

American Chemical Society
Division of Medicinal Chemistry
ABSTRACTS

228th ACS National Meeting

Philadelphia, PA
August 22-26, 2004

D. L. Flynn, Program Chair

SUNDAY MORNING

• **Amino Acid Neurotransmitters**

W. J. Porter, Organizer

Papers 1-5

• **General Oral Session I**

B. S. J. Blagg, Presiding

Papers 6-16

SUNDAY AFTERNOON

• **Transporters in Drug Discovery**

M. R. Myers, Organizer

Papers 17-21

• **Nicotinic ACH Receptors**

S. Ananthan, Organizer

Papers 22-27

SUNDAY EVENING

• **Poster Session I**

D. L. Flynn, Presiding

Papers 28-152

MONDAY MORNING

• **Alfred Burger Award Symposium - Recent Advances Towards Novel Cardiovascular Therapeutics**

R. R. Wexler, Organizer, Presiding; K. A. Jacobson, Presiding

Papers 153-157

MONDAY AFTERNOON

• **Diversity and Chemogenomics**

P. Wipf, Organizer

Papers 158-162

• **Conventional and Non-Conventional Nucleosides**

V. E. Marquez, Organizer

Papers 163-167

MONDAY EVENING

• **Sci-Mix Session**

D. L. Flynn, Presiding Papers 11, 33, 35, 62, 68, 74-75, 87-88, 96, 102-103, 108, 129-131, 150, 173, 216, 220, 225, 232, 236, 241, 244, 249, 253, 258, 266, 274-275, 281, 299, 301-302, 304-305, 312, 327, 329, 333

TUESDAY MORNING

• **Graduate Student Award Symposium**

K. A. Jacobson, Presiding

Papers 168-172

• **General Oral Session II**

D. Rotella, Presiding

Papers 173-182

TUESDAY AFTERNOON

• **David Robertson Memorial Symposium**

B. K. Trivedi, Organizer

Papers 183-187

WEDNESDAY MORNING

• **Inflammation Part I, Emerging Small Molecule Inhibitors for Treatment of Autoimmune and Inflammatory Diseases**

J. Kozlowski, Organizer

Papers 188-192

- **Anti-Obesity Therapy**

M. J. Bishop, Presiding

Papers 193-197

WEDNESDAY AFTERNOON

- **Inflammation Part II, Emerging Small Molecule Inhibitors for Treatment of Autoimmune and Inflammatory Diseases**

L. McQuire, Organizer; R. J. Cherney, Presiding

Papers 198-203

- **Dipeptidyl Peptidase IV Inhibitors**

A. E. Weber, Presiding

Papers 204-208

WEDNESDAY EVENING

- **Poster Session II**

D. L. Flynn, Presiding

Papers 209-308, 309-323

THURSDAY MORNING

- **General Oral Session III**

D. L. Flynn, Presiding

Papers 324-333

- **Gamma-Secretase Inhibitors, Sponsored by Eli Lilly & Company**

D. G. Brown, Organizer; M. S. Wolfe, Presiding

Papers 334-338

DIVISION OF MEDICINAL CHEMISTRY

1. AMINO ACID TRANSPORTERS AS TARGETS FOR THERAPEUTIC INTERVENTION. *Beth J. Hoffman*, Neuroscience Discovery Research, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-7741, hoffman_beth@lilly.com

Amino acid transporters are critical for the tight regulation and recycling of amino acids as evidenced by redundant systems of low and high affinity, multiple gene families and gene products, for glutamate, GABA, glycine, proline, D-serine, aspartate and taurine. Recent studies have provided insight into the biology of amino acid transporters, suggesting that they may be attractive targets for therapeutic intervention. Following a review of gene families and associated proteins, this presentation will focus on high affinity transporters. Aspects of transporter biology and regulation will be exemplified using data from cellular localization, structure-function studies, mechanisms of regulation, transport kinetics and genetic manipulation *in vivo*. An overview of our current understanding of the role of amino acid transporters in regulating neurotransmission will be used to highlight those aspects of biology that remain to be elucidated. Identification of potent, selective pharmacological tools should aid in focusing on the most promising therapeutic targets.

2. COMBINING FLUORESCENCE AND ELECTROPHYSIOLOGY TO PROBE GLUTAMATE TRANSPORTER STRUCTURE AND FUNCTION. *G. Leary, J.B. Ross, and M.P. Kavanaugh*, NIH COBRE Center for Structural and Functional Neuroscience, University of Montana, Missoula, MT 59803, Fax: 406-342-5228, michael.kavanaugh@umontana.edu

Although there is little direct evidence, most models of neurotransmitter transporter function postulate a cyclical gating scheme with mutually exclusive states for internal and external substrate binding. A conformational transition between these states needs to occur every time a transmitter molecule is transported across the membrane. Charge movements across the membrane may occur during this conformational switch and/or during binding and unbinding of transmitter and cotransported ions. In order to test the idea of a conformational transition linked to a charge moving transport cycle, we constructed neuronal glutamate transporter mutants that could be covalently labeled at the mouth of the transporter pore with a fluorescent probe to allow simultaneous monitoring of fluorescence and currents under voltage clamp. GFP-fusion constructs were also analyzed. The data show that fluorescence photometry and lifetime analysis represents a novel and useful approach to monitor glutamate transporter structure and function. Support Contributed By: NCRP P20RR15583 and NS3270

3. PHARMACOPHORE DEVELOPMENT FOR THE GLUTAMATE VESICULAR TRANSPORTER (VGLUT1). *Charles M. Thompson¹, Richard J. Bridges¹, and John M. Gerdes²*. (1) Center for Structural and Functional Neuroscience, University of Montana, Dept of Biomedical and Pharmaceutical Sciences, Missoula, MT 59812, Fax: 406-243-4643, charles.thompson@umontana.edu, (2) Center for Structural and Functional Neuroscience, Department of Chemistry, University of Montana

L-Glutamate is transported into presynaptic vesicles in an ATP-dependent manner by the glutamate vesicular transporter (VGLUT). VGLUT is a specific transporter for glutamate but it is low affinity ($K_m = 1$ to 3 mM), which is in contrast to the excitatory amino acid transporters (EAATs; $K_m = 5$ -50 μ M). VGLUT is an integral membrane protein but, until recently, very little was known about its structure, binding and pharmacology. This presentation will briefly review the features of VGLUT-mediated uptake of glutamate, advances in the pharmacology, known and optimized substrate and inhibitor structures, our recent efforts to develop selective and potent inhibitors of VGLUT, and the development of a new pharmacophore model for VGLUT1.

4. DISCOVERY AND SAR OF SELECTIVE INHIBITORS OF THE HGLYT-1B TRANSPORTER. *Samuel Gibson¹, Robert Gilfillan¹, David Jaap¹, David Miller¹, Glenn Walker², and Grant Wishart¹*. (1) Department of Medicinal Chemistry, Organon Research, Newhouse, United Kingdom, s.gibson@organon.co.uk, (2) Department of Pharmacology, Organon Research

Alteration of glycine levels in the mammalian central nervous system may influence inhibitory activity mediated by the strychnine-sensitive glycine receptor (SSGR) or excitatory neurotransmission through the glycine site on the NMDA complex. SSGR's are located in the spinal cord and brainstem and are closely associated with the neuronal GlyT-2 transporter whereas GlyT-1 is distributed more widely in the CNS and may play a role in controlling concentrations of the co-agonist glycine in the vicinity of NMDA receptors. This affords an opportunity for inhibition of the transporter to enhance NMDA receptor function through elevated concentrations of the co-agonist glycine. This mechanism may have relevance in addressing hypoglutaminergic function associated with psychosis. We describe here three series of selective GlyT-1b inhibitors. *In vitro* SAR is discussed for all three series, together with some conclusions concerning the interactions of these ligands with the transporter.

5. SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIP OF NOVEL CHIRAL LIGANDS FOR THE GLYCINE REUPTAKE TRANSPORTER TYPE-2 (GLYT-2). *Methvin Isaac*, Medicinal Chemistry, NPS Pharmaceuticals Inc, 6850 Goreway Drive, Mississauga, ON L4V 1V7, Canada, Fax: 905-677-9595, misaac@npsp.com

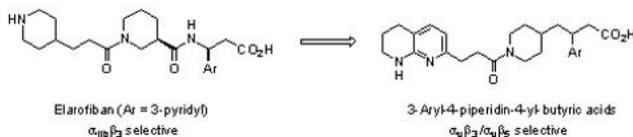
The amino acid glycine is a major neurotransmitter in the mammalian central nervous system (CNS) functioning at both inhibitory and excitatory synapses. Two distinct glycine transporters, GlyT-1 and GlyT-2, have been recently cloned and share 50% identity at both the nucleotide and amino acid levels. GlyT-1 (four isoforms: Gly-T1a, Gly-T1b, Gly-T1c, Gly-T1d) is expressed in the hippocampal and cortical regions of the brain as well as in the spinal cord and brainstem. In contrast, GlyT-2 is expressed primarily in the spinal cord and cerebellum and is absent in the hippocampus and cortex. Compounds, which selectively inhibit the glycine transporter, GlyT-2 would thus be expected to alter receptor, function and therefore provide therapeutic benefit in a variety of disease states such as neuropathic pain and spasticity. This presentation describes the synthesis and biological activity of novel classes of selective GlyT-2 reuptake inhibitors highlighting the significance of double bond geometry and chirality on GlyT-2 activity.

