecules that are involved in a diverse range of physiological processes. The intracellular concentration of cyclic nucleotides is tightly regulated by the balance of their synthesis by adenylyl and guanylyl cyclases and their degradation by phosphodiesterase enzymes. The twenty one phosphodiesterases can be arranged into eleven families based on sequence homology and enzymatic properties. Some members of family act on cyclic AMP (PDEs 4, 7 & 8), some on cyclic GMP (PDEs 5, 6 & 9), and some are dual substrate enzymes (1, 2, 3, 10 & 11). Further complexity is added by splice

variants that can result in tissue and subcellular specificity. Currently, there are marketed drugs that inhibit PDE3, PDE4 and PDE5. It is clear that there is ample scope to develop selective inhibitors for other members of the family to provide therapies for a range of conditions.

MEDI 262

Development of PDE4 inhibitors for CNS indications

***Allen T. Hopper**, Medicinal Chemistry, Memory Pharmaceuticals Corporation, 100 Philips Parkway, Montvale, NJ 07645, Fax: 210-802-7190, hopper@memorypharma.com*

A growing body of evidence supports the utility of PDE4 inhibitors for treating Alzheimer's disease and other neurodegenerative and neuropsychiatric diseases by enhancing synaptic plasticity. PDE4 is an enzyme that regulates intracellular concentrations of cAMP, an important second messenger, by catalyzing its hydrolysis to AMP. Selective inhibition of PDE4 is one method to increase levels of cAMP and enhance synaptic plasticity. This enzyme is localized within key brain structures associated with learning and memory such as the hippocampus and prefrontal cortex. Increasing cAMP concentrations within these structures drives the PKA-CREB pathway leading ultimately to the synthesis of proteins that help to strengthen connections among neurons and enhance synaptic plasticity. Rolipram, the first generation prototypical selective PDE4 inhibitor was developed originally for depression, but was discontinued due to several factors including the side effect of emesis, high in vivo clearance and synthetic issues. Second generation PDE4 inhibitors (e.g., Cilomilast and Roflumilast) have generally targeted peripheral indications with an inflammatory component such as asthma and COPD. This talk will discuss optimization strategies and approaches toward achieving ‘on target' mechanism of action with PDE4 inhibitors for CNS activity.

MEDI 263

Discovery of selective PDE7 and PDE7 and 4 dual inhibitors and their role in T cell activation

***William J. Pitts**, Department of Chemistry, Bristol-Myers Squibb Research and Development, Route 206 and Province Line Rd, Princeton, NJ 08543, pittsw@bms.com*

Based on a non-selective screening lead we have developed selective PDE7 inhibitors as well as a series of less selective compounds which inhibit both PDE7 and PDE4. Compounds were evaluated in a model of T cell proliferation as well as in a PDE7 knock out background in an effort understand the relative contributions of PDE7 and PDE4 to activity.

MEDI 264

Inhibition of the striatal phosphodiesterase PDE10A: Biochemical, behavioral and pharmacological predictors of antipsychotic potential

***Christopher J Schmidt**, CNS Discovery, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340, christopher.j.schmidt@pfizer.com*

PDE10A is a dual substrate, cyclic nucleotide phosphodiesterase identified by homology screening and molecular cloning in 1999. Based upon reports of high levels of PDE10A expression in the brain, we have characterized the biological function of PDE10A to evaluate its potential as a CNS drug target. Localization studies across species demonstrate that striatal PDE10A is expressed exclusively in medium spiny neurons of both striatal output pathways. Biochemical and behavioral evaluation of both KO mice and putative inhibitors lead to the hypothesis that PDE10A normally functions to dampen striatal output. Based upon the view that many of the symptoms of schizophrenia are the result of reduced striatal activity, our observations suggest that PDE10A inhibitors would be useful as antipsychotic agents. Consistent with an overall enhancement of striatal function, PDE10A inhibitors potently increase biochemical markers of striatal activity and demonstrate efficacy in preclinical models of antipsychotic activity. Both the biochemical and behavioral effects of PDE10A inhibitors are selectively absent in PDE10A KO mice confirming the mechanism of these activities. As predicted by the presence of PDE10A in both the D2 and D1 receptor expressing pathways, and in contrast to the effects of D2 antagonists, PDE10A inhibitors enhance gene transcription in both striatal output pathways. The opposing effects of these two pathways on motoric function suggest that PDE10A inhibitor may have low EPS liability; an expectation supported in experiments evaluating the cataleptic activity of selective inhibitors. In conclusion, the potent activation of the striatal output indicates that PDE10A inhibitors may be very effective in the treatment of the same symptoms of schizophrenia affected by currently marketed agents. In addition, the unique ability of PDE10A inhibitors to activate both striatal output pathways offers the possibility that these agents will have an improved clinical profile both in terms of safety and efficacy.

MEDI 265

Scaffold-based discovery of selective PDE4 inhibitors

***Kam Y. J. Zhang**, Graeme L. Card, Jinyu Liu, Landy Blasdel, Bruce P. England, Chao Zhang, Yoshihisa Suzuki, Sam Gillette, Byunghun Lee, Daniel Fong, Ben Powell, Davin Hsieh, Joshua Neiman, Michael V. Milburn, Brian L. West, Prabha N. Ibrahim, Dean R. Artis, and Gideon Bollag, Plexxikon, Inc, 91 Bolivar Dr, Berkeley, CA 94710, Fax: (510)548-4785, kzhang@plexxikon.com*

Phosphodiesterases (PDEs) catalyze the hydrolysis of cAMP or cGMP which regulate a variety of cellular processes and are prime targets for drug development. We have shown that an invariant glutamine functions as the key specificity determinant by a “glutamine switch” mechanism for recognizing the purine moiety in cAMP or cGMP. We have found a common scheme of inhibitor binding to the PDEs: (i) A hydrophobic clamp formed by highly conserved hydrophobic residues that sandwich the inhibitor in the active site; (ii) hydrogen bonding to an

invariant glutamine that controls the orientation of inhibitor binding. A scaffold can be readily identified for any given inhibitor based on the formation of these two types of conserved interactions. We describe a scaffold-based drug design approach applied on the discovery of several new classes of PDE4 inhibitors. This method starts with low affinity screening of a low molecular weight compound library followed by high throughput co-crystallography of the screening hits to select compounds that exhibit a dominant binding mode and have appropriate sites for substitution. These scaffolds compounds serve as the starting point for lead development. We report two lead series with different profiles of PDE4 selectivity discovered using our scaffold-based drug discovery platform, which have been evaluated in preclinical studies.

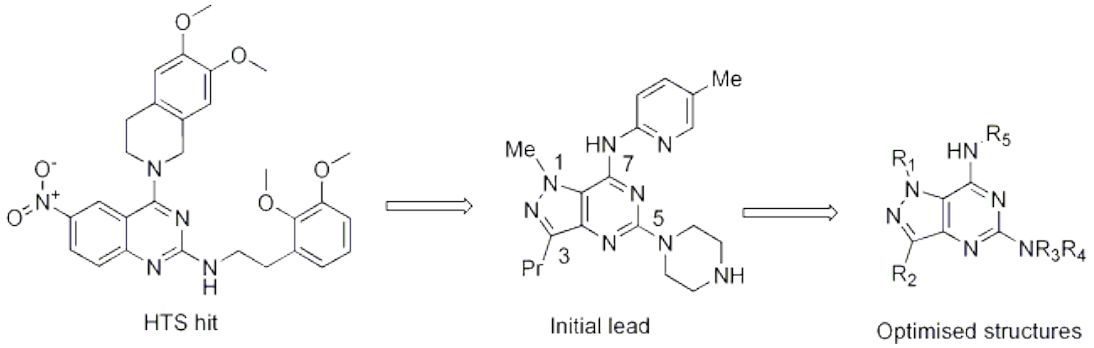
MEDI 266

Structure based design of second generation long-acting PDE5 inhibitors

Michael J Palmer[1]*, Andrew S. Bell*[2]*, David N. A. Fox*[3]*, and David G Brown*[2]*. (1) Sandwich Discovery Chemistry, Pfizer Global Research & Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom, mike.palmer@pfizer.com, (2) Sandwich Chemistry, Pfizer Global Research & Development, Sandwich, Kent CT13 9NJ, United Kingdom, (3) Pfizer Global Research and Development, United Kingdom*

The clinical knowledge gained from the pioneering PDE5 inhibitor sildenafil and subsequent agents, has highlighted the potential of PDE5 inhibition for treatment of additional indications beyond male erectile dysfunction. Such indications would be best treated by highly selective agents suitable for chronic once daily oral dosing. This talk details the discovery and progression of a pyrazolopyrimidine PDE5 inhibitor series designed to display inherently good physicochemistry, and targeting a chronic once daily treatment goal. Key features of the talk are:

1. Rationalisation of SAR in the pyrazolopyrimidine series with emphasis on the C3 substituent. Rationalisation includes the use of co-crystal structure information to guide design for potency and selectivity. 2. An assessment of physical properties in the series with emphasis on optimising permeability and clearance to drive long half-life oral pharmacokinetics. 3. In depth assessment of a PDE5 selective and physicochemically optimised lead with the potential for once daily dosing in man.

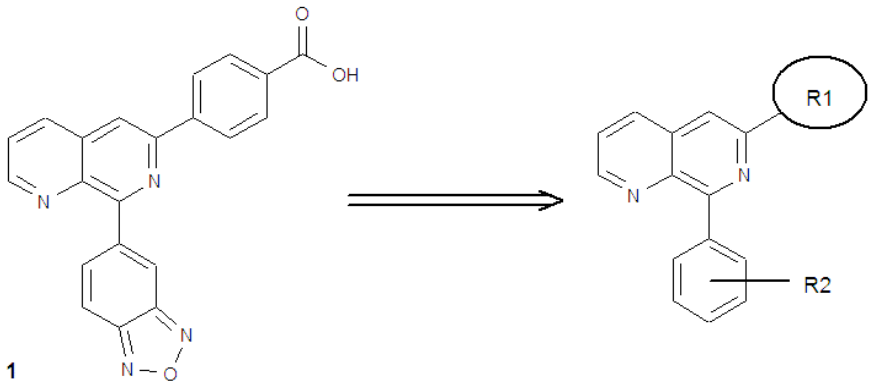


MEDI 267

The development of PDE4 inhibitors with improved therapeutic index for the treatment of COPD and asthma

Neil J. Press[1], *Clive McCarthy*[2], *Roger Taylor*[2], *Rene Hersperger*[3], *Thomas Keller*[4], *Joe Fullerton*[3], *Nicola Arnold*[3], *Lyndon Brown*[3], *Julia Hatto*[3], *Mark Mercer*[3], *Helen Oakman*[3], *Cathy Ritchie*[3], *Peter Gedeck*[3], *Martin Gosling*[3], *Andrea Hankin*[3], *Denise Head*[3], *Alexandra Smith*[3], *Rowan Stringer*[3], *Brian Everatt*[3], *Louise Dalrymple*[3], *Janet Maas*[3], *Elisabeth Schaeublin*[3], *Keith Butler*[3], *John R. Fozard*[5], *Lazzaro Mazzoni*[3], *Nicolaou Beckmann*[3], *Frederic Bernard*[3], *Olivier Bonneau*[3], *David Farr*[3], *Deborah Hynx*[3], *Morris Tweed*[3], *Daniel Wyss*[3], *Thomas Buhl*[3], *Moise Azria*[3], *Beate Vogel*[3], *and Alexandre Trifilieff*[3]. *(1) Dept. of Chemistry, Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, United Kingdom, Fax: +44 1403 323 837, neil.press@novartis.com, (2) GDC Horsham, Novartis Institutes for BioMedical Reasearch, Horsham, RH12 5AB, United Kingdom, (3) Novartis, (4) Novartis Institute for Tropical Diseases, 138670, Singapore, (5) Institute of Biomedical Research, Novartis Pharma Ltd, CH-4002 Basel NA, Switzerland*

Building on a previously disclosed PDE4 inhibitor, NVP-ABE171 (1), new compounds were synthesised with significant improvements in physico-chemical properties, pharmacokinetics and therapeutic index. Thus, NVP-ABE171 was a low solubility (pH 6.8 = 0.002g/L; pH 1 = 0.00004g/L) compound with highly variable bioavailability (rat BAV=10% +/-5%). Rational optimisation of physico-chemical properties led to the synthesis of several development candidates with much improved solubility (>10g/L) and pharmacokinetic parameters (rat BAV 65-97%). Potency at the PDE4 enzyme was retained (IC50<100nM) and excellent in vivo efficacy was demonstrated in several models of inflammation. Screening for toxicological side effects was carried out in the rat and the ferret model of emesis, and led to the nomination of the compound with the greatest therapeutic ratio for further development.



1

IC50 PDE4A = 630nM
IC50 PDE4B = 32nM
IC50 PDE4D = 1nM
Solubility pH6.8 = 0.002g/L
Rat BAV = 10% +/-5

Typical profile:
IC50 PDE4A = 165nM
IC50 PDE4B = 93nM
IC50 PDE4D = 3nM
Solubility pH6.8 >10g/L
Rat BAV = 97% +/-5

MEDI 268

Periodic classification of human immunodeficiency virus inhibitors

***Francisco Torrens**, Institut Univesitari de Ciencia Molecular, Universitat de Valencia, Edifici d'Instituts de Paterna, P. O. Box 22085, Valencia 46071, Spain, Fax: 34-96-354-3274, Francisco.Torrens@uv.es, and Gloria Castellano, Facultad de Ciencias Experimentales, Universidad Católica de Valencia San Vicente Mártir, Valencia 46003, Spain*

Classification algorithms are proposed based on information entropy. It is studied the feasibility of mixing a given human immunodeficiency virus type 1 (HIV-1) inhibitor with dissimilar ones, in a complex drug. The 31 inhibitors are classified by structural chemical properties. Many classification algorithms are based on information entropy. An excessive number of results appear compatible with the data, suffering combinatorial explosion. However, after the equipartition conjecture one has a selection criterion. According to this conjecture, the best configuration of a flowsheet is that in which entropy production is most uniformly distributed. The analysis includes inhibitors fitting the general scheme: (base derivative)-(furan ring). The base portion is often a guanine or cytosine derivative; the furan normally contains one O heteroatom. The structural elements of an inhibitor can be ranked according to their inhibitory activity, in the order: base > furan.

MEDI 269

99mTc-Labeled SDF as a target-specific molecular probe for noninvasive imaging of myocardial infarction

***Preeti Misra**[1], Alison D Schecter[2], Djamel Lebeche[3], Hung Ly[3], Roger J Hajjar[3], and John V. Frangioni[4]. (1) Haematology/Oncology, Beth Israel Deaconess medical Center, Harvard Medical school, 330 Brookline Ave, SLB-05, Boston, MA 02215, pmisra@bidmc.harvard.edu, (2) Department of Medicine and Immunobiology, Mount Sinai School of Medicine, New York, NY 10029, (3) Cardiovascular Research Center, Mount Sinai School of Medicine, New York, NY 10029, (4) Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, MA 02215*

Stromal-Cell-Derived Factor 1 (SDF-1) and its chemokine receptor CXCR4 have been proposed as key mediators of cardiac physiology. To image CXCR4 expression in vivo, we have synthesized 99mTc-SDF in one-step, using solid-phase preparation of the reactive intermediate [99mTc-MAS3]-NHS. The specific activity of [99mTc-MAS3]-SDF was 1086 Ci/mmol. Affinity for adenovirus-expressing CXCR4-positive cells was 1.85 ± 0.15 nM, with a BMax of 2.6 x 105 receptors per cell. For neonatal rat cardiomyocytes affinity was 2.9 ± 0.1 nM, with a BMax of 4.8x 104. After intravenous injection, blood clearance was rapid via the kidneys. Rats with induced myocardial infarctions had uptake of 0.57 ± 0.07 %ID/g in injured myocardium vs. 0.11 ± 0.01 %ID/g in non-injured myocardium. In conclusion, solid-phase chemical strategies for [99mTc-MAS3-NHS] pre-loading permit one-step preparation of disease-targeting radiotracers, which in turn, can be used to study important physiologic/pathologic processes in vivo.

MEDI 270

Synthesis of Littorachalcone

***Ganesh L Kumar**, Department of Chemistry, Iowa state university, 1605, Gilman hall, Chemistry department, Ames, IA 50014, lganeshk@iastate.edu, and George Kraus, Department of Chemistry, Iowa State University, Ames 50011*

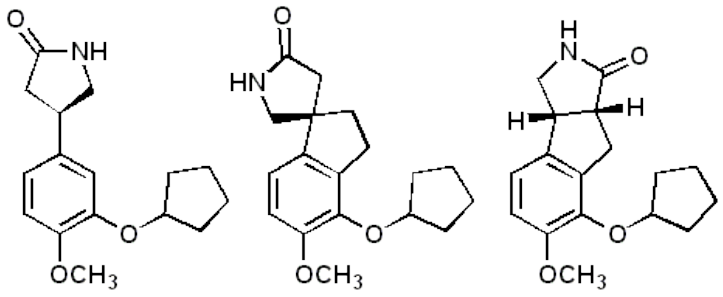
Littorachalcone, a biologically active polyphenol, was found to be useful in the treatment of various neurological disorders including Parkinson's and Alzheimer's disease. A direct and convergent synthesis of littorachalcone will be presented. A bis-aldol reaction was used as a key step involving 2,4-dimethoxyacetophenone and suitably functionalized 4,4'-oxybisbenzaldehyde. Reduction of resulting bis-enone by NiCl2-NaBH4 followed by removal of protecting groups furnished the target molecule in an efficient manner.

MEDI 271

Synthesis of structural probes for the PDE4 catalytic site

***Barbara Lindsay** and David R Adams, School of Engineering and Physical Sciences, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, United Kingdom, Barbara.Lindsay@hw.ac.uk*

Phosphodiesterase type 4 (PDE4) enzymes catalyse the removal of the key intracellular messenger molecule, cyclic adenosine monophosphate (cAMP), and PDE4 inhibitors are currently being developed as therapeutic agents for respiratory diseases such as asthma. Inhibition of PDE4 by the archetypal inhibitor, (R)-rolipram (**1**), is complicated by the existence of two distinct conformational states for the enzyme with distinct affinities for it: a High Affinity Rolipram-Binding State (HARBS) and a Low Affinity Rolipram-Binding State (LARBS). Rolipram and some other inhibitors have been found to cause a profound intracellular relocation of PDE4 sub-type A into foci. To probe a possible link between HARBS-PDE4 and foci formation, we are synthesising conformationally constrained analogues (**2** and **3**) of **1** that may resemble its HARBS- and LARBS-PDE4-bound conformations.

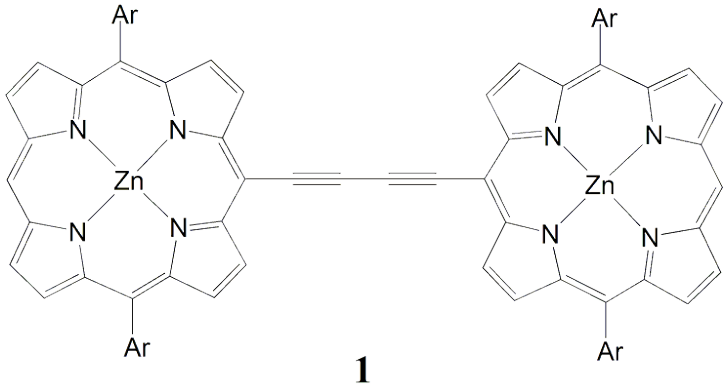


MEDI 272

Two-photon excited photodynamic therapy using water-soluble porphyrin dimers

Milan Balaz[1]*, Hazel A. Collins*[1]*, Marina K. Kuimova*[2]*, Emma Dahlstedt*[1]*, Mamta Khurana*[3]*, Aliaksandr Karotki*[4]*, David Phillips*[2]*, Brian Wilson*[4]*, and Harry L. Anderson*[1]*. (1) Department of Chemistry, University of Oxford, Mansfield Road, OX1 3TA Oxford, United Kingdom, milan.balaz@chem.ox.ac.uk, (2) Department of Chemistry, Imperial College, London, United Kingdom, (3) University of Toronto and Ontario Cancer Institute, Toronto, Canada, (4) University of Toronto and Ontario Cancer Institute, Toronto M5G 1X5, Canada*

Two-photon excited photodynamic therapy (TPE-PDT) is the use of a chromophore with a high TPE cross section as a photosensitizer in PDT. The quadratic dependence of 2PE on the laser intensity allows high spatial selectivity by focusing the laser beam at a target point and thus preventing damage to healthy adjacent tissue. Additionally, near-infrared light of twice the wavelength of the absorption band can be used to produce the excited state of the sensitizer facilitating biological tissue penetration. Recently we have shown that porphyrin dimer such as **1** has an exceptionally high two photon absorption cross-section of ca 6,000 GM at 780 nm and high singlet oxygen yields. The challenge now is to synthesize biocompatible porphyrin dimers with good cellular uptake while keeping their excellent photophysical properties. We will present the synthesis of new water-soluble dimers, their in vitro one- and two-photon PDT results, intracellular localization, and fluorescence lifetime imaging microscopy.



1

MEDI 273

Design and synthesis of some multitargeted ligands as potential antihypertensive agents

Bishram Singh Chouhan*, Pharmaceutical Chemistry Laboratory, Pharmacy department, The Maharaja Sayajirao University of Baroda, Faculty of Tech. & Engg, Kalabhawan, Vadodara 390002, India, Fax: +91-265-2423898, cbishram@yahoo.co.uk, Mange Ram Yadav, Department of pharmacy, The M.S University of Baroda, Baroda 390001, India, and Rajani Giridhar, Pharmacy Department, The M.S University of Baroda, vadodara 390002, India*

Since the mid-90s, antihypertensive compounds, which act simultaneously on several targets, have been the subject of intensive research, and this led to the discovery of several agents

with different dual antihypertensive mechanisms of action. They include simultaneous action on various receptors ranging from calcium channel, β1 adrenergic blockers, α1 adrenergic blockers, 5HT 2A antagonist, endothelin and angiotensin receptor antagonists. In our ongoing research for the development of novel potential antihypertensive agents we have designed and synthesized some dual acting compounds as alpha-1 and angiotensin-II (A-II) receptor antagonists. 2 and/or 3-Substituted-6,7-dimethoxyquinazolinones were prepared using a novel synthetic route which include cyclization of un/substituted diamides to the corresponding quinazolinone derivatives using microwave irradiations. The synthesized compounds were subjected to in vivo and in vitro screening for alpha-1 and A-II receptor antagonistic activity. Out of the series of compounds screened two compounds showed promising activity in nanomolar range against alpha-1 as well as A-II receptors.

MEDI 274

Discovery and synthesis of novel *N*-(hetero-biaryl)piperazine adenosine A_{2a} receptor antagonists

Joel M. Harris[1]*, Hong Liu*[1]*, Jinsong Hao*[1]*, Bernard Neustadt*[1]*, Hongtao Zhang*[2]*, Jean Lachowicz*[2]*, Mary Cohen-Williams*[2]*, Geoffrey Varty*[2]*, Kathleen Cox*[3]*, Andrew W. Stamford*[1]*, and William J Greenlee*[4]*. (1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033-1300, Fax: 908-740-7152, joel.harris@spcorp.com, (2) CV/CNS Biology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, (4) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, Kenilworth, NJ 07033*

Adenosine is an important neuromodulator in the central and peripheral nervous systems. Adenosine modulates its effects through the activation of four subtype receptors located on cell membranes, known as A_1, A_{2a}, A_{2b}, and A_3. The adenosine A_{2a} receptor is a member of the G-protein-coupled receptor family and is abundant in discrete brain regions, such as the striatum. Antagonism of the A_{2a} receptor may provide a means of modulating the dopaminergic system without the associated motor side effects of direct dopamine D2 receptor interaction. Thus, adenosine A_{2a} receptor antagonists could provide treatment of neurodegenerative diseases such as, Parkinson's disease. The design, synthesis, and evaluation of *N*-(hetero-biaryl)piperazine adenosine A_{2a} antagonists will be presented. Highly potent A_{2a} receptor antagonists were discovered with excellent selectivity versus the A_1 receptor and exhibited good *in vivo* activity.

MEDI 275

Toward multivalent GPCR signaling from poly(amidoamine) dendrimer conjugates

Yoonkyung Kim[1]*, Athena M. Klutz*[1]*, Béatrice Hechler*[2]*, Christian Gachet*[2]*, and Kenneth A. Jacobson*[1]*. (1) Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0810, kimyoonk@niddk.nih.gov, (2) INSERM U311, Etablissement Français du Sang-Alsace, Strasbourg, France*

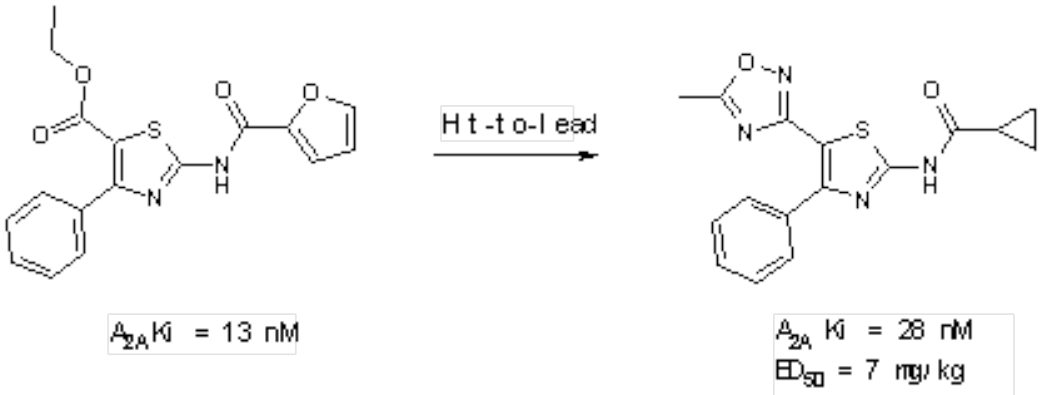
Adenosine receptors (ARs) are members of G-protein-coupled receptor (GPCR) family. A_{2A} AR is one of the four identified AR subtypes and is relevant to various disease conditions including thrombosis, nervous system disorders, and ischemic reperfusion damage. In an effort to develop advanced therapeutics to act through ARs, PAMAM dendrimers were used to conjugate at the periphery varying numbers of receptor-selective nucleoside moieties for activation of the A_{2A} AR and characterized spectroscopically. Dendrimers are treelike macromolecular architectures that possess unique size, shape, and physical properties. We envision that dendrimers may act as nanoscaffolds for attachment of multiple ligands for synergistic receptor binding and improved overall pharmacological profiles compared to the monovalent ligands. Indeed, PAMAM-nucleoside conjugates exhibited binding affinities at the human A_{2A} AR with submicromolar K_i values. Furthermore, an enhanced antiaggregatory effect on ADP-induced platelet aggregation, characteristic of A_{2A} AR agonists, was observed in our preliminary in vitro experiments.

MEDI 276

Hit to lead optimization of a series of 2-([2-amino]-4-phenyl-thiazole-5-carboxylic acid ethyl ester)carboxamides identified as A2A antagonists

***Gitte Mikkelsen**, Anette Graven Sams, Mogens Larsen, Benny Bang-Andersen, Morten Langgaard, Tenna Juhl Schroeder, and Lars Thorup, Lundbeck Research Denmark, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark, gmi@lundbeck.com*

The neuromodulator adenosine acts on a family of G protein-coupled receptors receptors termed A_1, A_{2A}, A_{2B} and A_3. The A_{2A} receptor is predominantly expressed in the striatum, closely co-localized with dopamine D_2 receptors. The A_{2A} receptors interact with D_2 receptors, causing a decrease in affinity of D_2 receptors for dopamine, upon stimulation. Thus, A_{2A} antagonists are capable of enhancing the effect of dopamine or dopamine agonists, making A_{2A} receptor antagonists interesting as drugs for the treatment of Parkinsons Disease. An HTS campaign to identify A_{2A} antagonists in our lab resulted in the discovery of a series of non-drugable hits containing an ester functionality. Herein, the result of a hit optimisation, replacing the ester group with isosteric groups is presented. This optimisation resulted in the identification of A_{2A} antagonist lead compounds, possessing good PK properties, acceptable selectivity towards A_1, and with a demonstrated effect in a mechanistic *in vivo* model.



MEDI 277

Design and characterization of dimeric ligands cross-linking two identical modulatory AMPA receptor sites

Birgitte H. Kaae[1]*, Kasper Harpsøe*[1]*, Alberto Contreras Sanz*[2]*, Darryl S. Pickering*[2]*, Per Sauerberg*[3]*, Rasmus P. Clausen*[1]*, Jette S. Kastrup*[1]*, Tommy Liljefors*[1]*, and Ulf Madsen*[1]*. (1) Dept. of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, 2 Universitetsparken, 2100 Copenhagen, Denmark, bhk@farma.ku.dk, (2) Dept. of Pharmacology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark, (3) Medicinal Chemistry Research II, Novo Nordisk A/S, 2760 Måloev, Denmark*

AMPA receptors belong to the class of excitatory amino acid receptors, and play important roles in physiological functions, and in many neurological disorders. E.g. modulators are of great therapeutic interest as cognitive enhancers. AMPA receptors are composed of four subunits assembled as two subunit-dimers. Ligands were designed to cross-link two identical modulatory binding sites by the use of computational chemistry. The designed dimeric ligands were synthesized in excellent yields. Pharmacological characterization of these allosteric positive modulators revealed potent EC_{50} values (0.5-3.5 μM) on $GluR1_i$-4_i, and no subunit selectivity. The preferred stereoisomer was co-crystallized with (*S*)-glutamate and GluR2-S1S2J (N754S), and the x-ray structure revealed cross-linking of two identical binding sites by the dimeric ligand as predicted.

MEDI 278

Mechanism of interaction of multivalent antimicrobial peptide with model membranes

Anne Young*, Zhigang Liu, Chunhui Zhou, and Neville R. Kallenbach, Department of Chemistry, New York University, Box29, Rm1001,100 Washington Square East, New York, NY 10003, anneyoung@nyu.edu*

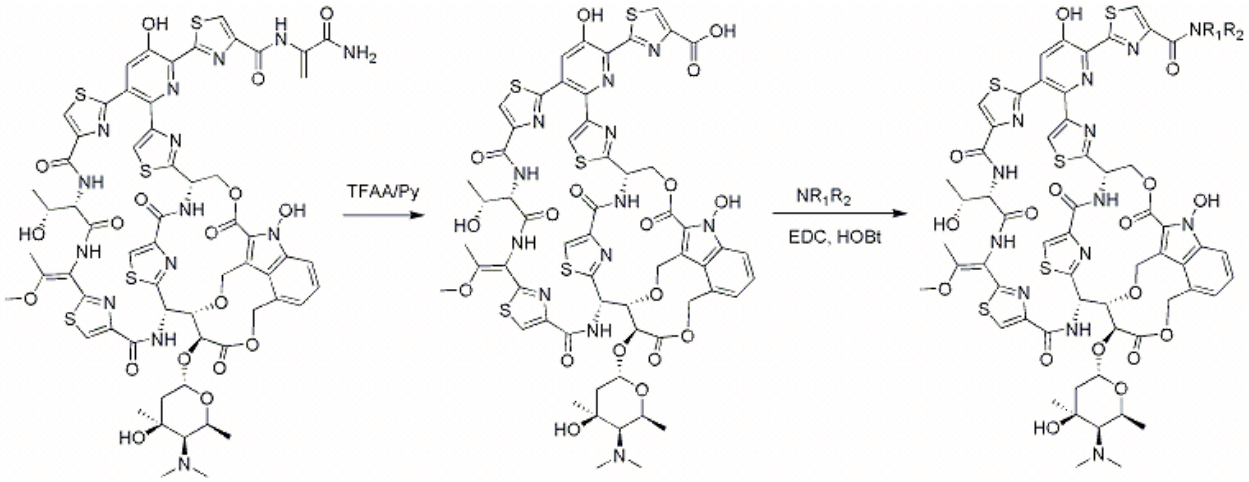
Natural antimicrobial peptides (AMPs) secreted by most organisms have been investigated as a potential source of new antibiotics. Our recent studies indicate that a multivalent strategy of polymerized AMPs can enhance the potency of monomeric peptides. However, the mechanism by which multivalent AMPs kill bacterial pathogens has yet to be explored. It is generally accepted that AMPs lead to permeation of the bacterial cell membrane. Two phases of interaction between AMPs and membranes have been detected: (1) binding by electrostatic interactions, and (2) assembly of bound AMPs to the membrane. Our results support this biphasic model, we find adding charges can enhance binding without facilitating assembly. Initial attachment of arginine peptides are electrostatically driven, while presence of typtophan favors an intercalation process at the interface between the headgroups and core of the membrane. Promoting assembly requires a different interaction, and we will describe models that alter the balance between them.

MEDI 279

Novel water-soluble nocathiacin analogs as potent antibacterial agents

Libo Xu[1], *Kun Liu*[2], *Amy Farthing*[2], *Sheryl Debenham*[2], *Fengqi Zhang*[2], *Guo Q. Shi*[3], *James F. Dropinski*[2], *Peter T. Meinke*[2], *Christrine McCallum*[4], *and Emily Hickey*[5]. *(1) Department of Medicinal Chemisty, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, libo_xu@merck.com, (2) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, (3) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ NJ 07065, (4) Infectious Diseases, Merck Research Laboratories, Rahway, NJ 07065, (5) Merck Research Laboratories, Rahway, NJ 07065*

Nocathiacin I is a new member of the thiazolyl peptide antibiotics family and displays potent antibacterial activity against a variety of Gram-positive and drug resistant bacteria. Nocathiacin I disrupts bacterial protein biosynthesis by interacting directly with the ribosomal site. Poor water solubility is the key limitation to the development of this compound as an IV drug. Several approaches trying to obtain analogs of nocathiacins with increased water solubility have been reported in the literature. In this presentation, we will describe novel synthetic strategies to instill water-solubilizing groups onto nocathiacins. We discovered a mild and selective method to transform nocathiacin I to the highly desirable carboxylic acid intermediate which allowed for easy access to a variety of novel amides. The in vitro and in vivo antibacterial activities of nocathiacin analogs will be presented.



MEDI 280

WITHDRAWN

MEDI 281

ESI/MS study on sulfur containing ß-lactams and their interactions with glutathione

***Maya Kostova**, Carey J. Myers, and Monika Konaklieva, Department of Chemistry, American University, 4400 Massachusetts Ave NW, Washington, DC 20016, Fax: 202.885.1752*

Glutathione is a small intracellular protein that functions as a free radical scavenger, amino acid transporter and cell life cycle regulator. It also plays a role in the body's antioxidant defense system and in drug detoxification. Glutathione is mostly present in the cell in its reduced form. As a thiol, it is likely to form disulfide bonds with other thiol compounds. This study examines the interactions of several sulfur-containing ß-lactams with glutathione using ESI/MS. The experimental results of this preliminary study assisted in broadening our knowledge of ß-lactam-glutathione interactions.

MEDI 282

Synthesis and SAR of 4-(benzylideneamino)benzenesulfonamides as selective COX-2 inhibitors

*Shwu-Jiuan Lin, Department of Medicinal Chemistry, College of Pharmacy, Taipei Medical University, 250 Wu-Hsing St., Taipei 110, Taiwan, shwu-lin@tmu.edu.tw, and **Li-Ming Yang**, Division of Medicinal Chemistry, National Research Institute of Chinese Medicine, 155-1, Li-Nong St., Sec. 2, Taipei 112, Taiwan, Fax: +886-2-2826-4276, lmyang@nricm.edu.tw*

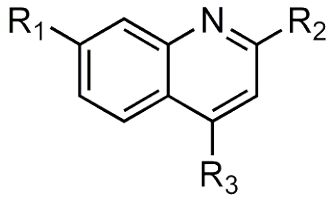
Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used to treat pain, fever and inflammation. COX-2 selective inhibitors have proven to be effective anti-inflammatory and analgesic medicines with lower bleeding and ulcerogenic effects than traditional NSAIDs, which nonselectively inhibit COX-2 and COX-1. Recently, rofecoxib and valdecoxib has been withdrawn from the market due to the increased risk of heart attack and stroke. Thus, it is highly desirable to develop new selective COX-2 inhibitors to prevent the cardiovascular side effects. In the present study, a series of 4-(benzylideneamino)benzenesulfonamide derivatives was designed and synthesized for the evaluation as selective COX-2 inhibitors in a cellular assay using human whole blood. The design, synthesis and SAR among these compounds will be presented and discussed.

MEDI 283

Synthesis and biological profile of substituted quinolines as potent 5-Lipoxygenase inhibitors

Marc Gagnon[1], *Christine Brideau*[2], *Elizabeth Cauchon*[2], *Anne Chateauneuf*[2], *Yves Ducharme*[3], *Richard Frenette*[3], *Richard W. Friesen*[3], *Sebastien Guiral*[2], *Pierre Hamel*[1], *Joseph A. Mancini*[2], *Marc Ouellet*[2], *David Percival*[2], *Angela Styhler*[2], *and Elizabeth Wong*[2]. *(1) Department of Medicinal Chemistry, Merck Frosst Canada & Co, 16711, Trans Canada Hwy, Kirkland, QC H9H 3L1, Canada, Fax: 514-428-4900, (2) Department of Biochemistry, Merck Frosst Canada & Co, Kirkland, QC H9H 3L1, Canada, (3) Merck Frosst Canada & Co, Kirkland, QC H9H 3L1, Canada*

Leukotrienes are derived from the biotransformation of arachidonic acid through the action of 5-lipoxygenase and FLAP. Compounds that inhibit one of those key enzymes for the biosynthesis of leukotrienes, are postulated to be implicated in a variety of disorders including inflammatory and allergic diseases, artherosclerosis and cancer. As part of an ongoing effort, we have synthesized and evaluated a number of novel quinoline and 2-cyanoquinoline derivatives. A structure activity relationship (SAR) study led to the discovery of compounds that exhibit good to excellent in vitro activity against the human 5-LO enzyme. These compounds are also potent inhibitors of the calcium ionophore stimulated production of LTB4 in whole blood and in cell based assays. The design, the synthesis and the activity of these 5-LO inhibitors will be presented.



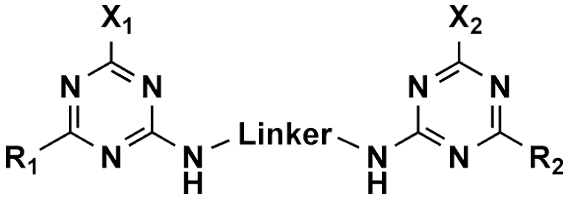
MEDI 284

1,3,5-Triazine derivatives with improved solubility for the treatment of inflammatory diseases

Boulos Zacharie, ***Daniel Fortin****, Shaun D. Abbott, Jean-François Bienvenu, Alan Cameron, Josée Cloutier, Jean-Simon Duceppe, Abdallah Ezzitouni, Karine Houde, Caroline Lauzon, Joël Lechasseur, Nancie Moreau, Valérie Perron, Nicole Wilb, Marie-Ève Fafard, Dannyck Gaudreau, Lilianne Geerts, Brigitte Grouix, François Sarra-Bournet, Lyne Gagnon, and Christopher Penney, ProMetic BioSciences Inc, 500, boul. Cartier Ouest, Laval, QC H7V 5B7, Canada, Fax: 450-781-1403, b.zacharie@prometic.com*

Protein A (MW = 42,000) binds with high affinity to the tail portion of human and mouse antibodies. This bacterial protein has potential therapeutic utility but its toxicity and cost limit its therapeutic use. Nonetheless, it has been approved by the FDA for the treatment of autoimmune diseases (arthritis, ITP), whereby protein A is used covalently linked to a silica column. The patient's blood is passed through this column in a manner similar to kidney dialysis (apheresis). So there is a definite need for a nontoxic small molecule mimetic to

protein A which can be administrated as a drug. We have shown that a series of low molecular weight triazine derivatives (1) displays significant activity relative to protein A in a competitive ELISA assay. These derivatives also demonstrate interesting activity in vivo in inflammatory disease models. Described herein is a series of more soluble analogues that show improved oral activity. The structure-activity relationships of these compounds will be presented.



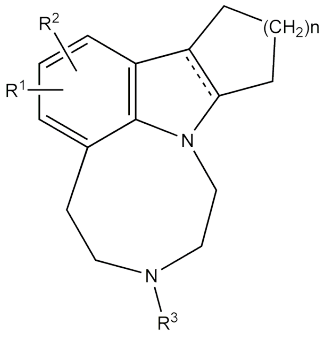
1

MEDI 285

[1,4]Diazepine[7,8,1-hi]indole derivatives as antipsychotic and antiobesity agents

Hong Gao[1]*, Gary Stack*[2]*, Boyd L. Harrison*[1]*, Hossein Mazandarani*[3]*, Jean Zhang*[3]*, Sachin Kalgonkar*[3]*, Sharon Rosenzweig-Lipson*[3]*, John Dunlop*[3]*, Terry Andree*[3]*, and Lee Schechter*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, gaoh1@wyeth.com, (2) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, (3) Wyeth Neuroscience, Princeton, NJ 08543*

5-HT_{2C} agonists and partial agonists represent a novel therapeutic approach toward the treatment of schizophrenia. At present, the most widespread treatments for schizophrenia are the ‘atypical' antipsychotics, which combine dopamine (D_2) receptor antagonism with serotonin (5-HT_{2A}) receptor antagonism. Despite the reported advances in efficacy and side-effect liability of atypical antipsychotics over typical antipsychotics, these compounds do not adequately treat all of the symptoms of schizophrenia and are accompanied by problematic side effects including weight gain. Novel antipsychotics which are effective in treating the symptoms in schizophrenia without producing weight gain would represent a significant advance in the treatment of schizophrenia. A series of benzodiazocinoindoles (I) were investigated and several analogs found to be potent and selective 5-HT_{2C} agonists and partial agonists with affinities in the 10 nM range. Herein we report the synthesis and SAR of these novel benzodiazocinoindoles.



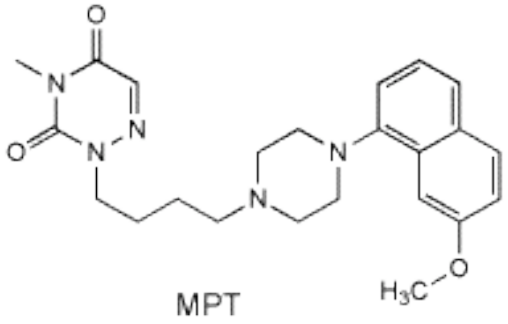
I

MEDI 286

Synthesis and structure activity relationship of novel azaurazil and pyridopyramidine derivatives of arylpiperazine as potential and selective 5-Ht1a receptor agonists

Vattoly J Majo[1]*, Jaya Prabhakaran*[1]*, Lyudmila Savenkova*[1]*, J. John Mann*[2]*, and J. S. Dileep Kumar*[2]*. (1) Department of Psychiatry, Columbia University, 1051 Riverside Drive, Box:42, New York, NY 10032, (2) Department of Psychiatry and Division of Neuroscience, Columbia University and New York State Psychiatric Institute, New York, NY 10032*

The serotonin 5-HT1A receptor is implicated in the pathophysiology of major neuropsychiatric disorders including depression, suicidal behavior, panic disorder, epilepsy, bulimia, schizophrenia, Parkinson's disease, and Alzheimer's disease and is therefore an important target for drug therapy. 5-HT1A receptor agonists are being evaluated as antipsychotic drugs (APDs) with fewer side effects. We have recently found [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 5-HT1A receptor agonist in vivo radiotracer. However, the lack of favorable kinetics at later time points of this ligand prompted us to evaluate the affinity and agonist profile of a series of arylpiperazines tethered to azauracil and pyridopyrimidine derivatives. The design, synthesis, SAR and in vivo efficacies of selected compounds will be presented.



MPT

MEDI 287

Synthesis of D-amino acid oxidase inhibitors and their effects on the plasma and brain levels of D-serine

Bridget Duvall[1]*, Dana Ferraris*[1]*, Yao-sen Ko*[1]*, Ajit Thomas*[1]*, Pavel Majer*[1]*, Camilo Rojas*[1]*, Takashi Tsukamoto*[1]*, and Kenji Hashimoto*[2]*. (1) Department of Research, MGI Pharma, Inc, 6411 Beckley Street, Baltimore, MD 21224, Fax: 410-631-8189, bridget.duvall@mgipharma.com, (2) Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan*

The preclinical and clinical evidence supporting the role of NMDA receptor hypofunction in schizophrenia has prompted clinical trials of agents that enhance NMDA receptor function. For example, schizophrenic patients receiving D-serine, a full agonist at the glycine site of the NMDA receptor, with concomitant neuroleptic therapy have shown significant improvements in their positive, negative, and cognitive symptoms. In humans, however, D-serine is believed to

be metabolized substantially by D-amino acid oxidase (DAAO), diminishing its bioavailability. To address this issue, we have designed small molecule DAAO inhibitors which can be co-administered with D-serine to minimize its metabolism by DAAO. Through our SAR studies, we found that small molecules based on a benzo[d]isoxazol-3-ol core structure potently inhibit DAAO. The most potent compound was tested for its ability to enhance the plasma and brain levels of co-administered D-serine in rats.

MEDI 288

Design, synthesis and in vivo results of chemically-modified antisense oligonucleotides targeting microRNA-122

Garth A. Kinberger[1]*, Stephanie Propp*[2]*, Scott Davis*[2]*, Susan Freier*[2]*, Christine Esau*[2]*, Eric E. Swayze*[1]*, C. Frank Bennett*[3]*, and Balkrishen Bhat*[1]*. (1) Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc, 1891 Rutherford Road, Carlsbad, CA 92008, (2) Department of Biology, Isis Pharmaceuticals, Inc, Carlsbad, CA 92008, (3) Isis Pharmaceuticals, Inc, Carlsbad, CA 92008*

MicroRNAs (miRNAs) are short non-coding RNAs which regulate gene expression during development by binding to the 3'-untranslated region of the mRNA and inhibiting translation. The most abundant microRNA in liver is miR-122. Using an antisense oligonucleotide (ASO) to inhibit miR-122 in normal and diet induced obesity mouse models we showed reduction in cholesterol synthesis and improvement in liver steatosis, respectively. These data point to miR-122 as a potential therapeutic target for the treatment of cardiovascular disease. To further improve in vivo activity, a number of antimiR-122 ASOs consisting of modifications in sugar, heterocycle and backbone were designed and synthesized, and their ability to inhibit miR-122 activity were evaluated. SAR studies resulted in molecules that displayed an earlier onset of action as well as several fold increase in activity compared to parent uniform 2'-O-MOE modified ASO. The results from the miR-122 SAR will be presented.

MEDI 289

Multifunctional proligands for Alzheimer's disease therapy

Lauren E Scott[1]*, David E. Green*[1]*, Tim Storr*[2]*, Meryn L. Bowen*[1]*, Michael Merkel*[1]*, Gavin H Tansley*[3]*, Harvey Schugar*[4]*, Cheryl L. Wellington*[3]*, and Chris Orvig*[1]*. (1) Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Fax: 604-822-2847, lescott@chem.ubc.ca, (2) Department of Chemistry, Stanford University, Stanford, CA 94305-5080, (3) Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC V5Z 4H4, (4) Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8087*

The brain pathology of Alzheimer's disease is typified by the presence of insoluble protein plaques (of beta-amyloid peptide, Aß) associated with elevated levels of brain metal ions such as Cu, Zn and Fe. Dysfunctional interactions of the aggregated peptide and redox-active metal ions (Cu, Fe) are implicated in the development of highly oxidative conditions in the brain, leading to neurological decline; thus, small molecule metal-binding agents with antioxidant

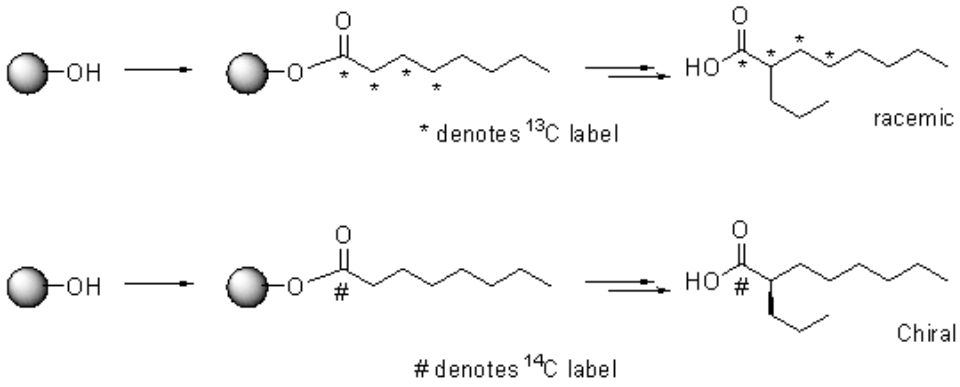
activity have been developed as potential Alzheimer's therapeutics. Targeting to the brain through appended sugar moieties completes the multifunctionality of these new compounds. The synthesis, characterization and in vitro assay of these pro-drugs will be discussed.

MEDI 290

Solid-phase synthesis of isotope-labeled 2-propyloctanoic acid, a therapeutic agent for stroke and Alzheimer's disease

***Jonathan Z. Ho**, Cheng Tang, and Matthew P Braun, Department of Drug Metabolism, Merck & Co., Inc, 126 East Lincoln Avenue, Rahway, NJ 07065, Fax: 732-594-6921, jonathan_ho@merck.com*

Solid-Phase organic synthesis plays an important role in modern drug discovery. This technique is widely used as a tool for development of target structure-activity-relationship (SAR) toward lead compounds for drug development. However, utilization of solid-phase synthesis in obtaining small molecule isotopically labeled compounds has only been scarcely explored. Hence, we sought to develop an efficient solid-phase synthetic strategy that would allow the preparation of carboxylic acids, particularly, those for which standard purification and isolation would be difficult due to lack of a UV chromophore. We report herein a convenient method that takes advantage of the oxime resin as a solid support. Two C-isotope labeled compounds were made by application of this technology.



MEDI 291

Discovery and SAR study of a novel anti-Alzheimer compound family acting on APP

*Stéphane Burlet[1], Bénédicte Grasland[2], Marie-Ange Debreu-Fontaine[1], Marie-Eve Grosjean[2], André Delacourte[2], and **Patricia Melnyk**[1]. (1) Team 3, UMR8161 CNRS, Lille1 University, Lille2 University, Pasteur Institute of Lille, 1, Rue du Pr Calmette, BP447, 59021 Lille, France, Fax: 33 3 20 87 12 33, stephane.burlet@ibl.fr, patricia.melnyk@ibl.fr, (2) Inserm U837, JPARC, 59045 Lille, France*

Alzheimer's disease (AD) is the most well known age related neurodegenerative dementia which is characterized by two main pathological hallmarks: intracellular neurofibrillary tangles

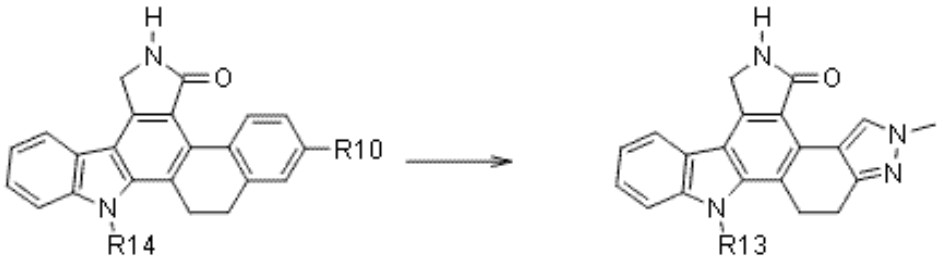
and amyloid plaques (consisting of Abeta), a catabolic product of APP. This latter can be proceeded in two different ways. The first one leads to Abeta with the sequential action of beta and gamma secretase. In contrast, in the non-amyloidogenic pathway, APP is cut in the middle of Abeta sequence and releases metabolites that could have potential physiological and/or neurotrophic activities: sAPPalpha and AICD. Chloroquine was first reported to show the desired effects i.e decrease of Abeta and boost of AICD and sAPPalpha. Based on a screening oriented approach, a new family of compounds exhibiting the required effects but with powerful action was discovered. More than one hundred compounds was then synthesized and tested on cellular models then SAR studies lead to structural prerequisites for biological activity.

MEDI 292

Synthesis and structure-activity relationships of novel, potent mixed lineage kinase (MLK) inhibitors for Alzheimer's disease

Ming Tao[1]*, Chung Ho Park*[2]*, Reddeppareddy Dandu*[1]*, Allison Zulli*[1]*, Kurt Josef*[1]*, James L. Diebold*[1]*, Diane E. Gingrich*[1]*, Matthew Curry*[1]*, Jean Husten*[3]*, George Gessmen*[3]*, Thelma Angeles*[3]*, and Robert L. Hudkins*[1]*. (1) Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: 610-738-6558, mtao@cephalon.com, (2) Cephalon, Inc, West Chester, PA 19380, (3) Department of Biochemistry, Cephalon, Inc, West Chester, PA 19380*

The c-Jun amino-terminal kinase (JNK) signaling pathway leads to activation of transcription factor and proapoptotic genes. The cascade plays an important role in neuronal apoptosis and may contribute to the neuronal loss associated with Alzheimer's disease and Parkinson's disease. The JNKs are stress activated protein kinases and are activated by the dual specificity MAP kinases MKK4 and MKK7, which are activated by upstream signals including the mixed lineage kinases (MLKs). The first generation compound from our program, CEP-1347, is a semi synthetic derivative of the indolocarbazole K-252a. CEP-1347, a potent inhibitor of the MLKs, displays a broad neuroprotective profile. In the search for potent synthetic MLK inhibitors, we identified dihydronaphthyl[3,4-a]pyrrolo[3,4-c]carbazole core 1 as novel MLK1/3 selective inhibitors. Toward our objective to further improve the MLK potency and bring DLK activity into the core, we prepared F-ring dihydroindazole analogs 2. The synthesis and SAR of this new dihydroindazole scafford will be discussed.



1 2

MEDI 293

WITHDRAWN

MEDI 294

Pyridinylaminohydantoins as small molecule BACE1 inhibitors: Exploration of the S3 pocket

Ping Zhou[1], *Jonanthan Bard*[2], *Rajiv Chopra*[1], *Kristi Yi Fan*[1], *Yun Hu*[2], *Yanfang Li*[1], *Ronald L. Magolda*[1], *Michael S. Malamas*[1], *Menelas Pangalos*[2], *Peter Reinhart*[2], *Jim Turner*[2], *Zheng Wang*[1], *and Albert J Robichaud*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, Fax: 732-274-4505, zhoup@wyeth.com, (2) Department of Neuroscience, Wyeth Research, Princeton, NJ 08543*

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is the leading cause of dementia. Although the cause of AD is still unclear, deposition of b-amyloid peptide (Ab) in the brain is a hallmark of AD pathogenesis, and it is believed that therapeutic agents that lower Ab will be beneficial in the treatment of AD. Ab is produced from membrane-bound b-amyloid precursor protein (APP) by sequential proteolytic cleavage by b-secretase (BACE1) and g-secretase. Therefore, BACE1 is an attractive therapeutic target for AD. In this poster we will present novel pyridinylaminohydantoins as potent BACE1 inhibitors. X-ray crystal structure of pyridinylaminohydantoin compound in complex with BACE1 demonstrated that the aminohydantoin moiety interacts with the two aspartic acids in catalytic domain of BACE1, while pyridine nitrogen forms hydrogen bonding with Trp 76 at S2'. The optimization of the S3 pocket via parallel synthesis approach led to many very potent compounds. The synthesis, SAR and x-ray structure of the series will be presented.

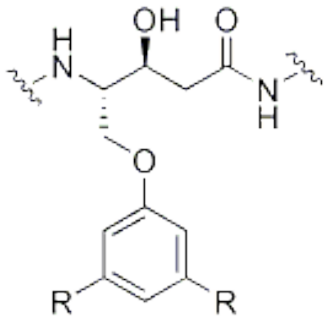
MEDI 295

Design, synthesis and SAR of potent statin-based β-secretase inhibitors: Exploration of P1 phenoxy and benzyloxy residues

Marcus Bäck[1], *Jonas Nyhlén*[2], *Ingemar Kvarnström*[1], *Åsa Rosenquist*[3], *and Bertil Samuelsson*[3]. *(1) Department of Chemistry, Linköping University, Campus Valla, S-58183 Linköping, Sweden, Fax: +4613281399, marba@ifm.liu.se, (2) Department of Organic Chemistry, Stockholm University, SE-10691 Stockholm, Sweden, (3) Medivir AB, S-14144 Huddinge, Sweden*

The human aspartic protease, β-secretase (BACE), is generally considered to play an initiating role in the neurodegenerative cascade ultimately leading to Alzheimer's disease (AD). The amyloid precursor protein (APP) is cleaved by different proteases along two major pathways, the α-secretase pathway and the amyloid forming β-secretase (BACE) pathway. The amyloid forming pathway is dependent on two proteolytic cleavages perfomed by β-secretase and γ-secretase, resulting in the release of amyloid-β40 (Aβ40) and the insoluble pathogenic amyloid-β42 (Aβ42). In this study we present several potent and promising BACE inhibitors, displaying low nanomolar activity, which were identified from a series of statine-based

inhibitors incorporating novel methylphenyloxy- and methylbenzyloxy residues in the P1 position.



R = H or F

MEDI 296

Pyrrolidines as conformationally constrained diaminopropanes: A versatile scaffold for potent inhibitors of BACE-1

Jason M. Guernon[1], *Lorin A. Thompson III*[1], *John E. Macor*[1], *Andrew J. Tebben*[2], *Andrew Good*[2], *Catherine R. Burton*[3], *Donna M. Barten*[3], *Jovita Marcinkeviciene*[4], *Jeremy H. Toyn*[3], *Charlie Albright*[3], *Jodi K. Muckelbauer*[5], *Daniel Camac*[5], *Tatyana Zvyaga*[6], *James Grace*[7], *Kimberly Lentz*[7], *and Kenneth M. Boy*[1]. *(1) Neuroscience Chemistry, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492, jason.guernon@bms.com, (2) Computer Assisted Drug Design, Bristol-Myers Squibb, (3) Neuroscience Biology, Bristol-Myers Squibb, (4) Chemical Enzymology, Bristol-Myers Squibb, (5) X-Ray Crystallography, Bristol-Myers Squibb, (6) Lead Profiling, Bristol-Myers Squibb, (7) MAP Discovery, Bristol-Myers Squibb*

The production of the amyloidogenic A-beta 1-42 protein fragment from Amyloid precursor protein (APP) is postulated to initiate the pathology characteristic of Alzheimer's disease. Beta-secretase (BACE) and Gamma-secretase are responsible for the liberation of A-beta 1-42, so inhibition of these enzymes would be of potential therapeutic benefit. Previously reported Gamma-lactam-diaminopropanes were potent *in-vitro* inhibitors of BACE. A conformationally restricted pyrrolidine template was successfully incorporated. Crucial properties including CYP profile, PGP efflux, and selectivity versus other aspartyl proteases were attenuated by functionalization of the 4- and 5-positions of the pyrrolidine. The rationale for these compounds will be discussed as well as their synthesis and properties.

MEDI 297

Synthesis and SAR of hydroxyethylamine-based phenylcarboxyamides as BACE-1 inhibitors

Yong-Jin Wu[1], *Yunhui Zhang*[1], *Andrew Good*[2], *Lorin A. Thompson*[1], *Catherine R. Burton*[3], *Jeremy H Toyn*[3], *Charles F. Albright*[3], *and John E. Macor*[1]. *(1) Department of Neuroscience*

Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06443, yong-jin.wu@bms.com, (2) Department of Computer-Aided Drug Design, Bristol-Myers Squibb Company, Wallingford, CT 06443, (3) Department of Neuroscience Biology, Bristol-Myers Squibb Company, Wallingford, CT 06443

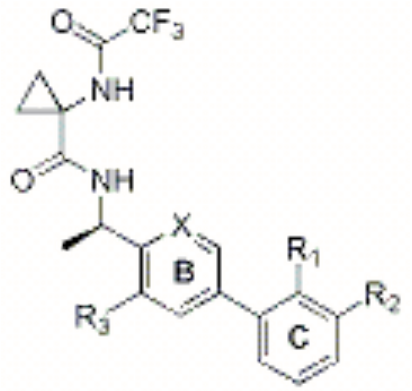
A series of N-((2S,3R)-1-(3,5-difluorophenyl)-3-hydroxy-4-(3-methoxybenzylamino)-butan-2-yl)benzamides has been synthesized as BACE-1 inhibitors. A variety of P2 and P3 substituents have been explored, and these efforts have culminated in the identification of several 3,5-disubstituted benzamides with potent BACE-1 inhibitory activity.

MEDI 298

Bradykinin B1 antagonists: Biphenyl SAR studies in the cyclopropanecarboxamide series

Christina Ng Di Marco[1]*, Robert M. DiPardo*[1]*, Ronald K. Chang*[1]*, Kathy L. Murphy*[2]*, Richard W. Ransom*[2]*, Duane Reiss*[3]*, Cuyue Tang*[4]*, Thomayant Prueksaritanont*[5]*, Douglas Pettibone*[2]*, Mark G. Bock*[1]*, and Scott D. Kuduk*[1]*. (1) Department of Medicinal Chemistry, Merck & Co., Inc, WP14-3, Sumneytown Pike, Post Office Box 4, West Point, PA 19486, christina_ng@merck.com, (2) Neuroscience Drug Discovery, Merck Research Laboratories, West Point, PA 19486, (3) Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, (4) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (5) Department of Molecular Endocrinology, and Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

Bradykinin (BK) peptides are involved in pain and inflammation resulting from tissue injury and noxious stimuli. There are two distinct G-protein-coupled bradykinin receptors, designated as B1 and B2, that regulate these effects. The B1 receptor is rapidly induced after such trauma, and BK B1 antagonists have been shown to be efficacious in animal pain models, demonstrating their potential to serve as a novel pathway for the treatment of pain. We have previously reported the preparation of a series of biphenylcyclopropane carboxamide based bradykinin B1 receptor antagonists with excellent affinity for the human B1 receptor. The modulation of the biphenyl region to improve the receptor occupancy and pharmacokinetic properties of this series will be presented.

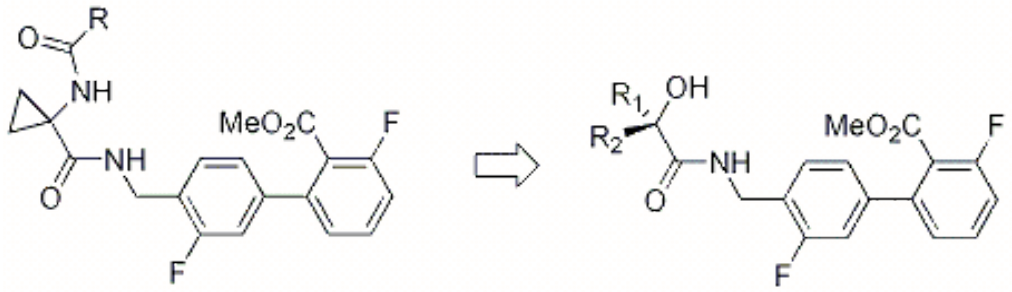


MEDI 299

Development of alpha-hydroxy amides as a novel class of Bradykinin B1 antagonists

***June J. Kim**, Michael R. Wood, Kathy Schirripa, and Mark G. Bock, Department of Medicinal Chemistry, Merck & Co., Inc, WP 14-3, P.O. Box 4, Sumneytown Pk, West Point, PA 19486, Fax: 215-652-3971, june_kim@merck.com*

The bradykinin (BK) family of G-protein coupled receptors contains two subtypes, (BK B1 and BK B2), which function in pain and inflammation pathways. The constitutively expressed B2 receptor is activated by the peptides bradykinin and kallidin to evoke acute pain subsequent to tissue damage. These peptides are metabolized by carboxypeptidases to form [des-Arg(9)] BK and [des-Arg(10)] kallidin, which activate the BK B1 receptor. The inducible BK B1 receptor is generally detected at very low levels in healthy tissue, but is expressed at higher levels in injured tissues and is believed to play a role in chronic pain and inflammation. Additionally, the BK B1 receptor appears to be constitutively expressed in the central nervous system (CNS) of numerous mammals and this localization suggests a potential central mode of action. To target a potential central mediator of chronic pain, novel antagonists incorporating alpha-hydroxy amides were designed, which display high receptor affinity, good oral bioavailability, and good CNS exposure. These medicinal chemistry and biological results are described.



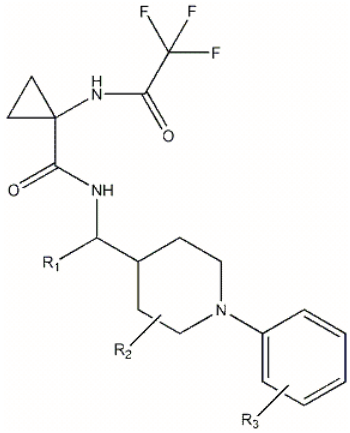
MEDI 300

Bradykinin B1 receptor antagonists: SAR studies of the aryl-piperidines on the cyclopropane carboxamide scaffold

***Jenny Wai**[1], Scott D. Kuduk[1], Michael R Wood[1], Ronald K. Chang[1], Dong-Mei Feng[1], Kathy L. Murphy[2], Richard W. Ransom[2], Cuyue Tang[3], Thomayant Prueksaritanont[4], Roger M. Freidinger[1], Douglas Pettibone[2], and Mark G. Bock[1]. (1) Department of Medicinal Chemistry, Merck & Co., Inc, WP14-3, Sumneytown Pike, Post Office Box 4, West Point, PA 19486, Fax: 215-652-3971, jenny_wai@merck.com, (2) Neuroscience Drug Discovery, Merck Research Laboratories, West Point, PA 19486, (3) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (4) Department of Molecular Endocrinology, and Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

Bradykinin B1 receptor antagonists are targeted as potential therapeutic agents for the treatment of chronic pain and inflammation. A series of cyclopropane carboxamides containing arylpiperidines as a new scaffold were evaluated. Several of these antagonists showed sub-

nanomolar binding affinities for the human bradykinin B1 receptor, and exhibited good pharmacokinetic profiles in both dog and rat.



MEDI 301

Synthesis and SAR study of a new series of Bradykinin B1 receptor antagonists containing allylic amines

Qingyian Liu[1]*, Wenyuan Qian*[2]*, Jian Jeffrey Chen*[1]*, Christopher Fotsch*[1]*, Nianhe Han*[1]*, Aiwen Li*[1]*, Chester Yuan*[1]*, Gloria Biddlecome*[1]*, Eileen Johnson*[1]*, Carlo van Staden*[1]*, Dianna Lester-Zeiner*[1]*, Gordon Ng*[1]*, Gondi Kumar*[1]*, Randall W. Hungate*[1]*, and Benny C. Askew*[1]*. (1) Department of Chemistry Research & Discovery, Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, qingyian@amgen.com, (2) Amgen Inc, CA*

The bradykinin receptors (subtypes B1 and B2) are two G-protein-coupled receptors. B2 receptors are expressed constitutively in central and peripheral tissues, while B1 receptors are not usually expressed under physiological conditions, but may be quickly upregulated under several inflammatory stimuli. It has been shown that B1 peptide antagonists are efficacious in reversing neurogenic pain induced by capsaicin as well as inflammatory pain induced by UV irradiation, carrageenan, CFA or LPS. More importantly, B1 receptor knockout mice exhibit hypoalgesia to chemical and thermal noxious stimuli. They show attenuated inflammatory responses and reduced neutrophil accumulation following tissue injury. Therefore, B1 receptor antagonists are potentially useful agents in the treatment of chronic pain and inflammation. In this poster, we describe our continuing exploration of the structure-activity relationship (SAR) of B1 receptor antagonists and discuss the discovery of a new series of potent and selective small molecule antagonists. One of these compounds showed modest oral bioavailability in rats.

MEDI 302

Inhibitors of NF-Kappa B derived from thalidomide

Bulbul Pandit[1]*, Esperanza Carcache de Blanco*[2]*, Zhigen Hu*[1]*, and Pui Kai Li*[1]*. (1) Department of Medicinal Chemistry and Pharmacognosy, The Ohio State University, College of Pharmacy,*

500 W 12th Avenue, Columbus, OH 43210, Fax: (614) 688-8556, pandit.6@osu.edu, (2) Department of Pharmacy Practice and Administration and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210

Nuclear factor kappa B (NF-κB) is a group of transcription factors that initiates up regulation of growth factors, cytokines, cell adhesion molecules, and antiapoptotic proteins which mediate promotion, angiogenesis, metastasis and chemoresistance of tumor. As part of a collaborative drug design and discovery effort to search for inhibitors of NFκB, we used Thalidomide and its modified analogs for the design of NFκB inhibitors. Thalidomide and twenty analogs were evaluated. Thalidomide and two active analogs 5HPP-33 and compound 20 inhibited the TNF-α induced activation of NFκB by inhibiting translocation of (p50/p65) to the nucleus in an ELISA-based assay. They also demonstrated stabilization of IκB α following TNF-α activation, in Hela and DU-145 cells by immuno-blot method. The stabilization of IκB α was demonstrated to be a result of inhibition of its phosphorylation following TNF-αactivation.

MEDI 303

Identification of a peptoid inhibitor of the proteasome that targets Sug2/Rpt4 Sub-unit

Hyun-Suk Lim[1]*, Chase T. Archer*[1]*, Di Cai*[1]*, Deirdre Brekken*[1]*, and Thomas Kodadek*[2]*. (1) Division of Translational Research, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, hyun-suk.lim@utsouthwestern.edu, (2) Department of Internal Medicine and Division of Translational Research, University of Texas Southwestern Medical Center, Dallas, TX 75390*

The 26S proteasome is a large, multi-protein complex comprised of a 20S catalytic complex capped on each end with a 19S regulatory particle (RP) that is responsible for most non-lysosomal proteolysis in mammalian cells. The 19S RP, which have protein unfolding activity, play non-proteolytic roles independent of the 20S core particle (CP) in transcription and DNA repair. The active site in the 20S CP is the target of recently developed drugs for the treatment of cancer. However, there have been no reports of pharmacological mediators of the 19S RP, which might also be interesting as research tools or perhaps even drug leads. Here we describe the isolation of such a molecule, called RIP-1, from a combinatorial library. RIP-1 is shown to inhibit the activity of the 19S RP in vitro as well as the proteolytic activity of the proteasome in living cells. Chemical cross-linking experiments identified the molecular target of RIP-1 as Sug2/Rpt4, one of the six ATPases.

MEDI 304

Synthesis and biological evaluation of 2-arylthiazolidine-4-caboxylic acid amides for melanoma and prostate cancer

Yan Lu[1]*, Zhao Wang*[1]*, Chien-Ming Li*[2]*, Wei Li*[1]*, James T. Dalton*[2]*, and Duane D. Miller*[1]*. (1) Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, 847 Monroe Ave., Room 327, Memphis, TN 38163, Fax: 901-448-6828, ylu11@utmem.edu, (2) Division of Pharmaceutics, Ohio State University, Columbus, OH 43210*

Single-agent chemotherapy has been ineffective in the treatment of advanced melanoma. Dacarbazine (DTIC), the only drug approved by FDA for treatment of melanoma, has a response rate of 10% to 20%. 2-Arylthiazolidine-4-carboxylic acid amide (ATCAA) was designed and synthesized in an effort to develop potential and selective anti-melanoma compounds. We prepared ATCAA derivatives with modifications of the aliphatic chain, thiazolidine ring and various aryl substitutents. The antiproliferative activity of ATCAA derivatives was examined and compared with Sorafenib, DTIC and Taxol. In vitro assay indicated that the synthesized analogues were about 10 times more potent than Sorafenib against two melanoma cell lines (SKMEL-188 and WM-164). The best selectivity ratio between Melanoma cell lines and control (Fibroblast cells) is about 1:35. We also examined the cytotoxicity of synthesized compounds in five human prostate cancer lines. One of our compounds showed a 27 fold ability to inhibit the PPC-1 cell line compared to RH7777 (control) cell. Synthesis, SAR and Biological evaluation of ATCAA will be presented.

MEDI 305

Trisubstituted isoalloxazines: A new class of G-quadruplex binding agents

Mallesham Bejugam[1]*, Pravin Shirude*[1]*, Sven Sewitz*[2]*, Raphael Rodriguez*[2]*, and Shankar Balasubramanian*[2]*. (1) Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom, mb591@cam.ac.uk, (2) University of Cambridge, Department of Chemistry, Cambridge CB2 1EW, United Kingdom*

Certain guanine rich DNA sequences, under physiological concentration of Na+ and K+, can fold into stable G-quadruplex structures, in vitro. Such G-rich sequences are found in the telomeric regions of eukaryotes, e.g. (GGGTTA)n in humans. Putative G-quadruplex structures have also been identified in upstream regions associated with the initiation of transcription notably in several oncogenes, including c-myc, VEGF, bcl2 and two G-quadruplexes have been identified in the c-kit promoter from our laboratory. We are investigating the hypothesis that such promoter G-quadruplexes are involved in transcriptional gene regulation, and small molecules that interact with promoter G-quadruplexes may act as gene regulators.

The c-kit oncogene that encodes a tyrosine kinase receptor, which regulates key signal transduction cascades in order to control cell growth and proliferation. Gain-of-function mutations of c-kit are found in several highly malignant human cancers, in particular gastrointestinal stromal tumors (GIST). A small molecule that binds a c-kit promoter G-quadruplex and alters the c-kit gene expression would provide further evidence to promoter-quadruplex hypothesis and serve as proof-of-concept for a therapeutic approach to address GIST.

We have designed and synthesised tri-substituted isoalloxazines (1) and examined their potential as G-quadruplex ligands (Figure 1). The binding affinity of isoalloxazines with G-quadruplexes was evaluated by Surface Plasmon Resonance (SPR). The best ligands show submicromolar G-quadruplex binding affinity and no binding to duplex DNA. Fluorescence Resonance Energy Transfer-melting analysis was employed to measure G-quadruplex stabilising potential of these ligands. These results revealed that isoalloxazines possesses a high degree of G-quadruplex stabilisation. The interaction of isoalloxazines with G-quadruplex DNA was also explored by circular dichroism spectroscopy that revealed a preference for

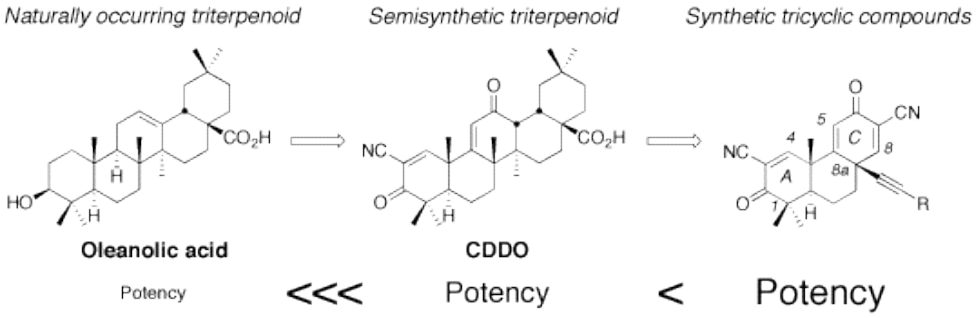
isoalloxazines binding to the parallel folded form of G-quadruplex DNA. Preliminary cellular studies using the MCF-7 (breast cancer cell line) suggest that isoalloxazines alter the expression of the c-kit gene.

MEDI 306

Novel tricyclic compounds having acetylene groups at C-8a and cyano enones in rings A and C: Highly potent anti-inflammatory and cytoprotective agents

Tadashi Honda[1]*, Chitra Sundararajan*[1]*, Hidenori Yoshizawa*[1]*, Xiaobo Su*[1]*, Yukiko Honda*[1]*, Karen T. Liby*[2]*, Michael B. Sporn*[2]*, and Gordon W. Gribble*[1]*. (1) Department of Chemistry, Dartmouth College, Hanover, NH 03755, Fax: 603-646-3946, th9@dartmouth.edu, (2) Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH 03755*

Novel C-8a functionalized tricyclic compounds having cyano enones in rings A and C have been synthesized and biologically evaluated. Among them, compounds with acetylene groups at C-8a show extremely high potency in in vitro and in vivo bioassays for anti-inflammatory and cytoprotective activities. Both in vitro and in vivo potencies are markedly higher than those of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO), which is currently being evaluated in phase I clinical trials for the treatment of leukemia and solid tumors.



MEDI 307

Nick-containing oligonucleotide as human Topoisomerase I inhibitor

Ming Li *and Tianhu Li, Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore, mingli05@nus.edu.sg*

As a specific enzyme releasing the topological stress of DNA generated by several cellular press such as replication and transcription, human topoisomerase I has been known to be a molecular target of various anticancer agents, such as the camptothecins, indolocarbazoles and indenoisoquinolines. Moreover, it has also been shown in the past few years that apart from the supercoiled structures, a few linear duplex oligonucleotides can act as substrate of eukaryotic topoisomerase I in vitro as well. Subsequent investigation in this research field demonstrated to a further step that when a nick was present in the topoisomerase I-binding sequence near its cutting sites, one strand of duplex oligonucleotide substrates could generate covalent linkage with the enzyme in an irreversible manner. Inspired by the previous discoveries, we herein developed a series of nick-containing unimolecular oligonucleotides as

irreversible inhibitors of human topoisomerase I and examined their inhibitory effect on the relaxation reaction of negatively supercoiled DNA catalyzed by human topoisomerase I. The correlation between the position of nick site and inhibitory effect as well as between the length of these nicked oligonucleotides and IC50 values will be discussed during our poster presentation.

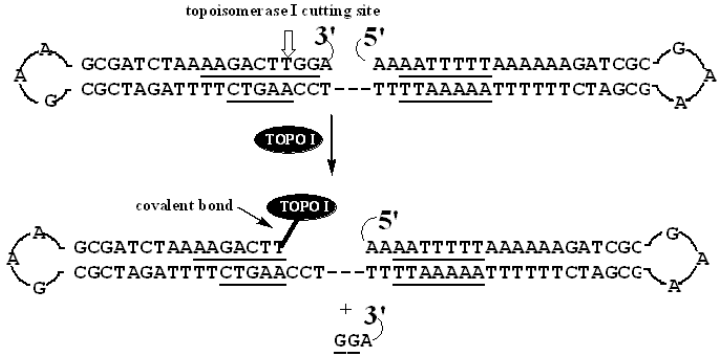


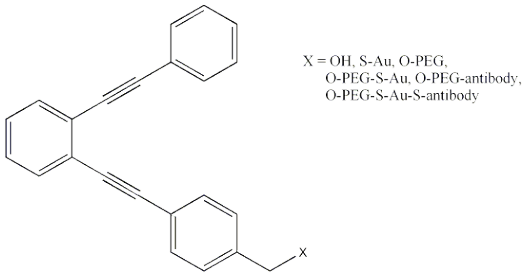
Figure 1. Schematic illustration of inhibitory effect of nicked oligonucleotides on the activity of topoisomerase I, the underlined tracts denote the topoisomerase I-binding tracts, and the cutting site by topoisomerase I is indicated by ⇩.

MEDI 308

PMSA antibody-toxin conjugates as antiprostatic agents

Danielle Falcone[1]*, Glenn J. Bubley*[2]*, and Graham Jones*[1]*. (1) Department of Chemistry and Chemical Biology, Northeastern University, 360 Huntington Ave, Boston, MA 02446, falcone.da@neu.edu, (2) Genitourinary Oncology Group, Beth Israel Deconess Medical Center, Boston, MA 02215*

Enediynes are a class of naturally occurring cytotoxic compounds. Their potency is derived from their ability to undergo molecular rearrangement to convert the ene-di-yne pharmacohore into chemically reactive diradical species, which have propensity to cleave duplex DNA and induce apoptosis. The first FDA approved monoclonal antibody conjugate was Wyeth's Mylotarg® which is composed of the enediyne cytotoxin calicheamicin coupled through a linker group to an anti CD33 antibody. One of the goals of our research is to apply targeting techniques in the synthesis of second generation antiprostatic agent. A novel photoactivated enediyne cytotoxin was synthesized through a series of Sonogashria reactions. Targeting abilities are being investigated through the use of gold nanoparticles, polyethylene glycol (PEG), and prostate membrane specific antibody (PMSA). By coupling PMSA with a clinically proven toxin (enediyne), which is activated photochemically, it is expected that a new line of antiprostatic agents can be identified.



MEDI 309

Regulation of the topoisomerase II alpha gene using polyamides that binds to the inverted CCAAT box present in the promoter

*Jim Sexton[1], Hilary Mackay[2], Toni Brown[2], Minal Kotecha[3], Caroline O'Hare[3], Jerome Kluza[3], Daniel Hochhauser[3], John Hartley[3], Binh Nguyen[4], David Wilson[4], and **Moses Lee**[2]. (1) Chemistry, Furman University, Greenville, SC 29613, (2) Department of Chemistry, Hope College, Natural Sciences Division, 35E. 12th. Street, Holland, MI 49422, Fax: 616-395-7923, lee@hope.edu, (3) Oncology, Royal Free & University College Medical School, London W1W 7BS, United Kingdom, (4) Department of Chemistry, Georgia State University, Atlanta, GA 30303*

Small molecules that bind with strong affinity to specific DNA sequences, such as distamycin and its polyamide analogs, are important for the development of novel agents for specific gene regulation. In a side-by-side dimer binding motif, a stacked pyrrole (Py)/pyrrole pair recognizes an A•T or T•A base pair, an imidazole (Im)/Py pair binds to a G•C site. Polyamides can, thus, be tailor-made to target any DNA sequence. In an ongoing program aimed at developing gene-targeted compounds, polyamides were specifically designed to target the inverted CCAAT box-2 (ICB2) of the topoisomerase II alpha gene. Our primary objectives are the following: design of polyamides that bind reversibly and selectively to ICB2, have strong affinity for the target site, and exhibit slow rates of dissociation from the target ligand/DNA complexes. Polyamides that bind DNA in either the stacked side-by-side motif or hairpin motif were investigated. In addition, studies on the use of intercalating moieties, such as naphthalimide, to affect the rate of association and dissociation were conducted. The synthesis, biophysical properties of JS-I-93 (f-IPP-Nap), as well as its ability to inhibit the binding of NF-Y to ICB2 have been achieved. Furthermore, this compound was able to enter cells and move into the nucleus, interact with genomic DNA, and induce confluent cancer cells to express the topoisomerase II alpha gene. Results from these studies will be presented.

MEDI 310

New N-substituted phenoxazines as specific inhibitors of Akt in cancer cells

*Parimala B. Hanumesh[1], Bharathalaxmi Pulluru[1], Kuntebommanahalli N. Thimmaiah[2], and **Netkal M. Made Gowda**[1]. (1) Department of Chemistry, Western Illinois University, 1 University Circle, Macomb, IL 61455, PB-hanumesh@wiu.edu, GN-Made@wiu.edu, (2) Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN 38105*

Drug resistance is always a major obstacle in the clinical treatment of cancer. Several pharmacological agents including some phenoxazines have been shown to reverse multi drug resistance in vitro and there is still a need to identify more potent, more specific, and less toxic modulators for clinical use. We hypothesize that by increasing the alkyl side chain length, the phenoxazine derivative's potency as anticancer agent will be enhanced.

In this project, we have synthesized a series of N-substituted phenoxazines with pentylamino and hexylamino side chains and are screening them to find out whether they are more/less potent than the previously reported derivatives. In order to predict the mechanism of anticancer action, cell screening for Akt inhibition is being started in Rhabdomyosarcoma cell lines (Rh1 and Rh30). Furthermore, to determine the inhibitory concentration of each drug, a standard growth inhibition assay is being performed.

Acknowledgement: We thank the NIH (AREA grant # 5-20860) for support

MEDI 311

Synthesis and characterization of N-hexylamino phenoxazines as potential anticancer drugs

*Bharathalaxmi Pulluru[1], Parimala B. Hanumesh[1], Kuntebommanahalli N. Thimmaiah[2], and **Netkal M. Made Gowda**[1]. (1) Department of Chemistry, Western Illinois University, 1 University Circle, Macomb, IL 61455, B-Pulluru@wiu.edu, GN-Made@wiu.edu, (2) Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN 38105*

Phenoxazines are known for anti-multidrug resistance (MDR) activities. We hypothesize that by increasing the alkyl side chain length, the derivative's potency as anticancer agent will increase. We are synthesizing and characterizing a series of seven hydrophobic N-substituted phenoxazines with a six carbon alkyl side chain and different amino functionalities. Each synthesis is based on the ability of N-(10-chloroalkyl)phenoxazines to undergo iodide catalyzed nucleophilic substitution reactions with secondary amines such as N,N-diethylamine, N-diethanolamine, pyrrolidine, piperidine, morpholine, thiomorpholine, and (â-hydroxyethyl)piperazine. The products are characterized by UV, IR, 1H and 13C NMR, mass spectral and elemental data. The lipophilicities are to be determined. The purified compounds also are to be evaluated for anticancer activity.

In this study, in addition to the synthesis of seven hexylamino phenoxazine derivatives, we plan to determine their IC50 and screen them for inhibition of the phosphorylation of AKT and downstream targets.

Acknowledgement: We thank the NIH (AREA grant # 5-20860) for support

MEDI 312

Discovery of YM155, a novel survivin suppressant for the treatment of cancer

***Isao Kinoyama**, Akira Matsuhisa, Takahito Nakahara, Masahiro Takeuchi, Kenna Shirasuna, Tsuyoshi Minematsu, Norio Asai, Shunichiro Matsumoto, Kenichi Kawaguchi, Junichi Kazami, Akira Toyoshima, Aya Kita, Fumiko Tominaga, Minoru Okada, and Mitsuaki Ohta, Drug Discovery Research, Astellas Pharma Inc, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan, Fax: +81-29-854-1519, isao.kinoyama@jp.astellas.com*

Survivin is a key member of the family of inhibitors of apoptosis (IAP) that suppress apoptosis through inhibition of caspases and procaspases. Survivin is selectively expressed in most solid tumors but not expressed in most normal tissues. Through the lead optimization of the HTS hit compound, we identified YM155 as a highly potent survivin suppressant. YM155 demonstrated antiproliferative activity against various human tumor cell lines, and induced in vivo antitumor activity without showing severe systemic toxicity in mice. YM155 is currently in Phase II clinical trials for the treatment of cancer. The syntheses and biological activities of YM155 derivatives will be presented.

MEDI 313

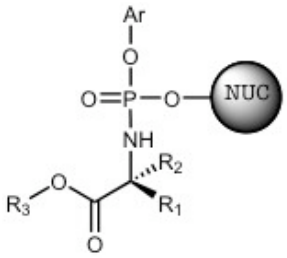
Enhancement of the anticancer activity of cladribine by application of the phosphoramidate protide approach

Rocco Valente[1]*, Costantino Congiatu*[1]*, Elisabeth Walsby*[2]*, Kenneth Mills*[2]*, and Christopher McGuigan*[1]*. (1) Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3XF, United Kingdom, valenter@cardiff.ac.uk, (2) School of Medicine, Cardiff University, Cardiff CF14 4XN, United Kingdom*

2-chlorodeoxyadenosine (2CdA, cladribine) is a potent anticancer and immunosuppressive agent used as the drug of choice for hairy-cell leukaemia but can also be used in other neoplasms. As with most nucleoside drugs, it needs to be phosphorylated into the active triphosphate form. In this work we report the application of the phosphoramidate prodrug approach[1] in order to improve cellular penetration and to by-pass the first step of kinase-mediated activation. We describe the synthesis of different “protides” where the phosphate in 5' is masked as a phosphate prodrug, containing an aromatic ester and a protected amino acid. All the final compounds are obtained as mixture of two diasteroisomers, in variable ratio, due to the stereochemistry of the phosphorus centre.[2] The results of biological evaluation, in different leukaemia cell lines, provide evidence for an increase in activity for the phosphoramidate analogues, with an average 10-fold enhancement in potency shown by the most active derivates, when compared to the parent nucleoside.