6. 4-PIPERIDINYL-SUBSTITUTED β -ARYL BUTYRIC ACIDS: A NEW CLASS OF POTENT α 11b β 3/ α 5 β 5 INTEGRIN ANTAGONISTS. *Bart L. De Corte*, William A. Kinney, Li Liu, Shyamali Ghosh, Livia Brunner, William J. Hoekstra, Rosemary Santulli, Jef C. Proost, Bruce P. Damiano, Bruce E. Maryanoff, Dana L. Johnson, and Robert A. Galemme, Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, P.O.Box 776, Spring House, PA 19477, Fax: 215-628-4985, bdecorte@prdu.jnj.com

Integrins are a family of heterodimeric cell-surface glycoproteins that are involved in cell-cell interactions and communication between cells and the extracellular matrix. The integrins α 11b β 3, α v β 3, α v β 5, α v β 6, and α 5 β 1 recognize adhesive proteins that contain the Arg-Gly-Asp (RGD) tripeptide sequence, which is critical for binding to the integrin extracellular domain. Hence, selective and bioavailable non-peptide mimics of the RGD recognition motif have been pursued in attempts to modulate integrin-mediated biological processes and treat a variety of diseases, such as cancer, osteoporosis, restenosis, and diabetic retinopathy.

A drug discovery program in our laboratory that targeted the platelet fibrinogen receptor, α 11b β 3 (GPIIb/IIIa), produced elarofiban, a potent, selective,

orally bioavailable α 11b β 3 antagonist, which was selected for human clinical evaluation. In the course of structure-activity relationship studies, we found that minor structural modifications to the elarofiban core resulted in major differences in the integrin binding profile. This exercise led to the discovery of a new class of piperidine-based α v β 3/ α v β 5 integrin antagonists. The synthesis and biological activity of these compounds will be discussed.

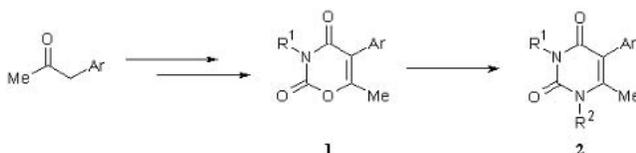


7. IDENTIFICATION AND BIOLOGICAL ACTIVITY OF A NEW SERIES OF ANTAGONISTS OF HMCH-R1. *Graeme Semple¹, Bryan Kramer¹, Debbie Hsu¹, Martin Casper¹, Sonja Strah Pleyne¹, Bill Thomsen¹, Thuy Anh Tran¹, Christina Bjennig¹, Kevin Whelan¹, Kosuke Kanuma², Katsunori Omodera², Mariko Nishiguchi², Takeo Funakoshi², Shigeyuki Chaki², and Yoshinori Sekiguchi².* (1) Arena Pharmaceuticals Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121, *GSemple@arenapharm.com*, (2) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd

From screening of our in-house collection of GPCR-directed ligands, we identified a series of alkyl-amino quinazolines as functional antagonists of the CART form of the human MCH-R1. A hit-to-lead expansion of the SAR of this series led to a number of sub-series with potent and selective MCH-R1 antagonist activity culminating in the identification of our lead compound, ATC0175 (AR224349). Highlights from the SAR expansion will be presented along with the *in vivo* and *in vitro* pharmacological profiles of several examples that will demonstrate that compounds from this series are able to inhibit food intake and body weight increase in sub-chronic feeding models in both normal rats and in rats fed a high-fat diet.

8. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SUBSTITUTED 5-ARYL-6-METHYLURACILS AS HUMAN GnRH RECEPTOR ANTAGONISTS. *Martin W. Rowbottom¹, Fabio Tucci², Yun Fei Zhu², Zhiqiang Guo², Timothy Gross², Greg Reinhart³, Qui Xie³, R. Scott Struthers³, John Saunders², and Chen Chen².* (1) Department of Medicinal Chemistry, Neurocrine Biosciences Inc, 10555 Science Center Drive, San Diego, CA 92121, Fax: 858 658 7601, *mrowbottom@neurocrine.com*, (2) Department of Medicinal Chemistry, Neurocrine Biosciences, Inc, (3) Department of Exploratory Discovery, Neurocrine Biosciences, Inc

A number of disease states, including endometriosis and prostate cancer, can be controlled via the suppression of gonadotropin-releasing hormone (GnRH) stimulated production of both follicle-stimulating hormone and luteinizing hormone. This can be achieved via agonism or antagonism of the GnRH receptor. Recent efforts have been directed toward the development of orally bioavailable small-molecule GnRH antagonists and previously we reported the discovery of a new class of uracil derived GnRH receptor antagonists, exemplified by 2. A rapid and efficient synthesis of substituted uracils (2), via the condensation of amines with oxazin-2,4-diones (1) will be described. This allowed for facile modification of a key substituent at N-1 (of 2) and led to the discovery of a number of potent compounds. The SAR of this series and how the results may lead to a better understanding of small-molecule-GnRH receptor binding will also be discussed.



9. DISCOVERY OF A NOVEL CLASS OF THIOPHENE-DERIVED ANTAGONISTS OF THE HUMAN GLUCAGON RECEPTOR. *Joseph L. Duffy¹, Brain A. Kirk¹, Zenon Konteatis¹, Elizabeth Campbell¹, Rui Liang¹, Nancy J. Kevin¹, James R. Tata¹, Kevin T. Chapman¹, Alka Bansal², Sharon Tong¹, Song Zheng¹, Sheila M. Cohen³, Corin Miller³, Mari Rios Candelore⁴, Victor Ding⁴, Richard Saperstein⁵, Edward J. Brady⁵, Guoqiang Jiang⁴, Dan Xie⁴, Xiaodong Yang⁴, Sajjad A. Qureshi⁴, and Bei B. Zhang⁴.* (1) Department of Basic Chemistry, Merck & Co., Inc, PO Box 2000, RY123-234, Rahway, NJ 07065, Fax: 732-594-5350, *joseph_duffy@merck.com*, (2) High Throughput Screening, Merck & Company, Inc, (3) Research Imaging, Merck & Company, Inc, (4) Metabolic Disorders - Molecular Endocrinology, Merck & Company, Inc, (5) Pharmacology, Merck & Company, Inc

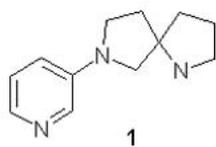
Diabetes mellitus arises from inappropriate secretion and activity of the two major hormones that control glucose homeostasis, insulin and glucagon. While many therapeutic approaches to the treatment of this disease have focussed on the normalization and utilization of plasma insulin, an alternative or additional therapy may be realized by blocking hepatic glucose production using glucagon antagonists. We have identified a novel series of thiophene-derived competitive antagonists of the human glucagon receptor. The discovery and SAR of this lead class will be discussed, resulting in compounds with a functional IC₅₀ < 50 nM against the human glucagon receptor, and bioavailability of > 30% (rat). Furthermore, a method has been developed for the direct observation (NMR) of the efficacy of glucagon antagonists in transgenic murine perfused liver expressing the human glucagon receptor. The use of this method for the investigation of compounds in the entire organ of interest will also be presented.

10. IMMUNOCONJUGATES COMPRISED OF DRUGS WITH IMPAIRED CELLULAR PERMEABILITY: A NEW APPROACH TO TARGETED THERAPY. *Svetlana Doronina, Brian Mendelsohn, Brian Toki, Steven Alley, Damon Meyer, Kevin Hamblett, Joe Francisco, Charles Cerveny, Alan Wahl, and Peter Senter, Seattle Genetics, 21823 30th Dr SE, Bothell, WA 98021, sdoronina@seagen.com*

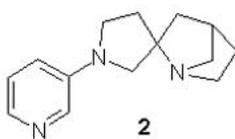
Previous studies have shown that monoclonal antibody-valine-citrulline-monomethyl auristatin E (mAb-Val-Cit-MMAE) conjugates have pronounced antitumor activity *in vitro* and *in vivo* on a wide range of models for human cancer. Here we present a new series of auristatins that are relatively non-toxic, yet are highly potentiated in activity when conjugated to internalizing mAbs. One such example is MMAF, a C-terminated phenylalanine auristatin derivative that contains a free carboxyl group. MMAF is 10 - 200 times less potent than MMAE as a free drug. However, mAb-Val-Cit-MMAF conjugates are approximately 10 times more potent than corresponding MMAE conjugates. Treatment of mice with low and well tolerated doses of these conjugates leads to cures and regressions of established carcinoma and hematologic tumor xenografts in nude mice. The results illustrate how mAbs that bind to tumor antigens and subsequently internalize can be used to enhance the potency of relatively impermeable, but highly active drugs.

11. DIAZASPIROCYCLIC COMPOUNDS AS SELECTIVE LIGANDS FOR THE α 4 β 2 NICOTINIC ACETYLCHOLINE RECEPTOR: SYNTHESIS AND PHARMACOLOGICAL STUDIES. *B.S. Bhatti¹, G.D. Hawkins¹, Scott R. Breining², Teresa Y. Phillips³, Anatoly Mazurov³, and C. Miller¹.* (1) Targacept Inc, 200 East First Street, Suite 300, Winston-Salem, NC 27101-4165, Fax: 336-480-2113, *bhattib@Targacept.com*, (2) Targacept, Inc, (3) Department of Medicinal Chemistry, Targacept, Inc

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that are prominent in both the central nervous system (CNS) and the peripheral nervous system (PNS). Compounds that modulate these receptors (nicotinic modulators) are considered to be potentially therapeutic in a variety of conditions and disease states (e.g., pain, cognitive deficits, Alzheimers and Parkinsons diseases, ulcerative colitis, anxiety, depression, Tourettes syndrome). We will discuss a new class of nAChR modulators, exemplified by the structures 1 and 2, with partial agonist properties at the α 4 β 2 nAChR subtype. These diazaspirocyclic compounds show high affinity (<100 nM) for α 4 β 2 nAChRs, with high selectivity for CNS over PNS subtypes. Synthetic routes and pharmacological profiles will be provided.