[1]Cahard, D.; McGuigan, C.; Balzarini, J. Aryloxy Phosphoramidate Triester as Pro-Tide. Mini-Reviews in Medicinal Chemistry 2004, 4, 371-382

[2]Congiatu, C.; Brancale, A.; Mason, M.; Jiang, W.; McGuigan, C. Novel potential anticancer naphtyl phosphoramidates of BVdU: separation of diasteroisomers and assignment of the absolute configuration of the phosphorus center. J. Med. Chem. 2006, 49, 452-455



MEDI 314

Experimental and systems biology studies of the radioresistance of prostate carcinoma cells

*Ana Niciforovic[1], Jelena Djordjevic[1], Miroslav Adzic[1], Vesna Vucic[1], **Petar M Mitrasinovic**[2], and Marija B. Radojcic[1]. (1) Laboratory of Molecular Biology and Endocrinology, VINČA Institute of Nuclear Sciences, POBox 522-090, Belgrade 11000, Yugoslavia, (2) Department of Information Technologies and Artificial Intelligence, Center for Multidisciplinary Studies, University of Belgrade, Kneza Viseslava 1, Belgrade 11030, Yugoslavia, petar.mitrasinovic@cms.bg.ac.yu*

Molecular mechanisms for the gamma-ionizing radiation (IR) resistance of human prostate cancer cells, PC-3, are not quite clear. The low-IR effects are primarily manifested by the generation of reactive oxygen species (ROS) and the expressions both of ROS-metabolizing antioxidant enzymes, such as Mn and CuZn superoxide dismutases (SODs) and catalase (Cat), and of the NF-kappaB transcription factor. A substantial increase in the concentrations of SODs was observed in the cells irradiated by 10 and 20 Gy relative to those irradiated by 0 and 2 Gy, while the Cat and NF-kB expressions were fairly stable. A systems biology model was developed to shed more light on how MnSOD affects the biological state of cells depending upon the production of H2O2. By raising the initial presence of MnSOD in the 0.7-10 x 10^{-6} M concentration range, the nuclear NF-kappaB (NF-kappaB_n)-H2O2 interplay was elucidated. Both the time-dependent and steady-state concentrations of H2O2 for various initial levels of MnSOD were contrasted. The systems biology model has been compared with our experimental data suggesting that, in the absence of Cat, the expression enhancements of MnSOD and CuZnSOD may form a positive feed-forward relation with the antiapoptotic NF-kappaB gene regulator, which leads to a relatively successful PC-3 cell adaptation to prooxidative conditions induced by IR. In this light our systems biology model indicates that a possible mechanism for the adaptation of prostate cancer cells to IR is assocciated with a decreasing trend of effective concentrations of H2O2 due to MnSOD induction. It is believed that our results provide a experimental and systems biology framework upon which a promising therapeutic strategy of metastatic prostate cancer should rely.

MEDI 315

Lead identification to generate isoquinolinedione inhibitors of insulin-like growth factor receptor (IGF-1R) for potential use in cancer treatment

***Scott C. Mayer**[1], Annette L. Banker[1], Frank Boschelli[2], Li Di[3], Mark Johnson[4], Cynthia Hess Kenny[5], Girija Krishnamurthy[6], Kristina Kutterer[5], Franklin Moy[4], Susan Petusky[1], Malini Ravi[5], Diane Tkach[2], Hwei-Ru Tsou[5], and Weixin Xu[4]. (1) Chemical & Screening Sciences, Wyeth Research, Princeton, NJ, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, mayers@wyeth.com, (2) Oncology, Wyeth Research, Pearl River, NY, Pearl River, NY 10965, (3) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ 08543, (4) Chemical & Screening Sciences, Wyeth Research, Cambridge, MA, Cambridge, MA, (5) Chemical & Screening Sciences, Wyeth Research, Pearl River, NY, Pearl River, NY 10965, (6) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965*

Insulin-like growth factor receptor (IGF-1R) is a growth factor receptor tyrosine kinase that acts as a critical mediator of cell proliferation and survival. This receptor is over-expressed or activated in tumor cells and is emerging as a novel target in cancer therapy. Efforts in our “Hit to Lead” group have generated a novel series of submicromolar IGF-1R inhibitors based on a isoquinolinedione template originating from a Lance enzyme HTS screen. Chemical triage and parallel synthesis incorporating focused library arrays were instrumental in moving these investigations through the Wyeth exploratory medicinal chemistry process. The strategies, synthesis, and SAR behind this interesting kinase scaffold will be discussed in more detail.

MEDI 316

Withdrawn

MEDI 317

Microwave-expediated synthesis of 5-aminosubstituted camptothecin analogs: Inhibitors of hypoxia inducible factor HIF-1ƒÑ

Blair T Lapointe[1]*, Joelle Torregrossa*[1]*, Kristen Bailey*[2]*, Christopher Barone*[1]*, Ryan T Coccia*[1]*, Catherine Y Cote*[1]*, Conor P Davern*[1]*, Theresa A Dunstan*[1]*, Benjamin J Durant*[1]*, Nisal U Gajadeera*[1]*, David A Garcia*[1]*, Daniel I Gotleib*[1]*, Andrea I Lebed*[1]*, Emily A Lewis*[1]*, Steven L Mathieu*[2]*, Melissa L McNeel*[1]*, Stephanie E Muser*[1]*, Catherine M Norwood*[1]*, Samantha M Rupert*[1]*, Timothy F Siclari*[1]*, Jason M Silverberg*[1]*, Zachary P Thompson*[1]*, Danielle Falcone*[2]*, Glenn J. Bubley*[3]*, and Graham Jones*[2]*. (1) Department of Chemistry & Chemical Biology, Northeastern University, 360 Huntington Ave. 102HT, Boston, MA 021115, lapointe.b@neu.edu, (2) Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02458, (3) Genitourinary Oncology Group, Beth Israel Deconess Medical Center, Boston, MA 02215*

The camptothecins are a class of topoisomerase I inhibitors which also have the ability to inhibit HIF-1á. The parent compound camptothecin, isolated from Camptotheca acuminata, consists of a planar, pentacyclic ring system with considerable scope for refinement using classical QSAR methods. Camptothecin exhibited significant anti-tumor activity in in vivo studies initiating human clinical trials, however due to high toxicities and low water solubility; it failed to receive FDA approval. Two derivatives of camptothecin however,topotecan and irinotecan, are now FDA approved drugs used in the treatment of ovarian and colon cancer respectively. In an effort to identify new analogs of this class with improved biological profiles, a number of C-5 aminoalkyl derivatives were synthesized using microwave enhanced methodology. The analogs were screened using a variety of biological assays, and a 5-fluoroethyl analog with potent HIF inhibitory activity was identified.

MEDI 318

Novel duocarmycin-analog based antibody drug conjugate for targeted cancer therapy

Vincent Guerlavais[1], *Qian Zhang*[1], *Kilian Horgan*[1], *Sharon Boyd*[1], *Bilal Sufi*[1], *Liang Chen*[1], *Lynae Green*[2], *David Passmore*[2], *Janette Sung*[2], *Rangan Vangipuram*[2], *Lourdes Thevanayagam*[2], *Mohan Srinivasan*[2], *Mary Do*[3], *Rory Dai*[3], *Eilene Kwok*[3], *Colin Chong*[3], *Carol Soderberg*[3], *Chin Pan*[3], *Mary Huber*[4], *Peter Sattari*[4], *Chetana Rao*[4], *Shrikant Deshpande*[2], *Pina Cardarelli*[3], *David J. King*[4], *and Sanjeev Gangwar*[1]. *(1) Department of Medicinal Chemistry, Medarex Inc, 1324 Chesapeake Terrace, Sunnyvale, CA 94089, Fax: 408-545-5912, vguerlavais@medarex.com, (2) Department of Protein Chemistry, Medarex Inc, (3) Department of Pharmacology and Cell Biology, Medarex Inc, (4) Department of Molecular Biology and Biochemistry, Medarex Inc*

Duocarmycins and its analogues are the parent members of extremely potent antitumor antibiotics that derive their biological properties through sequence selective alkylation of DNA. These analogues have considerable potential as drugs that can be targeted to tumors by monoclonal antibodies. These analogues are also shown not to be a substrate for the major mechanisms of drug resistance, suggesting that targeted delivery may be effective in drug resistant tumors. We have designed and synthesized several water-soluble synthetic DNA alkylating agents and linked them to a number of anti-tumor antibodies of potential interest using both peptide linkers and hydrazone linkers which are readily cleaved by lysosomal proteases and at endosomal pH respectively for cancer therapy. Here we describe the design and synthesis of a water soluble dipeptide prodrug of an extremely potent duocarmycin derivative (Med-2338). The in vitro and in vivo properties of human monoclonal antibody (mAbs)-drug conjugates consisting of Med-2338 linked to an anti PSMA antibody (PSMA is expressed in primary and metastatic prostate cancers) or anti CD70 antibody (CD70 is highly expressed in lymphomas, glioblastomas, and clear cell renal cell carcinoma) will be presented. These conjugates have shown an excellent stability profile in human plasma. Anti-PSMA or CD70 conjugates have demonstrated the capabilities of selective and potent antigen-dependent cell killing (EC50 =20 pM, 72H LNCap and 786-O cytotoxicity assay). Treatment of established tumor xenografts (LNCap and 786-O) with these conjugates at a single dose of 0.1 umol/kg resulted in complete tumor regression with no associated weight loss by the end of the study (60 days). The results described in this presentation will suggest that conjugates of Med-2338 have significant clinical potential for the treatment of PSMA and CD-70 expressing tumors and may well be applicable to many other antigen targets expressed in multiple cancer types.

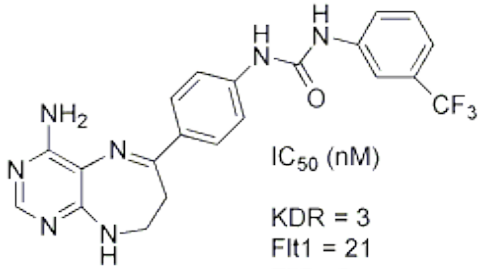
MEDI 319

Pyrimido[4,5-b][1,4]diazepines as novel multitargeted inhibitors of receptor tyrosine kinases

Zhiqin Ji[1], *Vijaya Gracias*[2], *Irini Akritopoulou-Zanze*[2], *Daniel H. Albert*[1], *Keith B. Glaser*[1], *Patrick M. Marcotte*[1], *Pease Lori*[1], *Nirupama B. Soni*[3], *Kent D Stewart*[1], *Stevan W. Djuric*[2], *Steven K. Davidsen*[1], *and Michael R. Michaelides*[1]. *(1) Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064,*

zhiqin.ji@abbott.com, (2) Abbott Laboratories, Abbott Park, IL 60064, (3) Abbott Laboratories, Abbott Park, IL 60064-6112

Interruption of receptor tyrosine kinases (RTKs) signaling pathways has become an important aspect of anti-cancer drug discovery. The multi-targeted agents SutentTM and NexavarTM demonstrate that clinical benefit with manageable side effects is possible with broad-acting kinase inhibitors. As a part of our continuing efforts to identify backup compounds of Abbott's RTK clinical candidate ABT-869, we have developed a novel series, pyrimido[4,5-b][1,4]diazepine, as inhibitors of RTKs. Structure-activity relationship studies led to N,N'-biphenyl urea analogs that potently inhibit both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) families of kinase as exemplified by compound 1.



1

IC_{50} (nM)

KDR = 3
Flt1 = 21
Flt3 =3
CSF1R = 619

MEDI 320

Synthetic methods for the preparation of novel ARQ501 human metabolites

***Rui-Yang Yang**, Darin Kizer, Hui Wu, Erika Volckova, Xiusheng Miao, Khanh Nguyen, Syed Ali, Manish Tandon, Ron Savage, and Mark A. Ashwell, ArQule, Inc, 19 Presidential way, Woburn, MA 01801*

The synthesis and characterization of novel metabolites of ARQ 501 (3,4-dihydro-2,2-dimethyl-2H-naptho[1,2-b]pyran-5,6-dione, beta-lapachone) are described.

ARQ 501 is an anti-cancer drug candidate currently in Phase 2 clinical trials. ARQ 501 elevates E2F-1 levels leading to the activation of the cell cycle checkpoint which results in the selective apoptotic cell death of cancer cells.

In this poster, we describe ARQ501 metabolites found in human blood. Structures of several major human blood metabolites were postulated based on high-resolution HPLC/MS/MS with 14C labeled and non-labeled ARQ501; postulated structures were synthesized and compared with metabolites through high resolution HPLC/ MS/MS. The structure of several metabolites, including novel ring contracted and ring opened structures, were confirmed.

MEDI 321

Design and synthesis of carbocyclic nucleoside analogs as anticancer and antiviral drugs

Naresh K Sunkara *and Katherine L. Seley, Department of Chemistry and Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, naresh1@umbc.edu*

Enzymatic inhibition of biological methylation pathways essential for viral and cancer replication has shown promise in the design of chemotherapeutics. Disruption of some critical enzymes like S-adenosyl-L-homocystine hydrolase (SAHase), Adenosine Deaminase (ADA) and methyltranferases (MeTase) has been shown to control viral and cancer cell multiplication. As a class, carbocyclic nucleoside derivatives are structurally modified such that they mimic the natural nucleosides enough to be recognized, but ultimately disrupt subsequent biological processes. These targets feature three specific modifications: 1) replacement of the ribose sugar with a cyclopentyl ring to create stability that previously synthesized IsoA analogues lacked; 2) alteration of the connectivity between the sugar and the heterocyclic base moiety 3) alteration of the heterocyclic ring, making them possible targets for Adenosine Deaminase (ADA). These combined features have the potential to theoretically produce inhibition on biological methylations and may exhibit synergistic inhibition and subsequently, greater potency as antiviral and anticancer agents.

MEDI 322

Design, synthesis and preliminary evaluation of an antiestrogen-mitomycin C hybrid agent

Robert N. Hanson[1]*, Edward Y. Hua*[1]*, David C. Labaree*[2]*, Richard B. Hochberg*[2]*, John M. Essigmann*[3]*, and Robert G. Croy*[4]*. (1) Department of Chemistry and Chemical Biology, Northeastern University, 360 Huntington Avenue, Boston, MA 02115, Fax: 617-373-8795, r.hanson@neu.edu, (2) Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT 06510, (3) Departments of Chemistry and Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, (4) Department of Chemistry and Biological Engineering Division, Massachusetts Institute of Technology, Cambridge, MA 02139*

A convergent synthesis of a novel estradiol hybrid was developed based on structures of the potent anti-proliferative mitomycin C and the steroidal anti-estrogen RU 56688. A multi-step synthesis provided the key 11-beta- (omega-azido-triethyleneglycoloxy)-phenyl-estradiol in good overall yield. The N-propargyl-N'-methyl –mitomycin C was prepared in five steps from mitomycin C using a variation of a literature procedure. The two components were ligated using “click” chemistry to give the triazole hybrid agent in 81% yield. Biological assays demonstrated that both potent antiestrogenic and antiproliferative activities were retained in the final hybrid compound.

This research was supported in part through grants from the National Institutes of Health [PHS 1R01 CA81049 (R.N.H.) and PHS 1R01 CA 37799 (R.B.H.)], and the U.S.Army Breast Cancer Research Program [DAMD 17-00-1-00384 and W81HW0410544(R.N.H.)] .

MEDI 323

Mechanism of action of bioactive tamoxifen conjugates

Emily L. Rickert[1]*, Xinghua Long*[2]*, Anton C. Peterson*[1]*, Joseph P. Trebley*[1]*, Melinda M. Morrell*[1]*, Ken P. Nephew*[2]*, and Ross Weatherman*[3]*. (1) Department of Medicinal Chemistry & Molecular Pharmacology, Purdue University, 575 Stadium Dr, West Lafayette, IN 47907, Fax: 765-494-1414, erickert@pharmacy.purdue.edu, (2) Medical Sciences, Indiana University School of Medicine, Bloomington, IN, (3) Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907-2091*

One of the key unanswered questions in estrogen signaling concerns the role of non-classical signaling pathways in the overall function of estrogen receptor (ER) modulators. We hypothesize that development of molecules that localize to specific subcellular areas offers a potential way to study non-classical ER signaling mechanisms. Poly(methacrylic acid) conjugated to 4-hydroxytamoxifen (PT) was shown to have high ER affinity in vitro and function with similar potency to 4-hydroxytamoxifen in ER-mediated transcriptional assays. PT was found to inhibit estradiol-induced proliferation of both MCF-7 cells and a tamoxifen-resistant MCF-7 cell line. This suggested that PT may have a mechanism of action involving ER downregulation, but we found no change in ER levels. This leads us to believe that the activity and localization may be the result of a novel mechanism of action. The implications of this unique mechanism on tissue dependent estrogen responses and anti-estrogen resistance are currently being explored.

MEDI 324

Synthesis and biological evaluation of cytotoxic decapeptide macrocycles

Melinda R. Davis*, Thomas J. Styers, Rodrigo A. Rodriguez, and Shelli R McAlpine, Department of Chemistry and Biochemistry, San Diego State University, 5500 Campanile Drive, San Diego, CA 92182-1030, Fax: 619-594-4634, melindarenee@gmail.com*

Less than 20% of pancreatic cancers respond to current chemotherapeutic agents, and as the fifth most deadly cancer in the U.S., it is essential to devise new treatments in order to selectively target this cancer. Large macrocyclic peptides are a class of novel molecules that have shown tremendous potential as immunosuppressants, anti-cancer agents, and antibiotics. Sansalvamide A (San A) derivatives are a class of macrocycles that have proven to be cytotoxic in pancreatic cell lines. Inspired by the San A pentapeptide, di-sansalvamide A is a new class of macrocyclic decapeptides that show selectivity against multiple pancreatic cancer cell lines over non-cancerous cell lines, and comparable potency to their San A counterparts. Our laboratory has optimized the synthesis of these decapeptides and shown their potential as an important anti-tumor agent.

MEDI 325

Synthesis and cytotoxicity studies of novel sansalvamide A derivatives

Yalda S. Mostofi[1]*, Suchitra Ravula*[2]*, Stephanie Lapera*[2]*, Melinda R. Davis*[2]*, William S. Disman*[2]*, Katerina Otrubova*[2]*, Erinprit Signh*[2]*, and Shelli R McAlpine*[2]*. (1) Department of chemistry and biochemistry, SDSU, 5500 Campanile Drive, San Diego, CA 92182-1030, Fax: 619-594-4634, aztec_yalda@hotmail.com, (2) Department of Chemistry and Biochemistry, San Diego State University, San Diego, CA 92182-1030*

Colon cancer is the third most common form of cancer and the second leading cause of death among cancers. Pancreatic cancer is the fifth most deadly cancer each year 32,000 individuals in the U.S. are diagnosed with this condition. It has been shown that Sansalvamide A (San A), which is a depsipeptide isolated from marine fungus, exhibits anti-tumor activity. In recent years, we have synthesized a series of San A derivatives that have been optimized for potency against drug-resistant pancreatic and colon cancers. Results from our laboratory indicate that molecules belonging to our San A library produce effective inhibitors in the nanomolar concentration ranges against these cancers. These molecules represent a significant breakthrough because the clinically used agent for these drug-resistant cancers manifest significantly greater IC50 values against these same cell lines proving San A to be a promising class of anti-tumor agents.

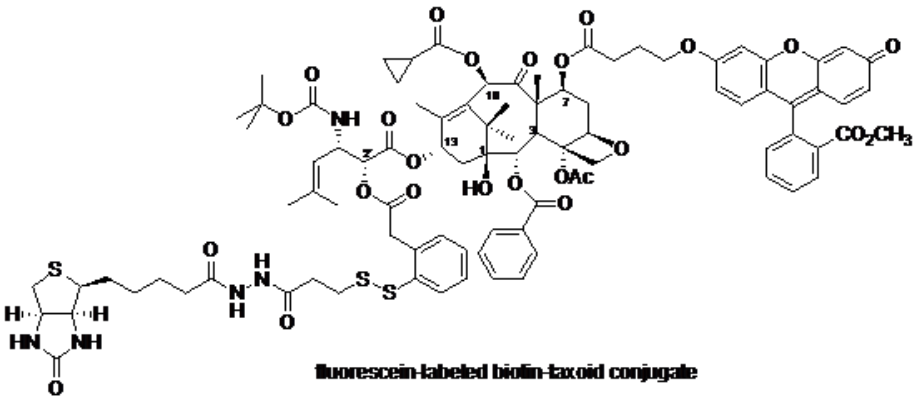
MEDI 326

Synthesis and application of fluorescence-labeled biotin-taxoid conjugate for the investigation into efficacious tumor-targeting drug delivery system

Xianrui Zhao[1]*, Shuyi Chen*[1]*, Jin Chen*[1]*, Jingyi Chen*[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, xizhao@ic.sunysb.edu, (2) Department of Condense Matter Physics and Materials Science, Brookhaven National Laboratory, Upton, NY 11973, (3) Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

A series of biotin-taxoid conjugates were designed and prepared for evaluation of their efficacy in tumor-targeting drug delivery. Recently, it has been shown that biotin receptors are overexpressed in numbers of cancer cell surface. Thus, the biotin receptor is an excellent biomarker for tumor-targeting drug delivery *via* receptor-mediated endocytosis. A novel disulfide-containing linker was designed and used for conjugating biotin and a taxoid, which would release the original taxoid inside of tumor cell by the action of intracellular glutathione. Three conjugates were systematically designed to verify the three stages of the whole process, *i.e.*, internalization of biotin conjugate, cleavage of the linker, and release of the taxoid, respectively. At each stage, a fluorescent or fluorogenic moiety was recruited to visualize the

progress. The syntheses of these conjugates and the cell-based evaluation of their tumor-targeting efficacy by confocal fluorescence microscopy using L1210FR cell line, which overexpresses biotin receptors, will be presented.

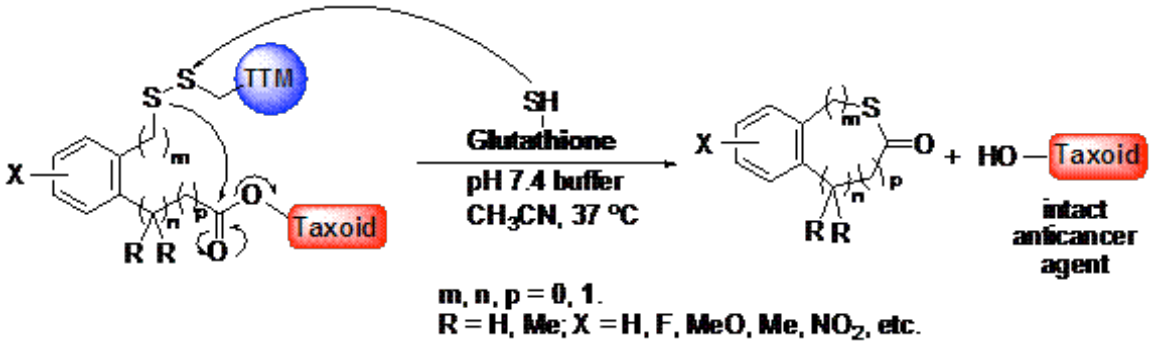


MEDI 327

Novel disulfide linkers for tumor-targeting drug delivery

Xianrui Zhao[1], *Jin Chen*[1], *Shuyi Chen*[1], *Stanislav Jaracz*[1], *Manisha Das*[1], *and Iwao Ojima*[2]. *(1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, Fax: 631-632-7942, xizhao@ic.sunysb.edu, (2) Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

Mechanism-based cleavable linkers, stable in blood circulation but efficient in drug release inside of tumor cells, are essential for efficacious tumor-targeting drug delivery. We have been successfully developing such linkers involving strategically designed disulfide linkage, which form thiolactones to release anticancer agents upon cleavage by intracellular glutathione. These novel bi-functional linkers can be connected to a variety of tumor-targeting molecules (TTM) and cytotoxic agents. To further investigate the stability in blood plasma and efficacy of the self-immolative disulfide linkers, a series of novel linkers were designed, synthesized and evaluated in a model system. Several factors, e.g., ring size, pH, and substituents, were found to play critical roles in the stability, self-immolative process, and drug release. The synthesis and structure-function relationships of these novel linkers will be presented.

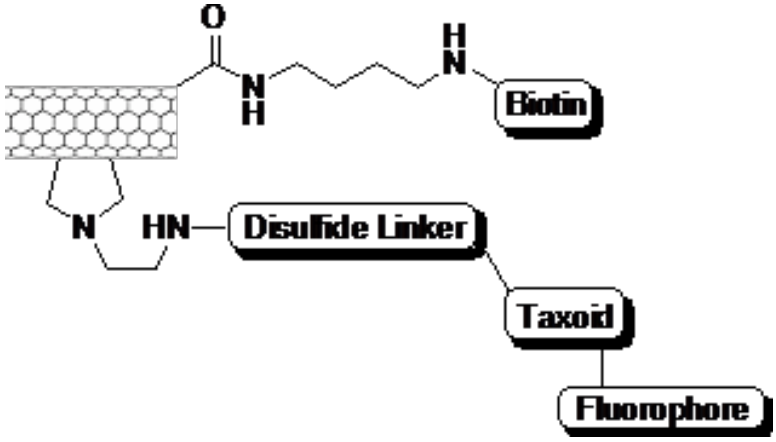


MEDI 328

Synthesis and evaluation of functionalized SWNT as transporter for tumor-targeting drug delivery

Shuyi Chen[1]*, Jingyi Chen*[2]*, Xianrui Zhao*[1]*, Stanislaus S. Wong*[3]*, and Iwao Ojima*[4]*. (1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, shcchen@ic.sunysb.edu, (2) Department of Condense Matter Physics and Materials Science, Brookhaven National Laboratory, Upton, NY 11973, (3) Department of Chemistry, SUNY at Stony Brook and Materials Science Department, Brookhaven National Laboratory, Stony Brook, NY 11794, (4) Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

A SWNT-based biotin-taxoid conjugate, in which biotin was introduced as the tumor-targeting moiety, was designed and synthesized for tumor-specific drug delivery. The conjugate includes a novel self-immolative disulfide-containing linker to trigger the drug release. The cellular uptake of the fluorescence-labeled conjugate and the drug release were investigated by means of confocal fluorescent microscopy using L1210FR leukemia cell line, which overexpresses biotin receptors. The successful real-time observation of the receptor-mediated endocytosis and the intracellular drug release of the fluorescence-labeled biotin-SWNT-taxoid conjugate will be presented.



MEDI 329

Rational design, synthesis, and bioassay of small molecules for inhibition of the mTOR signaling pathway

Jun Yong Choi[1]*, Elzbieta S. Selinger*[2]*, Lisa M. Ballou*[2]*, Richard Z. Lin*[2]*, and Dale G. Drueckhammer*[1]*. (1) Department of Chemistry, Stony Brook University, Stony Brook, NY 11794, jychoi@ic.sunysb.edu, (2) Department of medicine, Stony Brook University, Stony Brook, NY 11794*

The mammalian target of rapamycin (mTOR) is an attractive target for cancer treatment, as the signaling mediated by mTOR is hyperactivated in many human cancers. mTOR forms two

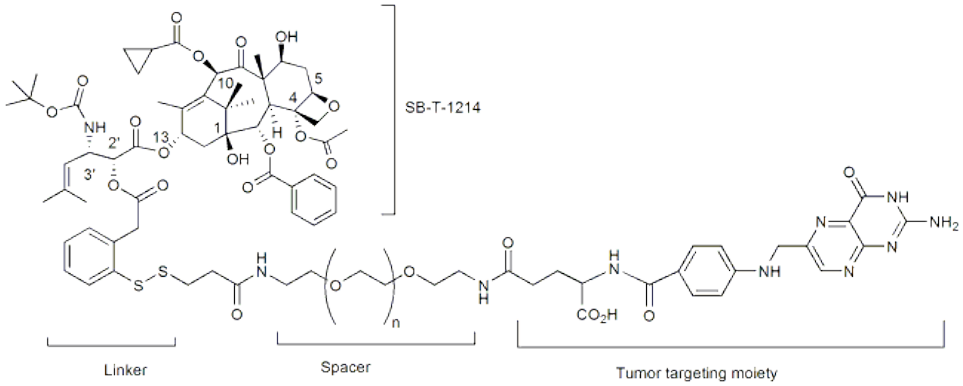
multiprotein complexes (mTORC1 and mTORC2) that have different activities. It has been shown that rapamycin only inhibits the mTORC1 complex, with mTORC2 being rapamycin-insensitive. Small molecules that bind directly to the mTOR catalytic site and block the activities of both mTOR complexes are expected to have broader anti-cancer activity than the rapamycin. Homology modeling was performed to identify active site differences between mTOR and the homologous phosphoinositide-3-kinases (PI3Ks) and DNA-dependent protein kinase. The lead compounds have been further modified based on these modeling results. The designed compounds have been synthesized and tested against mTOR and PI3Ks. Inhibitors having increased potency and selectivity against mTOR have been obtained, supporting the modeling approach and providing improved compounds for further development of potential anti-cancer agents.

MEDI 330

Design, synthesis and evaluation of tumor-targeting folate-taxoid conjugate

Manisha Das *and Iwao Ojima, Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, mdas@ic.sunysb.edu*

As a part of our ongoing research program on the tumor-targeting drug delivery systems, we chose folic acid as the tumor-targeting molecule in this study. It has been shown that the folate receptors are overexpressed in numerous cancers, which makes this receptor an excellent target for cancer drug delivery. Accordingly, we designed a folate-taxoid conjugate to target these tumor cells specifically. A highly potent second-generation taxoid, SB-T-1214, was conjugated to folic acid through a novel mechanism-based cleavable linker developed in our laboratory as well as a PEG-spacer to increase aqueous solubility. Once the drug conjugate is internalized into the tumor cell the free taxoid would be released by the action of glutathione present in the tumor cell. The syntheses as well as the study on the drug internalization and release using fluorescence-labeled drug conjugate will be presented.



MEDI 331

WITHDRAWN

MEDI 332

Synthesis of 17-alpha-substituted arylvinyl estradiols and evaluation as ligands for the estrogen receptor ligand binding domain (ER-LBD)

*Robert N. Hanson[1], **Sandra Olmsted**[2], Pakamas Tongcharoensirikul[1], Emmett McCaskill[1], David C. Labaree[3], and Richard B. Hochberg[3]. (1) Department of Chemistry and Chemical Biology, Northeastern University, 360 Huntington Avenue, Boston, MA 02115, Fax: 617-373-8795, r.hanson@neu.edu, (2) Deaprtment of Chemistry, Augsburg College, 2211 Riverside Avenue South, Minneapolis, MN 55454, Fax: 612-330-1649, olmsteds@augsburg.edu, (3) Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT 06510*

As part of our program to probe the ligand binding pocket of the estrogen receptor we have prepared and evaluated new examples of 17-alpha-(substituted phenyl) vinyl estradiols. Previous results from competitive binding assays indicated that the affinity for the ER-LBD is dependent upon the nature and site of substitution but that translation to efficacy in Ishikawa cells was often inconsistent. In this study we describe the preparation of different (substituted phenyl) vinyl analogs and their evaluation as ligands for the ER-LBD in order to explore the relationship between binding and stimulation.

Supported by grants from NIH [PHS 1RO1 CA81409] and the U.S. Army Breast Cancer Research Program [DAMD 17-99-1-9333 and 17-00-1-00384].

MEDI 333

Histone deacetylase inhibition activity of resveratrol and its analogs

***Didem Dayangac-Erden**[1], Peruze Ayhan[2], Gamze Bora[1], Kemal Yelekci[3], Sevim Dalkara[4], Ayhan S. Demir[2], and Hayat Erdem-Yurter[1]. (1) Department of Medical Biology, Hacettepe University Faculty of Medicine, Sihhiye, 06100 Ankara, Turkey, Fax: +90-312-3096060, didayan@hacettepe.edu.tr, (2) Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey, (3) Faculty of Arts and Sciences, Kadir Has University, Istanbul, Turkey, (4) Department of Pharmaceutical Chemistry, Hacettepe University Faculty of Pharmacy, 06100 Ankara, Turkey*

Histone deacetylases (HDAC) are enzymes that play an important role in modifying chromatin structure and regulating gene expression. A number of HDAC inhibitors have been developed as anti-cancer agents. Resveratrol which is a molecule produced by plants in response to stress, is known to have anti-inflammatory, antioxidant and anti-cancer effects. In this preliminary study, HDAC inhibition activities of resveratrol and its analogues were investigated in vitro by using HeLa nuclear extract in a fluorimetric assay. High HDAC inhibitory activity was found in resveratrol in a concentration dependent manner. It showed more inhibitory effect than known HDAC inhibitors like short chain fatty acids. To display inhibitor positioning in the active site of HDAC enzyme, molecular docking studies were performed and results showed that resveratrol had the most favorable free energy of binding and inhibition constant values.

Demonstration of HDAC inhibitory effect of resveratrol will provide new insights into pharmaceutical applications.

MEDI 334

Discovery, optimization and biological evaluation of novel, potent and selective histone deacetylase (HDAC) inhibitors

Nivedita D Namdev[1]*, Manish Tandon*[1]*, Rao Akireddy*[1]*, Hernan Orgueira*[1]*, David Vensel*[1]*, Ming Kung*[1]*, Hui Wu*[1]*, Patrick Hutchins*[1]*, Magdi Moussa*[1]*, Jeffrey Link*[1]*, Yanbin Liu*[1]*, Robb Nicewonger*[1]*, Charles Bruseo*[2]*, Julie Gorenstein*[2]*, Enkeleda Nakuci*[2]*, Denise McSweeney*[2]*, Karen Bresciano*[3]*, Yunxia Wang*[3]*, Dennis France*[2]*, and Mark A. Ashwell*[4]*. (1) Medicinal Chemistry, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, nnamdev@arqule.com, (2) Molecular Oncology, ArQule, Inc, Woburn, MA 01801, (3) Preclinical Development, ArQule Inc, Woburn, MA 01801, (4) ArQule Inc, Woburn, MA 01801*

Histone deacetylase inhibitors (HDACi) have been pursued as a new class of targeted therapeutic agents for human cancer therapy. Here we describe the use of a high content screening assay measuring hyperacetylation together with HDAC enzyme inhibition data (IC50). Several series of potent HDAC in vitro inhibitors have been identified with differentiated HDAC isoform selectivity and anti-proliferative activity against cultured human cancer cell lines. The optimization of these series with parallel in vitro ADME assays is described.

MEDI 335

Design, synthesis and evaluation of the first highly selective sigma-2 receptor ligand

Sanju Narayanan[1]*, Christophe Mesangeau*[1]*, Jamal Shaikh*[2]*, Rae R. Matsumoto*[3]*, Jacques H. Poupaert*[4]*, and Christopher R. McCurdy*[5]*. (1) Department of Medicinal Chemistry and Laboratory for Applied Drug Design and Synthesis, University of Mississippi, 417 Faser Hall, University, MS 38677, Fax: 662-915-5638, slnu@olemiss.edu, (2) Department of Pharmacology, School of Pharmacy, University, MS 38677, (3) Department of Pharmacology, School of Pharmacy, Research Institute of Pharmaceutical Sciences, University, MS 38677, (4) Universite Catholique de Louvain, Avenue Emmanuel Mounier 73,B-1200,Brussels, Belgium, Brussels, Belgium, (5) Department of Medicinal Chemistry and Laboratory for Applied Drug Design and Synthesis, RIPS, University of Mississippi, University, MS 38677*

Sigma receptors (σ-1 and σ-2) are a well-defined receptor class, distinct from opioid and phencyclidine binding sites. They are present in the central nervous system as well as in various peripheral tissues. The σ-1 receptor has been demonstrated to be involved in acute and chronic effects of cocaine and methamphetamine toxicities, while activation of the σ-2 receptor induces growth arrest and cell death in various tumour cell lines. The mechanism by which σ-2 ligands induce cytotoxicity, however, remains unknown. This is partially due to the fact that several σ-2 signaling studies have been done by existing nonselective σ ligands that bind both σ-1 and σ-2 receptor. In this regard, searching for selective high affinity σ-1 and σ-2

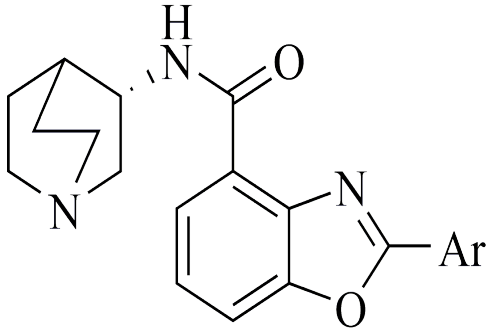
ligands led to the design and synthesis of the first highly selective σ-2 ligand derived from a series of compounds developed in our lab.

MEDI 336

Discovery of 2-arylbenzoxazole carboxamides as 5-HT3 receptor antagonists

*Catherine M. Beer[1], Lisa H. Borden[1], Kevin L. Christensen[2], Svetlana Dobritsa[2], David J. Fairfax[1], Soshanna Isaacson[1], John P. Lindsay[3], Jun-Ho Maeng[4], **David D. Manning**[4], Liaqat Masih[4], Vadim V. Mozhaev[3], Dana A. Razzano[1], W. Martin Rennells[1], Justin Richardson[1], Timothy Rust[1], Alexander Usyatinsky[4], Zhicai Yang[4], and Julianne V. Zaremba[3]. (1) Medicinal Chemistry, Albany Molecular Research Incorporated, 21 Corporate Circle, Albany, NY 12212-5098, (2) Discovery R&D In Vitro Biology, Albany Molecular Research Incorporated, Bothell, WA 98011, (3) Metabolism and Biotransformations, Albany Molecular Research Incorporated, Albany, NY 12203, (4) Discovery R&D Chemistry, Albany Molecular Research Incorporated, 21 Corporate Circle, Albany, NY 12212-5098, David.Manning@albmolecular.com*

Serotonin type-3 receptor (5-HT_3) antagonists revolutionized the chemotherapy field being safe and effective agents for the acute treatment of chemotherapy-induced nausea and vomiting (CINV). Functionally, the 5-HT_3 receptor is a ligand-gated ion channel which mediates fast synaptic neurotransmission in the CNS and periphery. Its structural uniqueness within the serotonin receptor family has made the 5-HT_3 receptor an attractive target for disease intervention. Recently, firm clinical support has emerged for the treatment of irritable bowel syndrome (IBS) and schizophrenia with 5-HT_3 modulators. The opportunity to add treatment options for chronic diseases like IBS prompted us to search for a new class of 5-HT_3 receptor antagonists. 2-Arylbenzoxazole carboxamides were discovered as potent, orally active 5-HT_3 receptor antagonists with good metabolic stability. Early structure-activity relationships and efficacy assessment will be described.



MEDI 337

Novel indole-3-carbinol-derived antitumor agents

***Jing-Ru Weng**[1], Chen-Hsun Tsai[2], Samuel K. Kulp[2], Dasheng Wang[2], Chia-Hui Lin[2], Yihui Ma[2], and Ching-Shih Chen[2]. (1) Department of Biological Science and Technology, China Medical University, 91 Hsueh-Shih Road, Taichung, 40402 NA, Taiwan,*

jrweng@mail.cmu.edu.tw, (2) Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, OH 43210

Purpose. The chemopreventive potential of indole-3-carbinol has attracted much attention because of its demonstrated ability to protect against chemical-induced carcinogenesis in different experimental animal models. From a mechanistic perspective, the ability of indole-3-carbinol to target a broad range of signaling pathways underlies its translational potential for cancer prevention and/or treatment. Therefore, this study was aimed at pharmacologically exploiting indole-3-carbinol as a molecular platform to develop structural variants with improved chemical stability and apoptosis-inducing potency. Methods. Structural optimization was carried out by structure-activity correlations in conjunction with molecular modeling. The in vitro effects of structural variants vis-à-vis indole-3-carbinol were evaluated in PC-3 and LNCaP human prostate cancer cell lines. Cell viability, apoptosis, and signaling targets were determined by immunoblotting, and chemical stability was assessed by nuclear magnetic resonance spectrometry. Results. Among a series of indole-3-carbinol derivatives examined, OSUMC-A9 represented the optimal agent with IC50 of 2 μM and 3.8 μM for reducing the viability of PC-3 and LNCaP cells, respectively, which were two-order-of-magnitude lower than that of indole-3-carbinol (respective IC50, 512 μM and 267 μM). Despite a 100-fold difference in antitumor potency, the pharmacological profiles of OSUMC-A9 and indole-3-carbinol in interfering with target signaling pathways were virtually identical. Both agents facilitated dose-dependent dephosphorylation of Akt and and Bad, accompanied by increased phosphorylation of MAPβits substrates GSK3 kinases. Moreover, the effects of OSUMC-A9 on suppressing the expression of Bcl-2, Bcl-xL, Mcl-1, survivin, NF-kB, and cyclin D1, and on up-regulating the expression of Bax, p27, and p21 paralleled those of indole-3-carbinol. The growth of existing PC-3 tumor xenografts was completely suppressed after i.p. treatment with OSUMC-A9 at 25 mg/kg. Conclusion. OSUMC-A9 is a potent antitumor agent with pleotropic mode of mechanisms by affecting multiple signaling pathways, which might have translational potential in cancer therapy.

MEDI 338

Lipophilic antitumor drug compounds: Cholesterol-modified camptothecins

*Yuehua Zhang and **Lisa B. Brungardt**, Drug Discovery, Sonus Pharmaceutical, Inc, 22026 20th Ave SE, Bothell, WA 98021*

A new series of lipophilic camptothecin derivatives have been synthesized by attaching a cholesteryl group to camptothecin and camptothecin derivatives through a linker. The structure of new compounds has been characterized by ^{1}H NMR, MS, FT-IR and elemental analysis. The new compounds are more soluble in biocompatible organic solvents such as soybean oil and vitamin E, and easily loaded into emulsion nanodroplets. *In vitro* cytotoxicty, as measured by GI_{50} values (50% of growth inhibition), of cholesterol-modified camptothecin compounds was investigated. The compounds with a cholesteryl group at C-10 show more anti-tumor effect, but those with a group at C-20 are less anti-tumor effect. It is interesting to note that the choice of linker had an effect on which cell types were most susceptible to our C-10 constructs.

MEDI 339

Study of conformationally biased oligodeoxyribonucleotides designed to induce bending and/or novel secondary structures in DNA

***Hisao Saneyoshi**, Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, Frederick, MD 21702, saneyoshih@ncifcrf.gov, and Victor E. Marquez, Laboratory of Medicinal Chemistry, Center for Cancer Reserch, NCI-frederick, Frederick, MD 21702*

G-tetrads are unusual structures that result from the self-association of guanosines. In the present work, we focus on the relationship between sugar pucker and the alternating syn-anti base orientation of guanine bases in G-tetrads. We have incorporated North and South bicyclo[3.1.0]hexane nucleosides on the thrombin binding aptamer [d(G2T2G2TGTG2T2G2)] as a model of an intramolecular anti-parallel G-tetrad, by alternating locked North- and South-methanocarba-deoxyguanosines in two sequences. The first sequence mimics the naturally observed pattern beginning with a syn-South-G, while the second has the opposite orientation beginning with an anti-North-G. The middle TGT and all the T's are natural nucleosides. We expect the modified oligonucleotides would be effective in either promoting or inhibiting the proper folding by affecting the local and global conformation. The corresponding North-type and South-type guanosine phosphoramidites and solid supports for DNA synthesis were successfully prepared. The chemical synthesis and biophysical properties will be presented.

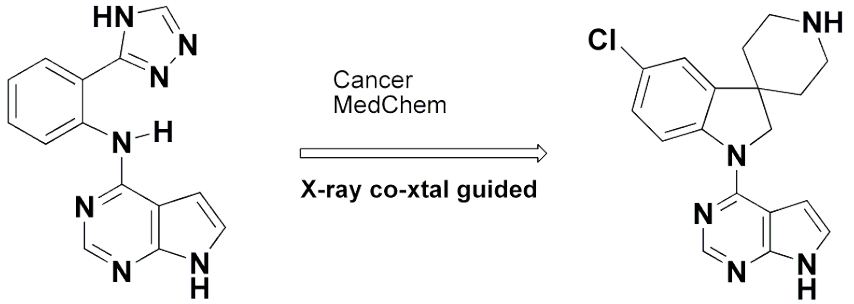
MEDI 340

Design, synthesis and evaluation of a potent class of spiroindoline pyrrolopyrimidines targeting Akt as anticancer agents

***Goss S. Kauffman**[1], Joel T. Arcari[2], Chris Autry[1], Deborah Baker[1], Gaby Barbacci[1], Vincent Bernardo[1], Merin Boehm[1], Gary Borzillo[2], David Briere[2], Chiliu Chen[2], Tracey Clark[2], Kevin G. Coleman[1], Matthew Corbett[2], Kevin Freeman-Cook[2], Catherine Hulford[2], John Jakubczak[1], Shefali Kakar[2], Lissie Knauth[2], Chao Li[2], Jing Lin[2], Blaise Lippa[2], Yong Lu[2], Michael Luzzio[2], Eric Marr[2], Gary Martinelli[2], Matthew A Marx[2], Joel Morris[1], Kendra Nelson[2], Gonghua Pan[2], Jay Pandit[2], Kristina Rafidi[1], Shaughn Robinson[2], Eric Soderstrom[2], Kosta Tsaparikos[2], Patrick W Vincent[2], and Liuqing Wei[2]. (1) Department of Cancer Research, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, Fax: 860-686-0605, goss.s.kauffman@pfizer.com, (2) Pfizer Global Research and Development, Groton, CT 06340*

The Akt (PKB) serine threonine protein kinases (Akt1, 2 and 3) are key components of cellular growth and survival signaling pathways and have been widely accepted as promising targets for anticancer drug discovery. An HTS of the Pfizer compound library resulted in only one hit: the pyrrolopyrimidine - Compound I (below). Early analoging around this pyrrolopyrimidine lead showed very tight SAR. Utilization of co-crystal structures along with High Speed

Analoging(HSA) ultimately led to Compound II (below). This compound has been shown to have potent Akt1 activity in vitro and in vivo, and lead to tumor regressions when dosed in a mouse xenograft model. The chemistry to prepare these compounds will be presented along with our understanding of the SAR around this series.



I II

MEDI 341

Increase in oxidative stress via glutathione reductase inhibition as a novel approach to enhance cancer sensitivity to radiation

***Yong Zhao**, Teresa Seefeldt, Wei Chen, Laura Carlson, Adam Stoebner, Sarah Hanson, Ryan Foll, Srinath Palakurthi, and Xiangming Guan, Department of Pharmaceutical Sciences, South Dakota State University, Brookings, SD 57007, Fax: 605-688-5993, yzhao1788@jacks.sdstate.edu*

Radiation is one of the major therapies in cancer treatment. The main obstacle in treating cancer by radiation is cancer resistance. Therefore, developing novel approaches to reverse cancer resistance or to increase cancer sensitivity to radiation is an ongoing research effort. In this poster, we would like to report that an increase in oxidative stress by inhibition of glutathione reductase (GR) significantly increased the sensitivity of OVCAR-3 cells, a human ovarian cancer cell line, to radiation. When the cells were treated with 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonyl-amino)phenylthiocarbamoylsulfanyl]propionic acid (2-AAPA), an irreversible GR inhibitor developed in this laboratory, followed by radiation in a 96 well plate, a significant synergistic effect was observed suggesting that inhibition of GR could be a novel approach to increase ovarian cancer sensitivity to radiation. The synergistic effect was correlated with an increase in cell oxidative stress which was measured by the levels of intracellular reduced glutathione and oxidized glutathione.

MEDI 342

N-Acetyl-S-(p-chlorophenylcarbamoyl)cysteine and its analogs as a novel class of anticancer agents

***Wei Chen**[1], Teresa Seefeldt[1], Yong Zhao[1], Zhiling Zhang[1], Alan Young[2], and Xiangming Guan[1]. (1) Department of Pharmaceutical Sciences, South Dakota State University, Brookings,*

SD 57007, Fax: 605-688-5993, vigo688@hotmail.com, (2) Department of Veterinary Sciences, South Dakota State University, Brookings, SD 57007

N-Acetyl-S-(p-chlorophenylcarbamoyl)cysteine (NACC) was identified as a metabolite of sulofenur, an anticancer agent reported by Lilly Research Laboratories against solid tumors. NACC was found to exhibit anticancer activity against a colon cancer cell line and low toxicity against CV-1 cells - a normal monkey kidney cell line. More interestingly, our preliminary data revealed that the compound caused an accumulation of the colon cancer cells in the G0/G1 phase of the cell cycle thus preventing the cells from entering the S phase. This is a different anticancer mechanism than most other cell cycle active chemotherapeutic agents that block cancer cells at the S or M phase. Various analogs of NACC have been synthesized. The synthesis and anticancer activity evaluation of these compounds will be presented.

MEDI 343

Evaluation of the effect of 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid (2-AAPA) on doxorubicin induced cardiotoxicity

Sarah Hanson[1]*, Teresa Seefeldt*[1]*, Qiangrong Liang*[2]*, and Xiangming Guan*[1]*. (1) Department of Pharmaceutical Sciences, South Dakota State University, Brookings, SD 57007, Fax: 605-688-5993, shanson@jacks.sdstate.edu, (2) Cardiovascular Research Institute, Sanford Research/USD, The Sanford School of Medicine of University of South Dakota, Sioux Falls, SD 57105*

Doxorubicin is a commonly used chemotherapeutic agent. Development of tumor resistance to doxorubicin is a major problem in the use of this medication. Additionally, cardiotoxicity is the dose-limiting factor in the therapeutic use of doxorubicin. Data obtained from this laboratory indicate that 2-AAPA, a glutathione reductase inhibitor, can enhance the anticancer activity of doxorubicin in OVCAR-3, a human ovarian cancer cell line, by augmenting doxorubicin induced oxidative stress. The objective of this investigation was to evaluate the effect of 2-AAPA on doxorubicin induced cardiotoxicity. H9c2 cells, rat heart cells, were treated with 2-AAPA, doxorubicin, or a combination of the two agents. The data demonstrate that the drug combination that exhibits the best synergistic effect in inhibiting OVCAR-3 produced no additional heart cell cytotoxicity as compared to doxorubicin alone. This data demonstrates that glutathione reductase inhibition can effectively increase cancer sensitivity to doxorubicin without enhancing doxorubicin induced cardiotoxicity.

MEDI 344

Increase in oxidative stress via glutathione modulation as a novel approach to enhance cancer sensitivity to doxorubicin

Teresa Seefeldt*, Yong Zhao, Wei Chen, Laura Carlson, Adam Stoebner, Sarah Hanson, Ryan Foll, Srinath Palakurthi, and Xiangming Guan, Department of Pharmaceutical Sciences, College of Pharmacy, South Dakota State University, Box 2202 C, Brookings, SD 57007, Fax: 605-688-5993, Teresa.Seefeldt@sdstate.edu*

Drug resistance is a major cause of cancer treatment failure. Doxorubicin induces the production of damaging reactive oxygen species as part of its mechanism of action, and resistance to doxorubicin can develop through increased levels of the intracellular antioxidant glutathione. Mechanisms of increasing the state of oxidative stress could enhance the sensitivity of cancer cells toward doxorubicin. Modulation of intracellular glutathione via a combination of glutathione reductase inhibition and glutathione synthesis inhibition is a novel approach to increasing oxidative stress and improving the activity of cancer chemotherapy. A novel irreversible glutathione reductase inhibitor, 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid (2-AAPA), and a glutathione synthesis inhibitor, buthionine sulfoximine (BSO) were used to increase the oxidative state in OVCAR-3 cells followed by treatment with doxorubicin. The combination exhibited a higher synergistic effect with doxorubicin than either compound alone. The methods and results will be presented.

MEDI 345

Interference of echinacea on cancer chemotherapy

***Jeremy Jensen**, Chemistry and Biochemistry Department, South Dakota State University, 121 Shepard Hall Box 2202, Brookings, SD 57006, jeremy.jensen@sdstate.edu, Fathi T. Halaweish, Department of Chemistry and Biochemistry, South Dakota State University, Brookings, SD 57007, and Christopher Chase, Department of Veterinary Science, South Dakota State University, Brookings, SD 57006*

Echinacea is one of the best selling herbal supplements on the market today and known for its immunostimulatory and antibacterial effects. Recent studies showed that Echinacea angustifolia compounds and preparations interfere with doxorubicin chemotherapy. An evaluation of Echinacea interference with other chemotherapy agents is needed.

Several Echinacea preparations (fingerprinted, standardized), compounds (chichoric acid, cynarine and echinacoside), and fractions of total extract were tested on cervical cancer (HeLa) and breast cancer (MCF-7) cell lines for anti-hyaluronidase activity and the interference of 5-fluorouracil and melphalan. Interference of Echinacea compounds and preparation with vinblastine and vincristine chemotherapy will be tested. Data indicated the Echinacea compounds, preparations and extracts showed a significant anti-apoptotic effect toward the chemotherapeutic agent in this study. Cynarine and dichloromethane fractions showed a significant increase of cell growth of HeLa and MCF-7 cells in the presence of 5-fluorouracil. Interference of Echinacea compounds and preparations with chemotherapeutic agents will be presented.

MEDI 346

Synthesis and characterization of pyrrolidine dithiocarbamate-copper complex: Proliferation inhibition, cell cycle arrest, apoptosis induction activities on cisplatin-resistant neuroblastoma cells

Haiyuan Zhang *and Fangyu Peng, Pediatrics and Radiology, School of Medicine, Wayne State University, 4901 Beaubien Blvd, Detroit, MI 48201, hazhang@med.wayne.edu*

Neuroblastoma (NB) is a malignant tumor originated from the peripheral sympathetic nervous system in children. Despite initial response to induction chemotherapy, acquired resistance to conventional chemotherapeutic drugs such as cisplatin and carboplatin is rapidly developed which is one of major causes of treatment failure in many patients. New effective drugs are urgently needed for treatment of those children suffering refractory NB. Pyrrolidine dithiocarbamate (PDTC) is a copper-binding ligand which was reported to have strong anti-tumor activity on many human tumor cells highly resistant to conventional chemotherapeutic agents. In current study, PDTC copper complexes (Cu-PDTC) were synthesized and showed strong anticancer activity against BE(2)C cells, a human neuroblastoma cell line highly resistant to cisplatin. The data from this study suggest that the CuPDTC complex holds potential to be used for treatment of refractory neuroblastoma in children.

MEDI 347

Synthesis and evaluation of novel bifunctional ligands for antibody targeted radiation cancer therapy and MRI

Hyuna Song*, Chemistry Division, Department of Biological, Chemical, Physical Sciences, Illinois Institute of Technology, 3101 S. Dearborn St, LS 182, Chicago, IL 60616, hsong12@iit.edu, and Hyun-Soon Chong, Chemistry Division, Biological, Chemical, and Physical Sciences Department, Illinois Institute of Technology, Chicago, IL 60616*

We previously reported the synthesis and biological evaluation of the structually new bifunctional ligand, C-NETA possessing both a macrocyclic cavity and an acyclic pendant binding group for use in MRI and RIT. C-NETA analogues having longer alkyl spacer have been synthesized, characterized, and evaluated for T1 relaxivities, MRI, and complexation kinetics and stability. We will present synthesis and chemical and biological evaluation of the new bifunctional ligands in this paper.

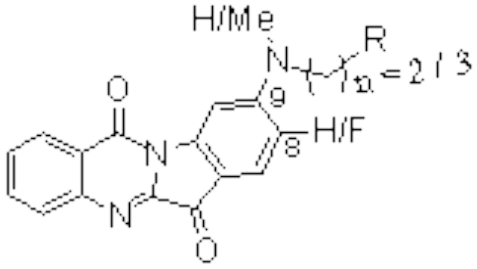
MEDI 348

Synthesis of 9-substituted Tryptanthrin derivatives and their activity against different cancer cell lines

Bhalchandra V. Bhagwat[1]*, Grace Shiahuy Chen*[2]*, Meng-Ling Chen*[1]*, Pei-Yun Liao*[1]*, and Ji-Wang Chern*[1]*. (1) School of Pharmacy, National Taiwan University, Taipei 100, Taiwan, bvbhagwat@yahoo.com, (2) Department of Applied Chemistry, Providence University, Sha-Lu 43301, Taiwan*

Tryptanthrin, indolo[2,1-b]quinazolin-6,12-one, is reported for its anticancer activity, while polyamines play important role in cell cycle proliferation and triplex DNA stabilization. In our research, we substituted aliphatic amine chains with different terminal functionality group (amine-alkyl-terminal functional group) at 9th position of tryptanthrin to study their combine inhibitory activity against different cancer cell lines. Terminal functionalities of these chains

were changed by different groups like ester, hydroxyl, NHTs, NH2, NH3+ salts, etc. These derivatives were synthesized by substituting relevant aliphatic amine chains at 6th position of 5,6-difluoroisatin or 6-fluoroisatin, and reacting with isatoic anhydride, which then transformed into the desired derivatives. Many compounds found to be active in μM range against stomach AGS cell line while some compounds showed significant activity against hepatoma cell Hep-G2 in sub-μM. The active derivatives were observed to stabilize 14C3 triplex. These results might be useful to develop a novel anti-cancer drug in future



R = OH, CN, COOEt, NH_2, NHTs, NHAc, $NHCOCF_3$, NH_3^+ salt.

MEDI 349

Synthesis, characterization, and anticancer activity of new copper thiosemicarbazone compound holding ONNS quadridentate system

Haiyuan Zhang *and Fangyu Peng, Pediatrics and Radiology, School of Medicne, Wayne State University, 3901 Beaubien Blvd, Detroit, MI 48201, Fax: 313-993-3845, hazhang@med.wayne.edu*

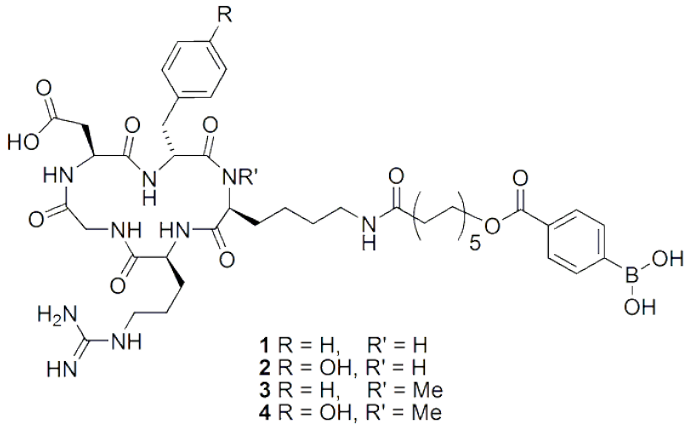
Many metal complexes were found to be highly potent against various types of human cancer cells. However, clinical application of majority of anti-cancer metal complexes tested in vitro was hampered by lack of tumor specificity. One of promising approaches to overcome this limitation is targeted delivery of these anti-cancer metal complexes to tumor tissues. Anti-cancer copper complex is especially attractive for targeted cancer therapy because targeted delivery of anticancer copper complexes may be monitored non-invasively by positron emission tomography (PET) when positron emitting copper isotopes, such as copper-64, are used to radio-label the compound. In current study, 8-hydroxyquinoline was coupled to 2-carboxaldehyde–thiosemicarbazide to make 8-hydroxyquinoline-2-carboxaldehyde–thiosemicarbazide (HQTS) holding a unique ONNS quadridentate system. The HQTS-copper complex suppressed proliferation and induced apoptosis of human neuroblastoma and malignant glioblastoma cells. The CuHQTS complex holds potential for targeted cancer therapy monitored by PET imaging.

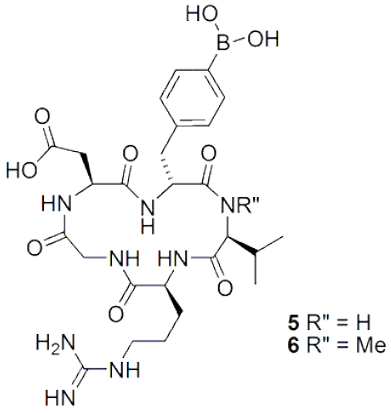
MEDI 350

Targeting cancer cells with boronated cyclic peptides for BNCT

Erin J. Ziolkowski, *Katrina A. Jolliffe, and Louis M. Rendina, School of Chemistry, The University of Sydney, F11, Eastern Ave, 2006 The University of Sydney NA, Australia, Fax: 61-2-9351-3329, ziolko_e@chem.usyd.edu.au*

Anticancer agents with tumor selectivity are the holy grail of cancer research. The present study focuses on combining peptidic ligands with boron-containing entities to afford novel conjugates for use in Boron Neutron Capture Therapy (BNCT). In BNCT, ^{10}B-containing agents are delivered to tumor cells and undergo rapid fission upon irradiation with neutrons to produce energetic $^{7}Li^{3+}$ and $^{4}He^{2+}$.[1] To maximise cell destruction, the compound must exhibit tumor selectivity.[1] This requirement may be addressed by using cyclic RGD peptides which bind to integrin receptors that are over-expressed on tumor cells,[2] and hence have the potential to deliver boron selectively to tumour cells. We are synthesizing a series of compounds (**1** - **6**) consisting of a cyclic RGD peptide and boron moiety. Key results will be presented.





References

[1] Soloway, A. H. *et al, Chem. Rev.* **1998**, *98*, 1515-1562. [2] Haubner, R. *et al*, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461-7472.

MEDI 351

Toward "best-in-class" Hsp90 inhibitors: Design, biosynthesis and preclinical profiles

Christine J Martin[1], Sabine Gaisser[1], William A Vousden[1], Lesley S Sheehan[1], Teresa Foster[1], Rose M Sheridan[1], Mohammad Nur-E-Alam[1], Nigel Coates[1], ***Steven J Moss***[1]*, Christoph Beckmann[1], Barrie Wilkinson[1], Matthew A Gregory[1], Chris Prodromou[2], Laurence Pearl[2], Thomas Greiner[3], Niko Bausch[3], and Ming Q Zhang[1]. (1) Biotica Technology Ltd, Chesterford Research Park, Little Chesterford CB10 1XL, United Kingdom, Fax: +44 1799 532921,*

christine.martin@biotica.com, steven.moss@biotica.com, (2) Institute of Cancer Research, London, United Kingdom, (3) Oncotest GmbH, Freiburg, Germany

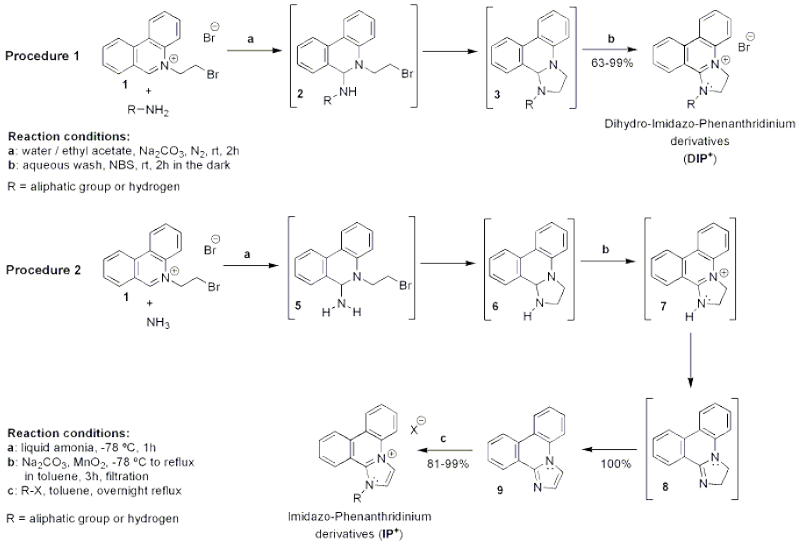
Hsp90 inhibitors in advanced development for cancer can broadly be classified into two groups: semi-synthetic derivatives of naturally occurring ansamycins and small molecules, such as mimetics of adenosine and non-purine based resorcinol compounds. Semi-synthetic ansamycins such as 17-DMAG and 17-AAG, contain a common quinone ‘toxicophore'. Through genetic engineering of the macbecin biosynthetic pathway we have now prepared a series of derivatives that lack the undesired quinone moiety. The most potent compound of this series has a binding affinity (Kd) of 3 nM to Hsp90, and is much better tolerated in vivo than 17-AAG (MTTD ≥ 250 mg/kg vs ~50 mg/kg i.p. in mice). It showed equivalent in vivo tumor growth inhibition in xenograft models at ≤ 1/3 MTTD to that of 17-AAG at MTTD. The improved therapeutic index coupled with its potent inhibition of Hsp90 makes the compound potentially the ‘best-in-class' Hsp90 inhibitor described to-date.

MEDI 352

One-pot synthesis of dihydro-imidazo and imidazo-phenanthridinium DNA intercalating platforms as promising anticancer agents

*Leroy Cronin and **Alexis D. C. Parenty**, Department of Chemistry, The University of Glasgow, Joseph Black Building, University Avenue, G12 8QQ, Glasgow, United Kingdom, L.Cronin@chem.gla.ac.uk, alexisp@chem.gla.ac.uk*

Two highly efficient and general one-pot annulation reactions are described for the synthesis of two DNA-Intercalating platforms Dihydro-Imidazo and Imidazo Phenanthridinium salts (Respectively DIPs and IPs). DNA affinity of the resulting products was determined using Isothermal Titration Calorimetry (ITC). In vitro tests show promising anti-cancer activity, with unexpected higher cytotoxicity on Cis-platin resistance cell lines A2780/cp70 and MCP1 than our Cisplatin-sensitive control cell line A2780.



MEDI 353

Development of potent inhibitors of B-Raf kinase

***Jianmei Wei**, Johnson & Johnson Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, Fax: 858-784-3116, and Ronald Wolin, Schering-Plough Research Institute, NJ*

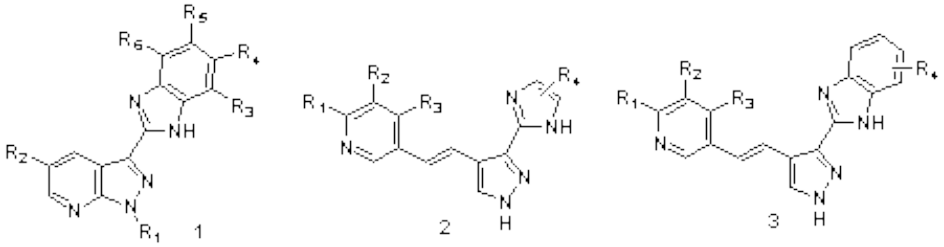
The recently approved anti-cancer agent Sorafinib, is a pan-kinase inhibitor used for the treatment of renal cell carcinoma. One of the kinases that Sorafinib affects is B-Raf kinase, an enzyme involved in cell growth and differentiation. Clinically, mutations to this protein have been linked to >60% of observed melanomas. With the availability of the x-ray crystal structure of B-raf kinase, and our interest in identifying a selective inhibitor of this enzyme, we designed a series of diarylimidiazoles and their isosters to interact with both the ATP and allosteric binding domains of the protein in a effort to obtain a selective B-raf inhibitor. The chemistry and the SAR detailing our efforts at discovering novel B-Raf inhibitors with improved activities will be presented.

MEDI 354

Design, synthesis, and evaluation of 3,4-disubstituted pyrazole analogs as antitumor CDK inhibitors

***Ronghui Lin**, Peter Connolly, George Chiu, Yang Yu, Shengjian Li, Stuart Emanuel, and Lee Greenberger, Johnson & Johnson Pharmaceutical Research & Development L.L.C, 1000 Route 202, Raritan, NJ 08869, Fax: 908-526-6469, Ronghui.Lin@yahoo.com*

Cyclin-dependent kinases (CDKs) are members of a family of serine-threonine protein kinases responsible for regulation of the eukaryotic cell cycle. A number of CDK inhibitors, such as flavopiridol, 7-hydroxystaurosporine (UCN-01), roscovitine (CYC202), BMS-387032 (SNS-032), PD0332991, and R547, have been studied in clinical trials for the treatment of cancer. Towards developing CDK inhibitors as anti-cancer agents, we recently reported that 3-benzoimidazoyl pyrazolopyridines (**1**) are novel potent anti-cancer CDK inhibitors and anti-proliferative agents. To discover structurally different CDK inhibitors with improved pharmacokinetic and solubility properties, we have designed, synthesized, and evaluated two related series of 3,4-disubstituted pyrazole analogs, in particular, 3-(imidazol-2-yl)-4-(2-pyridin-3-yl-vinyl)-pyrazole analogs (**2**) and 3-(benzoimidazol-2-yl)-4-(2-pyridin-3-yl-vinyl)-pyrazole analogs (**3**), as novel CDK inhibitors. The design, synthesis, and preliminary biological evaluation of these pyrazole compounds will be presented.



MEDI 355

Aurora kinase inhibitors: Lead structure identification from the Tetrahydrobenzo[b]thiophene class

Alexander C. Backes[1]*, Matthias Baumann*[1]*, Tilmann Brandstetter*[1]*, Doris Hafenbradl*[1]*, Roland Köstler*[1]*, Lars Neumann*[1]*, Joachim Vogt*[1]*, Peter C. Sennhenn*[1]*, Gerhard Müller*[1]*, and Gabriele Zybarth*[2]*. (1) GPC Biotech AG, Fraunhoferstrasse 20, D-82152 Martinsried, Germany, Fax: +49-89-8565-2610, alexander.backes@gpc-biotech.com, (2) GPC Biotech Inc, Waltham, MA 02451, USA*

Protein kinases play essential roles in controlling and modulating signal transduction pathways in the cell. Mutations in the corresponding encoding genes can lead to upregulation of protein kinase function, and this has been observed in a large number of different types of cancer as well as in inflammation. The members of the Aurora family of protein kinases play an important role in cell division and are required for multiple aspects of mitosis. Aurora A and Aurora B are both over-expressed in a wide range of different human tumours, including breast, lung, colon, ovarian, and pancreatic cancers. Inhibition of the Aurora kinases has been shown to suppress tumour growth in vivo, and the first small-molecule inhibitors of the Aurora kinases have progressed into phase II clinical trails.

Here we report on the design, synthesis, structure-activity and structure-selectivity relationships of tetrahydrobenzo[b]thiophene derivatives that were initially derived from a screening hit targeted against a mycobacterial kinase. Re-purposing by application of a Chemical Proteomics technology and systematic exploration of the core structure and its molecular periphery allowed us to establish initial structure-activity relationships. By establishing a pharmacophore model the key features for mediating the inhibitor-Aurora A interaction were elaborated. The majority of synthesized analogues led to the initial assumption that substituents linked to the 2-position of the underlying core were accommodated by the hydrophobic backpocket of Aurora A. Only with the support of protein X-ray crystallography the final binding mode of the tetrahydrobenzo[b]thiophenes in complex with Aurora A could be determined, revealing a striking contrast to the initially derived binding model. The value of high-resolution complex structures of inhibitor-kinase complexes will be highlighted together with the molecular interaction details that now provide a sound basis for any further optimization programs.

MEDI 356

P38 MAP kinase naphthyridinone inhibitors

Rowena Ruzek*, Department of Medicinal Chemistry, Merck & Co., Inc, WP14-2, PO Box 4, 770 Sumneytown Pike, West Point, PA 19486, Fax: 215-652-7310, rowena_ruzek@merck.com*

Rheumatoid arthritis (RA) is a disease of the connective tissue characterized by inflammation of the peripheral joints resulting in stiffness and pain. This condition may lead to deformation and destruction of the joints. One biological target of interest is the p38 MAP (mitogen

activated protein) kinase. This enzyme has been implicated as a factor in inflammatory and autoimmune diseases such as RA and Crohn's disease. P38 is an integral part of a biochemical pathway that leads to the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), both of which are known to cause inflammation and pain. Inhibition of p38 activity should also inhibit TNF-α release. Small molecule inhibitors of p38 MAP kinase have been synthesized in an effort to provide a treatment for RA with increased enzymatic and cellular potency, as well as a more convenient dosing regimen for patients.

MEDI 357

Design and SAR of pyrimidine-based inhibitors targeting the ABL-T315I mutation

Elena Dneprovskaia[1]*, Jianguo Cao*[1]*, Chun P. Chow*[1]*, Richard Fine*[2]*, Ehab Hanna*[1]*, John Hood*[1]*, Xinshan Kang*[2]*, Boris Klebansky*[2]*, Dan Lohse*[1]*, Chi-Ching Mak*[1]*, Andrew McPherson*[1]*, Glenn Noronha*[1]*, Moorthy S. S. Palanki*[1]*, Ved P. Pathak*[1]*, Joel Renick*[1]*, Richard Soll*[1]*, Binqi Zeng*[3]*, and Hong Zhu*[3]*. (1) TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830, (2) BioPredict, Inc, Oradell, NJ 07649-1525, (3) TargeGen, Inc, San Diego, CA 92121*

Imatinib, a BCR-ABL kinase inhibitor, is the standard of care for patients with chronic myelogenous leukemia. Mutations in the ABL kinase domain of the BCR-ABL protein result in interference with imatinib binding. Resistance to imatinib treatment leads to 50-90% of relapses of the disease. The T315I mutation accounts for 10-20 % of all observed mutations and is resistant to all approved and clinically advanced kinase inhibitors. TargeGen has designed and synthesized a new series of compounds based on a pyrimidine template by exploiting a unique binding interaction with Glu286 of the αC helix deep within the hydrophobic pocket. Optimization efforts guided by molecular modeling resulted in compounds with low nM ABL and ABL-T315I activity. Here we present the design and SAR of inhibitors with low nM activity against the ABL-T315I.

MEDI 358

Design and SAR of thiazole-based inhibitors for the ABL-T315I enzyme

Chun P. Chow[1]*, Jianguo Cao*[1]*, Elena Dneprovskaia*[1]*, Richard Fine*[2]*, Ehab Hanna*[1]*, John Hood*[1]*, Linda Hwang*[3]*, Xinshan Kang*[2]*, Boris Klebansky*[2]*, Dan Lohse*[1]*, Chi-Ching Mak*[1]*, Andrew McPherson*[1]*, Glenn Noronha*[1]*, Moorthy S. S. Palanki*[1]*, Ved P. Pathak*[1]*, Joel Renick*[1]*, Richard Soll*[1]*, Binqi Zeng*[3]*, and Hong Zhu*[3]*. (1) TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830, Fax: 858-678-0029, chow@targegen.com, (2) BioPredict, Inc, Oradell, NJ 07649-1525, (3) TargeGen, Inc, San Diego, CA 92121*

Imatinib, a BCR-ABL tyrosine kinase inhibitor, is the standard of care for patients with chronic myelogenous leukemia (CML). Unfortunately refractory response due to Imatinib treatment arises because of point mutations within the ABL kinase domain of BCR-ABL. These mutations interfere with Imatinib binding. Specifically, the T315I mutation accounts for about 15 percent of cases in which CML patients develop resistance to Imatinib. The T315I mutation also shows resistance to Dasatinib, a newer drug that has demonstrated effectiveness in Imatinib resistant

patients by targeting all the clinically relevant mutants except the T315I mutant. Using molecular modeling, we have identified elements in Imatinib and Dasatinib that prevent effective binding to the ABL-T315I mutant. We have developed and optimized a series of ABL-T315I inhibitors to mediate the deficiency found in Dasatinib. We will present design elements that provide potency against the T315I mutant along with our optimization strategy.

MEDI 359

Strategies involved in the construction of two series of novel potent inhibitors of ABL-T315I

Binqi Zeng[1]*, Jianguo Cao*[2]*, Chun P. Chow*[2]*, Chi-Ching Mak*[2]*, Elena Dneprovskaia*[2]*, Richard Fine*[3]*, Hong Gu*[4]*, Ehab Hanna*[2]*, John Hood*[2]*, Xinshan Kang*[3]*, Boris Klebansky*[3]*, Ge Li*[4]*, Dan Lohse*[2]*, Andrew McPherson*[2]*, Glenn Noronha*[2]*, Joel Renick*[2]*, Moorthy S. S. Palanki*[2]*, Ved P. Pathak*[2]*, Richard Soll*[2]*, Suhan Tang*[4]*, and Hong Zhu*[1]*. (1) TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121, Fax: 858-678-0029, (2) TargeGen, Inc, San Diego, CA 92121-3830, (3) BioPredict, Inc, Oradell, NJ 07649-1525, (4) Wuxi PharmaTech Co. Ltd, Shanghai, China*

Although Gleevec has been a remarkable success for treatment of CML, a significant number of patients develop drug resistance. It is estimated that 50-90% of resistance is drug related and due to mutations that alter the affinity of Gleevec to the mutated enzyme. The T315I (gatekeeper) mutation stands out among the >40 clinically identified mutations because it shows highest prevalence (>20%), and maintains resistance to all recently developed BCR-ABL inhibitors (Tasigna, Sprycel) that target most other mutations. Using molecular modeling, we have developed two series of novel ABL-T315I inhibitors to target the ABL-T315I mutant both in enzyme and cell-based assays. We will present the synthetic strategies that enabled optimizations of nM inhibitors of ABL-T315I in both series.

MEDI 360

Azaindazole ureas as potent VEGFR/PDGFR multitargeted receptor tyrosine kinase inhibitors

Yujia Dai*, Kresna Hartandi, Daniel H. Albert, Jennifer J. Bouska, Gail T. Bukofzer, Cherrie K. Donawho, Keith B. Glaser, Jun Guo, Junling Li, Patrick A. Marcotte, Amanda M. Olson, Donald J. Osterling, Lori J. Pease, Niru B. Soni, Kent D. Stewart, Paul Tapang, David R. Reuter, Steven K. Davidsen, and Michael R. Michaelides, Global Pharmaceutical Research & Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-935-5165, yujia.dai@abbott.com*

The vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) tyrosine kinases, and in particular KDR, are thought to play a prominent role in tumor angiogenesis, a process required for tumor growth and metastasis. Inhibition of VEGFR/PDGFR activation has become a compelling approach in the development of anticancer agents. In our continued efforts to identify potent and novel kinase inhibitors, we have discovered a series of azaindazole ureas that potently inhibit KDR and other VEGFR/PDGFR tyrosine kinases. These compounds also inhibit cellular KDR phosphorylation

and demonstrate oral activity in an estradiol-induced mouse uterine edema model. This poster presentation will describe the synthesis, structure-activity relationships (SARs) and characterization of this series of multit-argeted kinase inhibitors.

MEDI 361

Design and synthesis of c-met kinase inhibitors based on an in silico screen-derived lead

Sung-Eun Kim[1]*, Zhen-Dan Shi*[1]*, Megan Peach*[1]*, Alessio Giubellino*[2]*, Marc C Nicklaus*[1]*, Donald Bottaro*[2]*, and Terrence R Burke Jr.*[1]*. (1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, 376/217 NCI, Frederick, MD 21702, Fax: 301-846-6053, kims@ncifcrf.gov, (2) Urology Oncology Branch, CCR, NCI, NIH, Bethesda, MD 20892*

c-Met is a prototypic member of a subfamily of receptor tyrosine kinases (RTKs), which regulates a variety of cellular functions dealing with cellular growth and morphogenesis. Abnormal function of c-Met has been detected in a number of cancers, among which are breast, lung, melanoma, colorectal, prostate, ovarian and pancreatic cancers. Recently, several c-Met RTK inhibitors, including PHA665752, SU11274, SU11271 and PF-02341066 have been examined as potential new anticancer therapeutics. Using an in silico screen carried out on a database of commercially-available compounds, several potential c-Met RTK inhibitors were identified and evaluated for their ability to inhibit the c-Met RTK in whole cell systems. These compounds were hypothesized to bind in the ATP binding cleft of c-Met though interaction with a lipophylic area, while serving as a hydrogen bond acceptor with a key tyrosyl residue. Additionally, pi-stacking with the aromatic ring of a tyrosyl residue was also envisioned. Structural exploration of one of these in silico-derived c-Met RTK inhibitors will be presented.

MEDI 362

Design and synthesis of luminescent terbium(III) chelates: Application for kinase assay development

George Guoliang Yi*, Sukanta Bhattacharyya, Annegret Boge, Francisco Ramirez, and J. Richard Sportsman, Reagents R & D, MDS Analytical Technologies, 1311 Orleans Drive, Sunnyvale, CA 94089, Fax: 408-747-0965, george.yi@moldev.com*

Development of time-resolved fluorescence (TR-FRET) probes for kinase assays is of current interest. We have synthesized a set of luminescent terbium(III) chelates derived from cyclen-triacetic acid and differently substituted 1-azaxanthones. These complexes have been tethered with a phosphopeptide, and the resulting compounds tested as TR-FRET donors for kinase assays on IMAP® platform. The synthesis of the terbium(III) donors as well as their applications in kinase assays will be discussed.

MEDI 363

Discovery and SAR of a series of 3-[(6-piperidine-4-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-ones as IGF-1 receptor kinase inhibitors

Peiying Liu[1], *Upender Velaparthi*[1], *Mark D. Wittman*[2], *Mark G. Saulnier*[1], *K. Zimmermann*[3], *Xiaopeng Sang*[1], *David B. Frennesson*[4], *Francis Y. Lee*[5], *Joan Carboni*[6], *Ann Greer*[6], *Aixin Li*[6], *Ricardo Attar*[6], *Marco Gottardis*[7], *Zheng Yang*[8], *and Dolatrai M. Vyas*[9]. *(1) Discovery Chemistry, Bristol Myers Squibb Co, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, peiying.liu@bms.com, (2) Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Wallingford, CT, Wallingford, CT 06492-7660, (3) Pharmaceutical Research Institute, Bristol-Myers Squibb, Wallingford, CT 06492, (4) Infectious Disease Chemistry, Bristol Myers Squibb, Wallingford, CT 06492, (5) Oncology Drug Discovery, Bristol Myers Squibb Co, Pharmaceutical Research Institute, Princeton, NJ 08543, (6) Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Princeton, NJ, Princeton, NJ 08543, (7) Oncology Drug Discovery, Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Princeton, NJ, Princeton, NJ 08543, (8) Bristol-Myers Squibb Co, Pharmaceutical Research Institute, Princeton, NJ, Princeton, NJ 08543-4000, (9) Discovery Chemistry, Bristol Myers Squibb Co, Pharmaceutical Research Institute, Wallingford, CT 06492*

Signaling through the insulin-like growth factor I (IGF-1R) pathway mediates events which promote the malignant phenotype such as mitogenisis (via stimulation of signaling cascades through Ras/Raf/MARK kinase) and cell survival (via activation of the PI3K/Akt/mTor kinase pathway). Epidemiological studies have shown that elevated IGF-1 levels correlate with increased risk of developing colon, breast, prostate, and lung tumors. Previously we reported BMS-536924 as a new small molecule kinase inhibitor of IGF-1R with robust efficacy in IGF-Sal tumor model. As part of our continuous efforts toward the identification of IGF-1 receptor kinase inhibitors with improved enzyme and cell potency, we have recently identified a novel series of 3-[(6-piperidine-4-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one derivatives. The synthesis and detailed SAR of this series as IGF-1 receptor kinase inhibitors are presented.

MEDI 364

Synthesis of cis-fused indolocarbazole pyran derivatives as multikinase inhibitors

Françoise M. Perron-Sierra[1], *Roy Golsteyn*[1], *Nathalie Kucharczyk*[1], *Patrick Casara*[1], *and Céline Boucley*[2]. *(1) Medicinal Chemistry, Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy sur Seine, France, Fax: 33.1.55.72.24.70, françoise.perron@fr.netgrs.com, (2) Finorga, Chasse sur Rhône 38670, France*

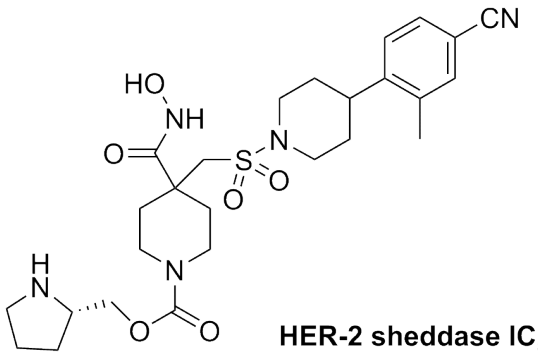
An efficient scale synthesis of enantiomerically pure N_{12},N_{13}-pyran-bridged indolocarbazoles is disclosed, starting from an indole-indoline derivative. Functional diversity is presented through 15 examples allowing SAR on FLT3 and Chk1 inhibitory properties. In vitro pharmacological data are presented for the most potent compounds.

MEDI 365

Discovery of ß-sulfonamide piperidine hydroxamates as potent and selective HER-2 sheddase inhibitors

David M. Burns[1]*, Chunhong He*[1]*, Yanlong Li*[1]*, Peggy Scherle*[1]*, Maryanne Covington*[2]*, Max Pan*[1]*, Richard Wynn*[1]*, Sharon Turner*[1]*, Jordan S. Fridman*[1]*, Steve Friedman*[1]*, Brian Metcalf*[1]*, and Wenqing Yao*[3]*. (1) Medicinal Chemistry, Incyte Corporation, Experimental Station-E336/212, Route 141 and Henry Clay Road, Wilmington, DE 19880, Fax: 302-425-2704, dburns@incyte.com, (2) Bristol-Myers Squibb Company, (3) Incyte Corporation, Wilmington, DE 19880*

The human epidermal growth factor receptor-2 (HER-2) is a tyrosine kinase receptor that is activated upon homo-and heterodimerization with another member of the HER family or by proteolytic cleavage (shedding) of the extracellular domain (ECD). Overexpression of the oncogene HER-2/neu has been associated with aggressive pathogenesis, poor prognosis, and decreased responsiveness to conventional chemotherapeutic and hormonal treatment regimes in non-small cell lung cancer, ovarian cancer, and breast cancer patients. In addition, elevated plasma levels of HER-2 ECD have been associated with increased metastatic potential and a decrease in disease-free and overall survival in patients with breast cancer. Therefore, inhibition of the protease responsible for HER-2 ECD shedding, which has recently been identified as ADAM-10, may be therapeutically desirable for treating cancer patients that overexpress HER-2. Several ß-sulfonamide piperidine hydroxamates were identified to be potent inhibitors of HER-2 sheddase with excellent selectivity over other matrix metalloproteases (MMPs).



HER-2 sheddase IC_{50} 6.5 nM

MEDI 366

Identification of multikinase inhibitor using a multistep computer aided approach

Sivanesan Dakshanamurthy[1]*, Mikell Paige*[2]*, Todd Hansen*[2]*, Salimuddin Shah*[2]*, Stephen Byers*[2]*, and Milton Brown*[2]*. (1) oncology, Lombardi Cancer Center, Georgetown University, reservoir road, E401/W225, NRB, washington, DC 20057, sd233@georgetown.edu, (2) oncology, Georgetown University, washington, DC 20057*

In recent years, computer based virtual screening has become a powerful tool for the drug discovery. However, major challenge in the Computer Aided Drug Design (CADD) is obtaining

accurate protein-ligand binding affinity because conventional scoring functions fails to include protein flexibility, solvation penalty, and conformational entropy. In some cases, the binding modes that correspond to the largest calculated binding free energy are not necessarily the actual binding modes found in the crystallographic complexes. Thus, free energy simulations are good alternative to rescore the binding complexes. In this study, we formulated a multi-step CADD approach in which each step acts as a filter that employs step by step filters to identify only the most promising candidates. We successfully applied this multi-step approach to the identification of multi-kinase inhibitors.

MEDI 367

Nanomedicinal chemistry: Preparation of novel tyrosine kinase inhibitor-targeted linkers for nanoparticle targeting

Robert N. Hanson*, Kristin Bailey, Marah Elston, and J. Adam Hendricks, Department of Chemistry and Chemical Biology, Northeastern University, 360 Huntington Avenue, Boston, MA 02115, Fax: 617-373-8795, r.hanson@neu.edu*

As part of our program for applying nanotechnology to biomedicine we have focused on the design and preparation of multivalent nanoparticles. Our strategy involves a modular-convergent approach in which we develop terminally functionalized nanoparticle binding groups and separately prepare, using structure-based drug design, derivatives of ligands that bind to specific cellular markers. In this project, we selected tyrosine kinase inhibitors (TKI) of the anilinoquinazoline family as our targeting molecules onto which we would append a substituent that would interact with the nanoparticle binding moiety. In this presentation we will describe the synthesis of each module, the ligation using “click” chemistry and our preliminary efforts toward labeling the nanoparticles.