1



2

12.

DEVELOPMENT OF SUBSTITUTED INDOLES AS IONOTROPIC GLUTAMATE RECEPTOR LIGANDS. Xiaohong Shou and A. Richard Chamberlin, Department of Chemistry, University of California, Irvine, Irvine, CA 92697, shoux@uci.edu

Glutamate receptors (GluRs), including ligand-gated cationic channels (ionotropic glutamate receptors: iGluRs) and G-protein-coupled metabotropic receptors (mGluRs), are responsible for excitatory synaptic neurotransmission in the mammalian central nervous system (CNS). AMPA, KA, and NMDA receptors constitute the iGluR family. In search for receptor sub-type selective ligands, a series of conformationally constrained kainic acid analogues has been designed based on modeling studies of kainic acid complexed with the binding domain of GluR2 (X-ray, Armstrong, 1998). In vitro biological assays identified reasonably potent substituted indoles, the pharmacophore of which guides further library synthesis in a search for more active and selective iGluR ligands. Our screened ligands are intended to serve as pharmacological tools for iGluR characterization and provide novel insight into both structural and functional properties of iGluRs.

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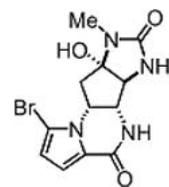
DISCOVERY, DESIGN, SYNTHESIS AND SAR OF VR1 ANTAGONISTS. Scott L. Dax¹, Michele C. Jetter¹, Mark McDonnell¹, Mark A. Youngman¹, James J. McNally¹, Sui Po Zhang¹, Adrienne Dubin², Leslie Moser¹, Nadia Nasser², Ellen E. Codd¹, and Christopher M. Flores¹. (1) Johnson & Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-3297, sdax@prdu.jnj.com, (2) Johnson & Johnson Pharmaceutical Research and Development LLC

Starting from a FLIPR-based HTS utilizing a transfected cell line, several series of potent vanilloid type 1 receptor (hVR1) antagonists were developed. The design, synthesis and Structure-Activity Relationships of naphthol-, isoquinolinyl- and quinolinyl- derived amides and ureas will be presented. Congeners containing a novel aminotetrafin scaffold will also be discussed.

14.

CHEMICAL BIOLOGY AND MECHANISM OF ACTION STUDIES ON THE ANTITUMOUR AGENT, (-)-AGELASTATIN A. Karl J. Hale¹, Mathias M. Domostoj¹, Edward Irving², Feodor Scheinmann², Mohamed El-Tanani³, Charlene Mason³, and Charles Campbell³. (1) The Christopher Ingold Laboratories, The Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom, Fax: 0208-952-8111, k.j.hale@ucl.ac.uk, m.domostoj@ucl.ac.uk, (2) The Medicinal Chemistry Department, Ultrafine, (3) Department of Surgery, Cancer Research Centre, Queen's University of Belfast

(-)-Agelastatin A is a tetracyclic alkaloid obtained from the axinellid sponge *Agelas dendromorpha*. It functions as a selective inhibitor of glycogen synthase kinase 3 β (GSK-3 β), an enzyme that plays a central role in the regulation of metabolism, embryonic development, and oncogenesis. It also inhibits the proliferation of human KB nasopharyngeal cancer cells at low drug concentrations (IC₅₀ = 0.075 μ g/mL), and increases the life-span of mice with L1210 leukemia when administered at doses of 2.6 mg/kg. Recently, we completed an enantioselective total synthesis of (-)-agelastatin A from D-glucosamine for the purpose of evaluating its antitumour and toxicological effects in mice xenografted with human bladder and colon carcinomas. The results of our tests will be presented in this lecture along with preliminary mechanism of action studies which indicate that (-)-agelastatin A potently downregulates the expression of β -catenin and osteopontin.



(-)-Agelastatin A

15.

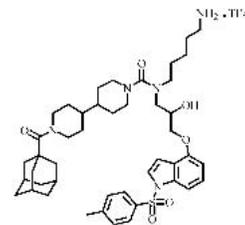
DISCOVERY OF INHIBITORS OF THE CORE BINDING FACTOR β -SMOOTH MUSCLE MYOSIN HEAVY CHAIN FUSION PROTEIN AS A TREATMENT OF ACUTE MYELOID LEUKEMIA. Michael J. Gorczyński, Department of Chemistry, University of Virginia, Charlottesville, VA 22904, Fax: 434-924-0798, mjg6d@virginia.edu

Core-binding factors (CBF) are DNA-binding transcriptional regulators consisting of a α and a β subunit. CBF α binds DNA whereas CBF β does not. However, CBF β enhances the DNA-binding affinity of CBF α and protects it from proteolytic degradation. Both subunits are essential for hematopoietic development. An inv(16), associated with 12% of acute myeloid leukemia cases, produces a chimeric protein fusing CBF β to the tail region of smooth muscle myosin heavy chain (SMMHC). The fusion protein causes dysregulation of CBF function by means of anomalously tight binding to CBF α . Since binding of CBF β -SMMHC to CBF α is required for dysfunction, this binding represents an excellent target for a small molecule inhibitor. LUDI was used to screen a virtual database and all hits possessed a 2-aminothiazole ring attached to an aromatic moiety. A library of 2-aminothiazoles was synthesized and screened for activity using both heteronuclear ¹⁵N-¹H correlation NMR spectroscopy and fluorescence resonance energy transfer.

16.

WRENCH-SHAPED SYNTHETIC MOLECULES THAT MODULATE GENE TRANSCRIPTION. Youngjoo Kwon¹, Hiroki Shimogawa², Qian Mao¹, Yoshinori Kawazoe¹, Yongmun Choi¹, Hideo Kigoshi², and Motonari Uesugi¹. (1) Biochemistry, Baylor College of Medicine, One Baylor Plaza, Alkek N410, Houston, TX 77030, Fax: 713-798-1625, ykwon@bcm.tmc.edu, (2) Chemistry, University of Tsukuba

Development of synthetic molecules that provide external control over the transcription of a given gene represents a challenge in medicinal and bioorganic chemistry. Here we discuss design and analysis of a series of wrench-shaped molecules that modulate gene transcription in cells. These unique cell-permeable molecules target protein-protein interactions between coactivators and transcription factors in the nucleus. Our case studies foreshadow the promise and the challenge of targeting protein-protein interactions in the nucleus and may lead to the development of synthetic modulators of gene expression relevant to human diseases.



Wrenchnolol

17.

MEMBRANE TRANSPORTERS AND PRODRUG ACTIVATING ENZYMES: MODERN MOLECULAR PHARMACEUTICS. Gordon L. Amidon, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109, glamidon@umich.edu

Our understanding of the membrane transport mechanisms of drugs has undergone a revolution. Epithelial cells, in particular, lining the gut, liver, and kidney represent the principle barrier for drug entry and exit from the body, are an essential determinant of the ADME properties of a drug. A second discovery was that prodrugs could be carrier mediate. Today it is firmly established that several peptidomimetic prodrugs utilize the peptide carriers, hPEPT1 or HPT for

entry into the mucosal cell. The demonstration that nucleoside prodrugs utilize a carrier mediated pathway for mucosal cell entry, explains the high bioavailability of valacyclovir. However, a second step is required that of activation. This step is often relegated to ubiquitous 'esterases'. Recently we have identified and cloned a new esterase enzyme referred to as Valacyclovirase (also known as VACVase or BPHL) and shown it to efficiently hydrolyze the esters of valacyclovir and valganciclovir. This presentation will provide an overview of membrane transporters, focusing on epithelial cell transporters and report the recent results of our studies on transport and activation of a variety of nucleoside prodrugs. We conclude that, with the tools available today, prodrug design can be based on detailed molecular mechanisms and strategies.

18.

CHEMICAL APPROACHES TO OVERCOMING MULTIDRUG RESISTANCE AT THE BLOOD-BRAIN BARRIER. **Kenneth L. Audus¹, Antonie Rice¹, Yanbin Liu², MaryLou Michaelis³, Richard H. Himes⁴, and Gunda I. Georg².** (1) Department of Pharmaceutical Chemistry, The University of Kansas, School of Pharmacy, 2095 Constant Avenue, Lawrence, KS 66047, Fax: 785-864-5736, audus@ku.edu, (2) Department of Medicinal Chemistry, University of Kansas, (3) Department of Pharmacology and Toxicology, University of Kansas, (4) Department of Molecular Biosciences, University of Kansas

Chemical modifications were introduced into the taxol structure to reduce interactions with the product of the multidrug resistant type 1 (MDR1) gene, P-glycoprotein (Pgp), and to improve blood-brain barrier (BBB) permeability. Taxane analog, Tx-67, with a succinate group added at the C10 position of taxol was synthesized and identified as such a candidate. Tx-67 had no interactions with Pgp as demonstrated by the lack of enhanced uptake of rhodamine 123 by brain microvessel endothelial cells (BMECs). The transport across BMEC monolayers was polarized for Tx-67 with permeation in the apical to basolateral direction greater relative to basolateral to apical permeation across BMECs. In an in situ rat brain perfusion study, Tx-67 was demonstrated to permeate across the BBB at a substantially greater rate than taxol. Results demonstrate that Tx-67 had a reduced interaction with Pgp and as a consequence, enhanced permeation across the blood-brain barrier in vitro and in situ.