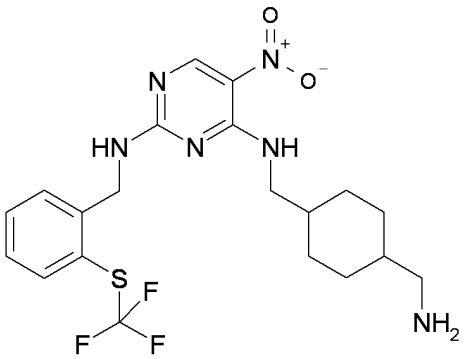
MEDI 368

Potent and selective PKC-θ inhibitors: Advancement from LI to LO

Anthony S. Prokopowicz III*[1], Charles L. Cywin[1], Georg Dahmann[2], Erick R. R. Young[1], Ronald L. Magolda[1], Mario G. Cardozo[1], Derek A. Cogan[1], Darren DiSalvo[1], John D. Ginn[1], Mohammed A. Kashem[1], John P. Wolak[1], Carol A. Homon[1], Thomas M. Farrell[1], Heather Grbic[1], Hanbo Hu[1], Paul V. Kaplita[1], Lisa H. Liu[1], Denice M. Spero[1], Deborah D. Jeanfavre[1], Kathy M. O'Shea[1], Della M. White[1], Joseph M. Woska Jr.[1], and Maryanne L. Brown[1]. (1) Department of Research, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877-0368, (2) Department of Medicinal Chemistry, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss D-88397, Germany*

An uHTS campaign identified a series of 2,4-diamino-5-nitropyrimidines as potent and selective PKC-θ inhibitors. Hit to lead data is presented showing that we were able to achieve

selectivity over multiple kinases, including closely related kinases CDK-1, PLK-1, and PKC-δ. Several highly selective analogues showed cellular potency. The overall profile of this series made it attractive for advancement to lead optimization.



MEDI 369

Novel pyrimidine alkynyl phenyl ureas as potent Tie-2 inhibitors

Clifford D Jones*, Kevin Blades, Matthew Box, Leonie Campbell, Paula Daunt, Richard Grant, Alison Griffen, Lorraine Hassall, Barry Hayter, Keith Johnson, Darren Jones, Jane Kendrew, Kieran Lennon, Richard WA. Luke, William McCoull, Linette Ruston, Michael L. Swain, Andy Wright, and John A. Stawpert, Cancer and Infection Research, AstraZeneca UK, Mereside, Alderley Park, Macclesfield SK10 4TG, United Kingdom, cliff.jones@astrazeneca.com*

The receptor tyrosine kinase Tie-2 is involved in the maturation and maintenance of blood vessels and acts in a complementary and coordinated fashion with VEGF receptor signalling. Inhibition of Tie-2 signalling is expected to prevent vessel differentiation, maturation and persistence and impair the capability for further tumour growth. Screening of the AstraZeneca compound collection identified a novel diaminopyrimidine alkynyl phenyl urea that inhibited the phosphorylation of Tie-2 in cells and was a suitable start point for further elaboration. Initial efforts focussed on the optimisation of the potency and pharmacokinetic (PK) parameters of the series. Issues encountered with a lack of photostability and poor oral bioavailability led to the development of a 2-aminopyrimidine alkyne phenyl urea series with much improved properties. The synthesis and structure-activity relationships (SAR) of both of these classes of kinase inhibitors will be described.

MEDI 370

Evolution of selective, potent, and orally bioavailable small molecule Tie-2 kinase inhibitors

Philip R Olivieri II[1]*, Stephanie D Geuns-Meyer*[1]*, Paul E Hughes*[2]*, Brian K Albrecht*[1]*, Steve Bellon*[3]*, James Bready*[2]*, Sean Caenepeel*[2]*, Victor J Cee*[1]*, Stuart C Chaffee*[1]*, Angela Coxon*[2]*, Maurice Emery*[4]*, Jenne Fretland*[4]*, Paul Gallant*[5]*, Yan Gu*[5]*, Brian L Hodous*[1]*, Doug Hoffman*[6]*, Rebecca E Johnson*[1]*, Richard Kendall*[2]*, Joseph L Kim*[3]*, Alexander M Long*[3]*, Michael Morrison*[5]*, Vinod F Patel*[1]*, Anthony Polverino*[2]*, Paul Rose*[5]*, Paul Tempest*[1]*, Ling Wang*[2]*,*

Douglas A Whittington[3], and Huilin Zhao[5]. (1) Department of Medicinal Chemistry, Amgen, One Kendall Square, Building 1000, Cambridge, MA 02139, (2) Department of Oncology Research, Amgen, Thousand Oaks, CA 91320, (3) Department of Molecular Structure, Amgen, Cambridge, MA 02139, (4) Department of Pharmacokinetics and Drug Metabolism, Amgen, Thousand Oaks, CA 91320, (5) Department of Molecular Pharmacology, Amgen, Cambridge, MA 02139, (6) Department of Pharmaceutics, Amgen, Thousand Oaks, CA 91320

Inhibition of angiogenesis is a promising and clinically validated approach for limiting tumor growth and survival. The receptor tyrosine kinase Tie-2 is expressed primarily in the vascular endothelium and is required for developmental angiogenesis and vessel maturation. Interference with the Tie-2 pathway by diverse ligand/receptor blocking agents such as soluble Tie-2 receptors, antibodies, and peptide-Fc conjugates has been shown to suppress tumor growth in mouse xenograft studies. An alternative strategy for interfering with the Tie-2 signaling pathway involves targeting the ATP-binding site of the Tie-2 kinase domain with small molecule inhibitors. Potent, orally bioavailable kinase inhibitors with selectivity over other kinases implicated in angiogenesis are required in order to properly evaluate the therapeutic utility of this approach. Towards this end, several selective DFG-out binding scaffolds evolved from a designed multi-kinase inhibitor with the aid of X-ray co-crystal structures of Tie-2 and KDR. These structurally diverse molecules demonstrated on-mechanism activity in in vivo models.

MEDI 371

WITHDRAWN

MEDI 372

Pyridyl-pyrimidine benzimidazole derivatives as potent, selective, and orally active inhibitors of Tie-2 kinase

***Karina Romero**[1], Stephanie Geuns-Meyer[1], Paul Hughes[2], Annette Bak[1], Steve Bellon[1], James Bready[2], Sean Caenepeel[2], Victor J Cee[3], Stuart C Chaffee[1], Angela Coxon[2], Holly L. Deak[1], Maurice Emery[2], Jenne Fretland[2], Paul Gallant[1], Yan Gu[1], Brian L Hodous[1], Doug Hoffman[2], Rebecca E Johnson[1], Richard Kendall[2], Joseph L Kim[1], Jasmine Lin[1], Alexander M Long[1], Michael Morrison[1], Hanh N Nguyen[1], Philip R Olivieri II[1], Vinod F Patel[1], Anthony Polverino[4], David Powers[2], Paul Rose[1], Mary K Stanton[1], Ling Wang[2], and Huilin Zhao[1]. (1) Amgen, Inc, 1 Kendall Square, Bldg 1000, Cambridge, MA 02139, romerok@amgen.com, (2) Amgen, Inc, Thousand Oaks, CA 91320, (3) Department of Medicinal Chemistry, Amgen, Thousand Oaks, CA 91320, (4) Amgen, Inc, Seattle, WA 98119*

Inhibition of angiogenesis is a promising and clinically established approach for limiting tumor growth and survival. The receptor tyrosine kinase Tie-2 is expressed primarily by vascular endothelial cells and is critical for developmental angiogenesis and vessel maturation. Interference with the Tie-2 pathway by diverse blocking agents such as soluble Tie-2 receptors, anti-Tie-2 intrabodies, anti-Ang-2 antibodies and peptide-Fc conjugates has been shown to suppress tumor growth in xenograft studies. An alternative strategy for interfering with the Tie-2 signaling pathway involves targeting the ATP binding site of the Tie-2 kinase

domain. Potent, orally bioavailable, and selective kinase inhibitors are essential in assessing the therapeutic utility of this approach. Toward this end, we describe the development of pyridyl-pyrimidine benzimidazole derivatives as ATP-competitive inhibitors of Tie-2 autophosphorylation.

MEDI 373

Design and synthesis of dihydroindazolo[5,4-a]pyrrolo[3,4-c]carbazole oximes as potent dual inhibitors of VEGF-R2 and TIE-2 receptor tyrosine kinase

***Reddeppareddy Dandu**, Allison L. Zulli, Edward Bacon, Ted Underiner, Candy Robinson, Hong Chang, Sheila Miknyoczki, Jennifer Grobelny, Bruce A. Ruggeri, Thelma S. Angeles, Lisa D. Aimone, and Robert L. Hudkins, Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: NA, dreddy@cephalon.com*

Angiogenesis is not only a dynamic and very complex process that involves the formation of new blood vessels from the existing vasculature but is also a critical process during early embryonic development as well as in a number of processes including cancer, rheumatoid arthritis and psoriasis. The development of the normal vasculature is believed to be dependent on the vascular endothelial growth factor (VEGF) and its receptor tyrosine kinases, mainly VEGF-R2 and the angiopoietins (Ang-1 and Ang-2) and its receptor kinases, primarily TIE-2. Thus, the disruption of both VEGF-R2 and TIE-2 receptor signaling are an attractive targets to prevent tumor angiogenesis, which can then lead to the inhibition of tumor growth and metastasis. We have identified dihydroindazolocarbazole based oximes as low nanomolar potent dual VEGF-R2 and TIE-2 receptor tyrosine kinase inhibitors. We will present in detail the structure-activity relationships (SAR), pharmacokinetic, and the in vivo evaluation of lead dihydroindazolocarbazole oximes.

MEDI 374

The impact of physicochemical properties on sensorial dynamic: The cooling sensation

***Stefan M. Furrer**, Ingredient Systems, Givaudan Flavors R&D, 1199 Edison Drive, Cincinnati, OH 45216, Fax: 513-948-3582, stefan.furrer.sf1@givaudan.com*

Physicochemical properties represent a major factor in the design of new active ingredients. Although physicochemical properties (such as logP) are well studied in the flavour industry for volatile compounds, their impact on taste sensations is less known. Using cooling compounds as a case study, the impact of such properties on taste sensations and flavour applications was investigated.

MEDI 375

Pharmaceutical applications of cooling agents

***Sara Encisco**, Chemistry, Harvard University, 12 Oxford Street, Cambridge, MA 02138, sencisco@fas.harvard.edu, and Ahamindra Jain, Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138*

Cooling agents have found application over the years in a range of formulations, as lotions and creams for the skin, as well as treatments for pain relief. More recently, the receptor involved in transduction of the cooling sensation has been found in elevated levels in prostate cancer cells. We are in the process of preparing a range of structures, including phosphine oxides and menthol analogs, for application across the potential activities of these molecules.

MEDI 376

Synthesis and biological evaluation of 2,4-diaminoquinazoline derivatives and related compounds as novel CC chemokine receptor 4 (CCR4) antagonists

***Noriyuki Kawano**, Toru Kontani, Naoyuki Masuda, Yohei Koganemaru, Wataru Hamaguchi, Hiroyuki Kaizawa, Koji Kato, Susumu Igarashi, Hiroshi Nagata, Hiroshi Inami, Tadashi Terasaka, Noriko Ishikawa, Kazuhiro Yokoyama, Shinichi Ogino, Mitsuhiro Kondo, Makoto Takeuchi, and Mitsuaki Ohta, Institute for Drug Discovery Research, Astellas Pharma Inc, 21, Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan, Fax: +81-29-854-1519, noriyuki.kawano@jp.astellas.com*

The CC chemokine receptor 4 (CCR4) works together with its ligands, thymus and activation regulated chemokine (TARC), and macrophage-derived chemokine (MDC), to promote recruitment and homing of CCR4-expressing cells (T-cells, monocytes, macrophages, etc.). CCR4 antagonists are expected to have therapeutic potential in the treatment of diseases such as asthma, rheumatoid arthritis, and dermatitis since TARC, MDC, and CCR4-expressing cells are found to increase in asthmatic lungs, arthritic joints, and inflamed skin. In a search for small molecular CCR4 antagonists, *N*-cycloheptyl-6,7-dimethoxy-2-(4-pyrrolidin-1-ylpiperidin-1-yl)quinazolin-4-amine (AS1611113) was found as a lead compound during a high-throughput screening. We have designed and synthesized the related compounds of AS1611113, and finally identified 4,6-diaminopyrazolo[3,4-*d*]pyrimidine derivatives as highly potent CCR4 antagonists to show inhibitory activities against oxazolone-induced ear edema in mice at a dose of 30 mg/kg p.o. The synthesis and structure-activity relationships (SAR) of these compounds will be presented.

MEDI 377

Synthesis and SAR investigation of 3, 4-diamino derivatives of thiadiazole-1-oxides as CXCR1-CXCR2 dual antagonists

***Purakkattle Biju**[1], Younong Yu[1], Cynthia Aki[1], Junying Zheng[1], Jianhua Chao[1], Michael P. Dwyer[1], Rindgen Diane[2], Richard Bond[2], James Jakway[2], Hongchen Qiu[2], R. William Hipkin[2],*

James Fossetta[2], Waldemar Gonsiorek[2], Hong Bian[2], Xuedong Fan[2], Carol Terminelli[2], Jay Fine[2], J. Robert Merritt[3], Zhenmin He[3], Gaifa Lai[3], Minglang Wu[3], and Arthur Taveras[1]. (1) Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 9087407152, purakkattle.biju@spcorp.com, (2) Department of Biological Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Pharmacopeia Drug Discovery Inc, Cranbury, NJ 08512

Abstract: Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. In general, chemokines have been classified in to two main classes, the CXC-chemokines and the CC-chemokines. The CXC-chemokines include interleukin-8 (IL-8), neutrophilactivating protein-1(NAP-1), NAP-2, GRO-á and many more. These CXC-chemokines promote the accumulation and activation of neutrophils, hence, they have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis, RA and COPD. IL-8 mainly activates neutrophils through their G-protein coupled receptors, CXCR1 and CXCR2. Due to the obvious relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonist are targets of small molecule drug discovery. We have previously identified several 3, 4-diamino-3-cyclobut-3-ene-1, 2-diones as potent dual CXCR1-CXCR2 dual antagonists. This presentation will highlight the medicinal chemistry effort towards replacing the cyclobutene dione centre core and its detailed SAR.

MEDI 378

Synthesis and structure-activity relationships of heteroaryl-substituted 3,4-diamino-3-cyclobut-3-ene-1,2-dione CXCR2/CXCR1 receptor antagonists

Younong Yu[1]*, Michael P. Dwyer[1], Jianping Chao[1], Cynthia Aki[1], Jianhua Chao[1], Biju Purakkattle[1], Diane Rindgen[2], Richard Bond[3], Rosemary Mayer-Ezel[3], James Jakway[3], Hongchen Qiu[3], R. William Hipkin[3], James Fossetta[3], Waldemar Gonsiorek[3], Hong Bian[3], Xuedong Fan[3], Carol Terminelli[3], Jay Fine[3], Daniel Lundell[3], J. Robert Merritt[4], Zhenmin He[4], Gaifa Lai[4], Minglang Wu[4], and Arthur G. Taveras[1]. (1) Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033-0539, Fax: 908-740-7152, younong.yu@spcorp.com, (2) Department of Drug Metabolism, Schering-Plough Research Institute, (3) Department of Biological Research, Schering-Plough Research Institute, (4) Pharmacopeia Drug Discovery Inc, Cranbury, NJ 08512*

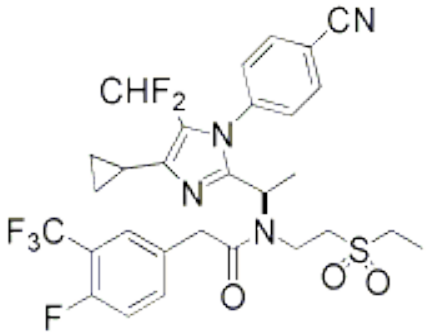
Interleukin-8 (IL-8, CXCL8) and related CXC chemokines have been implicated in controlling the trafficking of neutrophils to the sites of inflammation. In addition, CXCL8 and CXCL1 levels have been found to be elevated in human body fluids in various inflammatory conditions such as chronic obstructive pulmonary disease (COPD), arthritis, and psoriasis where neutrophil infiltration is observed. To date, two G-coupled protein receptors have been identified that are activated by CXCL8 (CXCR2 and CXCR1) making them attractive targets for therapeutic intervention for various inflammatory disorders. Using a previously identified 3,4-diamino-3-cyclobut-3-ene-1,2-dione motif as a template, we designed and synthesized a series of heteroaryl-substituted CXCR2/CXCR1 receptor antagonists. This presentation will highlight the medicinal chemistry efforts toward the optimization of the receptor binding affinities, cell-based potency, and oral bioavailability of this class of CXCR2/CXCR1 receptor antagonists.

MEDI 379

Imidazole derivatives as potent CXCR3 antagonists

Xiaohui Du[1], *Xiaoqi Chen*[1], *Jeffrey Mihalic*[1], *Jeffrey Deignan*[1], *Jason Duquette*[1], *An-rong Li*[1], *Bryan Lemon*[1], *Ji Ma*[2], *Shichang Miao*[1], *George Tonn*[1], *Tassie Collins*[1], *and Julio Medina*[1]. *(1) Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, xdu@amgen.com, (2) Amgen Inc, South San Francisco, CA 94404*

CXCR3 is a G-protein-coupled receptor expressed predominantly on activated Th1 cells and plays a role in their migration into sites of inflammation. CXCR3 and its ligands, MIG (CXCL9), IP-10 (CXCL10) and ITAC (CXCL11) have been implicated in a variety of inflammatory and autoimmune diseases such as transplant rejection, psoriasis, rheumatoid arthritis and multiple sclerosis. Thus, it has been postulated that blocking CXCR3 may prevent the recruitment of inflammatory cells and result in the beneficial treatment of autoimmune diseases. Here we describe the optimization efforts to increase CXCR3 antagonism, improve pharmacokinetic properties and reduce glutathione-mediated metabolism which led to the discovery of potent antagonists with improved pharmacokinetic properties as exemplified by (40).



(40)

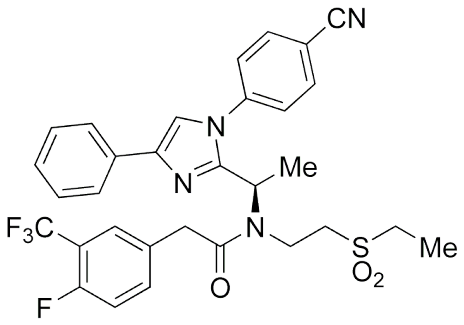
MEDI 380

Mono- and bicyclic small molecule antagonists of CXCR3

An-Rong Li[1], ***Michael G. Johnson***[1], *Jiwen Liu*[1], *Xiaoqi Chen*[1], *Xiaohui Du*[1], *Jeff Mihalic*[1], *Jeffrey Deignan*[1], *Darin J. Gustin*[1], *Jason Duquette*[1], *Zice Fu*[1], *Liusheng Zhu*[1], *Andrew P. Marcus*[1], *Phillipe Bergeron*[1], *Tassie Collins*[1], *Timothy Sullivan*[2], *Jay Danao*[1], *and Julio C. Medina*[1]. *(1) Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, anrongl@amgen.com, mgjohnso@amgen.com, (2) Amgen Inc, South San Francisco*

CXCR3 is a chemokine receptor expressed primarily on activated T cells and implicated in a variety of autoimmune diseases. In this poster we present a diverse set of CXCR3 antagonists bearing moncyclic and bicyclic ring systems that replace the 8-azaquinazolinone core ring

system found in the clinical candidate AMG 487. The N-phenyl substituted imidazole 16 exemplifies compounds with a core replacement that affords an improved CXCR3 in vitro activity profile relative to AMG 487.



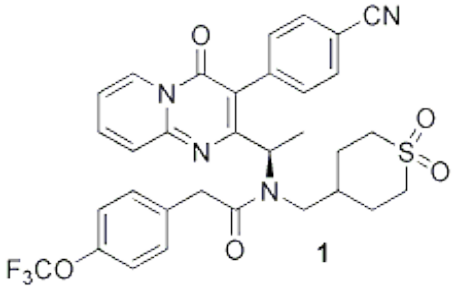
16

MEDI 381

Pyrido[1,2-a]pyrimidin-4-ones as potent CXCR3 antagonists

Jason Duquette[1]*, Xiaohui Du*[1]*, Johann Chan*[2]*, Bryan Lemon*[1]*, Tassie Collins*[1]*, George Tonn*[1]*, Julio Medina*[1]*, and Xiaoqi Chen*[1]*. (1) Amgen Inc, 1120 Veterans Blvd, South San Francisco, CA 94080, duquette@amgen.com, (2) Amgen Inc, Thousand Oaks, CA 91320*

Pyrido-[1,2-a]pyrimidine-4-ones were found to be a potent series of CXCR3 antagonists. However, compounds in this series displayed PXR mediated CYP-induction. In this presentation we describe the optimization that lead to the discovery of a potent CXCR3 antagonist with reduced PXR activity. Some observations on the relationship between lipophilicity and PXR activation will be presented. Furthermore, the synthetic routes that enabled the exploration of the SAR of this series will be highlighted along with the biological data. These efforts lead to the identification of compound **1** as a potent CXCR3 antagonist with good *in vitro* and *in vivo* pharmacokinetic properties.



1

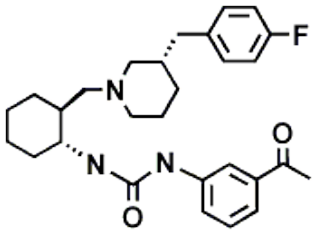
MEDI 382

Identification of potential back-ups for clinical candidate CCR3 antagonist DPC-168

Qing Shi[1]*, Ui Tae Kim*[1]*, Brian J. Vargo*[1]*, Patricia K. Welch*[1]*, Maryanne Covington*[1]*, Nicole C. Stowell*[1]*, Eric A. Wadman*[2]*, Paul Davies*[2]*, Kimberly A. Solomon*[1]*, Swamy Yeleswaram*[1]*,*

Danielle Graden[1], Ilona Kariv[1], Percy H Carter[2], Soo S. Ko[2], and George V. De Lucca[2]. (1) Research & Development, Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, NJ 08543, Fax: 609-252-3993, qing.shi@bms.com, (2) Bristol-Myers Squibb Company, Princeton, NJ 08543

We recently disclosed our clinical candidate DPC 168 as a potent and selective CCR3 antagonist. In order to develop back-up compounds for DPC 168, we investigated ways to improve the CYP2D6 and hERG selectivity. We explored the SAR of the urea substituent, the benzyl piperidine portion, and the cyclohexane core of the molecule. We discovered that analogs with polar substituents on cyclohexane, such as amines, amides or sulfonamides, in combination with heterocyclic ureas, exhibited improved CYP2D6 and hERG selectivity while maintaining the pharmacokinetic properties, CCR3 binding and chemotaxis potency of DPC-168. Several compounds were identified as potential back-ups.



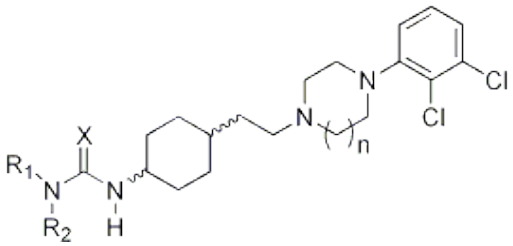
DPC-168

MEDI 383

Discovery of novel dopamine D3/D2 ligands for the treatment of schizophrenia

***György Domány**, Gedeon Richter Ltd, P.O.B. 27, Budapest H-1475, Hungary, gy.domany@richter.hu*

Our quest for new antipsychotics was based on three interrelated hypotheses: 1. dopamine D2 antagonism is required for antipsychotic activity; 2. dopamine D3 antagonism may carry favourable effects such as cognitive enhancement and lack of catalepsy; 3. simultaneous in vivo manifestation of D2 and D3 receptor antagonism requires higher affinity for D3 than D2 receptors. We started with known selective dopamine D3 antagonists and, after multiple structural modifications, a series of urea (thiourea) derivatives of general formula A were identified as high affinity ligands of both dopamine D3 and D2 receptors. In vivo studies revealed several highly potent members of this series in different antipsychotic tests with good pharmacokinetic properties. RGH-188 was selected as the best analogue for continued preclinical and then clinical development.



MEDI 384

Design and synthesis of potent and selective fluorinated dopamine D_3 receptor ligands

Zhude Tu[1]*, Shihong Li*[1]*, Michelle Taylor*[2]*, Robert R. Luedtke*[2]*, and Robert H Mach*[1]*. (1) Department of Radiology, Washington University School of Medicine, Division of Radiological Sciences, 510 S. Kingshighway Blvd., St. Louis, MO 63110, Fax: 314-362-8555, tuz@mir.wustl.edu, (2) Department of Pharmacology And Neurosicence, University of North Texas, Health Science Center, Forth Worth TX 76107*

D_3 dopamine receptor selective compounds may have therapeutic potential for the treatment of neuropsychiatic diseases, Parkinson's disease, and the abuse of psychostimulants. The lack of highly-selective D_3 receptor ligands in vivo has limited the development of PET radiotracers for imaging this receptor.

The goal of the present study was to systhesize analogues that could be labeled with fluorine-18 for imaging dopamine D_3 receptors with PET. The structure of [^{11}C]WC-10 was modified by: 1) replacing the 2-methoxyphenyl group in the piperazinyl ring with a 2-(2-fluoroethoxyphenyl group; 2) with a 2-fluoroethoxy or 2-fluoroethyl substituted the hydrogen on 2 or 4 position of aromatic ring in the aromatic group in the benzamide moiety; and, 3) using single or double bond links the amide moiety and the amino in piperazinyl ring. The results of this modification lead to the identification of a number of fluorinated compounds that displayed a high affinity for D_3 receptors (Ki: 0.52 - 5 nM) with reduced affinity for D_2 receptors (8.6 – 55 nM). The D_2:D_3 affinity ratio of these analogs ranged from 1 to 30. Function assays determined that these compounds are antagonists or partial antagonists at D_3 receptors. Several of these fluorinated compounds could provide two positions to radiolabel with F-18, which will be very useful for the metabolism studies of this class of D_3 compounds.

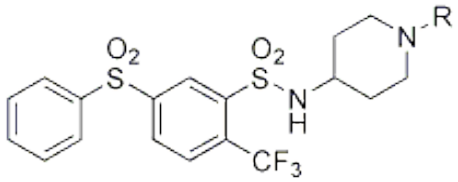
MEDI 385

Anabolic activity and pharmacokinetic profiles of secreted frizzled-related protein-1 (SFRP-1) antagonists

William J. Moore[1]*, Jeffrey C. Kern*[1]*, Thomas J. Commons*[1]*, Matthew A. Wilson*[1]*, Gregory S. Welmaker*[1]*, Eugene J. Trybulski*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, Shoichi Fukayama*[3]*, Alana L. Upthagrove*[4]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, Fax: 484-865-9398, moorew2@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (4) Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426*

Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1 is a negative regulator of the Wnt pathway and deletion of the SFRP-1 gene in mice results in osteoblast activation, proliferation and differentiation resulting in increases in trabecular bone. SFRP-1 antagonists (I) with good in vitro profiles were identified in our discovery program using FP

binding and TCF-luciferase assays. Some select molecules were evaluated in an ex vivo mouse calvaria tissue culture assay as well as pharmacokinetic experiments. The anabolic activities and PK profiles of the SFRP-1 inhibitors will be discussed.



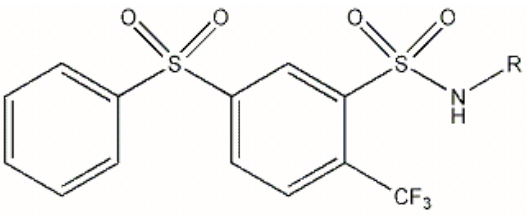
(I)

MEDI 386

Design, synthesis and biological activity of modulators of secreted frizzled related protein-1 (SFRP-1), an antagonist of the Wnt signaling pathway

Thomas J. Commons[1]*, Richard P. Woodworth*[1]*, Michael B. Webb*[1]*, William J. Moore*[1]*, Jeffrey C. Kern*[1]*, Eugene J. Trybulski*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, Shoichi Fukayama*[3]*, Alana L. Upthagrove*[4]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, commonT@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (4) Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426*

Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1 is a Wnt antagonist. In osteoblast cells antagonism of Wnt can lead to a decrease in bone formation. Consequently the goal of the program was to develop small molecule inhibitors of SFRP-1, which may be useful for the treatment of bone disorders such as osteoporosis. From the Exploratory phase of the program a diarylsulfone sulfonamide scaffold was identified. Subsequent SAR showed that replacing the hydrogen ortho to the sulfonamide with an alkyl group improved biological activity; however, this was also a major site of metabolism. Replacement of the alkyl group with the metabolically stable triflurormethyl group proved to be optimal for this position. The SAR within the sulfonamide (I), and the modifications to optimize the over all profile of the compounds prepared, will be discussed.



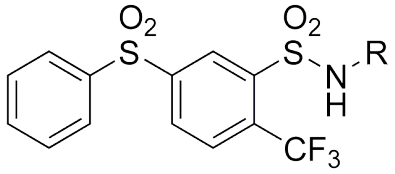
(I)

MEDI 387

Diaryl sulfone sulfonamides as secreted frizzled-related protein-1 (SFRP-1) antagonists: SAR and optimization

Jeffrey C. Kern[1]*, William J. Moore*[1]*, Thomas J. Commons*[1]*, Richard P. Woodworth*[1]*, Matthew A. Wilson*[1]*, Gregory S. Welmaker*[1]*, Eugene J. Trybulski*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, Fax: 484-865-9398, KernJ@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1 is a negative regulator of the Wnt pathway and deletion of the SFRP-1 gene in mice results in osteoblast activation, proliferation and differentiation resulting in increases in trabecular bone. Therefore, small molecule inhibitors of SFRP-1 are promising candidates for the treatment of bone related diseases such as osteoporosis. The SAR and optimization of a novel series of diaryl sulfone sulfonamides (I) as SFRP-1 inhibitors will be discussed.



(I)

MEDI 388

Biophysical methods to interrogate the interactions of secreted frizzled-related proteins with small molecule antagonists

Girija Krishnamurthy[1]*, Keith Pitts*[2]*, William J. Moore*[1]*, Matthew A. Wilson*[1]*, Gregory S. Welmaker*[1]*, Ariamala Gopalsamy*[1]*, and Peter V. N Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 401 North Middletown Road, Pearl River, NY 10965, Fax: 845-602-5687, Krishng@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA*

Secreted frizzled related protein (sFRP) is a biological receptor for Wnt, which is known to regulate important biological functions. sFRP-1, a member of this class of frizzled receptor proteins is a Wnt antagonist and is expressed in osteoclasts and osteocytes. sFRP consists of two major sequence domains including the N-terminal frizzled cysteine rich domain and heparin binding C-terminal domain. In a Discovery program aimed at developing small molecule antagonists of sFRP-1, fluorescence binding assays were developed to characterize

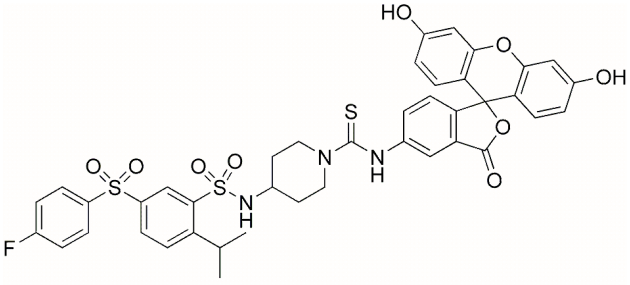
such agents. In the early phase of the program, the rank order binding potency of selected hits identified in the screen were profiled in fluorescence binding assays to confirm that the compounds interacted specifically with sFRP-1. The development of medium throughput fluorescent binding assays, evaluation of the binding stoichiometry with respect to the oligomeric state of the protein, and the utilization of photolabeling methods to characterize the antagonists will be discussed.

MEDI 389

Design and synthesis of fluorescent probes for the development of a binding assay for the identification of secreted frizzled-related protein-1 (SFRP-1) antagonists

Gregory S. Welmaker[1]*, Matthew A. Wilson*[1]*, William J. Moore*[1]*, Jeffrey C. Kern*[1]*, Eugene J. Trybulski*[1]*, Ronald L. Magolda*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, welmakg@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Studies have shown that certain Wnt proteins interact with a family of proteins named “frizzled” that can function as either direct receptors for Wnt proteins or as a component of a Wnt receptor complex. Secreted frizzled related protein-1 (SFRP-1) is expressed in osteoblasts and osteocytes and has been identified as a Wnt antagonist. SFRP-1 knockout mice demonstrate increased bone formation, possibly due to the observed decrease in osteoblast/osteocyte apoptosis. In an effort to identify modulators of SFRP-1, several probe compounds were prepared for the development of a competitive binding assay. The design and synthesis of these probes will be presented, ultimately leading to the identification of compound 1.



1

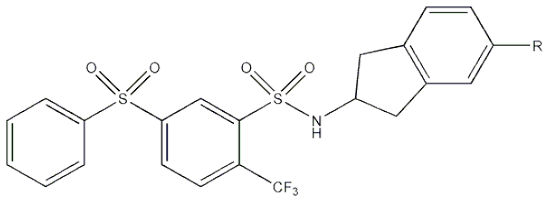
MEDI 390

Design, synthesis and biological activity of indane derivatives as modulators of secreted frizzled related protein-1 (SFRP-1), an antagonist of the Wnt signaling pathway

Richard P. Woodworth[1]*, Thomas J. Commons*[1]*, William J. Moore*[1]*, Jeffrey C. Kern*[1]*, Eugene J. Trybulski*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, Shoichi Fukayama*[3]*, Alana L. Upthagrove*[4]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's*

Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (4) Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426

Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1 is a Wnt antagonist. In osteoblast cells antagonism of Wnt can lead to decreased bone formation. The goal of the program was to develop small molecule inhibitors of SFRP-1, which may be useful for treating bone disorders such as osteoporosis. The program's exploratory phase identified a diarylsulfone sulfonamide scaffold. Subsequent SAR led to indane sulfonamide (I) as having potent binding to SFRP-1 (IC50 = 80 nM); however, it had both poor aqueous solubility and metabolic stability. Modifications of (I) led to (II) which had good binding (IC50 = 20 nM), functional activity (EC50 = 85 nM) as well as good aqueous solubility and metabolic stability. The synthesis of selected targets, the SAR leading to (II) as well as its full pharmaceutical profile will be discussed.



(I) R = H (II) R = -OCH_2CO_2H

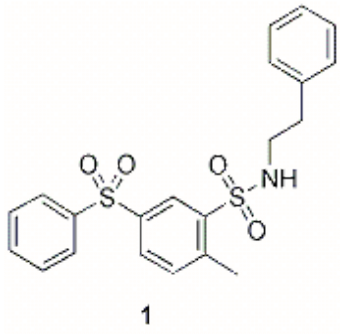
MEDI 391

Identification of diarylsulfone sulfonamides as secreted frizzled related protein-1 (SFRP-1) antagonist

Ariamala Gopalsamy[1]*, Mengxiao Shi*[1]*, Barbara Stauffer*[2]*, Ramesh Bhat*[2]*, Julia Billiard*[2]*, Helga Ponce-de-Leon*[2]*, Laura Seestaller-Wehr*[2]*, Shoichi Fukayama*[2]*, Annamarie Mangine*[2]*, Robert Moran*[2]*, Girija Krishnamurthy*[1]*, and Peter VN. Bodine*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

SFRPs are secreted receptors for Wnts that are important polypeptide growth factors known to regulate fundamental biological processes like tissue polarity, embryonic development and tumorigenesis. A SFRP was isolated in human osteoblast cells and identified as SFRP-1 (also known as SARP-2) and was regulated by osteogenic agents in the HOB cells in a differentiation selective manner modulating the life of osteoblasts and osteocytes. Hence, inhibition of SFRP-1 should increase the trabecular bone formation rendering itself as a novel osteogenic drug target for osteoporosis. High throughput screen was carried out using transfected U2-OS cells in SFRP-1-TCF-Luciferase Assay. The hits identified were further triaged based on their biochemical profile in the selectivity assays with different SFRPs and

Wnts, binding assay and cell death assay. Expansion of one of the hits diarylsulfone sulfonamide 1 to a viable selective lead series with reliable SAR with acceptable physical properties and ex-vivo activity will be discussed.



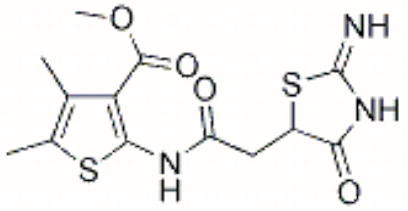
1

MEDI 392

Iminooxothiazolidines as secreted frizzled related protein-1 (SFRP-1) antagonists

Ariamala Gopalsamy[1]*, Mengxiao Shi*[1]*, Barbara Stauffer*[2]*, Ramesh Bhat*[2]*, Julia Billiard*[2]*, Helga Ponce-de-Leon*[2]*, Laura Seestaller-Wehr*[2]*, Shoichi Fukayama*[2]*, Annamarie Mangine*[2]*, Robert Moran*[2]*, Girija Krishnamurthy*[1]*, and Peter VN. Bodine*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

SFRPs are secreted receptors for Wnts that are important polypeptide growth factors that are known to regulate fundamental biological processes. Of the SFRPs, SFRP-1 isolated from human osteoblast cells has the potential to be a novel osteogenic drug target for osteoporosis. From high throughput screen we have identified a class of iminooxothiazolidines as secreted frizzled related protein-1 (SFRP-1) antagonists. The biochemical characteristics of this class along with the inferred SAR, selectivity, binding and ex-vivo activity will be discussed.

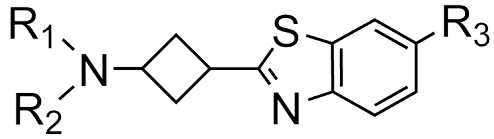


MEDI 393

Design, synthesis and SAR of potent substituted benzothiazole-cyclobutane histamine H3 receptor antagonists

Chen Zhao*, Minghua Sun, Thomas R. Miller, Timothy A. Esbenshade, Jill M. Wetter, Kennan C. Marsh, Jorge D. Brioni, and Marlon D. Cowart, Neuroscience Research, R4MN, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, chen.zhao@abbott.com*

The histamine H3 receptor is located mainly in the CNS on neurons, and is known to be both an autoreceptor that regulates the release and synthesis of histamine, and a heteroreceptor that regulates the release of other neurotransmitters, including acetylcholine, norepinephrine, dopamine and serotonin. H3 receptor antagonists have been shown to increase the levels of these neurotransmitters and have the potential as therapeutic agents for disorders such as attention deficit hyperactivity disorder, cognition, schizophrenia and Alzheimer's disease. A new series of benzothiazole-cyclobutane based H3 antagonists (1) was designed and evaluated. Many compounds in this series are more potent in vitro than most previously reported 5-arylbenzofurans (e.g. ABT-239) and other bicyclic heterocycles, yet the compounds retain the high druglikeness of the earlier series. The synthesis and preliminary in vitro SAR, along with their favorable pharmacokinetic properties of select analogs will be described.



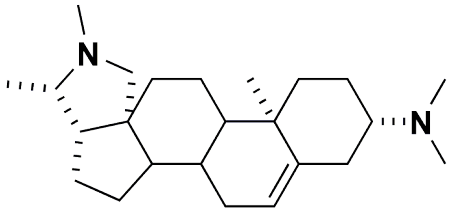
(**1**)

MEDI 394

Design and synthesis of novel, potent and selective H3 antagonists based on the natural product conessine

Jonathan A. Covel[1], *Rena Hayashi*[1], *Brian Hofilena*[1], *Jason Ibarra*[1], *Michelle Pulley*[1], *Michael Weinhouse*[1], *Dipanjan Sengupta*[1], *Jonathan Duffield*[1], *Vincent J. Santora*[1], *Graeme Semple*[1], *Robert R. Webb*[1], *Marissa Suarez*[2], *John Frazer*[2], *William Thompson*[2], *Jeffrey Edwards*[2], *Erin Hauser*[2], *Kevin Whelan*[2], *and Andrew Grottick*[2]*. (1) Medicinal Chemistry, Arena Pharmaceuticals, 6166 Nancy Ridge Dr, San Diego, CA 92121, jcovel@arenapharm.com, (2) Arena Pharmaceuticals, San Diego, CA 92121*

The H3 receptor is one of four distinct G-protein coupled histamine receptors. Histamine acts on hetero- and pre-synaptically located H3 receptors to regulate the synthesis and release of both histamine and other neurotransmitters in the central nervous system (CNS). It has been proposed that H3 antagonists may be useful in the treatment of disorders relating to feeding, wakefulness and cognition. The steroidal alkaloid natural product Conessine proved to be a potent non-imidazole H3 antagonist. We hypothesized that the relative positioning of the two amine functionalities of Conessine were key to its biological activity. Several core structures were evaluated on the basis of molecular modeling, novelty, and other characteristics. Herein we report initial investigations of a new class of H3 antagonist diamines discovered through this program.



Conessine

MEDI 395

Synthesis and biological evaluation of novel and potent H3 antagonists with improved pharmacokinetic profiles

Rena Hayashi[1], *Jonathan A. Covel*[1], *Brian Hofilena*[1], *Jason Ibarra*[1], *Michelle Pulley*[1], *Michael Weinhouse*[1], *Dipanjan Sengupta*[1], *Jonathan Duffield*[1], *Vincent J. Santora*[1], *Graeme Semple*[1], *Robert R. Webb*[1], *Albert Ren*[1], *Guilherme Pereire*[1], *Marissa Suarez*[2], *John Frazer*[2], *William Thompson*[2], *Jeffrey Edwards*[2], *Erin Hauser*[2], *Kevin Whelan*[2], *and Andrew Grottick*[2]*. (1) Medicinal Chemistry, Arena Pharmaceuticals, 6166 Nancy Ridge Dr, San Diego, CA 92121, rhayashi@arenapharm.com, (2) Arena Pharmaceuticals, San Diego, CA 92121*

H3 receptor antagonists have attracted considerable interest recently owing to their potential utility as treatments for several central nervous system (CNS) disorders including obesity, cognitive dysfunction, and excessive daytime sleepiness. We recently discovered a novel

family of diamine containing H3 antagonists, similar to the natural product Conessine, which display excellent potency and selectivity for the H3 receptor.

In order to further explore this series, the incorporation of terminal amides, sulfonamides or N-aryl groups as well as alteration of the polycyclic scaffold was investigated. Several of these analogs exhibit improved pharmacokinetic (PK) profiles compared to the original diamine compounds and display activity in histamine related in-vivo experiments. The binding, selectivity, and PK properties of these compounds will be presented.

MEDI 396

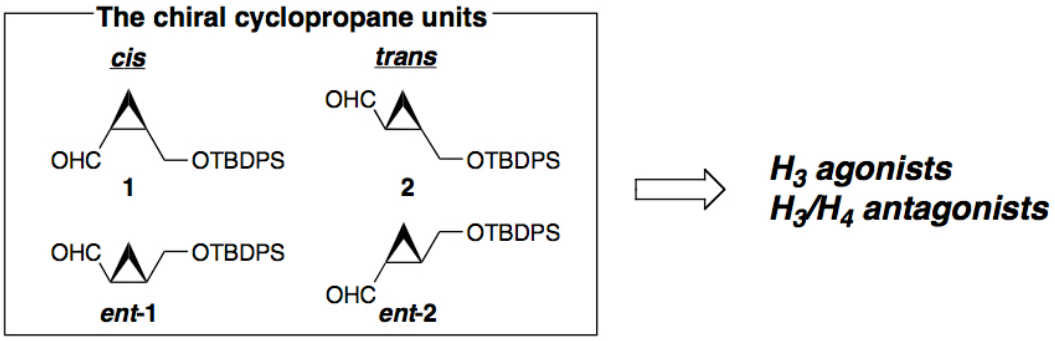
WITHDRAWN

MEDI 397

Development of potent histamine H_3/H_4 receptor ligands by the stereochemical diversity-oriented chiral cyclopropane-based conformational restriction strategy

Mizuki Watanabe, *Yuji Kazuta, Mitsuhiro Arisawa, Akira Matsuda, and Satoshi Shuto, Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo, Japan, shu@pharm.hokudai.ac.jp*

The stereochemical diversity-oriented chiral cyclopropane-based conformational restriction strategy can be an efficient method for developing specific ligands for drug target proteins. To develop potent H_3 and/or H_4 receptor ligands, a series of conformationally restricted analogues of histamine with a chiral *cis*- or *trans*- cyclopropane structure was designed on the basis of this strategy. Target compounds with stereochemical diversity were synthesized from the four chiral cyclopropane units, (1*S*,2*R*)- and (1*R*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (**1** and **2**, respectively) or their enantiomers ***ent*-1** and ***ent*-2**. Pharmacological profiles of these conformationally restricted analogues were shown to be different depending on the structure of the cyclopropane backbones, and highly selective H_3 receptor agonists and potent H_3 and/or H_4 receptor antagonists were successfully identified. These results show that when the structure of the target protein is unknown, the stereochemical diversity-oriented approach can be a powerful strategy in medicinal chemical studies.



MEDI 398

Histamine H_3 antagonists with serotonin reuptake transporter inhibitor activity

Kiev S. Ly[1]*, Michael A. Letavic*[1]*, Leslie A. Gomez*[1]*, Jill A. Jablonowski*[1]*, John M. Keith*[2]*, Jennifer M. Miller*[1]*, Emily M. Stocking*[1]*, Ronald L. Wolin*[2]*, Ann J. Barbier*[2]*, Jamin D. Boggs*[1]*, Pascal Bonaventure*[1]*, Brian Lord*[1]*, Kirsten L. Miller*[1]*, Sandy J. Wilson*[1]*, Timothy W. Lovenberg*[1]*, and Nicholas I. Carruthers*[1]*. (1) Neuroscience, Johnson & Johnson Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, Fax: 858-450-2089, kly@prdus.jnj.com, (2) Johnson & Johnson Pharmaceutical Research & Development, LLC, San Diego, CA 92121*

Depression is a major health issue, which affects over 300 million people worldwide. Many patients who suffer from depressive disorders are also diagnosed with cognitive impairment and/or fatigue. Depression is often treated with one of the currently marketed selective serotonin reuptake inhibitors (SSRIs), however these agents often fail to improve the cognitive impairment and fatigue observed with many patients even as mood improves. Numerous preclinical studies have shown that histamine H_3 antagonists have pro-cognitive effects and increase wakefulness without inducing nonspecific stimulant effects. This information led us to investigate the utility of histamine H_3 antagonists with serotonin reuptake transporter (Sert) inhibitor activity. Towards this end, we have discovered several series of potent histamine H_3 antagonists that are also serotonin reuptake inhibitors. Select compounds readily penetrate the CNS and several members of these series have potent in vivo activity. The medicinal chemistry, in vitro data, and in vivo pharmacology of these dual acting compounds will be presented.

MEDI 399

Synthesis of DAG-lactones containing heterocyclic moieties: Small focused libraries in search of C1-specific domain interactions

Saïd El Kazzouli[1]*, Nancy E. Lewin*[2]*, Peter M. Blumberg*[2]*, and Vicror E. Marquez*[1]*. (1) Laboratory of Medicinal Chemistry, National Institutes of Healt, Center for Cancer Research, National Cancer Institute-Frederick, Frederick, MD 21702, Fax: 301-846-6033, elkazzoulis@ncifcrf.gov, (2) Laboratory of Cancer Biology and Genetics, National Institutes of Health, Bethesda, MD 20892*

Although DAG binding to specific C1 domains of protein kinase C was regarded as unique to this family of isozymes, the discovery of homologous (PKC-like) C1 domains in other proteins has opened the possibility of directing DAG binding to other C1 domains as primary targets. Our research group has developed a series of diacylglycerol lactones (DAG-lactones) with Ki values for binding to PKC approaching those of phorbol esters, and our success in developing a specific DAG-lactone that selectively translocates RasGRP over PKC provides proof of principle for this concept. Herein, we described the syntheses of small, focused DAG-lactone libraries containing heterocyclic moieties (pyridines, quinolines and indoles) attached to the lactone at different positions on the heterocyclic ring, which were designed to explore

additional interactions between the ligand and the surrounding area of the C1 domain, including ligand-lipid and ligand-protein interactions.

MEDI 400

Discovery of new generation of photodynamic therapeutics by an efficient combinatorial synthesis using porphyrin platform

***Mikki Vinodu**, Diana Samaroo, Xin Chen, and Charles Michael Drain, Department of Chemistry, Hunter College of CUNY, 695 Park Avenue, New York, NY 10021, mvinodu@hunter.cuny.edu*

5,10,15,20-tetrakis-(2,3,4,5,6-pentafluorophenyl)-porphyrin (TPPF20) was used as a core platform to efficiently generate a variety of solution phase combinatorial libraries containing 21, 55, and 666 members. These porphyrin libraries have variety of substituents that includes carbohydrate, polar pyridyl, and alkane moieties. The choice of the substituents is made based up on the fact that sugar appended porphyrins are shown to be effective photodynamic agents in the induction of necrosis or apoptosis in several cancer cell lines. The pyridyl and alkyl chains are expected to provide appropriate amphiphathic characteristics to the porphyrin systems. These solution phase libraries are screened for binding to the MDA-MB-231 breast cancer cells by incubating the cells, washing away the unbound materials, and identifying the absorbed porphyrins in cell extracts by MALDI mass spectrometry. Porphyrin systems containing both thioglucose and pyridyl functions are effectively taken up by the cancer cells indicating that both glycosylation and amphipathicity are key properties in these selections. The compounds selected by the cancer cells were resynthesized directly. Fluorescence microscopy based cell binding assays of these winning compounds were made and were compared to the tetra (thioglucose) porphyrin derivative (TPPF16-Glu4) standard and confirm the selection criteria.

MEDI 401

Analysis of sample purity and integrity data using structural fragments: Patterns in the stability of compounds stored as solutions

***Lynne P. Greenblatt**, Dominick Mobilio, and Ramaswamy Nilakantan, Chemical and Screening Sciences, Wyeth Research, CN-8000, Princeton, NJ 08543, Fax: 732-274-4850, greenbl1@wyeth.com*

Fragment analysis was done on all compounds stored as solutions, and for which purity and integrity data were available. Certain structural fragments were found to be prevalent in compounds that degraded in solution over time. A description of the methods used in the fragment analysis, and the results, will be presented.

MEDI 402

New alkyl and aryl analogs of amodiaquine: Design, synthesis and antimalarial activity

*Emilia Paunescu[1], Sophie Susplugas[2], Emmanuelle Boll[1], Richard A. Varga[3], Elisabeth Mouray[2], Ion Grosu[4], Philippe Grellier[2], and **Patricia Melnyk**[1]. (1) Team 3, UMR8161 CNRS, Lille1 University, Lille2 University, Pasteur Institute of Lille, 1, Rue du Pr Calmette, BP447, 59021 Lille, France, Fax: 33 3 20 87 12 33, emiliapaunescu@yahoo.com, patricia.melnyk@ibl.fr, (2) Département "Régulations, Développement, Diversité Chimique", Muséum National d'Histoire Naturelle, 75005 Paris, France, (3) National Centre for X-Ray Diffractometry, "Babes-Bolyai" University, Faculty of Chemistry, 400028 Cluj-Napoca, Romania, (4) Organic Chemistry Department, "Babes-Bolyai" University Cluj-Napoca, Faculty of Chemistry, 400028 - Cluj-Napoca, Romania*

The use of chloroquine (CQ) for malaria treatment decrease in importance because of the development of CQ-resistant strains of Plasmodium falciparum. CQ and others 4-aminoquinolein drugs mode of action is based on their accumulation in the food vacuole and inhibition of heme degradation. Clinical use of amodiaquine (AQ), active against CQ-resistant strains, has been restricted for prophylactic use because of observed side effects reported in some cases. The observed drug toxicity is believed to be related to the formation of a quinone-imine oxidation metabolite. In order to block the 4' position and avoid the possible oxidation in vivo, to optimise the activity against CQ-resistant strains, a series of 4'-substituted new derivatives of 4'-deOHAQ have been designed. The products were synthesized using aryl-aryl and aryl-alkyl Suzuki coupling reactions. Antimalarial activities against CQ-resistant strains, inhibition of b-hematin polymerisation and cytotoxicity measurements on MRC-5 cell lines will be presented.

MEDI 403

Prion diseases and malaria: Similar SAR of an active Quinoline family

*Ralf Klingenstein[1], **Patricia Melnyk**[2], S. Rutger Leliveld[1], Adina Ryckebusch[3], and Carsten Korth[1]. (1) Institute for Neuropathology, Heinrich Heine University Duesseldorf, Moorenstrasse 5, 40225 Duesseldorf, Germany, ralf.klingenstein@uni-duesseldorf.de, (2) Team 3, UMR8161 CNRS, Lille1 University, Lille2 University, Pasteur Institute of Lille, 1, Rue du Pr Calmette, BP447, 59021 Lille, France, Fax: 33 3 20 87 12 33, patricia.melnyk@ibl.fr, (3) UMR8525 CNRS, Lille2 University, 59021 Lille, France*

Prion diseases are invariably fatal neurodegenerative diseases, in which the infectious agent consists of PrPSc, a pathogenic misfolded isoform of the normal cellular prion protein (PrPC). Until now, no pharmacological options exist for these novel pathogens. We will describe the screening of a series of polyquinolines and quinolines linked to a large variety of terminal groups for their ability to cure a persistently prion infected cell line (ScN2a). Several compounds showed antiprion activity in the nanomolar range. The most active molecule had a half-effective concentration (EC50) of antiprion activity of 50 nM. In a library of quinoline derivatives we were able to identify several structure-activity relationships (SAR). Remarkably, antiprion SAR in ScN2a cells were similar to antimalarial SAR in a cell model of malaria,

particularly for the sulphonamide quinoline derivatives, suggesting that some molecular targets of antiprion and antimalarial substances overlap.

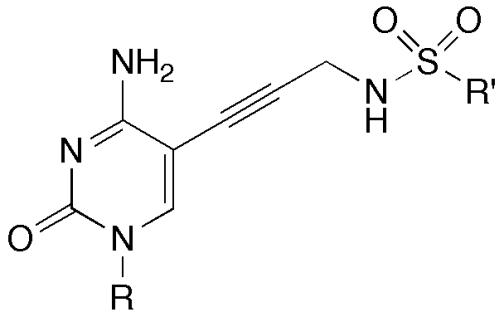
MEDI 404

Non-phosphate inhibitors of IspE, a kinase in the non-mevalonate pathway for isoprenoid biosynthesis and a potential target for antimalarial therapy

Anna K. H. Hirsch[1]*, Susan Lauw*[2]*, Philipp Gersbach*[1]*, W. Bernd Schweizer*[1]*, Felix Rohdich*[2]*, Wolfgang Eisenreich*[2]*, Adelbert Bacher*[2]*, and François Diederich*[1]*. (1) Department of Chemistry and Applied Biosciences, ETH Zurich, Laboratory of Organic Chemistry, Wolfgang-Pauli-Strasse 10, CH-8093 Zurich NA, Switzerland, Fax: 0041-44-6321109, hirsch@org.chem.ethz.ch, (2) Technische Universität München*

Malaria remains the most important and devastating tropical disease known with 300-500 million clinical cases and around one million deaths a year. Because of the emergence of drug and insecticide resistance the need for medicines with a novel mode of action has become increasingly important. *Plasmodium* parasites, the causative agents of malaria, use the non-mevalonate pathway for the biosynthesis of the common isoprenoid precursors, which is distinct from that used by humans. Hence, the enzymes of this pathway are ideal targets in the fight against this important infectious disease.[1] The kinase IspE, at the center of the non-mevalonate pathway, was chosen as the target of a structure-based drug design project leading to potent competitive inhibitors with K_i values in the nanomolar range.[2] The syntheses and biological activities of these compounds will be presented.

(1) Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Türbachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. Science **1999**, *285*, 1573. (2) Hirsch, A. K. H.; Lauw, S.; Gersbach, P.; Schweizer, W. B.; Rohdich, F.; Eisenreich, W.; Bacher, A.; Diederich, F. ChemMedChem **2007**, asap.



MEDI 405

Synthesis and biological activity of novel and potent C7 sancycline derivatives against Plasmodium falciparum

Beena Bhatia[1]*, Haregewein Assefa*[1]*, Laura Honeyman*[1]*, Atul Verma*[1]*, Michael Draper*[1]*, Phillip Rosenthal*[2]*, Jiri Gut*[2]*, Lynn Garrity-Ryan*[1]*, and Mark L. Nelson*[1]*. (1) Paratek Pharmaceuticals,*

Inc, 75 Kneeland Street, Boston, MA 02111, bbhatia@paratekpharm.com, (2) San Francisco Division of Infectious Diseases, University of California, San Francisco, CA 94143

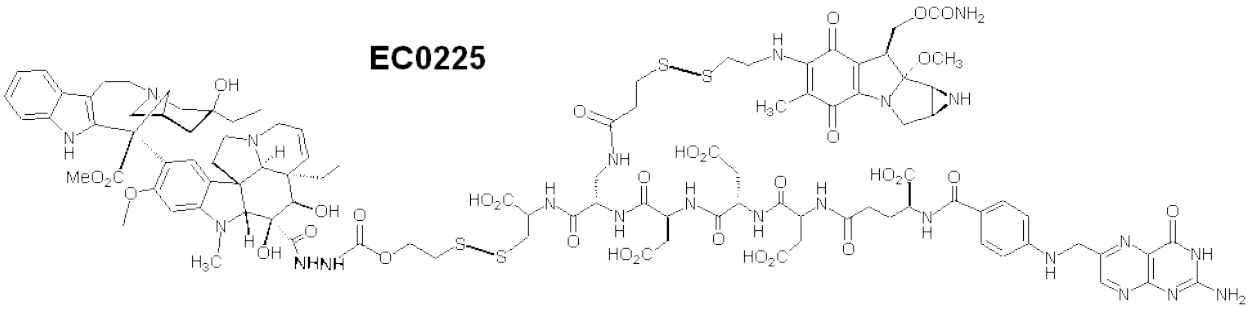
Current antimalarial drugs are limited by resistance due to some strains of malaria parasites, high cost, insufficient biological activity, and/or problems with toxicity. Doxycycline, a member of the tetracycline (TC) family of antibacterial therapeutics, is currently used clinically for both the treatment and prophylaxis of P. falciparum and P. vivax malaria. In order to discover new TCs with improved activity against malaria parasites, we screened our collection of novel TC derivatives in vitro to assess their antimalarial activity against P. falciparum, and examined them for their inherent cytotoxicity, phototoxicity, and antibacterial activity profiles, with the goal of deriving a potent, non-antibiotic antimalarial agent. Four different classes of C7-sancycline TC derivatives were found to be active against P. falciparum, suggesting a minimum pharmacophore required for enhanced antimalarial activity. The most potent compounds also were non-cytotoxic and non-phototoxic on a scale related to doxycycline, and possessed differing antibacterial profiles, depending upon the series. Herein, the synthesis and mechanisms of action related to in vitro activity against P. falciparum and mammalian cell safety indices will be presented, describing their potential as future antimalarial agents.

MEDI 406

Releasable dual-drug conjugates of folic acid (EC0225): An assembly concept for the consecutive introduction of unsymmetrical disulfide bonds

*Iontcho R. Vlahov[1], **Hari Krishna R. Santhapuram**[1], Yu Wang[1], Paul J. Kleindl[1], Fei You[1], Stephen J. Howard[1], Elaine Westrick[2], Joseph A. Reddy[2], and Christopher P. Leamon[2]. (1) Department of Discovery Chemistry, Endocyte Inc, 3000 Kent Ave., A1-100, West Lafayette, IN 47906, IN, Fax: 765-463-9271, hkrishna@endocyte.com, (2) Department of Discovery Biology, Endocyte Inc, West Lafayette, IN 47906, IN*

We describe the first synthesis of a dual-drug conjugate (EC0225) possessing two different biologically active agents attached to a folate receptor targeting ligand via two disulfide-based release systems. Our methodology allows for the introduction of a second disulfide bond into a molecular framework with a pre-existing disulfide system. EC0225 displayed potent anti-tumor activity.



MEDI 407

Chalcogen-containing cationic dyes for photosensitized cleavage of DNA with therapeutic applications

Michael K. Gannon II*, Jason J. Holt, Mao Ye, David J Donnelly, Tymish Y Ohulchanshyy, Bryan R Wetzel, and Michael R. Detty, Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, NY 14260*

We have designed and synthesized chalcogen-containing cationic dyes that have been found to promote DNA strand scission upon photosensitization with light of an appropriate wavelength. When bound to DNA we observed that the dyes absorb at wavelengths >600 nm and have greater quantum yields for singlet oxygen than free dye in solution. The dyes were unequivocally found to cause photodynamic damage to plasmid DNA through the indirect pathway of oxidation by singlet oxygen. Photochemical experiments with plasmid DNA and the dyes suggest that the genomic material contained in viral and bacterial pathogens are one possible target for photodynamic action. One useful therapeutic application for chalcogen-containing cationic dyes is the photodynamic reduction of blood-borne viral and bacterial pathogens for a risk-free blood supply.

MEDI 408

Gas-phase ion chemistry and tandem mass spectrometry for determination of alpha1 anti-trypsin inhibitor oxidation sites

Harsha P. Gunawardena*, Analytical Research, Talecris Biotherapeutics Inc, 1017 Main Campus Drive, Suite 1200, Raleigh, NC 27606, Fax: 919-508-9199, harsha.gunawardena@talecris.com*

Protein oxidation can impact the activity and efficacy when used as therapeutic drugs. Typically, methionine and tyrosine residues of a protein are susceptible to oxidation. However, only a few of these residues compose the catalytic site of a protein. For example, alpha-1-antitrypsin inhibitor (alpha-1) used in this study, consists of 7 methionine (met) and 1 tyrosine residues, of which, oxidation at met-351 and met-358 are the only known sites that decrease bioactivity. Most often, stability indicating methods lack the ability to discern such modifications at the molecular level. In the present study, alpha-1 oxidation is characterized by mass spectrometry and gas-phase ion chemistry methods involving electrons, protons, and collisions. Modification sites are examined in support of various oxidative forced degradation experiments. The complimentary nature of such methods, are utilized to localize the sites of alpha1 oxidation. This approach shows promise as an alternative stability indicating assay for alpha-1 oxidation.

MEDI 409

Discovery and optimization of a small molecule series that induces a novel isotropic growth phenotype in C. Albicans

Scott Collibee[1]*, Thomas Lila*[2]*, Bradley Morgan*[1]*, Penelope Chua*[3]*, Matthew Hamilton*[1]*, Takashi Nakai*[1]*, Daniel Pierce*[2]*, David J. Morgans Jr.*[4]*, Charles Vacin*[2]*, and David Clarke*[5]*. (1) Department of Medicinal Chemistry, Cytokinetics, Inc, 280 East Grand Ave, South San Francisco, CA 94080, (2) Assay Development, Cytokinetics, Inc, South San Francisco, CA 94080, (3) Department of Cancer Biology and Therepeutics, Cytokinetics, Inc, South San Francisco, CA 94080, (4) Cytokinetics, Inc, South San Francisco, CA 94080, (5) Cell Technologies, Cytokinetics, Inc, South San Francisco, CA 94080*

Yeast cells can respond to perturbation of the cell cycle or cytoskeleton with distinctive changes in extracellular and nuclear morphologies. An automated fluorescence-microscopic screen of 6800 known C. albicans pump mutant growth inhibitors was performed to identify small molecules that alter the morphology of Candida albicans. Compounds that caused diverse morphological phenotypes were identified, including one that induced an isotropic growth phenotype similar to that observed for a C. albicans cdc42 mutation strain. Optimization revealed members with broad activity against pathogenic yeast species (C. albicans, C. glabrata, and C. tropicalis) and low human cell toxicity.

MEDI 410

Examination of the blood compatibility of heparinized carbon nanotubes

Tae-Joon Park*, Departments of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Biotech Center 4005,110 8th Street, Troy, NY 12180, parkt@rpi.edu, Saravanababu Murugesan, Bristol-Myers Squibb Company, New Brunswick, NJ, Shaker Mousa, Pharmaceutical Research Instituted, Albany College of Pharmacy, Albany, NY 12208, Jawed Fareed, Departments of Pathology and Pharmacology, Loyola University Medical Center, and Robert J. Linhardt, Department of Chemistry, Chemical & Biological Engineering, Biology, Rensselaer Polytechnic Institute, Troy, NY*

The design of blood-compatible devices through the immobilization of the glycosaminoglycan (GAG) heparin, an anticoagulant has been pursued as an enabling “therapeutic delivery technology”. Blood compatibility is a vital property for biomedical devices and/or the applications of biomaterials due to the limitation in blood-contacting environments such as the problems of red blood cell disruption, platelet adhesion and activation, clot formation aggregation and thrombosis. We have herein characterized heparinized MWNTs using APTT to measure anticoagulant activity, carbazole assay to measure heparin concentration and octanol-water partition to determine the lipophilicity. Heparin, when immobilized to a nanomaterial through end-point attachment, should be more exposed, improving the protein ligand interaction of the nanomaterial and resulting in enhanced bioactivity. This covalent chemistry should be more stable, show higher accessibility and selectivity during binding to its protein ligand. In vivo half life experiments will be undertaken on end-point attached heparinized MWNTs.

MEDI 411

Effect of three volatile oils on percutaneous absorption of aconitine

*Li Yanjie[1], **Ma Yunshu**[2], and Bai Yicen[1]. (1) College of Chinese Traditional Medicine, Yunnan University of Traditional Chinese Medicine, Kunming 650220, China, Fax: +86 871 7154594, yanjieli@163.com, (2) College of Chinese Traditional Medicine, Yunnan University of Traditional Chinese Medicine, Kunming 650200, China, Fax: +86 871 7154594, ma.yunshu@yahoo.com.cn*

Purpose. The aim of this work was to study the effect of volatile oils from Fructus Litseae ,Rhizama Zingiberis and Rhizma Acori Tatarinowii on the percutaneous penetration of aconitine through rat skin. Methods. The physicochemical properties of prepared salts were investigated by using Franz diffusion cells and high performance liquid chromatography(HPLC). Their percutaneous absorption characteristics across hairless mouse skin and compared with Azone. the effect of various enhancers were studied using a flow-through diffusion cell system. Results. The three volatile oils enhanced remarkably the skin penetration of aconitine. It was shown that the penetration rate is strongly at the concentration of 7%v/v (the best concentration). However, the enhancement ratio of aconitine is dependent upon the enhancer type. Their enhancement ratio were 3.9,2.1,1.9,respectively. Conclusion. The Volatile oils of Fructus Litseae ,Rhizama Zingiberis and Rhizma Acori Tatarimowii improved the physicochemical properties and enhanced the skin permeability of aconitine..

Keywords: volatile oils; aconitine; Fructus Litseae; Penetration enhancers; percutaneous absorption

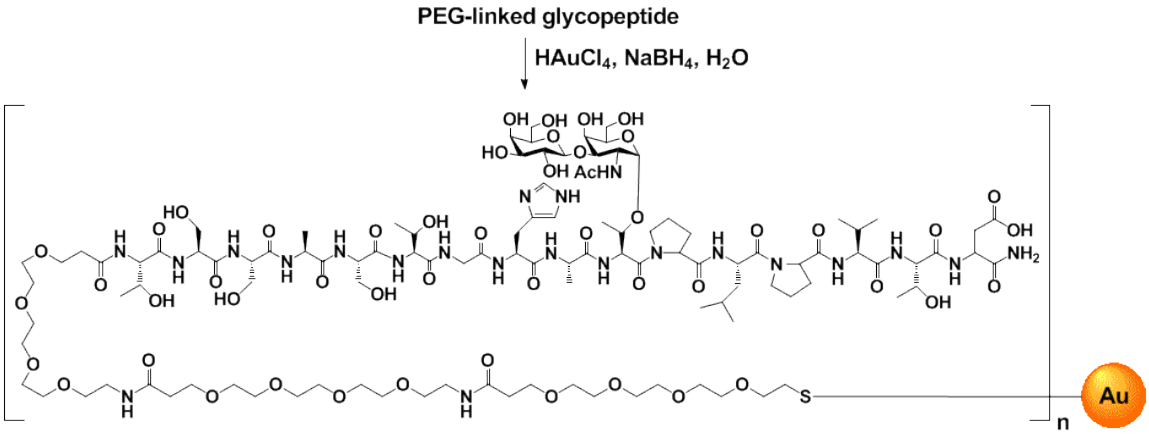
MEDI 412

Synthesis of gold nanoparticles bearing tumor antigens as novel anticancer therapeutics

***Andreas Sundgren**, Laboratory of Medicinal Chemistry, National Cancer Institute, 376 Boyles ST, Frederick, MD 21702, sundgrena@ncifcrf.gov*

It is well established that cell surface carbohydrates play unique roles in a host of biologically relevant events. The glycan structures on the surface of tumor cells are altered relative to those of a normal phenotype, and this altered expression creates “non-self” structures that can be recognized by the immune system and also contribute to tumor aggressiveness and metastasis. These modifications are evident in heavily O-glycoslylated cell surface mucins such as MUC4 which is highly expressed on pancreatic adenocarcinomas. In an effort to synthesize novel antitumor therapeutics, we have prepared gold nanoparticles that display multiple copies of PEG-linked carbohydrates and glycopeptides corresponding to a MUC4 peptide repeating unit on their surface. The density of these ligands has also been altered by

self assembly utilizing various passivating agents along with the mucin carbohydrates/glycopeptides. These particles will be used for the study of carbohydrate-mediated cellular events and for evaluation of their use as vaccines against various types of solid tumors.



MEDI 413

Targeted drug-delivery of an antibiotic bound to nanosized hydroxyapatite bone particles for treatment of bone injury

Royce R Runner[1], *Brian A Shapiro*[1], *James C McPherson III*[2], *and Thomas B Buxton*[1]. *(1) Department of Clinical Investigation, The Geneva Foundation, Building 38705, Fort Gordon, GA 30905, Fax: 706-787-2730, royce.runner@amedd.army.mil, (2) Department of Clinical Investigation, Eisenhower Army Medical Center, Fort Gordon, GA 30905*

We evaluated the ability of nanometer-sized NanOss™ vs micron-sized Skelite™ to carry, then release a “bone-seeking” antibiotic, a bisphosphonate-ciprofloxacin (E41) conjugate. E41 binding to NanOss™ was saturable (Bmax ca. 80%) and similar in avidity to Skelite™. Binding affinity of E41 to NanOss™ was about 8 fold higher than Skelite™ (Kd of 4.18 × 10-8 M, vs 4.67 × 10-7 M, respectively), a difference not explainable due to surface area differences. Acid elution of E41 from the compounds is important due to the low pH and high lactate of wounds. Lactic acid elution of E41 from NanOss™ was about twice as much as from Skelite™ (0.5 µg/mg vs 0.3 µg/mg, respectively, $p<0.01$). Quantitative microbiology showed E41-NanOss was more effective in killing Pseudomonas aeruginosa vs E41-Skelite ($p<0.002$). NanOss™ particles appear superior to Skelite™ as a local drug-delivery vehicle for bisphosphonate-containing antibiotics.

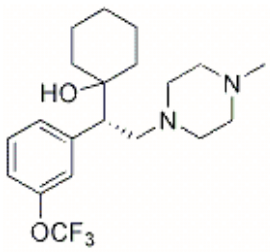
MEDI 414

Design and synthesis of heterocyclic cycloalkanol ethylamines as norepinephrine reuptake inhibitors

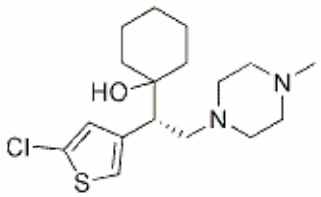
Joseph P. Sabatucci[1], *Paige E. Mahaney*[1], *Eugene J. Trybulski*[1], *Jenifer Leiter*[2], *Grace Johnston*[2], *Yingru Zhang*[3], *Darlene C. Deecher*[2], *and Oliver McConnell*[3]. *(1) Medicinal*

Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, sabatuj@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (3) Discovery Analytical Chemistry, Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426

The cycloalkanol ethylamine scaffold has been successfully utilized in the discovery and development of dual norepinephrine/serotonin reuptake inhibitors (SNRIs). Drugs possessing SNRI activity have been approved for major depressive disorder (MDD), and are in clinical development for the treatment of vasomotor symptoms (VMS) associated with menopause. A program to further expand the chemistry SAR by designing selective norepinephrine reuptake inhibitors (NRI) was evaluated. Efforts to discover novel selective NRIs using the cycloalkanol ethylamine scaffold resulted in the identification of WAY-256805 (1), a highly potent and selective NRI. Results from this series of compounds provided us with new insight to explore the scope and limitations of compounds selective for the norepinephrine transporter (NET). As part of our ongoing goal we have extended the SAR of this template to include a number of heterocyclic analogues e.g. (2). Design, synthesis and biological activity of this series will be presented.



1



2

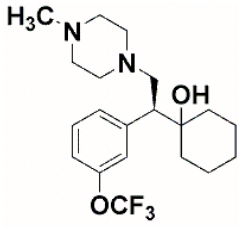
MEDI 415

SAR of the cycloalkanol ethylamine scaffold: 4-aminopiperidine reuptake inhibitors

Paige E. Mahaney[1]*, Lori K. Gavrin*[1]*, Fei Ye*[1]*, Eugene J. Trybulski*[1]*, Jenifer A. Bray*[2]*, Grace H. Johnston*[2]*, Jenifer Leiter*[2]*, Elizabeth Koury*[2]*, and Darlene C. Deecher*[2]*. (1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, mahanep@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Drugs that selectively inhibit norepinephrine reuptake, including reboxetine, nisoxetine and atomoxetine are marketed for the treatment of major depressive disorder and attention deficit hyperactivity disorder. In addition, these compounds have been reported to show efficacy for chronic pain disorders such as fibromyalgia and low back pain. In an effort to identify novel and selective norepinephrine reuptake inhibitors, we reinvestigated the structure-activity relationship (SAR) of the cycloalkanol ethylamine scaffold, of which venlafaxine is a member. These efforts led to the identification of a 2-(4-methylpiperzine) derivative, WAY-256805, a potent and highly selective norepinephrine reuptake inhibitor that exhibited efficacy in a variety

of in vivo models. Herein we report an extension of the SAR of this series by exploring the replacement of the piperazine ring in the cycloalkanol ethylpiperazine scaffold with a 4-aminopiperidine moiety, a common piperazine mimetic in medicinal chemistry. These efforts resulted in the synthesis of potent dual norepinephrine and dopamine reuptake inhibitors.



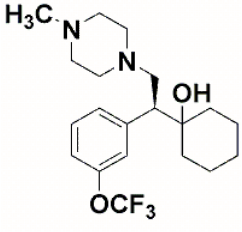
WAY-256805

MEDI 416

SAR of the cycloalkanol ethylamine scaffold: N-Substituted piperazine reuptake inhibitors

Paige E. Mahaney[1]*, Eugene J. Trybulski*[1]*, Gary Stack*[2]*, G. E. Morris Husbands*[2]*, Jenifer A. Bray*[3]*, Grace H. Johnston*[3]*, Jenifer Leiter*[3]*, Elizabeth Koury*[3]*, and Darlene C. Deecher*[3]*. (1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, mahanep@wyeth.com, (2) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, Princeton, Princeton, NJ 08543, NJ, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Norepinephrine (NE), a major neurotransmitter, is released from noradrenergic neurons during synaptic transmission. Norepinephrine reuptake inhibitors (NRIs) enhance the transmission of NE by increasing its synaptic availability through blocking its reuptake by the norepinephrine transporter (NET). Drugs that possess norepinephrine reuptake inhibition, either selectively or in combination with serotonin reuptake inhibition, have been approved for multiple indications including major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and pain disorders such as diabetic neuropathy and fibromyalgia. Other indications, including stress urinary incontinence (SUI) and vasomotor symptoms (VMS), are currently being assessed in clinical trials. In an effort to develop novel NRIs for evaluation in a variety of predictive animal models, the cycloalkanol ethylamine scaffold, of which venlafaxine is a member, was reinvestigated. Previously, we reported the identification of WAY-256805, a potent and highly selective norepinephrine reuptake inhibitor that exhibited activity in a variety of in vivo models. Herein, we report an extension of the structure-activity relationships of this series by investigating N-substituted piperazine analogs.



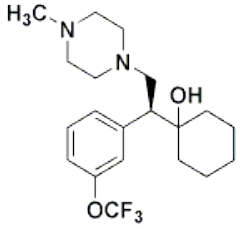
WAY-256805

MEDI 417

SAR of the cycloalkanol ethylamine scaffold: Alkyl analogs

Lori Krim Gavrin[1], *Paige E. Mahaney*[1], *Fei Ye*[1], *Joseph P. Sabatucci*[1], *Michael B. Webb*[1], *Eugene J. Trybulski*[1], *Jenifer A. Bray*[2], *Grace H. Johnston*[2], *Jenifer Leiter*[2], *Elizabeth Koury*[2], *and Darlene C. Deecher*[2]. *(1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd., Collegeville, PA 02140, gavrinl@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Drugs with varying amounts of both norepinephrine reuptake inhibition and serotonin reuptake inhibition have been developed and are currently being used as effective treatments in an assortment of therapeutic areas, including major depressive disorder, attention deficit disorder, and diabetic neuropathy. The goal of our program was to develop a selective norepinephrine reuptake inhibitor that could be used for the treatment of multiple indications. Through database mining and parallel synthesis, we identified WAY-256805, a potent and selective norepinephrine reuptake inhibitor (NRI). This poster will highlight the modifications made within the alkyl region of the cycloalkanol ethylamine analogs. These efforts include modifications such as ring size, ring substitution, heterocyclic replacements and replacing the ring with an acyclic moiety. The structure activity relationship (SAR) data for these analogs show the extreme sensitivity to changes within this region of the molecule.



WAY-256805

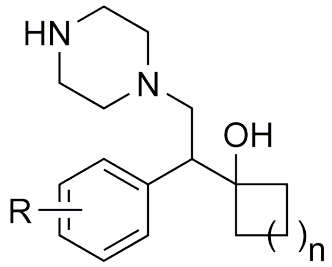
MEDI 418

Substituted phenylpiperazinylethyl cycloalkanols as selective norepinephrine reuptake inhibitors

An T. Vu[1], *Stephen T. Cohn*[1], *Lori K. Gavrin*[1], *Joseph P. Sabatucci*[1], *Paige E. Mahaney*[1], *Alison N. Campbell*[1], *Arthur A. Santilli*[1], *Eugene J. Trybulski*[1], *Richard E. Mewshaw*[1], *Jenifer A. Bray*[2], *Grace H. Johnston*[2], *Jenifer Leiter*[2], *Elizabeth Koury*[2], *and Darlene C. Deecher*[2]. *(1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, VuA@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Changes or decreases in the levels of key neurotransmitters such as serotonin, dopamine or norepinephrine in the brain have been implicated in a variety of neuropsychiatric disorders or dysfunctions. The most direct means of increasing local brain concentrations of these neurotransmitters is by blocking their reuptake after release into the synaptic cleft. Drugs that block the norepinephrine transporter (NET) thus inhibiting norepinephrine (NE) reuptake are

called norepinephrine reuptake inhibitors (NRIs), and have been developed to treat disorders such as major depression and attention deficit hyperactivity disorder (ADHD). Recently, these inhibitors have also been reported to demonstrate efficacy in other therapeutic indications including neuropathic pain, stress urinary incontinence and vasomotor symptoms. In our quest to develop novel NRIs, we reinvestigated the cycloalkanol ethylamine scaffold, of which venlafaxine, a dual acting serotonin and norepinephrine reupake inhibitor (SRI/NRI), is a member. The phenylpiperazinylethyl cycloalkanol series has been found to possess potent and selective NRI activity with limited SRI effects. In this report, we describe the synthesis and structure-activity relationships of the phenyl ring substitution and the cycloalkyl ring of this phenylpiperazinylethyl cycloalkanol series.

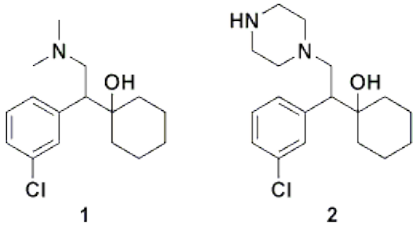


MEDI 419

SAR of the cycloalkanol ethylamine scaffold: Aminopyrrolidine and 3-aminopiperidine analogs

Lori Krim Gavrin[1]*, Douglas J. Jenkins*[1]*, Paige E. Mahaney*[1]*, Justin K. Belardi*[1]*, Eugene J. Trybulski*[1]*, Jenifer A. Bray*[2]*, Grace H. Johnston*[2]*, Jenifer Leiter*[2]*, Elizabeth Koury*[2]*, and Darlene C. Deecher*[2]*. (1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd., Collegeville, PA 02140, gavrinl@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

In our search for a selective norepinephrine reuptake inhibitor (NRI), we screened our extensive compound collection of cycloalkanol ethylamine analogs. Specifically, our group was looking for compounds that would be selective for the norepinephrine transporter (NET) over the serotonin transporter (SERT) in order to profile these compounds in various in vivo animal models. Our database mining revealed that replacing the dimethyl amine moiety of 1 with a piperazine group, as in 2, increased selectivity for NET over SERT. Further exploration of the amine region of the molecule confirmed that this moiety was crucial for achieving selectivity. This poster highlights additional analysis of this region of the molecule, specifically examining aminopyrrolidines and 3-aminopiperidines as piperazine mimetics. Compounds with submicromolar activity at NET and a favorable selectivity profile will be described.



1 2

MEDI 420

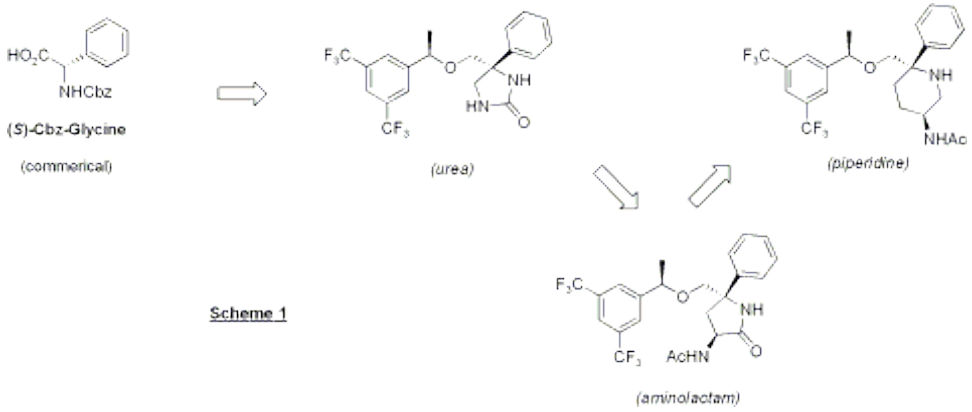
WITHDRAWN

MEDI 421

Practical asymmetric synthesis of potent NK_1 antagonists

Hon-Chung Tsui[1], *Sunil Paliwal*[1], *Gregory A. Reichard*[1], *Dong Xiao*[1], *Cheng Wang*[1], *Michelle Laci Wrobleski*[1], *Sapna Shah*[1], *Ruth A. Duffy*[2], *Jean Lachowicz*[3], *Cynthia Morgan*[3], *Amin Nomeir*[4], *Geoffrey Varty*[5], *and N-Y. Shih*[6]. *(1) Chemical Research Department, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, (2) Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) CV & CNS Biology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (4) Department of Drug Metabolism, Schering-Plough Research Institute, Kenilworth, NJ, (5) CV/CNS Biology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (6) Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033*

NK1 antagonists have potential therapeutic use in the treatment of a variety of central and peripheral diseases including pain, inflammation, depression, anxiety and emesis. Several novel and structurally different cores have been identified at SPRI as potent NK1 antagonists. A general synthetic route from commercially available (S)-Cbz-phenylglycine for these potent NK1 antagonists (Scheme 1) is described.



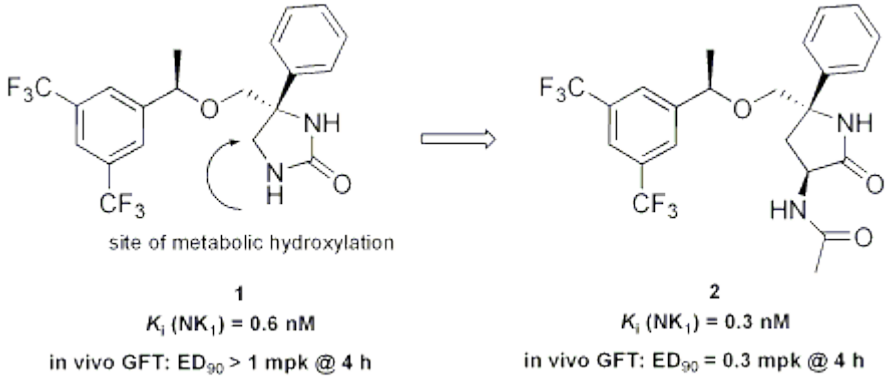
Scheme 1

MEDI 422

Novel γ-lactams as potent, selective and orally active NK_1 antagonists

Sunil Paliwal[1], *Gregory A. Reichard*[1], *Sapna Shah*[1], *Michelle Laci Wrobleski*[1], *Cheng Wang*[1], *Carmine Stengone*[1], *Hon-Chung Tsui*[1], *Dong Xiao*[1], *Ruth A. Duffy*[2], *Jean E. Lachowicz*[1], *Fei Liu*[1], *Amin A. Nomeir*[1], *Geoffrey B. Varty*[1], *and N-Y. Shih*[3]. *(1) Chemical Research Department, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, sunil.paliwal@spcorp.com, (2) Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033*

The use of NK_1 antagonists for the treatment of chemotherapy-induced nausea and vomiting has been demonstrated in clinic. We previously reported a cyclic urea based novel series of NK_1 antagonists. In vivo studies of the lead compound **1** in this series indicated oxidation next to the nitrogen was the major route of metabolism. Strategically replacing the nitrogen of cyclic urea compound **1** with a carbon resulted in the discovery of a novel and orally more efficacious γ-lactam series of NK_1 antagonists. Optimization of the γ-lactam series provided novel NK_1 antagonists (e.g. **2**) with high binding affinity and excellent oral CNS activity.



MEDI 423

Synthesis of a new anti-leishmanial lead structure by a novel Heck-type reaction

Christina Reichwald[1]*, Orly Shimony*[2]*, Nina Sacerdoti-Sierra*[2]*, Charles L. Jaffe*[2]*, and Conrad Kunick*[1]*. (1) Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstrasse 55, 38106 Braunschweig, Germany, Fax: +49-(0)531-391-2799, c.kunick@tu-bs.de, (2) Hadassah Medical School, Hebrew University, Jerusalem 91120, Israel*

In the course of a hit to lead campaign towards 7,12-dihydroindolo[3,2-*d*]benzazepin-6(5*H*)-ones with anti-leishmanial activity, derivatives with a chalcone substructure were designed. A new Heck-type reaction was developed for the synthesis of the target structures. For the new reaction, an iodo arene is reacted with a ketone Mannich base which serves as precursor for a terminal alkene. In the presence of $Pd(OAc)_2$ in DMF as solvent the reaction proceeds rapidly even without addition of a phosphine ligand. The so prepared compounds exhibited improved anti-leishmanial activity both on axenic amastigotes (GI_{50} < 1 µM) as well as on parasites in infected macrophages.