19.

NEW STRATEGIES IN MEDICINAL CHEMISTRY: HARNESSING NUTRIENT TRANSPORT MECHANISMS TO OPTIMIZE DRUG ABSORPTION AND DISPOSITION IN VIVO. **Mark A. Gallop, Xenoport, Inc, 3410 Central Expressway, Santa Clara, CA 95051, Fax: 408-616-7212, mgallop@xenoport.com**

Membrane-localized solute transporter proteins in intestinal, kidney, liver and brain tissues are increasingly understood to influence the absorption, distribution and clearance of drugs. Xenoport creates optimized therapeutic agents by applying medicinal chemistry design principles to control molecular recognition by transporter systems, thereby engineering more predictable drug disposition *in vivo*. This talk will examine aspects of this strategy, highlighting application to the design of actively transported prodrugs of gabapentin that show improved pharmacokinetic profiles relative to the parent drug. The actively transported prodrug XP13512 is currently undergoing clinical investigation for the treatment of neuropathic pain and other neurological disorders.

20.

PEPTIDE PRODRUG DESIGN FOR IMPROVING ORAL ABSORPTION. **Concepcion Pedregal, DCR&T, Lilly SA, Avda de la Industria 30, Alcobendas, 28108 Madrid, Spain, Fax: 34-91-6633411, Pedregal_Concepcion@Lilly.com**

Successful drug development requires not only optimization of specific and potent pharmacological activity but also efficient drug delivery to the target site. For orally administered drugs, the challenge of reaching their sites of action is even greater because they must first cross the intestinal epithelial cells to get into the systemic circulation. LY354740 was the first known, highly selective and potent agonist for group 2 metabotropic glutamate receptors: mGluR2 and mGluR3. Activation of presynaptic group 2 receptors inhibits glutamate release and therefore leads to normalized glutamate levels in the synaptic cleft compare with the case when overexcitation conditions take place. However, this compound has a main drawback low oral bioavailability (3-5%) in humans that is believed to arise from poor absorption through the GI tract. In this talk a discussion about specific prodrugs that deliver plasma concentration of LY354740 associated with efficacy in humans will be presented.

21.

GUANIDINIUM-RICH MOLECULAR TRANSPORTERS: MECHANISMS AND APPLICATIONS. **Paul A. Wender¹, Jonathan Rothbard², and Tad Jessop¹.** (1) Department of Chemistry, Stanford University, Stanford, CA 94305, wenderp@stanford.edu, (2) CellGate, Inc

Guanidinium-rich molecular transporters (GRMTs) have been shown to penetrate a variety of biological barriers, including membranes of adherent and non-adherent cells and various tissues, carrying a variety of cargoes including small molecules, peptides, proteins, nucleic acids, and magnetic particles. GRMTs have been advanced into clinical trials. This lecture will present results from a collaborative study (Stanford Chemistry Dept., Stanford Medical School, and CellGate, Inc.) bearing on the molecular mechanisms for GRMT entry into cells and an overview of applications of these versatile drug delivery agents.

22.

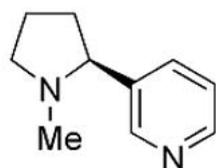
ADVENTURES IN THE RATIONAL DESIGN OF NICOTINIC ACETYLCHOLINE RECEPTOR THERAPEUTICS. **Jeffrey D. Schmitt¹, B.S. Bhatti², Scott R. Breining², Philip S. Hammond¹, Rebecca Harris¹, G.D. Hawkins², Josef Klucik¹, Lan Miao², Craig H. Miller², Yun De Xiao¹, Teresa Y. Phillips², Angela Seamans², and William S. Caldwell¹.** (1) Molecular Design Group, Targacept, Inc, 200 East First Street, Suite 300, Winston-Salem, NC 27101-4165, jeff.schmitt@targacept.com, (2) Medicinal Chemistry Group, Targacept, Inc

The nicotinic acetylcholine receptor (nAChR) family is highly complex, with respect to both subtype heterogeneity and binding-site structure. This fact, coupled with the promise of nAChR therapeutics, has motivated Targacept scientists to develop a dual ligand-based structure-based drug design strategy. Underpinning this strategy are novel virtual library design and QSAR techniques. Critical to our success has been the alignment of efforts between molecular modelers and medicinal chemists. Specific examples of the design and optimization of nAChR leads will be presented.

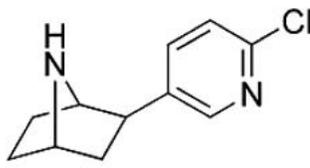
23.

DESIGN, SYNTHESIS AND PHARMACOLOGICAL CHARACTERIZATION OF SELECTIVE LIGANDS FOR NEURONAL NACHRS. **Alan P. Kozikowski¹, Zhi Liang Wei¹, Jianguang Lei¹, Yingxian Xiao², and Kenneth J. Kellar².** (1) Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, Fax: 312-996-7107, kozikowa@uic.edu, (2) Department of Pharmacology, Georgetown University

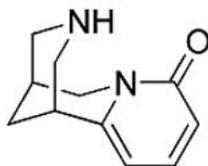
Neuronal nAChRs hold considerable promise as therapeutic targets in the search for new therapies for a host of central nervous system disorders. Drugs aimed at the nAChRs have marked potential for the treatment of neurodegenerative disorders, such as Alzheimers disease, Parkinsons disease, and nicotine addiction. nAChRs are comprised of combinations of one or more α and β subunits, and different subunit combinations define different receptor subtypes with distinct biophysical, physiological and pharmacological properties. Nine α and three β subunits have been cloned, which suggests the possibility of a very large number of receptor subtypes. Although we do not yet know all the rules of assembly, based on studies of subunit mRNA and protein distribution, 5 to 7 subtypes probably encompass the large majority of the nAChRs in the CNS and peripheral nervous systems. There are a number of nicotinic agonists and non-competitive antagonists (channel blockers); but, unfortunately, very few of these drugs are subtype-selective and therefore they do not discriminate very well among nAChR subtypes. Thus, the identification of specific agonists or antagonists based on selective modulation of nAChR subtypes may result in new and potentially useful therapeutic agents. Moreover, selective compounds are likely to find use in the diagnosis of certain CNS disorders through positron emission tomography (PET) imaging. While nicotine, epibatidine, cytisine, and some 3-pyridyl ethers show good affinity for the neuronal nAChRs, they generally lack selectivity. Our recent progress in the design, synthesis, and pharmacological characterization of ligands selective for the $\alpha 4\beta 2$ subtype, the most abundant nAChR subtype in the brain, will be presented. Attempts to use labeled forms of these ligands in PET imaging will also be discussed.



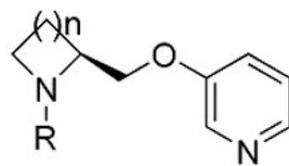
(-)-Nicotine



Epibatidine



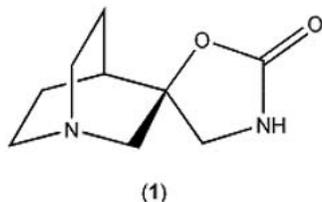
Cytisine



3-Pyridyl ethers

24. $\alpha 7$ -SELECTIVE COMPOUNDS AS NOVEL POTENTIAL THERAPEUTICS FOR CNS DISEASES. *Eifion Phillips*, Department of Chemistry, AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, Fax: 302-886-5382, eifion.phillips@astrazeneca.com

Emerging evidence suggests that the $\alpha 7$ nicotinic acetylcholine receptor (nAChR) plays an important role in the CNS, including in cognition and neuroprotection, and may be a valuable therapeutic target for the treatment of CNS diseases. Early small molecule nicotinic receptor ligands were selective for binding the $\alpha 4\beta 2$ sub-type over $\alpha 7$. This presentation will describe some recent developments in the discovery of novel $\alpha 7$ -selective compounds. (-)-Spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one] (**1**) (AR-R017779) an early such compound, and a selective $\alpha 7$ nAChR agonist, improved working memory, restored sensory gating, and possessed mild anxiolytic activity, while exhibiting reduced side effects relative to nicotine.



(1)

25. SUBTYPE SELECTIVE NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS. *Peter C Astles*, Medicinal Chemistry, Eli Lilly and Co, Erl Wood Manor, Sunninghill Road, Windlesham GU7 1XY, United Kingdom, astles_peter_c@lilly.com

Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand gated ion channels, which are found at the neuromuscular junction and in the central and peripheral nervous systems. The channels can be assembled from fourteen known subunits. The exact combination and function of all the channels are still not determined but in the CNS certain combinations have been identified which appear to modulate the release of specific neurotransmitters. Non-selective compounds like nicotine and epibatidine have demonstrated the therapeutic potential of nAChR agonists but their clinical value is limited by undesirable side effects. Selective ligands for different receptor subtypes are now emerging and the development of stable cell lines functionally expressing specific combinations of subunits has greatly improved our understanding of ligand specificity. This presentation will outline progress into the discovery of specific subunit selective compounds.