MEDI 424

Discovery of 2-quinolyl-oxazoles as potent inhibitors of phosphodiesterase 4

Rongze Kuang[1]*, Ho-Jane Shue*[1]*, David J. Blythin*[1]*, Neng-Yang Shih*[1]*, Li Xiao*[2]*, Danlin Gu*[1]*, Xiao Chen*[1]*, John Schwerdt*[1]*, Ling Lin*[1]*, Pauline C. Ting*[1]*, Xiaohong Zhu*[1]*, Robert Aslanian*[1]*, Daniel Prelusky*[3]*, Ping Wu*[4]*, Ji Zhang*[4]*, Xiang Zhang*[4]*, Chander Celly*[4]*, Michael Minnicozzi*[4]*, Motasim Billah*[4]*, and Peng Wang*[4]*. (1) Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7305, rongze.kuang@spcorp.com, (2) Department of Structural Chemistry, Schering-Plough*

Research Institute, Kenilworth, NJ 07033, (3) Department of Metabolism and Pharmacokinetics, Schering-Plough Research Institute, (4) Department of Inflammation and Infectious Diseases, Schering-Plough Research Institute, Kenilworth, NJ 07033

Phosphodiesterase 4 (PDE4), one of the cAMP-specific PDE isozymes, is expressed predominantly in inflammatory and immune cells. Inhibition of PDE4 effectively increases the intracellular cAMP level, which in turn provides critical negative regulation of various cellular functions in these cells. Therefore, the development of PDE4 inhibitors as anti-inflammatory drugs has attracted extensive research efforts. In this poster, we will present the discovery of a series of 2-quinolyl oxazoles as potent inhibitors of PDE4. The oxazole motif bearing the 4-carboxamide and 5-aminomethyl groups was found to be a novel pharmacophore for PDE4 inhibition. The synthesis and SAR of this novel series of PDE4 inhibitors will be described.

MEDI 425

Discrimination of (R)- and (S)-enantiomers of pyrroloquinolone derivatives by PDE5: A molecular docking/dynamics study

Maulik R Patel *and Tanaji T Talele, Department of Pharmaceutical Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, malkpatel@yahoo.com*

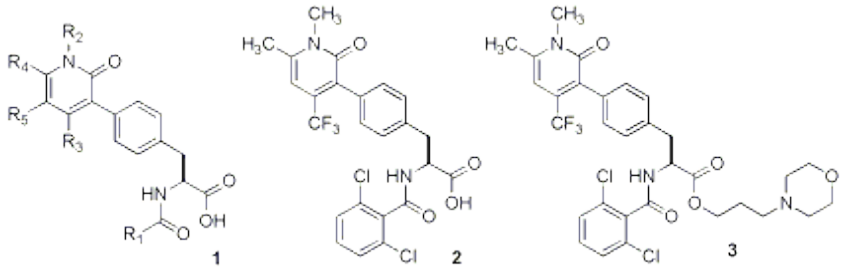
Molecular docking/dynamic simulations using the automated docking program Glide and generalized Born/solvent-accessible surface area (GB/SA) implicit water solvent model were carried out to investigate the binding modes of (R)- and (S)-enantiomers of known phosphodiesterase 5 inhibitors (PDE5Is). Evidence on the predictive accuracy of our docking procedure was obtained by studying the binding of crystallographic bound tadalafil, a known PDE5I, in which case the root mean square deviation was <1 Å. The higher PDE5 inhibitory activity of (R)-pyrroloquinolone enantiomers over the (S)-counterparts was rationalized on the basis of differences in the binding of a key methylenedioxyphenyl moiety substituted on a chiral carbon to the active site of PDE5. In an (R)-enantiomer, this moiety was found to fit nicely into the Q2 pocket formed by the hydrophobic amino acids Ala783, F786, F787, L804, Ile813, and Met816, while in (S)-enantiomer, it was mainly bound to the alternative pocket formed by Tyr612, His613, His657, and Leu681. An additional difference between an (R)- and (S)-enantiomers was the hydrogen bond formed between the –NH group of the quinolone moiety and the carbonyl oxygen of the side chain of an invariant Gln817, which was missing in the (S)-enantiomers. The binding energy (Emodel) of the (R)-enantiomers was relatively more negative than that of the (S)-enantiomers. In addition, a reasonably good correlation existed between the binding energy score of each of the inhibitors and the corresponding PDE5 inhibitory activity. The molecular docking/dynamics results for 41 pairs of enantiomers will be discussed in detail.

MEDI 426

Identification of N-acyl 4-(3-pyridonyl)phenylalanine derivatives and their orally active prodrug esters as dual acting alpha4-beta1 and alpha4-beta7 receptor antagonists

Jefferson W. Tilley[1], *Achyutharao Sidduri*[1], *Jian Ping Lou*[1], *Pam Rossman*[1], *Nadine Tare*[2], *Gary Cavallo*[2], *Aruna Railkar*[3], *Louise Gerber*[3], *Karl Frank*[3], *and Louis Renzetti*[2]. *(1) Discovery Chemistry, Roche Research Center, 340 Kingsland Street, Nutley, NJ 07110, jefferson.tilley@roche.com, (2) Repiratory, Inflammation and Autoimmune Disease, Roche Research Center, (3) Safety and Technical Sciences, Roche Research Center*

Alpha4 integrins are expressed on leukocytes with the exception of neutrophils and are involved in the trafficking of these cells to sites of inflammation. Clinical results generated with the anti-alpha monoclonal antibody Natalizumab and Roche's R411 indicate that they are important mediators of autoimmune diseases including multiple sclerosis, asthma and inflammatory bowel disease. From a series of N-acyl 4-(3-pyridonyl)phenylalanine derivatives 1, the trifluoromethyl derivative 2 was identified as a potent dual acting alpha4 integrin antagonist with activity in primate models allergic asthma. Invetigation of a series of prodrug esters lead to the discovery the morpholinopropyl derivative 3 demonstrating good intestinal fluid stability, solubility and permeability. Compound 3 gave high blood levels of 2 when dosed orally in non-human primates.



MEDI 427

Discovery and preliminary evaluation of 5-(4-phenylbenzyl)oxazole-4-carboxamides as prostacyclin receptor antagonists

Marc-Raleigh Brescia[1], *Laura L. Rokosz*[2], *Andrew G. Cole*[1], *Tara M. Stauffer*[2], *John M. Lehrach*[2], *Doulas S. Auld*[2], *Ian Henderson*[1], *and Maria L. Webb*[2]. *(1) Department of Chemistry, Pharmacopeia Drug Discovery, Inc, PO Box 5350, Princeton, NJ 08543, mbrescia@pcop.com, (2) Department of Biology, Pharmacopeia Drug Discovery, Inc, Princeton, NJ 08543-5350*

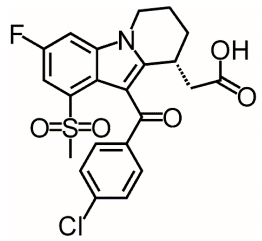
The discovery and evaluation of 5-(4-phenylbenzyl)oxazole-4-carboxamides as prostacyclin (IP) receptor antagonists is described. Analogs disclosed showed high affinity for the IP receptor in human platelet membranes with IC_{50} values of 0.05 to 0.50 μM, demonstrated functional antagonism by inhibiting cAMP production in HEL cells with IC_{50} values of 0.016 to 0.070 μM, and exhibited significant selectivity versus other prostanoid receptors

MEDI 428

Development of prostaglandin D2 receptor antagonist based on a tetrahydropyridoindole scaffold

Christian Beaulieu[1]*, Daniel Guay*[1]*, Zhaoyin Wang*[1]*, Yves Leblanc*[1]*, Patrick Roy*[1]*, Claude Dufresne*[1]*, Robert Zamboni*[1]*, Carl Berthelette*[1]*, Stephen Day*[1]*, Nancy N. Tsou*[2]*, Danielle Denis*[3]*, Gillian Greig*[3]*, Marie-Claude Mathieu*[3]*, Erika Vigneault*[3]*, and Gary O'Neill*[3]*. (1) Department of Medicinal Chemistry, Merck Frosst Canada Inc, P.O. Box 1005, Pointe Claire - Dorval, QC H9R 4P8, Canada, christian_beaulieu@merck.com, (2) Merck Research Laboratories, Rahway, NJ 07065-0900, (3) Department of Biochemistry, Merck Frosst Canada Inc, Pointe Claire - Dorval, QC H9R 4P8, Canada*

In our search of a new treatment for seasonal allergic rhinitis, we identified a new series of indoles as PGD2 receptor (DP1 receptor) antagonists. Herein, we report results from our structure-activity relationship studies and the identification of potent and selective DP1 receptor antagonists. A number of compounds with high intrinsic potency and selectivity were prepared. Of particular interest, the DP1 antagonist 1 has high affinity for the DP1 receptor with a Ki value of 1 nM. In a platelet rich plasma DP1 functional assay, compound 1 inhibits the PGD2-induced production of cAMP with an IC50 value of 4.6 nM.



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MEDI 429

Structure-activity relationship of 1,2,3,5-tetrasubstituted indoles as potent microsomal prostaglandin E_2 synthase-1 inhibitors

Sébastien Laliberté[1]*, Hélène Juteau*[1]*, Yves Gareau*[1]*, Renee Aspiotis*[2]*, Erich L. Grimm*[1]*, Marc Blouin*[1]*, D. Bruce Mackay*[1]*, Richard W. Friesen*[1]*, Diane Ethier*[3]*, Jocelyne Guay*[3]*, Chi-Chung Chan*[4]*, and Denis Riendeau*[3]*. (1) Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 Transcanada Highway, Kirkland, QC H9H 3L1, Canada, sebastien_laliberte@merck.com, (2) Merck Frosst Centre for Therapeutic Research, Kirkland, QC H9H 3L1, Canada, (3) Department of Biology, Merck Frosst Centre for Therapeutic Research, Kirkland, QC H9H 3L1, Canada, (4) Department of Pharmacology, Merck Frosst Centre for Therapeutic Research, Kirkland, QC H9H 3L1, Canada*

Microsomal prostaglandin E2 synthase-1 (mPGES-1) represents a potential target for novel analgesic and anti-inflammatory agents. We report herein the results of our SAR study on 1,2,3,5-tetrasubstituted indoles which led to the discovery of inhibitors that exhibit good in vitro activity against mPGES-1. Furthermore, one of these compounds was found to be efficacious in a rat arthritis in vivo model.

MEDI 430

Synthesis and structure-activity relationships of biarylimidazole derivatives as inhibitors of the microsomal prostaglandin E2 synthase-1

Hélène Juteau[1]*, Tom Y-H. Wu*[1]*, Yves Ducharme*[1]*, Richard W. Friesen*[1]*, Sebastien Guiral*[2]*, Lynn Dufresne*[3]*, Myriam Salem*[3]*, Hugo Poirier*[3]*, Daigen Xu*[3]*, and Laurent Audoly*[3]*. (1) Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 Transcanada Highway, Kirkland, QC H9H 3L1, Canada, (2) Department of Biochemistry, Merck Frosst Centre for Therapeutic Research, Kirkland, QC H9H 3L1, Canada, (3) Department of Pharmacology, Merck Frosst Centre for Therapeutic Research, Kirkland, QC H9H 3L1, Canada*

Microsomal prostaglandin E2 synthase (mPGES-1) appears to be the predominant prostaglandin synthase involved in inducible PGE2 production. As with COX-1/COX-2 inhibition, reduction of PGE2 level by inhibiting mPGES-1 may constitute an effective treatment of pain, inflammation, and fever. Thus, inhibitors of mPGES-1 have the potential to be novel analgesics and anti-inflammatory agents. Toward this end, a new class of mPGES-1 inhibitors bearing a biaryl imidazole scaffold has been identified. The synthesis and the in vitro biological evaluation of these mPGES-1 inhibitors will be presented.

MEDI 431

QSAR study of tacrine derivatives using variable selections

Yongnam Lee*, Youngae Jung, and Mankil Jung, Department of Chemistry, Yonsei University, Seoul, 120 Shinchondong, Seodaemungu, Seoul 120-749, South Korea, Fax: +82-2-364-7050, nami0209@yonsei.ac.kr*

Alzheimer's disease (AD) is one of the most widespread and prevalent diseases in Western societies. A diverse variable selection approach for a quantitative structure-activity relationship (QSAR) study of tacrine derivatives and suggest new analogues for the treatment of AD. We studied stepwise multiple linear regression (MLR), genetic algorithm (GA)-MLR, and simulated annealing (SA)-MLR in QSAR study of tacrines derivatives against acetylcholinesterase (AChE) activity. The results showed that AChE activity (logRA) of tacrine derivatives expressed with acceptable explanation (95.5-95.9%) and good predictive power (94.5-95.2%), repectively, in the models. The QSAR plays a key role in predictive power of biological activity using molecular descriptors. Our results will assist in understanding the hydrophobic and electrostatic interaction on increasing AChE activity and provide a tool for the QSAR study of tacrine derivatives against AChE activity.

MEDI 432

Structure guided virtual screening against dihydropteroate synthase

Kirk E. Hevener[1]*, Iain Kerr*[2]*, Mi Kyung Yun*[2]*, Jianjun Qi*[1]*, Stephen W. White*[2]*, and Richard E. Lee*[1]*. (1) Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Johnson Bldg, Suite 327, 847 Monroe Ave., Memphis, TN 38163, Fax: 901-448-6828, khevener@utmem.edu, (2) Department of Structural Biology, St Jude Childrens Research Hospital, Memphis, TN 38105*

Dihydropteroate synthase, DHPS, catalyzes the addition of p-amino benzoic acid (pABA) to dihydropterin pyrophosphate (DHPP) to form pteroic acid. It is a key step in bacterial folate biosynthesis, and is targeted by the sulfonamide class of antibiotics. Increased sulfonamide resistance has led to a renewed interest in the development of novel DHPS inhibitors. Utilizing a crystal structure of B. anthracis DHPS with a bound, pterin-like inhibitor, a structure-guided virtual screen was performed. Large, virtual libraries were pre-filtered by 3D pharmacophore and modified Rule-of-Three fragment constraints. A docking validation study was performed to identify the best docking and scoring combination to use. Over 5 million compounds were screened generating 5,093 fragment-like hits that were subsequently docked and ranked by score. Fragment hits with high predicted affinity for the pterin binding pocket, as determined by docking score, were selected for in vitro testing. Several compounds with micromolar activity were identified.

MEDI 433

Structure-based virtual screening: The discovery of novel inhibitors of hepatitis C virus NS5B RNA dependent RNA polymerase

Su Yeon Kim*, Yonsei Biomolecule Research Initiative, Yonsei University, B138A, Yonsei Engineering Research Complex, 134 Sinchon-dong, Seodaemun-gu, Seoul 120-749, South Korea, Fax: 82-2-393-9554, kimsy70@bmdrc.org, Jae Hong Shin, Drug Discovery Team, Bioinformatics and Molecular Design Research Center (BMDRC), Seoul 120-749, South Korea, and Kyoung Tai No, Department of Biotechnology, Yonsei University, Seoul 120-749*

We identified novel class of Hepatitis C virus NS5B (HCVNS5B) polymerase inhibitors by structure-based virtual screening. Virtual screening of commercially available chemical libraries has revealed 29 potential candidates with novel scaffolds as HCVNS5B polymerase inhibitors. The most active compound showed inhibitory activity against both in vitro HCV RNA-dependent RNA polymerase (RdRp) and in vivo HCV subgenomic RNA replicon R-1 cell with IC50 value range from 20 to 100 uM. Subsequent docking trials of new compounds into the binding pocket of the HCVNS5B polymerase catalytic domain identified the interactions between HCVNS5B polymerase and inhibitors. New inhibitors can serve as lead compounds for further lead identification and optimization.

MEDI 434

Computational investigation of direct antitumor cell activity of novel bisphosphonates

Michael P. Hudock[1], *Yonghui Zhang*[2], *Kilannin Krysiak*[2], *Fenglin Yin*[3], *Rong Cao*[4], *Yongcheng Song*[2], *Ermond van Beek*[5], *Socrates Papapoulos*[5], *and Eric Oldfield*[2]. *(1) Center for Biophysics and Computational Biology, University of Illinois at Urbana-Champaign, 607 S. Mathews Avenue, Urbana, IL 61801, hudock@uiuc.edu, (2) Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (3) Center for Biophysics and Computational Biology, University of Illinois at Urbana Champaign, Urbana, IL 61801, (4) Center for biophysics and computational biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, (5) Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden NA, Netherlands*

We report here a computational investigation of the direct effects of several novel classes of bisphosphonates in three tumor cell lines. For several such compounds, we have observed very low micro-molar anti-tumor cell activity and reduced bone affinity. The compounds were designed and synthesized in our laboratory and screened against breast adenocarcinoma (MCF-7), CNS glioblastoma (SF-268) and lung large cell (NCI-H460). In order to probe the mechanism of action of these compounds, we also performed enzyme screening against farnesyl diphosphate synthase (FPPS), a known target of other nitrogen containing bisphosphonates, and other enzymes in the mevalonate pathway. 3D-QSAR CoMSIA analysis of these compounds suggests the importance of hydrophobic features typical in our most potent species, and additional modeling suggests the possibility of multiple targets for these compounds. These results suggest that this new class of bisphosphonates could be used in future cancer therapies.

MEDI 435

Synthesis and profiling of a new multiple kinase inhibitor chemotype

Anne-Marie Egert[1], *Simone Kohfeld*[1], *Frank Totzke*[2], *Christoph Schächtele*[2], *Michael H. G. Kubbutat*[2], *Daniel W. Zaharevitz*[3], *and Conrad Kunick*[1]. *(1) Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstrasse 55, 38106 Braunschweig, Germany, Fax: +49-(0)531-391-2799, c.kunick@tu-bs.de, (2) ProQinase GmbH, 79106 Freiburg, Germany, (3) Information Technology Branch, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892*

Hyperactivity of kinases is involved in manifold tumor diseases and therefore the use of kinase inhibitors is an established option for cancer treatment. Recently, several drugs have been launched inhibiting simultaneously more than one cancer related kinase, e. g. sorafenib, sunitinib and dasatinib. By combining privileged heterocyclic scaffolds found in other kinase inhibitors we have designed a new multiple kinase inhibitor chemotype, 2-anilino-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one. Members of this new compound class exhibit antiproliferative activity in vitro when incubated with cancer cell lines. Synthesis and profiling of the new inhibitors both in an array of cancer related kinases and in the in vitro cell line screening of the National Cancer Institute will be presented in the poster.

MEDI 436

Synthesis and properties of novel stigmasterol-based cationic liposomes

Zhiping Le[1]*, Jia Qian*[1]*, Fei Yu*[2]*, Shaobo Deng*[2]*, Roger Ruan*[2]*, and Paul Chen*[2]*. (1) Department of Chemistry, Nanchang University, 999 Xuefu Road, Qianhu, Nanchang 330031, China, lzping@ncu.edu.cn, (2) Department of Bioproducts and Biosystems Engineering, University of Minnesota, Saint Paul, MN 55108*

Cationic liposomes as gene-carriers in non-viral gene therapy have attracted a great deal of interests due to their properties of low toxity, non-immunogenicity, conventional drug delivery and a potential of transfecting large pieces of DNA. Liposomes consist of a hydrophobic structure and a hydrophilic structure at each end. Liposomes can carry both hydrophobic molecules and hydrophilic molecules into the cell membrane.

In this work, a series of novel stigmasterol-based cationic liposomes, such as Stigmasta-5,22-dien-3-ol,4-[[2-(dimethylamino)ethyl]amino]-4-oxobutanoate,(3â,22E)-(9CI) and Stigmasta-5,22-dien-3-ol,4-[[2-(dimethylamino)ethyl]amino](2E)-4 -oxobutenoate,(3â,22E)-(9CI), were synthesized. These compounds were also characterized by Gas chromatography-mass spectrometry (GC-MS), Nuclear magnetic resonance (NMR) and Fourier Transform Infrared (FT-IR). In the future work, we will investigate the effect of the chemical structure of these lipids on lipofection. Furthermore, we will study their cytotoxicity and transfection efficiency in vitro and in vivo.

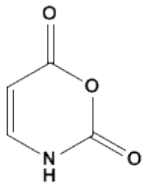
MEDI 437

Synthesis, structure and solution chemistry of 3-thia-uracil

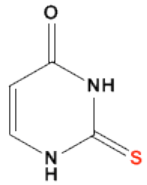
Jian Gao[1]*, Lei Shi*[2]*, Ryan Ermis*[2]*, Lawton Seal*[2]*, Duncan Aust*[2]*, and Braham Shroot*[2]*. (1) R&D, DPT Laboratories, DFB Pharmaceuticals, 330 Research Plaza, Brooks City Bases, San Antonio, TX 78235, Fax: 210-531-7283, (2) Health Point, DFB Pharmaceuticals, Fort Worth, TX 76107*

Previously, 2H-1,3(3H)-oxazine-2,6-dione, (3-oxa-uracil) [1], the oxazine analogue of uracil, was synthesized and shown to have potent antimicrobial effects as well as inhibiting cell growth. More recently, 2-thio-uracil-bearing nucleotides show potential as drug candidates in the field of interference RNAs (siRNAs). In the domain of sulfur-containing nucleotides we describe here the synthesis and characterization of the novel 3-thia-uracil [3] with in the context of evaluating the chemical and biological properties of this novel compound. Compound [3] was prepared by the reaction of thia-maleic anhydride with trimethylsily azide (TMSA), analogous to the procedure described for the synthesis of 3-oxa-uracil [1]. The desired compound was obtained as light yellow crystals, mp: 142-144 „aC and was characterized by IR, ESI-MS and HPLC. Solution chemistry studies indicated that, in both acid

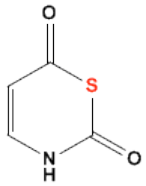
(HCl) and basic (NaOH) aqueous solution, this compound underwent acid or base catalyzed hydrolysis at similar rates to the oxygen analogue [1]. Given this surprising similarity in chemical properties we are furthering our research into pharmacological properties of this novel compound.



[1] 3-oxa-uracil



[2] 2-thio-uracil



[3] 3-thia-uracil

MEDI 438

Design and synthesis of unnatural DNA containing ring expanded purine analogs

***Orrette R Wauchope**, Dr. Zhibo Zhang, and Dr. Katherine Seley-Radtke, Department of Chemistry and Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, orrette1@umbc.edu*

As an extension of Nelson Leonard's work on benzene-expanded analogues, one focus for our research is aimed at utilizing a series of unnatural nucleosides to investigate nucleic acid structure and function . Expansion or extension of the width of the nucleobases, and subsequently the DNA helix, introduces diversity into the natural purine and pyrimidine scaffolds. In that regard, incorporation of a five membered heterocyclic spacer ring (pyrrole, furan or thiophene) possessing different hydrogen bonding traits will provide unique advantages for the heteroaromatic architecture not possible with previous studied unnatural base pairs. Consequently, one of the goals of this work will be to investigate the role that electrostatics and base stacking play in DNA helix stability as well as DNA polymerase replication. The synthesis and preliminary biophysical studies for several analogues are detailed herein.

MEDI 439

Synthesis of conformationally locked versions of puromycin as tools to understand the role of furanose conformation in the peptidyl transfer reaction

***Hisao Saneyoshi**[1], Yongseok Choi[2], Peter Strazewski[3], and Victor E. Marquez[1]. (1) Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, Frederick, MD 21702, saneyoshih@ncifcrf.gov, (2) Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, frederick 21702, (3) Laboratoire de Syntheses de Biomolecules, Universite Claude Bernard-Lyon 1, 69622 Villeurbanne cedex, France*

Use of conformationally locked bicyclo[3.1.0]hexane nucleosides with a defined sugar pucker that mimics either North- or South-type conformations in the pseudorotatinal cycle are proposed to help understand the role of conformation in the mechanism of inhibition of

puromycin in its mimicry of the 3'-terminus aminoacyl-t-RNA. We have already reported the synthesis of a conformationally locked version of a North-type puromycin analog via Mitsunobu coupling of a 3'-azide-substituted carbocyclic moiety with 6-chloropurine, with no interference from the azide group reacting with triphenylphosphine. In the case of the synthesis of the South-type version, the corresponding South carbocyclic amine was used as a starting material. However inversion of hydroxyl group at 3'-position by Mitsunobu reaction did not succeed in the case of the N-6-benzoyladenine nucleobase. Because participation of the adenine interfered with the reaction, an alternative sequence of reactions was employed to circumvent the problem.

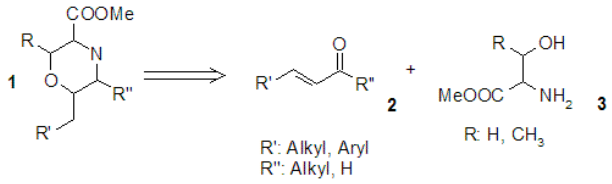
MEDI 440

Efficient one-pot synthesis of chiral polysubstituted morpholines

***Rana Adnan Bilbeisi**, Department of Chemistry, Mcgill University, 801 Sherbrooke St. W, Montreal, QC, QC H3A 2K6, Canada, rana.bilbeisi@mail.mcgill.ca, and Nicolas Moitessier, Department of Chemistry, McGill University, Montreal, QC H3A 2K6, Canada*

Functionalized morpholine derivatives are found in various natural products, biologically active compounds and are widely used in organic synthesis. Naturally occurring derivatized morpholines have shown a wide range of biological activity. Antitumor, antibiotic, anti-inflammatory and antimicrobial morpholine based compounds were extracted from natural resources.

Synthesis of chiral functionalized morpholine systems has not been fully explored, it has been a long term challenge and often requires a multi-step sequence. Stereoselective one-pot synthesis of chiral poly-substituted morpholine derivatives is being developed. The synthetic approach involves the reaction of enantiopure amino alcohols (2) with alpha,beta-unsaturated systems (3). The sequential one-pot approach is initiated by reductive amination of the alpha,beta-unsaturated system and is terminated by intramolecular hydroxyl attack on the olefin. The method and its scope will be presented.



MEDI 441

Paullones are rearranged to 11*H*-indolo[3,2-*c*]quinoline-6-carboxylic acids by a novel ring contraction reaction

Anja Becker[1]*, Simone Kohfeld*[1]*, Lutz Preu*[1]*, Tanja Pies*[2]*, Daniel W. Zaharevitz*[3]*, and Conrad Kunick*[1]*. (1) Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstrasse 55, 38106 Braunschweig, Germany, Fax: +49-(0)531-391-2799, c.kunick@tu-bs.de, (2) Institut für Pharmazie, Universität Hamburg, 20146 Hamburg, Germany, (3) Information Technology Branch, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892*

Paullones (7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-ones) are commercially available inhibitors of glycogen synthase kinase-3 (GSK-3). During investigations of the general chemistry of paullones we discovered a novel rearrangement reaction by which the starting materials are ring-contracted to furnish 11*H*-indolo[3,2-*c*]quinoline-6-carboxylic acids. The reaction proceeds in the presence of radical initiators under air atmosphere in DMF as solvent. A putative mechanism for the new reaction will be presented. Testing of the reaction products in the in vitro cell line screening of the National Cancer Institute revealed that some of the new compounds exhibit antiproliferative activity with preference for cell lines from the CNS and the leukaemia subpanels.

MEDI 442

Syntheses of UDP-GlcNYn, UDP-GalNYn and several analogs with utility to analyze sugar-transferase protein substrates

Ganesha Rai *and Craig J Thomas, NIH Chemical Genomics Center, National Human Genome Research Institute, National Institute of Helath, 9800 Medical Center Drive, Rockville, MD 20850, bantukallug@mail.nih.gov*

A major post-translational modification is the O-linked addition of N-acetylglucosamine and N-acetylgalactosamine by their complimentary transferases (analogous to phosphate addition by the various kinases). Glycosylation is a complex form of posttranslational modification and is known to control many aspects of protein function. Glycosyltransferases use sugar donors in which the activating group is typically a (substituted) phosphate such as a nucleotide or nucleoside. For both the addition of N-acetylglucosamine and N-acetylgalactosamine there are numerous isoforms of each transferase class and a major question involves the identification of the protein substrates of each isoform. A major first step in exploring this question involves the synthesis of modified Sugar-UDP constructs capable of labeling the relevant protein substrates in a manner such that each can be surveyed following this event. To this end, we report a generalized method for the syntheses of uridine diphosphate-N-pentynamide galactosamine (UDP-GalNYn), UDP-GlcNYn, cytosine diphosphate-N-pentynamide galactosamine (CDP)-GalNYn, CDP-GlcNYn and several analogous constructs starting from galactosamine and glucosamine. These unnatural sugar derivatives with native bases and non-native bases will be studied for their interactions with both the native and mutated sugar transferases.

MEDI 443

Synthesis of novel PNA building blocks for strain-promoted "click" chemistry

*J. S. Taylor and **Poulomi Sengupta**, Department of Chemistry, Washington University in St. Louis, Campus Box 1134, One, Brookings Drive, St. Louis, MO 63130, Fax: 314-935-4481, taylor@wustl.edu, sengupta@wustl.edu*

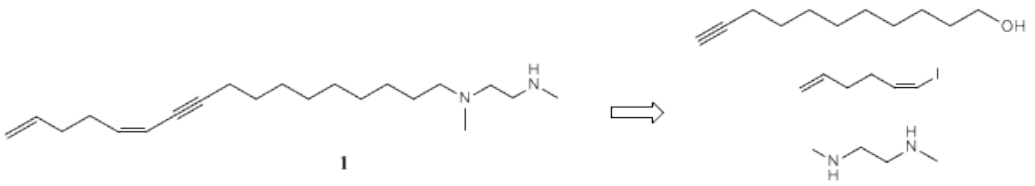
Synthesis of novel PNA building blocks for strain-promoted click chemistry Huisgen's 1, 3-dipolar cycloaddition of azides to multiple bonds is an old reaction, but has recently found extensive application in all fields of chemistry for joining molecules together selectively under the name of ‘click chemistry'. We have been exploring the use of a strain-promoted version of this reaction for the template-directed ligation of peptide nucleic acids. In this poster we shall describe the synthesis of a novel PNA building block which consists of a norbornene group linked to a uracil PNA monomer. The strain of the norbornene ring facilitates the reaction of this group with phenyl azides. (This work was supported by NIH grant PO1 CA104457-01). Synthesis of PNA building block

MEDI 444

Toward the synthesis of Clathculins A and B

***Susan Gail Brown**, Department of Chemistry, Macalester College, 1600 Grand Avenue, Saint Paul, MN 55105, sbrown@macalester.edu*

The two novel acyclic diaza alkenynes, clathculins A and B (1 and 2 respectively), were isolated from the Indo-Pacific sponge Clathrina aff. reticulum collected in Sodwana Bay, South Africa.1 They were isolated as an unstable mixture and their structures were reported via hydrogenation of the compounds to the saturated analogs. Our work done surrounding these compounds has been toward their synthesis and categorization. This involves the convergent route shown below



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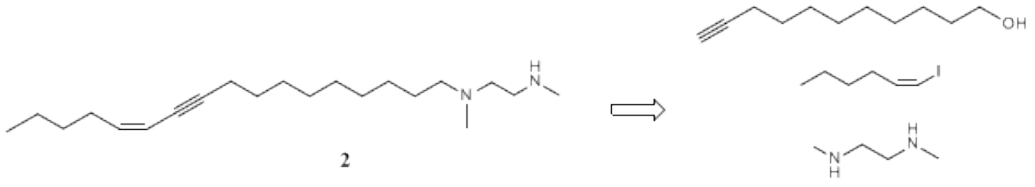

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MEDI 445

Utilizing a diazirine and alkyne containing probe in a proof of principle study to investigate small molecule interactions across the proteome

Christopher A. LeClair[1]*, William A. Prinz*[2]*, Sumana Raychaudhuri*[2]*, and Craig J. Thomas*[1]*. (1) NIH Chemical Genomics Center, NHGRI, National Institutes of Health, 9800 Medical Center Drive, Rockville, MD 20850, leclairc@mail.nih.gov, (2) Laboratory of Cell Biochemistry and Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892*

The potent, efficacious, and selective interaction of a small molecule and a protein target is a major tenet of drug design, pharmacology, and toxicology. Likewise, the disruption of the native interactions between small molecules and their protein counterparts often results in a disease state. While the ubiquitous event of a small molecule binding to a protein to initiate innumerable biochemical processes is understood, comprehension of any given small molecule's binding events across the proteome is limited. Methods are needed to explore these interactions with designed small molecule probes which maintain binding preference. As a proof of principle study, the binding of cholesterol to Osh4p, a known cholesterol-binding protein, was investigated. To this end, a cholesterol analogue containing diazirine and alkyne moieties was synthesized. Following binding to Osh4p, the derivative was covalently linked by light activation of the diazirine. The resulting conjugate was linked to a modified biotin containing an azide tether utilizing copper (I)-catalyzed Huisgen cycloaddition (click chemistry). The high affinity of biotin to streptavidin was exploited to isolate the small molecule/protein complex. Further investigation showed that this method was successful in protein isolation from a complex cellular extract. This initial study demonstrates the potential of diaziridine/alkyne conjugative protein isolation as a powerful new technique to ascertain and comprehend small molecule/protein interactions.

MEDI 446

Cholesterol lowering drugs inhibit Staphylococcus aureus virulence

Eric Oldfield*, Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, IL 61801, Fax: 217-244-0997, eo@chad.scs.uiuc.edu*

Staphylococcus aureus is the major cause of nosocomial as well as community-acquired staph infections. It produces a bright orange carotenoid pigment called staphyloxanthin which acts as a virulence factor, stopping reactive oxygen species produced by neutrophils from bacterial killing. The first step in staphyloxanthin biosynthesis involves condensation of two farnesyl diphosphate molecules to form diapophytoene, catalyzed by the enzyme CrtM. A knock-out of the CrtM gene is white and non-infective in mice, so CrtM is a candidate for new generation antibiotics which act by reversing S. aureus virulence. In this talk, I will show that a cholesterol-lowering drug which inhibits human squalene synthase inhibits CrtM, as well as S. aureus pigment formation, and that it augments ROS-based killing both in vitro and in vivo and increases host survival. I will also discuss the results of structural studies of CrtM, which are leading to more potent inhibitors.

MEDI 447

Current therapy and innovative targets for treatment of cardiac arrhythmias

***James K. Hennan**, Cardiovascular and Metabolic Diseases Research, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9394, hennanj@wyeth.com*

The management of cardiac arrhythmias is primarily concerned with restoring and maintaining sinus rhythm and preventing symptomatic and/or life-threatening arrhythmias. Cardiac arrhythmias are disorders of rate, rhythm, impulse generation or conduction that are driven by underlying cardiovascular disease. Currently available antiarrhythmic drugs have limited efficacy, documented risk of proarrhythmia and side effect profiles that limit tolerability. Over the last 15 years, antiarrhythmic drug use has declined and registrations of new chemical entities have literally come to a standstill. New advances in antiarrhythmic drug development are now focused on creating chemical entities with desired profiles of action and selectivity. Emerging therapeutic compounds hold the promise of superior efficacy and tissue selectivity with reduced potential for cardiac depression and proarrhythmia. Challenges in the regulatory environment and the burden of past failures make this therapeutic area difficult, but the growing unmet medical need makes it imperative to identify superior antiarrhythmic drugs. The goal of this symposium is to provide an overview of the emerging molecular targets that are being pursued in drug development today.

MEDI 448

Class III antiarrhythmic agents: Delayed cardiac repolarization by selective blockade of IKr, IKs or IKur

***Harold Selnick**, Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, hal_selnick@merck.com*

The treatment of life-threatening cardiac arhythmias remains a serious unmet medical need. Currently available therapies are suboptimal and carry serious risks of proarrhythmia. The realization that reentry is the most prominent mechanism underlying cardiac arrhythmias has prompted considerable efforts to modulate myocardial refractoriness. Several potassium channels that play important roles in cardiac repolarization have emerged as attractive targets for pharmacologic intervention over the years including IKr, IKs and IKur. The discovery of potent and selective blockers of these targets will be presented as well as potential advantages and disadvantages to these approaches.

MEDI 449

Design and synthesis of orally bioavailable Kv1.5 antagonists for the treatment of atrial fibrillation

***B. Wesley Trotter**, Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, bwesley_trotter@merck.com*

The development of ion channel blockers for the treatment of atrial fibrillation (AF) has attracted widespread interest in recent years. The prevalence of AF is rising as the population ages, and the disease has been identified as a major contributor to stroke and resultant morbidities and mortalities. Because current therapies can promote potentially lethal ventricular proarrhythmia, we have focused on antagonists of the Kv1.5 potassium channel and its associated current, IKur, which is observed in the human atrium but not in ventricle. We present here the synthesis and optimization of Kv1.5 antagonists guided by ion channel assay data, pharmacokinetic evaluation, and in vivo rat and dog cardiac electrophysiological experiments. Studies of key compounds have led to the identification of orally bioavailable antagonists that selectively increase atrial refractory period in a dog pharmacodynamic model.

MEDI 450

Discovery of potent gap-junction modifiers as novel antiarrhythmic agents: From stable hexa-peptides to orally available small molecules

***John A. Butera**[1], Bjarne Due Larsen[2], Edward Kerns[3], Li Di[4], James K. Hennan[5], Robert Swillo[5], Gwen Morgan[5], Christine Huselton[6], Ray J Unwalla[3], and Jørgen Petersen[7]. (1) Chemical & Screening Sciences, Wyeth Research, Princeton, NJ, CN 8000, Princeton, NJ 08543, Fax: 732-274-4129, buteraj@wyeth.com, (2) Medicinal Chemistry, Zealand Pharma A/S, Glostrup, Denmark, (3) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, (4) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ 08543, (5) Cardiovascular and Metabolic Diseases Research, Wyeth Research, Collegeville, PA 19426, (6) Biotransfomation Division, Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (7) Zealand Pharma A/S, Glostrup, Denmark*

Ventricular and atrial arrhythmias contribute significantly to overall morbidity and mortality in the developed world. Uncontrolled ventricular tachycardia (VT) can quickly cascade to ventricular fibrillation (VF) and then to sudden cardiac death. While less likely to induce sudden death, atrial fibrillation (AF) is a more prevalent form of cardiac arrhythmia which is associated with palpitations, dizziness, angina, hemodynamic impairment, and an increased risk of stroke. Pivotal failed clinical studies have illustrated the unmet medical need to discover safer and more efficacious antiarrhythmic agents. Impaired gap-junction intracellular communication has been implicated as an underlying mechanism for the propagation of unorganized cardiac electrical signals. Rotigaptide, a novel, stable hexapeptide shown to re-establish gap-junctional intercellular communication, is a first-in-class molecule being developed for the prevention (iv) of VT/VF. This presentation will review its discovery and its in vitro and in vivo characterization as a potent and efficacious antiarrhythmic agent. SAR from the hexapeptide series coupled with pharmaceutical profiling and focused screen of an internal small peptide library led to the identification and characterization of several structural classes of orally active small molecule

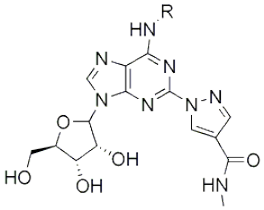
gap-junction modifiers possessing remarkable stability and potency. The second half of the talk will focus on the characterization of these leads as potential agents to treat chronic arrhythmias such as AF.

MEDI 451

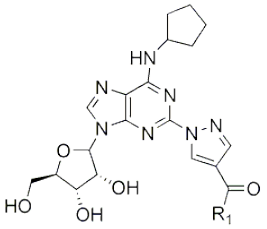
A1 Adenosine receptor agonists as ventricular rate control agents during atrial fibrillation

Jeff Zablocki[1]*, Elfatih Elzein*[1]*, Rao Kalla*[1]*, Xiaofen Li*[1]*, Thao Perry*[1]*, Tim Marquart*[1]*, Hugh Genin*[2]*, Mark Micklatcher*[1]*, John Shryock*[3]*, Lin Wu*[3]*, Yuan Li*[3]*, Yuzhi Wu*[3]*, Dewan Zeng*[3]*, Arvinder Dhalla*[3]*, Irene Lepist*[4]*, Brian Stafford*[4]*, and Kwan Leung*[4]*. (1) Department of Bioorganic Chemistry, CV Therapeutics, 3172 Porter Drive, Palo Alto, CA 94304, (2) Accelrys Inc, San Diego, CA 92121, (3) Department of Drug Research and Pharmacological Sciences, CV Therapeutics, (4) Department of Pre-Clinical Development, CV Therapeutics, Palo Alto, CA 94304*

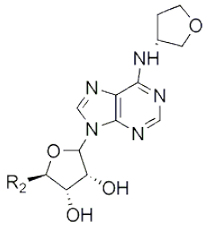
A1 Adenosine receptor agonists (AdoR) prolong atrioventricular (A-V) nodal conduction (i.e. ventricular rate control agent) and thus may provide benefit in the treatment of atrial fibrillation (AF) by reducing the number of impulses conducted from atria to the ventricles. Our goals were twofold: to discover a full A1 AdoR agonist with minimal blood brain barrier (BBB) penetration as an IV agent, and to discover a partial A1 AdoR agonist as a chronic oral agent. The full A1 AdoR agonist series was obtained from our A3 AdoR agonist series by enhancing the size and lipophilicity of the N-6 substituent as illustrated by 1 and 2, respectively. Compound 2 was further modified to incorporate a charge to diminish the propensity of BBB penetration in analogues 3–4. The genesis of the partial A1 AdoR agonist series is from Tecadenoson 5 through the 5'-hydroxyl replacement with an acetylenic group as illustrated by compound 6. Further details on the SAR of each series will be provided along with effects of selected members of each class on electrical conduction in isolated heart preparations (Langendorff, guinea pig).



1 R = Me
A_1 K_{iL} >6000 nM
A_3 K_{iH} = 73 nM
2 R = c-Pentyl
A_1 K_{iL} = 2 nM
A_3 K_{iH} = 1420 nM



3 R = O-
A_1 K_{iL} = 9 nM
A_3 K_{iH} = 4120 nM
4 R = $NHCH_2CH_2N(Me)_3$+
A_1 K_{iL} = 5 nM
A_3 K_{iH} = 95 nM



5 R_2 = CH_2OH
A_1 K_{iH} = 3 nM
6 R_2 = -ethynyl
A_1 K_{iH} = 393 nM

MEDI 452

Discovery of nicotinamides and related derivatives as potent and selective NCX reverse mode inhibitors

Akio Kakefuda[1], *Takahiro Kuramochi*[1], *Hiroyoshi Yamada*[1], *Ippei Sato*[1], *Issei Tsukamoto*[1], *Taku Taguchi*[2], *and Shuichi Sakamoto*[3]. *(1) Drug Discovery Research, Astellas Pharma Inc, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan, Fax: 81-29-852-5387, akio.kakefuda@jp.astellas.com, (2) QA, RA and Pharmacovigilance, Astellas Pharma Inc, Itabashi, Tokyo 174-8612, Japan, (3) Technology, Astellas Pharma Inc, Itabashi, Tokyo 174-8612, Japan*

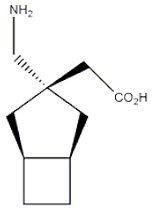
The Na+/Ca2+ exchanger (NCX) is one of the cation transporters and plays an important role in calcium handling in cardiomyocytes. NCX typically functions in a Ca2+ extrusion (forward) mode but can also function in a Ca2+ influx (reverse) mode. In myocardial ischemia and reperfusion, increases in [Na+]i lead to arrhythmogenic calcium overload via NCX reverse mode. Therefore, inhibition of NCX reverse mode could provide a novel therapeutic approach to the treatment of arrhythmias. In our research for novel NCX reverse mode inhibitors, we chose a known NCX inhibitor as a lead and performed conventional structural modifications on the compound resulting in the identification of potent, selective and orally active NCX reverse mode inhibitors. This presentation will describe the synthesis and pharmacological characterization of nicotinamides and related derivatives.

MEDI 453

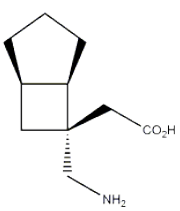
Design and synthesis of potent and efficacious 5-membered ring derivatives of gabapentin for the treatment of neuropathic pain

David C. Blakemore*, Simon A. Osborne, and Justin S. Bryans, Sandwich Chemistry, Pfizer Global Research and Development, Ramsgate Road, Sandwich CT13 9NJ, United Kingdom*

Gabapentin (Neurontin®) and pregabalin (Lyrica®) are highly effective in the treatment of neuropathic pain mediating their mode of action via an interaction with a binding site located on the α2δ subunit of a calcium channel. We have synthesized a number of 5-membered ring analogues of gabapentin, several of which show improved potency. Bicyclic analogue (i) has superior potency to gabapentin and pregabalin and has also proven to have superior efficacy to gabapentin and pregabalin in a key in vivo model of neuropathic pain. Synthesis of the regioisomers of this molecule led to the identification of the similarly potent and efficacious (ii). Both molecules have similar pharmacokinetic profiles to gabapentin. These compounds have progressed into clinical trials.