26. DEVELOPMENT OF SUBTYPE-SELECTIVE NICOTINIC RECEPTOR LIGANDS AS RECEPTOR ANTAGONISTS AT THE DOPAMINE-RELEASING RECEPTOR SUBTYPE. *Peter A. Crooks*, College of Pharmacy, University of Kentucky, Rose Street, Lexington, KY KY 40536-008, Fax: 859-257-7585, pcrooks@uky.edu

Few subtype-selective neuronal nicotinic acetylcholine receptor (nAChR) antagonists are available for use as pharmacological tools for investigating the

physiological roles of nAChR subtypes. Our research is aimed at the development of a new class of subtype-selective nAChR antagonist, which inhibits nAChRs mediating nicotine-evoked dopamine (DA) release (i.e the $\alpha 6\beta 2^*$ subtype). We have shown that alkylation of the pyridino N-atom of nicotine to form an N-n-alkylnicotinium analog, converts nicotine from a nAChR agonist into a potent nAChR antagonist. We have now expanded our SAR studies to investigate the effect of: a) simplification of the N-n-alkylnicotinium structure through removal of the N-methylpyrrolidino moiety, b) conformational restriction through the use of novel rigid rotameric analogs, c) N-alkyl group modification through introduction of unsaturation into the n-alkyl chain, and d) the use of dicationic bis-N,N-n-alkylnicotinium analogs, on nAChR inhibitory potency and selectivity at the $\alpha 6\beta 2^*$ subtype. The availability of selective $\alpha 6\beta 2^*$ antagonists may provide drug candidates for development as efficacious tobacco use cessation agents for the treatment of nicotine addiction.

27. DEVELOPMENT OF NEURONAL NICOTINIC RECEPTOR (NMR) AGONISTS AS NOVEL ANALGESICS. *William H. Bunnelle*, GPRD, Department R47W, AP9A-1, Abbott Laboratories, Abbott Park, IL 60064, William.H.Bunnelle@abbott.com

The analgesic properties of nicotine have been known for 70 years, but it was the 1994 discovery by Daly et al. that the profound analgesic properties of epibatidine are mediated by neuronal nicotinic receptors (NMR's) that clearly defined the potential of this pharmacology for discovery of novel analgesic agents. Research at Abbott Laboratories resulted in the development of ABT-594, a potent NMR agonist that provided clinical validation of this mechanism for treatment of pain. Ultimately, limited GI tolerability prevented further development of ABT-594. An improved understanding of the NMR subtypes involved in analgesia vs. those mediating adverse events has driven the search for a 2nd-generation NMR-based analgesic. Medicinal chemistry efforts to increase receptor subtype selectivity, resulting in compounds with improved therapeutic indices, will be described.

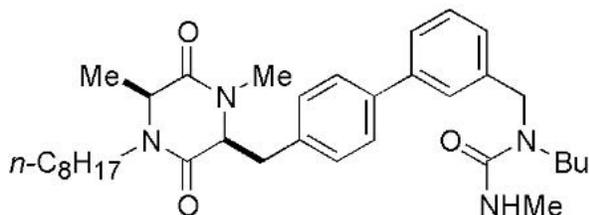
28. NOVEL ISOXAZOLE CARBOXAMIDES AS GROWTH HORMONE SECRETAGOGUE RECEPTOR (GHS-R) ANTAGONISTS. *Bo Liu¹, Gang Liu¹, Zhili Xin², Michael D. Serby², Hongyu Zhao², Douglas H. Falls², Christine A. Collins², Hing Sham³, Wiweka Kaszubska², and Verlyn G. Schaefer².* (1) Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, Fax: 847-938-1674, bo.x.liu@abbott.com, gang.liu@abbott.com, (2) Global Pharmaceutical Research and Development, Abbott Laboratories, (3) R47B, Cancer Research, Global Pharmaceutical R & D, Abbott Laboratories

Ghrelin, a 28 amino acid peptide with a unique n-octanoyl modification on Ser 3, was recently identified in rat stomach as an endogenous ligand for growth hormone secretagogue receptor (GHS-R), a G-protein coupled receptor (GPCR). Besides being a potent growth hormone secretagogue and regulator of other endocrine functions, ghrelin is also implicated in the short- and long-term regulation of energy balance. A selective small molecule GHS-R antagonist can potentially lead to reduced food intake, decreased adiposity, and body weight reduction in humans. An isoxazole carboxamide derivative was identified and confirmed as a pure GHS-R antagonist from a high throughput screening (HTS). Extensive medicinal chemistry efforts were initiated to explore the structure-activity relationship (SAR) of this series of compounds. This poster will specifically focus on synthesis and biological profiles of analogs through modification of the 5-position of the isoxazole core, which led to compounds with potent functional antagonism of GHS-R and good GPCR selectivity.

29. DISCOVERY OF POTENT BIARYL DIKETOPIPERAZINE FSH RECEPTOR AGONISTS: RAPID LEAD OPTIMIZATION THROUGH PARALLEL SYNTHESIS. *Tao Guo¹, Guizhen Dong¹, Dan Fitzpatrick¹, Peng Geng¹, Koc Kan Ho¹, Charles H. Jibilian¹, Steven G. Kultgen¹, Ruiyan Liu¹, Edward McDonald¹, Kurt W. Saionz¹, Kenneth J. Valenzano¹, Dan Xie¹, Anton E.P. Adang², Nicole C.R. van Straten², and Maria L. Webb¹.* (1) Pharmacoepia, Inc, PO Box 5350, Princeton, NJ 08543-5350, tguo@pharmacop.com, gdong@pharmacop.com, (2) Lead Discovery Unit, N.V. Organon, PO Box 20, 5340 BH Oss, The Netherlands

Follicle stimulating hormone (FSH), a 38 kDa heterodimeric glycoprotein hormone, plays an important role in human reproduction. FSH is responsible for ovarian follicle maturation in women and for spermatogenesis in men. FSH

signals through the FSH receptor (FSHR), a seven transmembrane G protein-coupled receptor (GPCR) expressed on granulosa cells in the female and Sertoli cells in the male. In an effort to develop a small molecule FSHR agonist as a potential oral therapy for treating infertility and spermatogenesis disorders, ECLiPS(TM) encoded combinatorial libraries were screened using FSHR transfected cells to provide micromolar agonist hits. Based on these hits, three parallel libraries were designed and synthesized on solid phase, resulting in the discovery of potent nanomolar biaryl diketopiperazine FSH receptor agonists. Details of the parallel synthesis and SAR will be presented.

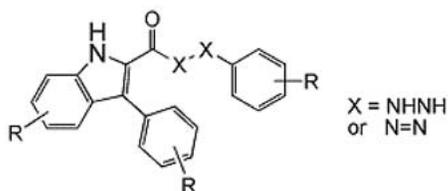


FSH EC₅₀ = 1.2 nM

30.

3-PHENYL-2-INDOLYL CARBOHYDRAZIDE AND THEIR AZO ANALOGUES AS POTENT ANTAGONISTS FOR THE GALR3 RECEPTOR. *Uendra P. Topiwala, Heidi Chen, Hermogenes Jimenez, Michael Reitman, John M. Wetzel, Mary Walker, Kiho Han, Noel Boyle, Gerald Caputo, Galina Muske, and Michael J. Konkel, Synaptic Pharmaceutical Corp., A Lundbeck Company, 215 College Road, Paramus, NJ 07652-1431, Fax: 201-261-0623, UPT@lundbeck.com, HIC@lundbeck.com*

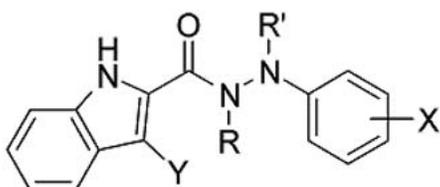
The previous poster describes our discovery of 3-phenyl-2-indolylcarbohydrazide as an antagonist at the GalR3 receptor. This poster describes SAR investigations on this series and efforts to replace the carbohydrazide moiety. These efforts revealed that azo analogues showed significantly enhanced affinity for the GalR3 receptor (e.g. SNAP 98529, 39 nM). This poster highlights the synthesis and SAR in these series.



31.

DISCOVERY OF 3-PHENYL-2-INDOLYL CARBOHYDRAZIDES AS ANTAGONISTS OF THE GALR3 RECEPTOR. *Heidi Chen, Uendra P. Topiwala, Lakmal W. Boteju, Eman Eldemenky, Hermogenes Jimenez, Michael Reitman, Mary W. Walker, Kiho Han, Noel Boyle, Gerald Caputo, Galina Muske, Jing Yang, Michael J. Konkel, and John M. Wetzel, Department of Chemistry, Synaptic Pharmaceutical Corporation, A Lundbeck Company, 215 College Road, Paramus, NJ 07652, Fax: 201-261-0623, HIC@lundbeck.com, UPT@lundbeck.com*

The endogenous ligand galanin has three identified receptors: GalR1, GalR2 and GalR3. In an effort to identify lead compounds for the GalR3 receptor, a screening effort identified SNAP 41176, a substituted indole carbohydrazide, as a lead compound (K_i = 1.8 μM). We report here our lead optimization and SAR studies on the carbohydrazide series, including the use of pharmacophore modeling and Hip-Hop alignment. This effort led to the discovery of SNAP 94927 (K_i = 147 nM). This poster highlights the synthesis and SAR.

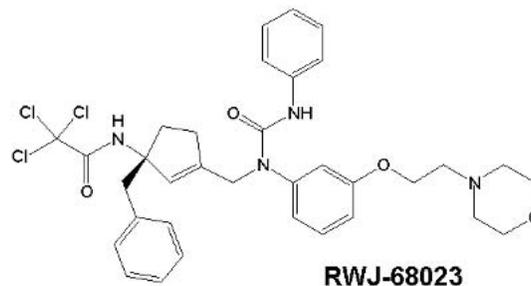


32.
WITHDRAWN.

33.

SYNTHESIS AND SAR STUDIES WITH A FIRST IN CLASS SERIES OF NON-PEPTIDE MOTILIN RECEPTOR ANTAGONISTS. *Min Amy Xiang, Philip Rybczynski, Robert H.K. Chen, Mary Pat Beavers, Donald W Combs, Joseph W Gunnet, William Hageman, John B Moore, Lubing Zhou, Maud Urbanski, and Keith T Demarest, Johnson & Johnson Pharmaceutical Research and Development, LLC, Raritan, NJ 08869, Fax: 908-203-8109, mxiang@prdus.jnj.com, prybczyn@prdus.jnj.com*

A novel scaffold for motilin receptor antagonists was discovered from the corporate compound library (IC₅₀ = 1 μM). The rationale for the selection of this series, the stepwise synthetic strategy used to increase the binding affinity of the initial lead 1000-fold, and the resolution of key intermediates toward the synthesis of the active enantiomer will be included. Compounds in this series of trisubstituted cyclopentenes were shown to inhibit the binding of motilin to human antral smooth muscle membrane, and to antagonize motilin-induced intracellular calcium mobilization in cells expressing the human motilin receptor. The most potent compounds were also effective in inhibiting motilin-induced contractility in rabbit duodenum.

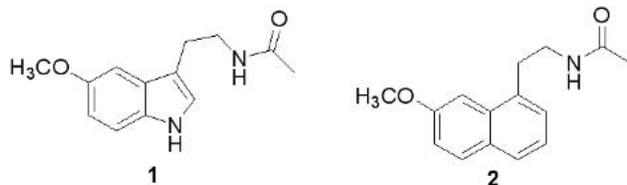


34.

SYNTHESIS OF AGOMELATONIN AND BIOLOGICAL ACTIVITY ON THE RAT DUODENUM MOTILITY AND CRAYFISH PHOTORECEPTORS. *Alfonso Lira-Rocha¹, Victor H. Pérez Castillo¹, Elia B. Naranjo-Rodríguez¹, Ofelia Espejo González¹, Beatriz Fuentes-Pardo², and Araceli De la O Martínez². (1) Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Cd. Universitaria, Coyoacán, México 04510, Mexico, Fax: 56225329, lira@servidor.unam.mx, (2) Facultad de Medicina, Universidad Nacional Autónoma de México*

The melatonin **1**, hormone secreted by pineal gland, has shown a short half-life period. Three types of melatonin receptors have been characterized (MT₁, MT₂, MT₃) but selective compounds for these receptors are not available. In the search of these, several types of compounds have been prepared. An important

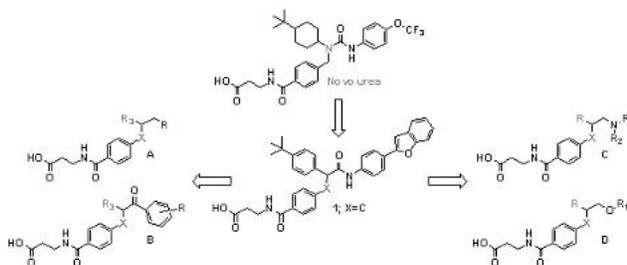
representative is agomelatonin **2**, a bioisoster of melatonin. Here we report a short synthetic route for the preparation of **2**. In addition, we evaluated the effect of this compound on the rat duodenum motility and on crayfish photoreceptors. Compared to melatonin, agomelatonin showed similar activity on the rat duodenum, but its effect on crayfish photoreceptors was different.



35. TOWARDS A POTENT SMALL MOLECULE GLUCAGON RECEPTOR ANTAGONIST.

Ravi Kurukulasuriya, Bryan K. Sorensen, and James T. Link, Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, Ravi.Kurukulasuriya@abbott.com

Glucagon, a 29-amino acid peptide, is the primary counter regulatory hormone to insulin in glucose homeostasis. In the postprandial state, patients with type 2 diabetes have elevated glucagon levels which lead to increased hepatic glucose output (HGO) and results in increased plasma glucose levels. Glucagon receptor antagonist have been efficacious in reversing the effects of glucagon challenge in animals and humans. We have discovered several series of small molecule glucagon receptor antagonists using a proprietary compound from Novo Nordisk as the lead. Initial medicinal chemistry strategies centered on acyclic linkers replacing the urea group yielded potent hGlucR antagonists. The biaryl amide **1**, an antagonist discovered by the project team showed a 50% decrease in glucagon induced plasma glucose levels in Sprague Dawley rats. Medicinal chemistry efforts to expand the strategy to generate urea like linkers with better physical properties such series A, B, C, and D will be discussed.



36. ANTAGONISTS OF GLUCAGON RECEPTOR FOR TYPE 2 DIABETES TREATMENT.

Hwan Soo Jae, Marty Winn, Bryan K Sorensen, James T. Link, Andy L Alder, Nelson D. Grihalde, Chun W. Lin, and Sham Hing, 4CB, AP10-LL, Metabolic Research and Drug Analysis Department, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064-6098, Fax: 847-938-1674, hwan-soo.jae@abbott.com

Glucagon which is a 29 amino acids peptide hormone is released into blood-stream when circulating glucose is low and stimulate hepatic glucose out to lead to increases in glycemia. Therefore glucogon raises plasma glucose levels in response to insulin-induced hypoglycemia¹. Glucagon receptor antagonists are contributed to attenuate endogenous glucose production and expect a useful tool of treatment of type2 diabetes. We have discovered a series of substituted 2-(phenoxy) phenyl acetamides that are glucogon receptor antagonists. They have demonstrated antagonism in a glucogon challenge model. Synthesis methods of these compounds and SAR will be discussed.

37. [11C]-SN003: A POTENTIAL PET LIGAND FOR IN VIVO IMAGING OF CRF1 RECEPTORS.

J. S. Dileep Kumar¹, Vattoly J Majo¹, Ramin V. Parsey¹, Victoria Arango¹, Mark D. Underwood¹, Norman R. Simpson², Suham Kassir¹, Jaya Prabhakaran¹, Julie Arcement¹, Ronald L. Van Heertum², and J. John Mann³. (1) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, Fax: 212-543-6017, dk2038@columbia.edu, (2) Department of Radiology, Columbia University, (3) Department of Psychiatry, Radiology & Division of Neuroscience, Columbia University & New York State Psychiatric Institute

Abnormal expression of CRF1, mostly up-regulation, is thought to comprise part of the pathogenesis of a diverse range of neuropsychiatric disorders such as anxiety, mood disorders, obsessive-compulsive disorder, posttraumatic stress and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Development of a high-specific radiolabeled, pharmacologically selective CRF1 receptor antagonists for Positron Emission Tomography (PET) would make it possible to quantify binding to CRF1 receptors in vivo, to study the pathophysiology of depression, anxiety and neurodegenerative diseases. Towards this we synthesized [O-methyl-11C]-N-[2-methyl-4-methoxyphenyl]-1-(1-(methoxymethyl)-propyl)-6-methyl-1H-1,2,3-triazolo[4,5c]pyridine-4-amine ([11C]SN003). 4-[1-(1-Methoxymethyl-propyl)-6-methyl-1H-[1,2,3]triazolo[4,5-c]pyridin-4-ylamino]-3-methylphenol, the precursor molecule for the radiolabeling was synthesized from 2,4-dichloro-6-methyl-3-nitropyridine in 7 steps with 20 % overall yield. The total time required for the synthesis of [11C]SN003 is 30 minutes from EOB using [11C]methyl triflate in presence of NaOH in acetone, with a 65 % yield (EOB) and >99% chemical and radiochemical purities along with a specific activity of >2000 Ci/ mmol. The preliminary PET studies with baboon suggest that the tracer penetrates blood brain barrier and accumulates in brain. The details of the synthesis and the in vivo and in vitro validation of [11C]SN003 will be presented.

38. 1,4,5,6-TETRAHYDROIMIDAZO[4,5-D][1]BENZAZEPINE DERIVATIVES 2: ORAL ACTIVE NON-PEPTIDE ANTAGONISTS OF ARGININE VASOPRESSIN RECEPTORS.

Hiroyuki Koshio¹, Akio Kakefuda¹, Ippei Sato¹, Ryutaro Wakayama¹, Masanao Sanagi¹, Junko Tsukada², Takeyuki Yatsu¹, Shuichi Sakamoto³, and Shin ichi Tsukamoto¹. (1) Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan, Fax: +81-29-852-5387, koshio@yamanouchi.co.jp, (2) Drug Development Div, Yamanouchi Pharmaceutical Co., Ltd, (3) Institute for Technology Development, Yamanouchi Pharmaceutical Co., Ltd

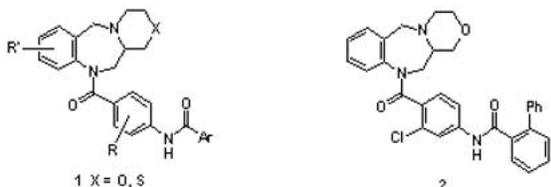
In the previous study, we reported 1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepine derivatives for dual arginine vasopressin (AVP) V1a and V2 receptor antagonists, including YM087 which is in the clinical stage. During continuing efforts to develop back-up candidates of YM087, we discovered new orally active non-peptide AVP antagonists derived from the 2-aryl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepine framework. A representative compound is YM-222546, which blocked the AVP-induced pressure response with a duration of over 8 hrs in conscious rats. Moreover, this compound increased urine volume in a dose-dependent manner in dehydrated conscious rats by oral administration. In this presentation, the synthesis, SAR and biological profiles of this series of antagonists will be discussed.