(i)



(ii)

MEDI 454

Discovery and SAR of orally active tri- and tetracyclic mGluR1 antagonists

Duane A. Burnett[1], *Deen Tulshian*[1], *Stephanie Cooke*[1], *Julius Matasi*[1], *Peter Korakas*[1], *Lisa S. Silverman*[1], *Thavalakulamgara K Sasikumar*[1], *Wen-Lian Wu*[1], *Chad Bennett*[1], *Chad Knutson*[1], *William J Greenlee*[2], *A. Reggiani*[3], *A. Veltri*[3], *R. Bertorelli*[3], *S. Fredduzzi*[3], *G. Lozza*[3], *G. Tarozzo*[3], *C. Foglia*[3], *and M. Grilli*[3]. *(1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, MS 2800, Kenilworth, NJ 07033, duane.burnett@spcorp.com, (2) Department of Chemical Research-CV/CNS, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Department of Neurobiological Research, Schering-Plough Research Institute, Milan, Italy*

Abstract: The role of metabotropic glutamate receptors in the perception of pain, in particular neuropathic pain, has been well established. A high affinity tricyclic mGluR1 antagonist was discovered during the course of a high throughput screen at SPRI. Optimization of the peripheral substituents and the core heterocycle led to the discovery of a number of highly potent, orally active mGluR1 antagonists with high selectivity over other metabotropic glutamate receptors. These compounds are very effective in animal models of neuropathic pain, including the spinal nerve ligation model. An overview of this discovery and SAR efforts will be presented.

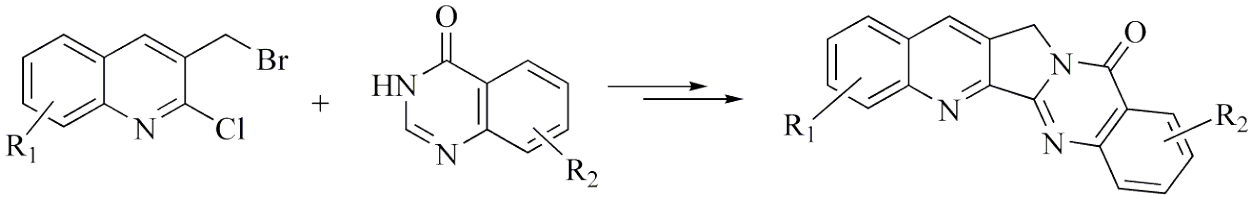
MEDI 455

Synthesis and topoisomerase poisoning activity of A-ring and E-ring substituted luotonin A derivatives

Kassoum Nacro[1], *Conxiang Zha*[1], *Peter R. Guzzo*[1], ***R. Jason Herr***[2], *Denise Peace*[3], *and Thomas D. Friedrich*[3]. *(1) Discovery Research & Development Department, Albany Molecular Research, Inc, P.O. Box 15098, Albany, NY 12212-5098, (2) Department of Medicinal Chemistry, Albany Molecular Research, Inc, P.O. Box 15098, Albany, NY 12212-5098, rjason.herr@albmolecular.com, (3) Center for Immunology and Microbial Disease, Albany Medical College, Albany, NY 12208*

Luotonin A, an alkaloid isolated from the Chinese medicinal plant Peganum nigellastrum, was first reported as a cytotoxic agent against the murine leukemia P-388 cell line. In late 2003 it was demonstrated that luotonin A was able to stabilize the covalent “cleavable complex” between the DNA phosphodiester backbone and topoisomerase I, resulting in cleavage of the resulting ternary DNA complex, similar to the mode of action of the structurally analogous alkaloid camptothecin. We sought to optimize the growth inhibitory activity of luotonin A through a rational design approach, and report here our results from the evaluation of several

A- and E-ring luotonin A analogs for in vitro growth inhibition in three human carcinoma cell lines. Several compounds were identified as being equipotent with luotonin A, and so were further analyzed for their ability to inhibit cell growth in human leukemic cell lines to asses the role of topoisomerase in cell proliferation.

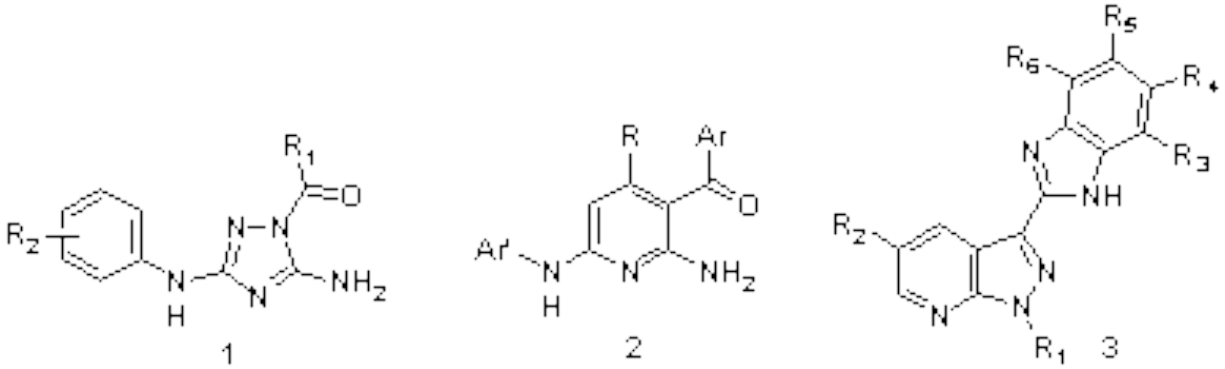


MEDI 456

Synthesis and evaluation of pyrazolo[3,4-b]pyridine CDK inhibitors as antitumor agents

Ronghui Lin[1]*, Yanhua Lu*[1]*, George Chiu*[1]*, Shengjian Li*[1]*, Yang Yu*[1]*, Shenlin Huang*[1]*, Peter Connolly*[2]*, Xun Li*[1]*, Stuart Emanuel*[1]*, Steve Middleton*[1]*, Mary Adams*[1]*, Angel Fuentes-Pesquera*[1]*, Robert Gruninger*[1]*, and Lee Greenberger*[1]*. (1) Johnson & Johnson Pharmaceutical Research & Development L.L.C, 1000 Route 202, Raritan, NJ 08869, Fax: 908-526-6469, Ronghui.Lin@yahoo.com, (2) Johnson & Johnson Pharmaceutical Research & Development L.L.C, NJ 08869*

Several cyclin-dependent kinase (CDK) inhibitors have entered clinical evaluation for the treatment of cancer. These include flavopiridol, 7-hydroxystaurosporine (UCN-01), roscovitine (CYC202), BMS-387032 (SNS-032), and R547. In our program to develop CDK inhibitors as anti-cancer agents, we recently reported that 1-acyl-1*H*-[1,2,4]triazole-3,5-diamine analogs (**1**) and 2-amino-3-benzoyl-6-anilinopyridine analogs (**2**) are novel anti-cancer CDK inhibitors and anti-proliferative agents. To discover structurally different CDK inhibitors with improved pharmacokinetic and solubility properties, we have designed, synthesized, and evaluated several other series of compounds. Herein a series of 3,5-disubstituted pyrazolo[3,4-b]pyridine analogs (**3**) were synthesized as novel CDK inhibitors. These compounds showed potent and selective CDK inhibitory activities and inhibited *in vitro* cellular proliferation in various human tumor cells. Selected compounds were evaluated for efficacy in *in vivo* tumor xenograft studies. The synthesis, SAR study, and biological evaluation of these pyrazolopyridine compounds will be presented.



MEDI 457

Design and synthesis of novel second generation HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs)

Thomas J Tucker[1], *Sandeep Saggar*[1], *John T Sisko*[1], *Robert M Tynebor*[1], *Peter J. Felock*[2], *Jessica A Flynn*[3], *Ming-Tain Lai*[2], *Yuexia Liang*[4], *Meiquing Liu*[2], *Mike Miller*[2], *Gregory Moyer*[3], *Vandna Munshi*[2], *Rebecca Perlow-Poehnelt*[1], *Sridhar Prasad*[5], *Rosa Sanchez*[4], *Maricel Torrent*[1], *Joseph P. Vacca*[1], *Theresa M. Williams*[1], *and Bang-LIn Wan*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 4/WP14-3, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-7310, tom_tucker@merck.com, (2) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) Vaccines and Biologics Research, Merck Research Laboratories, West Point, PA 19486, (4) Drug Metabolism Department, Merck Research Laboratories, West Point, PA 19486, (5) Department of Medicinal Chemistry/Structural Biology, Merck Research Laboratories, West Point, PA 19486*

Since their discovery in the early 1990's, Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been shown to be a key component of highly active anti-retroviral therapy(HAART). There are currently three commercially available NNRTIs : efavirenz, nevirapine, and delavirdine. The use of efavirenz and nevirapine has become part of standard combination antiviral therapies producing clinical outcomes with efficacy comparable to other antiviral regimens. There is however a critical issue with the emergence of clinical resistance, and a need has arisen for novel NNRTIs with a broad spectrum of activity against key HIV-1 RT mutations. The NNRTI program at Merck has been directed towards finding novel NNRTIs that possess high levels of antiviral potency against key clinically observed mutant viruses. Using a combination of traditional Medicinal Chemistry/SAR analysis, crystallography, and molecular modeling, we have designed and synthesized a series of novel, highly potent NNRTIs that possess broad spectrum antiviral activity and good pharmacokinetic profiles. This presentation will highlight the design and development of this series of compounds and will describe the progression of these compounds from early lead structures to mature second generation NNRTIs.

MEDI 458

Discovery and optimization of diphenyl ether nonnucleoside inhibitors of HIV reverse transcriptase

James P. Dunn[1], *Pete Dunten*[2], *Todd R. Elworthy*[1], *Xiaochun Han*[1], *Seth Harris*[2], *Gabrielle Heilek*[3], *Donald R. Hirschfeld*[1], *J. Heather Hogg*[1], *Ann Kaiser*[1], *Denis J. Kertesz*[1], *Woongki Kim*[1], *Klaus Klumpp*[3], *Yu Li*[3], *Taraneh Mirzadegan*[1], *Michael G. Roepel*[1], *Y. David Saito*[1], *Tania M. P. C. Silva*[1], *Steven Swallow*[1], *Zachary K. Sweeney*[1], *Jahari L. Tracy*[1], *Armando Villasenor*[2], *Harit Vora*[1], *Mark Smith*[1], *Dimitrios Stefanidis*[4], *Gouping Su*[3], *Alejandra Trejo-Martin*[1], *and Amy Zhou*[5]. *(1) Department of Medicinal Chemistry, Roche Palo Alto LLC, 3431 Hillview Avenue, Palo Alto, CA 94304, james.dunn@roche.com, (2) Department of Lead Discovery, Roche Palo Alto, Palo Alto, CA 94304, (3) Department of Viral Biochemistry, Roche Palo Alto LLC, Palo Alto Ca 94304, (4) Department of Pharmacetics, Roche Palo Alto LLC,*

Palo Alto, CA 94304, (5) Department of Drug Metabolism and Pharacokinetics, Palo Alto, CA 94304

A series of diphenyl ether compounds was discovered to inhibit the activity of HIV reverse transcriptase. Structure-based design was used to optimize the potency for both the wild-type and mutantant viruses of this novel series of non-nucleoside reverse transcriptase inhibitors (NNRTIs). This effort led to a 100-fold improvement in potency, and several compounds were discovered that showed excellent activity against both the wild-type virus and NNRTI-resistant viruses. Selected compounds had an IC50 value of <10nM against 92% of the viruses in a panel of 50 clinically derived mutant viruses. Pharmacokinetic studies in rat and dog demonstrated that these compounds have good oral bioavailability in animal species, The structure of a complex between HIV-RT and a pyridazinone inhibitor was also determined and will be described.

MEDI 459

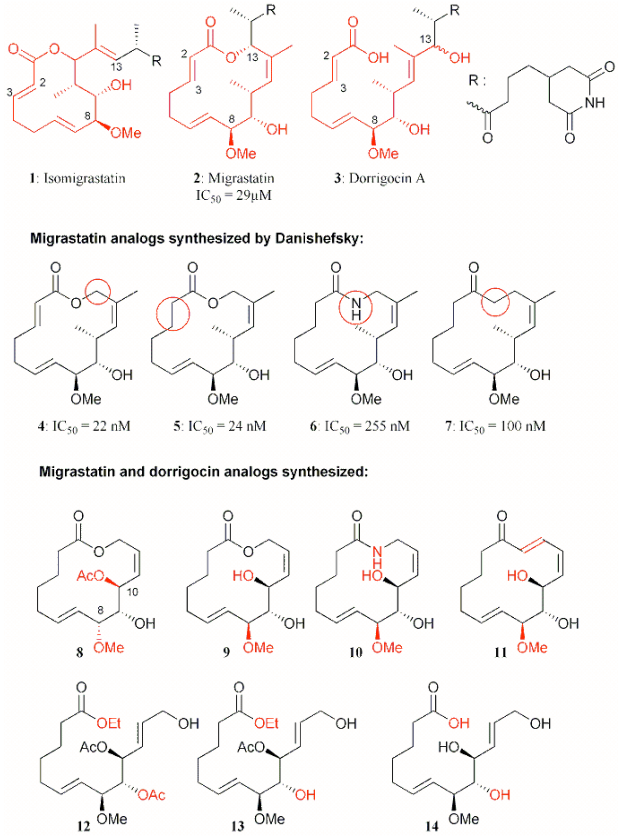
Synthesis and anticancer activity of new migrastatin analogs

Guillaume Anquetin[1]*, Sarah L. Rawe*[2]*, and Paul V Murphy*[1]*. (1) Center for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Dublin, Ireland, guillaume.anquetin@ucd.ie, (2) School of Chemical and Pharmaceutical Sciences, Dublin Institute of Technology, Dublin 8, Ireland*

Recently, the idea of targeting cell migration as an alternative strategy for the development of anti-cancer and potentially anti-angiogenic therapies has generated considerable interest. Migrastatin (2) is a natural product that inhibits cell migration. Migrastatin and dorrigocin (3) are shunt metabolites of iso-migrastatin (1) (Scheme 1). Although the total synthesis of migrastatin and its macrolide core have been achieved [1-4] there is still much to be learned about the structure activity relationships [5]. The initial biological evaluation of those analogues of the macrolide core structure of migrastatin has recently indicated much promise, providing agents ~1000 fold more potent than migrastatin itself in cell migration assays (4-7). To extend the understanding of the structure-activity relationships of the migratatin analogs synthesised, we investigated the impact of chemical modifications on positions C-8, C-10 and C-12 particulary. The synthesis of a range of analogues have been achieved from the carbohydrate precursor, tri-O-acetyl-D-glucal. Ring closing metathesis of intermediates with increased conformational constraint due to the presence of sterically hindered silyl protecting groups on oxygen has proven to be a key step in the synthetic routes to these types of analogues. Thus far, four migrastatin (8-11) and three dorrigocin (12-14) analogues have been synthesized, and their biological evaluation (anti-angiogenesis, anticancer activities, cytotoxic effects, ...) is currently

under investigation and preliminary results show that novel macrocyclic structures inhibit proliferation and migration of breast tumour cells.

[1] Danishefsky, S. J. et al, J. Am. Chem. Soc., 2003, 6042-6043. [2] Cossy, J. Et al, Eur. J. Org. Chem., 2006, 4800-4808. [3] Danishefsky, S. J. et al, Tetrahedron Letters., 2002, 9039-9042. [4] Iqbal, J. et al, Tetrahedron Letters, 2006, 6083-6086. [5] Danishefsky, S. J. et al, J. Am. Chem. Soc., 2004, 11326-11337.



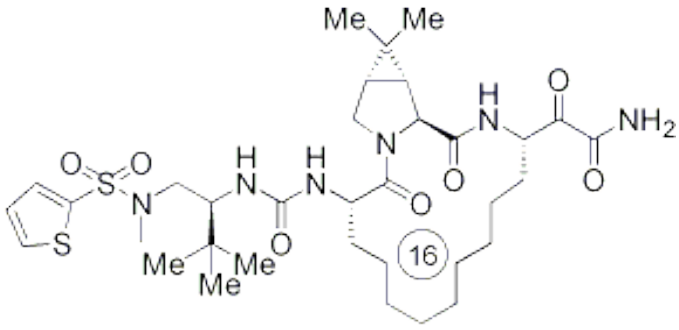
MEDI 460

Design and SAR of P1-P3 ketoamide derived macrocyclic inhibitors of HCV protease

Srikanth Venkatraman[1], *Francisco Velazquez*[2], *Wanli Wu*[1], *Melissa Blackman*[3], *Ashok Arasappan*[2], *Frank Bennett*[2], *Stephane L Bogen*[2], *Kevin Chen*[4], *Yuhua Huang*[2], *Edwin Jao*[2], *Latha Nair*[2], *Weidong Pan*[2], *Patrick Pinto*[2], *Mousumi Sannigrahi*[2], *Bancha Vibulbhan*[2], *Weiying Yang*[2], *Anil Saksena*[2], *Viyyoor Girijavallabhan*[5], *Xiao Tong*[6], *K-C. Cheng*[7], *Neng-Yang Shih*[8], *and F. George Njoroge*[2]. *(1) Chemical Research, Schering Plough Research Institute, 2015 Galloping Hill Road, A-301, MS 3545, Kenilworth, NJ 07033, Fax: 908-740-7152, Srikanth.Venkatraman@spcorp.com, (2) Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Chemical Research Department, Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, (4) Schering-Plough Research Institute, Kenilworth, NJ 07033, (5) Schering Plough Research Institute, Kenilworth, NJ 07033, (6) Virology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (7) Drug Metabolism,*

Schering-Plough Research Institute, (8) Department of Chemical Research, Schering Plough Research Institute, Kenilworth, NJ 07033

Hepatitis C Virus (HCV) infection is the major cause of chronic liver disease, leading to cirrhosis and hepatocellular carcinoma, which affects more than 200 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 genotype 1 and relapse patients is moderate at best, with only about 40% of the patients showing sustained virological response. Significant efforts are now directed towards development of therapies that target key enzymes vital to HCV replication and maturation. Macrocyclization strategy has been widely used to depetidize various peptidic inhibitors. X-ray structure of NS3 enzyme reveal a very shallow binding pocket at the catalytic site which makes development of inhibitors a daunting task. In this oral presentation we discuss, the design and the SAR of P1-P3 derived macrocyclic inhibitors that contain a ketoamide trap. Structure activity of the P1-P3 linker as well as the P3 capping region is extensively discussed. Compounds with excellent enzyme binding and cellular activities were identified. X-ray structure of inhibitor bound to the active site of the enzyme is also discussed. Macrocyclization proved to be an effective tool for depeptidization of these inhibitors, imparting enhanced metabolic stability and improved pharmacokinetic properties in the resultant molecules.



$K_i^* = 2$ nM

EC_{90} (rep) =70 nM

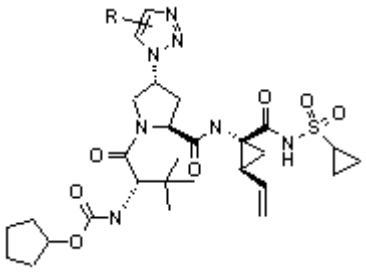
MEDI 461

Discovery of HCV protease inhibitors: Acyclic tripeptides containing novel P-2 substituted proline

Julie Naud[1]*, Pat Forgione*[2]*, Nathalie Goudreau*[3]*, Christopher Lemke*[1]*, and Montse Llinàs-Brunet*[3]*. (1) Departement of Chemistry, Boehringer Ingelheim (Canada) Ltd/Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, jnaud@lav.boehringer-ingelheim.com, (2) Department of Chemistry, Boehringer-Ingelheim Canada (Ltd), Laval, QC H7S 2G5, Canada, (3) Research and Development, Boehringer Ingelheim (Canada) Ltd, Laval (Quebec), QC H7S 2G5, Canada*

Hepatitis C virus (HCV) infections continue to be a major worldwide medical issue whereby current treatments are of limited efficacy and have with significant side effects. Therefore, a therapeutic need exists for a treatment regimen with improved efficacy and tolerability.

Towards the discovery of anti-HCV therapeutics, we have focused our efforts on the inhibition of the HCV NS3-4A protease an essential enzyme for viral replication. The N3-4A protease as a target has been previously validated. The first proof of concept in man for the HCV NS3-4A protease target was achieved with BILN 2061. In our search for a new generation of HCV protease inhibitors, we have focused on diverse acyclic tripeptide inhibitors which led to the discovery of novel acyclic P-2 substituted proline inhibitors. These inhibitors are characterized by a substituted-1-triazole moiety at the 4-proline. Details of the SAR and NMR binding mode studies will be presented, as well as the synthetic sequence for the preparation of these compounds.

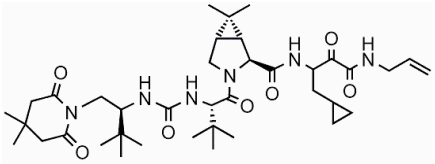


MEDI 462

Novel potent second generation HCV NS3 protease inhibitors

Kevin X Chen[1]*, Bancha Vibulbhan*[1]*, Weiying Yang*[1]*, Ashok Arasappan*[1]*, Frank Bennett*[1]*, Melissa Blackman*[2]*, Stephane L Bogen*[1]*, Yuhua Huang*[1]*, Latha Nair*[1]*, F. George Njoroge*[1]*, Angela Padilla*[2]*, Weidong Pan*[1]*, Patrick Pinto*[1]*, Mousumi Sannigrahi*[1]*, Francisco Velazquez*[1]*, Srikanth Venkatraman*[1]*, Xiao Tong*[2]*, Kuo-Chi Cheng*[2]*, and Neng-Yang Shih*[1]*. (1) Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Rd, K-15-3545, Kenilworth, NJ 07033, Fax: 908-740-7152, kevin.chen@spcorp.com, (2) N/A*

The hepatitis C virus (HCV) infection is the major cause of chronic liver disease. The HCV NS3 serine protease is essential for viral replication. It has been a target of choice for intensive drug discovery research in recent years. We have focused on developing novel moieties as the P3 capping group. It was found that tert-leucinol derived beta-diamino group was one of the best cappings examined. Further SAR on the primary amine led to the discovery of cyclic imide groups. This class of HCV protease inhibitors, represented by structure 1, had excellent enzyme assay potency (Ki* = 4 nM). They were highly selective against Human Neutrophil Elastase (HNE). They were also very potent in cell-based replicon assay (EC50 = 12 nM). Compound 1 had good rat and dog PK profile with moderate bioavailability. The SAR development and pharmacokinetic profiles of these compounds will be discussed.



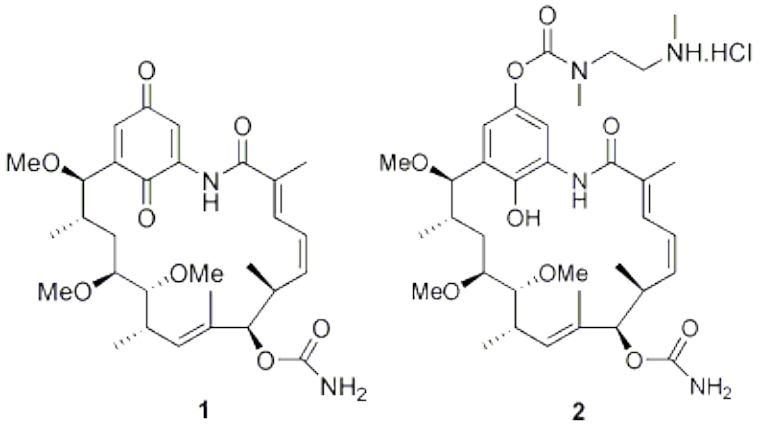
1 **Ki* = 4 nM**
HNE/HCV = 7100
EC_{50} = 12 nM

MEDI 463

Design, synthesis and biological evaluation of ansamycin prodrugs as water-soluble Hsp90 inhibitors

Steven J Moss[1], *Barrie Wilkinson*[1], *Alexander Guiblin*[1], *Alison McElhinney*[1], *Christoph Beckmann*[1], *Lesley S Sheehan*[1], *Jean-Philippe Crochard*[1], *Andrew J Kaja*[1], *Rose M Sheridan*[1], *Mohammad Nur-E-Alam*[1], *Nigel Coates*[1], *Matthew A Gregory*[1], *Thomas Greiner*[2], *Niko Bausch*[2], *Christine J Martin*[1], *and Ming Q Zhang*[1]. *(1) Biotica Technology Ltd, Chesterford Research Park, Little Chesterford CB10 1XL, United Kingdom, Fax: +44 1799 532921, steven.moss@biotica.com, (2) Oncotest GmbH, Freiburg, Germany*

We are developing water-soluble, ansamycin polyketides as potent Hsp90 inhibitors. Macbecin (1) has been characterized as an alternative lead to geldanamycin. (1) has a 5-fold higher affinity than geldanamycin for binding to Hsp90. Macbecin lacks a chemical ‘handle' for prodrug formation, so our strategy centered on the reduction of the quinone to a hydroquinone and then connection to ionisable groups to improve water solubility through either an ester or carbamate linkage. (2), from this chemical series, has aqueous solubility of >20 mM. It is stable at pH <6.5 but converts to macbecin under physiological conditions, e.g. in plasma with a t1/2 of 45-50 min. The conversion is not enzyme-dependent and therefore devoid of potential issues from metabolic polymorphism. (2) showed a significantly improved MTTD over (1). When given at 60 mg/kg to mice bearing DU145 prostate tumor xenograft, (2) produced potent inhibition in tumor growth.



1 **2**

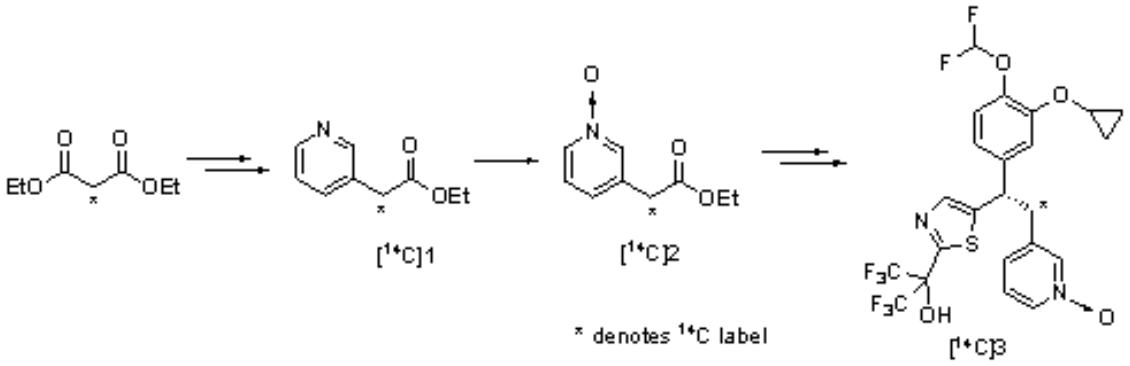
MEDI 464

Cu(I)Br-mediated preparation of 14C-labeled 3-pyridineacetate derivatives and synthesis of a novel 14C-labeled PDE-IV inhibitor

Jonathan Z. Ho, *Department of Drug Metabolism, Merck Research Laboratories, 126 East Lincoln Ave, Rahway, NJ 07065, Fax: 732-594-6921, Jonathan_ho@merck.com*

An efficient protocol for the synthesis of ^{14}C-labeled 3-pyridineacetate (**1**) and its *N*-oxide ([^{14}C]**2**) is described. Oxidation of this pyridine ([^{14}C]**1**) to its *N*-oxide ([^{14}C]**2**) proceeded in

high yield using H_2O_2 with $MeReO_3$ as a catalyst. The reaction employs readily available diethyl [2-^{14}C]malonate. This method has proven to be general in preparation of other pyridineacetate derivatives and their *N*-oxides which have been typically difficult to prepare by other means. Our development of the Cu(I)Br-coupling methodology as well as application to the synthesis of a ^{14}C-labeled phosphodiesterase-IV (PDE-IV) inhibitor, [^{14}C]**3**, are also reported.



MEDI 465

Evaluating small molecule•protein interactions in transcriptional activation

Sara J Buhrlage *and Anna K. Mapp, Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, buhrlage@umich.edu*

Protein•protein interactions regulate diverse and complex biological processes such as transcription and apoptosis. The ability to facilitate or inhibit protein•protein interactions with small molecules has tremendous promise in the development of therapeutics for diseases associated with the misregulation of protein assembly. A class of protein surfaces that remains particularly difficult to recognize is transcriptional co-activator proteins. Co-activator proteins serve as a bridge between DNA-bound transcription factors and components of the RNA polymerase holoenzyme. A variety of small molecule isoxazolidines and short isoxazolidine oligomers containing functionality similar to natural activators have been synthesized and evaluated for co-activator binding and ability to activate transcription. The ligands were found to bind the transcriptional co-activator CREB binding protein through its KIX domain using NMR spectroscopy and to activate transcription 70-80 fold in a cell based transcription assay. These results demonstrate the potential of small molecule based therapies for diseases caused by transcriptional misregulation.

MEDI 466

Identification and development of azolidinone vinyl-fused heteroaromatic derivatives: Second generation of potent PI3Kg inhibitors, with improved oral activity in models of Rheumatoid Arthritis

Thomas Ruckle*, Department of Chemistry, Merck Serono SA, 9 chemin des Mines, Geneva 1202, Switzerland, Fax: 41-22-414-9565, thomas.ruckle@merckserono.net*

PI3Kgamma is a key enzyme in leukocyte signalling, essentially responsible for mediating chemotaxis of leukocytes as well as degranulation of mast cells. PI3Kgamma functions mainly in response to G-protein coupled receptor activation and hence represents a high value target for autoimmunity and inflammation. There is an underlying body of evidence that inhibition of PI3Kgamma could be beneficial for the treatment of Rheumatoid Arthritis (RA). We have previously published potent, selective PI3Kgamma inhibitors orally active in murine models of RA (e.g. collagen induced arthritis, CIA). Our PI3Kgamma inhibitors suppress the progression of joint inflammation and cartilage damage. Here, we present a second generation of azolidinone vinyl-fused heteroaromatic derivatives as potent PI3Kgamma inhibitors with an improved pharmacokinetic and pharmacodynamic profile. Our Medicinal Chemistry efforts have led to the identification of a development candidate cpd 23, a potent PI3Kgamma inhibitor, which is fully orally available and shows efficacy in a mouse CIA model at 1mg/kg upon oral treatment.

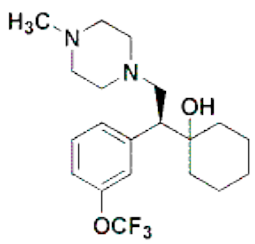
MEDI 467

Selective norepinephrine reuptake inhibitor WAY-260022 (NRI-022): Proposed therapy as a selective NRI for the treatment of neurological disorders and dysfunction

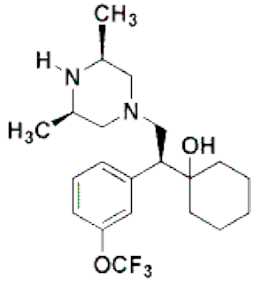
Eugene J. Trybulski[1]*, Paige E. Mahaney*[1]*, Lori K. Gavrin*[1]*, An T. Vu*[1]*, Gary Stack*[1]*, Stephen Cohn*[1]*, Douglas J. Jenkins*[1]*, Joseph P. Sabatucci*[1]*, Fei Ye*[1]*, Michael B. Webb*[1]*, Kimberly Sipe*[2]*, Jenifer Leiter*[2]*, Grace H. Johnston*[2]*, Kevin Burroughs*[2]*, Scott Cosmi*[2]*, Liza Leventhal*[3]*, Yingru Zhang*[4]*, Cheryl Mugford*[5]*, Brian Platt*[3]*, and Darlene C. Deecher*[2]*. (1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, trybule@wyeth.com, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (3) Department of Neuroscience, Wyeth Research, Princeton, NJ 08543, (4) Discovery Analytical Chemistry, Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426, (5) Biotransfomation Division, Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426*

Norepinephrine (NE) is a major neurotransmitter, which regulates body functions in both the central and peripheral nervous systems. Norepinephrine reuptake inhibitors (NRIs) increase extra cellular availability of the neurotransmitter by blocking its reuptake into the cell. Drugs that possess norepinephrine reuptake inhibition, either selectively or in combination with serotonin reuptake inhibition, have been approved for multiple indications including major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and pain disorders such as diabetic neuropathy and fibromyalgia. Other indications, including stress urinary incontinence (SUI) and vasomotor symptoms (VMS), are currently being assessed in clinical trials. Previously, we reported the identification of WAY-256805 as a selective norepinephrine reuptake inhibitor that exhibited activity in a variety of in vivo models. Optimization of this

structure for enhanced brain penetration by improved metabolic stability (rat oral bioavailability 49%) and lipophilicity has led to the discovery of WAY-260022. We will report the structure-activity relationships of this scaffold leading to the proposed development of WAY-260022 as a selective NRI for the treatment of neurological disorders and dysfunction.



WAY-256805



WAY-260022

MEDI 468

Discovery of LXR Modulator WAY-252623

Jay Wrobel[1]*, Robert J. Steffan*[1]*, Edward Matelan*[1]*, Stephen Marc Bowen*[1]*, Baihua Hu*[1]*, Michael Collini*[1]*, Christopher P Miller*[1]*, Ray J Unwalla*[1]*, Ponnal Nambi*[2]*, Elaine Quinet*[2]*, Liang Chen*[2]*, Anita Halpern*[2]*, Qiang-Yuan Liu*[2]*, Dawn Savio*[2]*, Eduoard Zamaratsky*[3]*, Lars Kruger*[3]*, Anna Wilhelmsson*[3]*, Annika Goos Nilsson*[3]*, Crina Ursu*[3]*, Erik Arnelof*[3]*, Johnny Sandberg*[3]*, Christopher Enroth*[3]*, Tomas Bonn*[3]*, and Mathias Farnegardh*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, wrobelj@wyeth.com, (2) Department of Cardiovascular and Metabolic Diseases, Wyeth Research, Collegeville, PA 19426, (3) Karo Bio AB, Huddinge, Sweden*

Liver X-Receptors (LXRa and LXRb) are members of the nuclear hormone receptor family of ligand-activated transcription factors that form obligate heterodimers with retinoid X receptors. LXRs act as a transcriptional master switches that coordinate the regulation of gene expression involved in cellular cholesterol homeostasis. LXR regulation of ABCA1, CETP, ApoE and several other key genes that mediate reverse cholesterol transport (RCT), validate LXR as a therapeutic target to promote RCT from atherosclerotic coronary lesions. Unfortunately, known LXR modulators share the undesirable side-effects of inducing hypertriglyceridemia by transactivating genes in the liver involved in fatty acid biosynthesis, including sterol regulatory binding element protein 1c (SREBP-1c) and fatty acid synthase (FAS). The pharmacological challenge therefore, is to identify LXR modulators that selectively activate desirable LXR target genes. The discovery, SAR and in vitro biology of a new LXR modulator WAY-252623 with minimal effects on triglycerides will be described.

MEDI 469

Synthesis, characterization, and nuclear receptor interaction profiles of enantiomeric bile acids

Bryson W. Katona[1], *Carolyn L. Cummins*[2], *Andrew D. Ferguson*[3], *David J. Mangelsdorf*[2], *and Douglas F. Covey*[1]. *(1) Department of Molecular Biology and Pharmacology, Washington University in St. Louis School of Medicine, Box 8103, 660 S. Euclid Ave., St. Louis, MO 63110, (2) Howard Hughes Medical Institute and Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX 75390, (3) Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390*

Bile acids are endogenous steroid detergents that modulate gene expression through interactions with nuclear receptors, which can lead to changes in the synthesis and metabolism of these steroids. Specific modulation of nuclear receptors could also have important therapeutic potential. In this study we report the first total synthesis of the enantiomers of lithocholic acid (LCA) and chenodeoxycholic acid (CDCA). *ent*-LCA was synthesized in 21 total steps with a 4.2% yield whereas *ent*-CDCA was obtained in 23 steps with a 0.8% yield. Furthermore, the critical micelle concentrations of *ent*-LCA and *ent*-CDCA were found to be identical to their natural counterparts. We also examined enantiomeric bile acid modulation of the FXR, PXR, and VDR nuclear receptors. Interestingly, *ent*-LCA and *ent*-CDCA showed differential interactions with these nuclear receptors compared to the natural steroids. This data highlights the potential utility of *ent*-bile acids in uncovering the non-receptor mediated functions of natural bile acids.

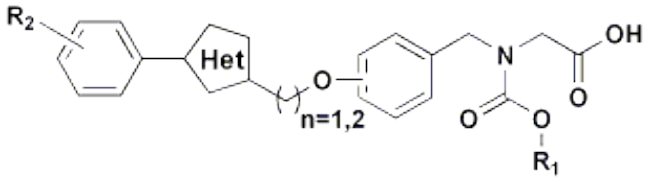
MEDI 470

Discovery of a novel, potent PPARa selective activator BMS-687453

Jun Li[1], *Lawrence J. Kennedy*[1], *Yan Shi*[2], *Shiwei Tao*[1], *Xiang-Yang Ye*[1], *Stephanie Y Chen*[1], *Ravikaran Raju*[1], *Ying Wang*[1], *Andres Hernandez*[1], *Hao Zhang*[1], *Wei Wang*[1], *Pratik V. Devasthale*[1], *Sean Chen*[1], *Zhi Lai*[1], *Shung Wu*[1], *Rebecca A. Smirk*[1], *Scott A. Bolton*[1], *Denis E. Ryono*[1], *Huiping Zhang*[1], *Ngiap-Kie Lim*[1], *Bang-Chi Chen*[1], *Kenneth T Locke*[3], *Kevin M. O'Malley*[3], *Litao Zhang*[3], *Rai Ajit Srivastava*[4], *Bowman Miao*[4], *Daniel S. Meyers*[4], *Hossain Monshizadegan*[4], *Debra Search*[4], *Denise Grimm*[4], *Rongan Zhang*[4], *Thomas Harrity*[4], *Lori K. Kunselman*[4], *Michael Cap*[4], *Vinayak Hosagrahara*[5], *Lisa Zhang*[5], *Pathanjali Kadiyala*[5], *Carrie Xu*[5], *Yi-Xin Li*[5], *Jodi K. Muckelbauer*[6], *Chiehying Chang*[6], *Stanley Krystek Jr.*[6], *Michael A. Blanar*[4], *Robert Zahler*[1], *Ranjan Mukherjee*[4], *Peter T. Cheng*[1], *and Joseph A. Tino*[1]. *(1) Discovery Chemistry, Bristol-Myers Squibb, P.O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-6810, jun.li@bms.com, (2) Bristol-Myers Squibb, Princeton, NJ 08543, (3) Lead Evaluation, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (4) Department of Biology, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (5) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton 08543, (6) Macromolecular Crystallography & CADD, Bristol-Myers Squibb, Princeton 08543*

Potent and efficacious peroxisome proliferator activated receptors alpha (PPARa) activators may represent an advance in the treatment of dyslipidemia/ atherosclerosis, which are major risk factors for cardiovascular disease. Herein we wish to disclose for the first time BMS-

687453, a development candidate from our PPARa program. BMS-687453 is a novel, potent PPARa selective activator. A systematic SAR study around an oxybenzylglycine skeleton 1 was explored in order to modulate PPARa and PPARg functional activity. We discovered that the regioisomeric 1,3-oxybenzylglycine compounds significantly enhanced PPARa functional activity and attenuated PPARg activity. The results of these SAR studies will be discussed in detail. BMS-687453 is a potent PPARa agonist (EC50 = 10 nM) with a high degree of selectivity vs. the PPARg receptor (EC50 = 4 μM; selectivity >400) in cell based transactivation assays. BMS-687453 has a promising pharmacokinetic profiles in preclinical animal models, with oral bioavailability of 88%, 91%, and 58% in mouse, rat, and cynomolgus monkeys, respectively. BMS-687453 also has an excellent profile in a panel of preclinical in vitro liability and toxicology assays. In pre-clinical in vivo efficacy studies, BMS-687453 robustly increased HDLc and ApoA1 levels in human ApoA1 transgenic mice and lowered VLDL and LDL cholesterol levels in dyslipidemic high fat fed hamsters. Based on its excellent potency, efficacy, pharmaceutical properties, and safety profile, BMS-687453 was advanced as a candidate for development as an agent for the treatment of dyslipidemia and atherosclerosis.



1

MEDI 471

Development of inhibitors of menaquinone biosynthesis: A new drug target in gram-positive bacteria

Michio Kurosu *and Dean C Crick, Microbiology, Immunology, and Pathology College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 1682 Campus Delivery, Fort Collins, CO 80523, Fax: 970-491-1815, michio.kurosu@colostate.edu*

Abstract: Potent inhibitors of menaquinones (2-methyl-3-polyprenyl-1,4-naphthoquinones) synthesis (specifically menaquinone A (MenA)) in Mycobacterium tuberculosis have been identified, which are also effective inhibitors of mycobacterial growth. Since utilization of menaquinone is a characteristic of Gram-positive organisms, these compounds are also active against organisms such as methicillin resistant Stapylococcus aureus and Staphylococcus epidermidis, and are expected to be effective against Bacillus anthracis and Listeria monocytogenes as well. The compounds identified as MenA inhibitors, ((alkylamino)octyloxyphenyl)(phenyl)methanones and their related molecules, were synthesized in a few steps via Friedel-Crafts acylation, alkylation, and amination reactions with high overall yields. A series of MenA inhibitors exhibited excellent growth-inhibitory activity against only Gram-positive bacteria (MIC values 2~8 microgram/mL). The MenA inhibitors were also effective against Mycobacterium spp. and showed MIC values as low as 1 microgram/mL. Interestingly, representative molecules were highly effective against the NRP stage 2 bacilli described in the Wayne low oxygen model (320-, 180-fold more activity against NRP stage 2 bacilli than ethanbutol and isoniazid, respectively). Growth of drug resistant Gram-positive organisms, including MRSA and MRSE, were sensitive to the MenA inhibitors,

indicating that menaquinone synthesis is a valid drug target in Gram-positive organisms. The results are expected to be of significance in terms of discovering new lead compounds that can be developed into new drugs to combat Gram-positive NIAID category A, B and C priority pathogens, as well as, emerging diseases caused by Gram-positive bacteria.

MEDI 472

Discovery of novel active site-directed pharmacological chaperones to increase the cellular activity of Gaucher disease associated glucocerebrosidase variants guided by virtual screening

Tingwei Mu[1]*, Yunfeng Hu*[2]*, Arthur J. Olson*[2]*, and Jeffery W. Kelly*[1]*. (1) Department of Chemistry, The Scripps Research Institute, 10550 N Torrey Pines Rd, BCC265, La Joll, CA 92037, Fax: 858-784-9611, tingwei@scripps.edu, (2) Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037*

Gaucher disease is the most prevalent lysosome storage disorder resulting from deficient lysosomal glucocerebrosidase (GC) activity. Clinically important GC mutant enzymes typically have reduced specific activity and reduced lysosomal concentration, the latter due to compromised folding in the endoplasmic reticulum (ER) and trafficking to the lysosome. Recently, we and others have demonstrated that pharmacological chaperones bind to the active site and assist folding of GC variants in the ER, enable their trafficking to the lysosome, and increase the cellular GC enzyme activity. Pharmacological chaperones represent a desirable alternative strategy because of the likelihood that orally available compounds that cross the blood-brain barrier can be developed. Here, we successfully combined in silico virtual screening methodology and experimental validation followed by rational drug design to discovery potent pharmacological chaperone leads. These leads are desirable for further optimization. The protocol presented here is also applicable to other areas of structure-based drug design.