39. POTENT, SELECTIVE, ORALLY ACTIVE, NONPEPTIDE VASOPRESSIN RECEPTOR ANTAGONISTS.

Jay M. Matthews¹, Alexey B. Dyatkin¹, Leonard Hecker¹, Dennis J. Hlasta¹, William J. Hoekstra¹, Brenda Poulter¹, Patricia Andrade-Gordon¹, Lawrence de Garavilla¹, Keith Demarest¹, Eric Ericson¹, Joseph Gunnet¹, William Hageman¹, Richard Look¹, John Moore¹, Charles H. Reynolds², and Bruce E. Maryanoff¹. (1) Drug Discovery, Johnson and Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, Spring House, PA 19477, Fax: 215-628-3297, jmatthew@prdus.jnj.com, (2) Computer Assisted Drug Discovery, Johnson and Johnson Pharmaceutical Research & Development

The nonapeptide arginine vasopressin (AVP) is responsible for numerous biological actions as both a hormone and a neurotransmitter. Three G-protein-coupled receptors, denoted as V1a, V1b, and V2, are involved in AVP binding

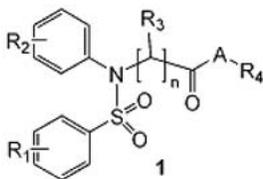
and cellular activation, resulting in important physiological responses such as reabsorption of water in the kidneys (V2), contraction of bladder, uterine, and vascular smooth muscle (V1a), breakdown of glycogen in the liver (V1a), aggregation of platelets (V1a), and release of corticotropin from the anterior pituitary gland (V1b). The V2 receptors on renal epithelial cells mediate AVP-induced antidiuresis to preserve normal plasma osmolality. Thus, selective, nonpeptide vasopressin V2 receptor antagonists have received attention for use in treating diseases with excessive renal reabsorption of water. We have developed a new family of tricyclic benzodiazepine compounds, **1**, which is exemplified by clinical candidate **2**. Our studies afforded receptor antagonists with good in vitro potency, selectivity for V2 over V1a, high oral bioavailability, and potent in vivo efficacy. We will discuss the chemical synthesis, assignment of enantiomers, and structure-activity relationships for the morpholine and thiomorpholine series, as well as the preclinical pharmacological activity of **2**.



40.

DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF A NOVEL CLASS OF POTENT, SELECTIVE OXYTOCIN RECEPTOR ANTAGONISTS. *Anna Quattropani¹, Jérôme Dorbais¹, David Covini¹, Serge Halazy¹, Alexander Scheer¹, Marc Missotten¹, Guidon Ayala¹, Anne Marie De Raemy-Schenk¹, Anthony Nichols¹, Rocco Cirillo², Enrico Gillio Tos², Lucia Golzio², Paolo Marinelli³, Claudio Giachetti², Claude Barberis⁴, André Chollet¹, and Matthias K. Schwarz¹.* (1) Serono Pharmaceutical Research Institute, CH-1228 Plan-les-Ouates, Geneva, Switzerland, Anna.Quattropani@serono.com, (2) Istituto di Ricerche Biomediche "A.Marxer", LCG-RBM, (3) RCC Ltd, (4) INSERM U469

Preterm labor, occurring in 7-10 % of deliveries in the developed world, is a major cause of perinatal mortality and morbidity. Several pharmacological agents to treat preterm labor have been developed but their use remains restricted due to lack of uterine selectivity, low efficacy and potentially serious side effects for mother and fetus. Oxytocin (OT) is a vital mediator of uterine contractility at the onset and during labor. An oxytocin receptor (OT-R) antagonist would have therapeutic use for the management of preterm labor by maintaining uterine quiescence and prolonging gestation. We will report a new class of small molecules of general structure **1** as selective and highly potent OT-R antagonists. The synthesis and SAR of these compounds will be described, as well as the optimization of their biopharmaceutical profile. Efficacy in different animal models of preterm labor via intravenous and oral route will be presented for the most potent compounds.



41.

ORAL hBNP CONJUGATES PART 1: DESIGN, SYNTHESIS AND CHARACTERIZATION. *Navdeep B. Malkar, Mark A. Miller, Mark J. Bednarcik, Monica E. Puskas, Kenneth D. James, and Nnochiri N. Ekwuribe, Nobex Corporation, PO Box 13940, Research Triangle Park, NC 27709, nmalkar@nobexcorp.com*

Congestive heart failure (CHF) is a common illness that affects over seven million Americans. CHF is the only cardiovascular disease that is increasing in prevalence worldwide, largely due to an older population and improved secondary prevention of acute myocardial infarction and hypertension. Recombinant human B-type natriuretic peptide (hBNP) is now being used to treat acutely decompensated CHF, but can only be administered via continuous infusion in a hospital setting.

NOBEX Corporation has developed a proprietary technology in which

amphiphilic oligomers are covalently attached to therapeutic agents, notably peptides, in order to facilitate oral delivery. In the present study, we report the design, synthesis and characterization of three different classes of hBNP conjugates. Through site-specific and oligomer-specific modification of the peptide, we have sought to alter the pharmacokinetic and pharmacodynamic properties of the compound while retaining its natural activity. The ultimate objective is the development of a derivative of hBNP that can be administered orally to treat patients suffering from chronic CHF.

42.

ORAL hBNP CONJUGATES PART 2: IN VITRO ACTIVITY AND BIOAVAILABILITY IN RATS. *Mark A. Miller, Navdeep B. Malkar, Kevin G. Yarbrough, David Surguladze, Jenn L. Boyer, Karen Polowy, Kenneth D. James, and Nnochiri Ekwuribe, Nobex Corporation, PO Box 13940, Research Triangle Park, NC 27709, mmiller@nobexcorp.com*

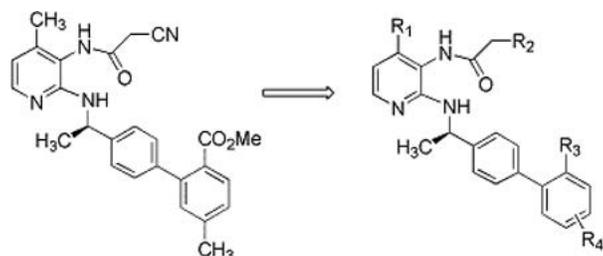
Human B-type natriuretic peptide (hBNP) is a treatment for acute congestive heart failure (CHF) that has been growing in use since its introduction in 2001. Human BNP binds to particulate guanylate cyclase receptors on vascular smooth muscle and endothelial cells. Binding to the receptor causes production of cyclic GMP, a secondary messenger important for maintaining cardiovascular and renal homeostasis. However, because it must be administered by continuous intravenous infusion, hBNP has not been used as a treatment for chronic CHF. Chronic CHF is currently treated with diuretics, digitalis drugs, Beta-blockers, ACE inhibitors, or ARBs, and the treatment often involves a combination of these drugs. An oral form of hBNP would be a desirable treatment for chronic CHF. However, proteins and peptides are not readily available for oral absorption and require modification or aid in the form of formulation. Nobex has developed proprietary technology in which amphiphilic oligomers are covalently attached to therapeutic agents, notably peptides in order to facilitate their oral delivery. Some goals of conjugation to hBNP are to provide protection from proteolysis, enhance bioavailability, and extend the circulating half life while retaining the activity of the natural peptide.

In Part 2 of our study, we report the results from testing of the hBNP conjugates. First, these conjugates were screened in vitro for agonist activity at the human natriuretic peptide receptor A (NPR-A). Although some conjugates were inactive at the receptor, many of the conjugates retained the activity of the native peptide. Conjugates showing activity were then assayed for bioavailability after oral dosing in rats.

43.

2,3-DIAMINOPYRIDINE BRADYKININ B1 RECEPTOR ANTAGONISTS. *Scott D. Kuduk¹, Christina Ng¹, Dong-Mei Feng¹, Jenny Wai¹, R. S. L. Chang², Charles M. Harrell², Kathy L. Murphy², R. W. Ransom², Duane Reiss², Thomayant Prueksaritanont³, Cuyue Tang³, Glenn Mason⁴, Susan Boyce⁴, Roger M. Freidinger¹, Douglas Pettibone², and Mark Bock¹.* (1) Department of Medicinal Chemistry, Merck & Co., Inc, WP14-3, Sumneytown Pike, Post Office Box 4, West Point, PA 19486, scott_d_kuduk@merck.com, (2) Department of Pharmacology, Merck Research Laboratories, (3) Drug Metabolism, Merck and Co., Inc, (4) Neuroscience Research Center, Merck & Co., Inc

The quest for improved treatments of chronic pain and inflammation continues to be an area of intense research. Human bradykinin B1 receptor antagonists embody a novel approach for the treatment for these disease states. A series of 2,3-diaminopyridine based BK B1 antagonists were optimized to have sub-nanomolar affinity for the human BK B1 receptor and good pharmacokinetic properties. The optimization was achieved by blocking a number of potential metabolic pathways, particularly through the use of various ester isosteres. Lead compounds were shown to exhibit good efficacy in rabbit in vivo models of pain and inflammation.



44.

C-TERMINAL TRUNCATION STUDY OF THE NOVEL CXCR4 CHEMOKINE

RECEPTOR LIGAND VMIP-II-(1-21)NH₂. Sandra C. Vigil-Cruz¹, Celia Amela-Cortés¹, Martha M. Rezende¹, Xin Wang¹, Elisabeth M. Perchellet², and Jean Pierre H. Perchellet². (1) Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, 4046 Malott Hall, Lawrence, KS 66045, Fax: 785-864-5326, svigil@ku.edu, amelacor@ku.edu, (2) Anti-Cancer Drug Laboratory, Kansas State University

Synthetic peptide fragments derived from viral macrophage inflammatory protein-II (vMIP-II) exhibit significant affinity for the CXCR4 chemokine receptor. Identification of the key structural features that contribute to this unique peptide binding to CXCR4 will provide further insight into ligand-receptor interactions. We designed and synthesized a series of analogues containing a systematic single amino acid C-terminal truncation in order to obtain optimal peptide length. We evaluated the series of peptides for CXCR4 receptor affinity using a radioligand binding assay. Results from this study demonstrate that the lead peptide can be significantly truncated without sacrificing target receptor affinity. The new lead peptide will be used for further structure-activity relationship (SAR) studies. This research was supported by the NIH COBRE award 1P20RR15563, matching support from the State of Kansas, and the University of Kansas.

45.

4-(9-ARYLTROPANYLIDENEMETHYL)BENZAMIDES AS OPIOID AGONISTS.

Philip M. Pitis¹, John R. Carson¹, Steven J. Coats², Ellen E. Codd¹, Scott L. Dax¹, Jung Lee¹, Rebecca P. Martinez¹, Linda A. McKnown³, Wu Nan Wu³, Sui Po Zhang¹, and Lou Anne Neilson⁴. (1) Analgesics Research Team, Johnson and Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Rds, P.O. Box 0776, Spring House, PA 19477-0776, Fax: 215-628-4985, ppitis@prdu.s.jnj.com, (2) Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, LLC, (3) Johnson and Johnson Pharm. Research and Development, LLC, (4) Department of Medicinal Chemistry, Merck Research Laboratories

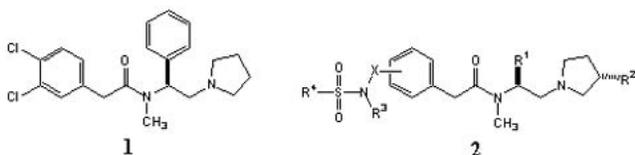
A series of N,N-dialkyl-4-(9-aryltropanylidene)methyl)benzamides was prepared. Certain of these compounds were extremely potent and selective delta opioid agonists and lacked the convulsive side effects associated with earlier delta agonists. In particular, (-)-N,N-Diethyl-4-[[8-phenethyl-8-aza-(1R, 5S)bicyclo[3.2:1]oct-3-ylidene]-phenyl-methyl]-benzamide was a potent, selective delta opioid agonist which elicited powerful antinociceptive effects. Unexpectedly, it was found that this substance underwent metabolic conversion to the corresponding monoethyl amide and that the monoethyl amide was a potent and selective mu opioid agonist. It is suggested that the secondary amide function, within this family of compounds, could be termed a "mu address".

46.

ARYLACETAMIDE κ AGONISTS WITH REDUCED CYTOCHROME P450 2D6

ACTIVITY. Christopher W. Ajello¹, Bertrand Le Bourdonnec¹, Joel A. Cassel², Gabriel Stabley², Serge Belanger², Robert N. DeHaven², and Roland E. Dolle¹. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, Fax: 484-595-1551, cajello@adolor.com, (2) Department of Pharmacology, Adolor Corporation

κ opioid receptor agonists of the arylacetamide class, e.g. ICI 199441 (**1**), were found to display potent affinity for cytochrome P450 2D6 (CYP2D6). Certain analogs bearing a substituted sulfonylamino group, e.g. **2**, were discovered to have significantly reduced affinity (IC₅₀ > 10 μ M) for CYP2D6 while retaining nanomolar affinity for the κ receptor. Synthesis, SAR and *in vitro* profile of this class of compounds will be presented.

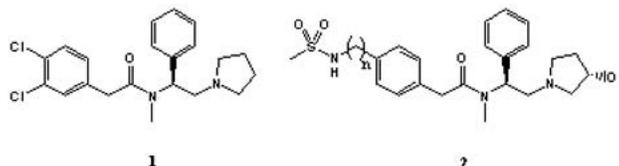


47.

MODELING STUDIES OF CYTOCHROME P450 2D6 ACTIVITY OF

ARYLACETAMIDE κ AGONISTS. Pamela R. Seida¹, Roberta G. Susnow², Christopher W. Ajello¹, Bertrand Le Bourdonnec¹, Joel A. Cassel³, Robert N. DeHaven³, and Roland E. Dolle¹. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, pseida@adolor.com, (2) independent consultant, (3) Department of Pharmacology, Adolor Corporation

κ opioid receptor agonists of the arylacetamide class, e.g. ICI 199441 (**1**), were found to display potent affinity for cytochrome P450 2D6 (CYP2D6). Certain analogs bearing a sulfonylaminoalkyl group, e.g. **2**, were discovered to have significantly reduced affinity (IC₅₀ > 10 μ M) for CYP2D6 while retaining nanomolar affinity for the κ receptor. A 3-D homology model of human CYP2D6 was developed, based on the recent crystal structure of rabbit CYP2C5, and used to explain the observed SAR of this class of compounds towards CYP2D6.

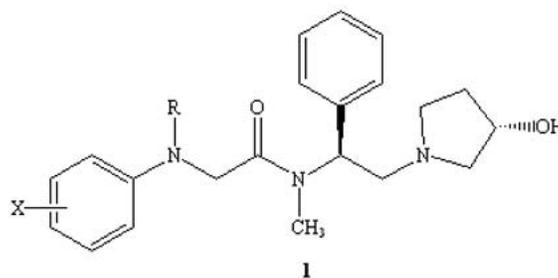


48.

NOVEL N-PHENYLAMINO ACETAMIDE DERIVATIVES AS POTENT AND

SELECTIVE KAPPA OPIOID RECEPTOR AGONISTS. Guo Hua Chu¹, Minghua Gu¹, Roland E. Dolle¹, Joel A. Cassel², Serge Belanger², Thomas M. Graczyk², and Robert N. DeHaven². (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

Kappa opioid receptor agonists display potent antinociceptive activity *in vivo*. As part of our discovery research program in this area, a novel series of phenyl-amino acetamide derivatives **1** with high affinity and selectivity for the kappa opioid receptor was synthesized. The details of the synthesis and biological activity of these novel kappa opioid receptor agonists will be presented.



49.

PARALLEL METHODS FOR THE PREPARATION OF N-ETHYL-4-[(8-ALKYL-8-AZA-BICYCLO[3.2.1]OCT-3-YLIDENE)-ARYL-METHYL]-BENZAMIDES,

POWERFUL MU AND DELTA OPIOID AGONISTS. Steven J. Coats¹, Mark J. Schulz¹, John R. Carson², Ellen E. Codd², Dennis J. Hlasta¹, Philip M. Pitis², Dennis J. Stone², Sui Po Zhang², and Scott L. Dax². (1) High-Throughput Chemistry, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Welsh & McKean Roads, P. O. Box 776, Spring House, PA 19477-0776, Fax: 215-628-3297, SCoats@prdu.s.jnj.com, (2) Analgesics Research Team, Johnson & Johnson Pharmaceutical Research & Development, L.L.C

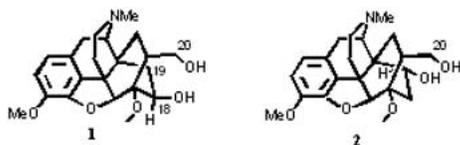
Two parallel synthetic methods were developed to explore the SAR of a series of potent opioid agonists. This series of tropanylidene benzamides proved extremely tolerant of structural variation while maintaining excellent opioid activity. Evaluation of several representative compounds from this series in the mouse hot plate test revealed potent antinociceptive effects upon oral administration.

50.

FUNCTIONALIZATION OF THE ETHANO BRIDGE OF ORVINOLS VIA AN

INTRAMOLECULAR BENZYL TRANSFER. *Huifang Wu¹, Weibin Chen¹, Deniz Bernard¹, Alexander D. MacKerell Jr.¹, Jeffrey R. Deschamps², and Andrew Coop¹.* (1) Department of Pharmaceutical Sciences, University of Maryland, School of Pharmacy, 20 Penn Street, Baltimore, MD 21201, huwu001@openwebmail.umaryland.edu, (2) Naval Research Laboratory

The orvinols, such as diprenorphine, etorphine, and buprenorphine, are a class of extremely potent opioids that have been extensively studied. Positions 18 and 19 have received little attention in terms of modification due to problems with severe steric hindrance, but we have recently shown that hydroxyl groups can be introduced into both the 18 and 19 positions (1 and 2). In an attempt to further functionalize these positions, we envisioned that selective protection of the less hindered 20-hydroxyl would allow the oxidization of the 18 and 19 hydroxyls. This was indeed the case for the 19-hydroxyl derivative 2, but when the 18-hydroxyl derivative 1 was treated with benzyl bromide, selective benzylation of the 18-hydroxyl resulted. We suggest that benzylation initially occurs at the least hindered 20-hydroxyl, followed by a benzyl transfer to the 18-hydroxyl due to their close proximity. Molecular modeling studies will be presented which add further insights into the mechanism of the reaction. The authors thank NIDA (DA-13583) for financial support.

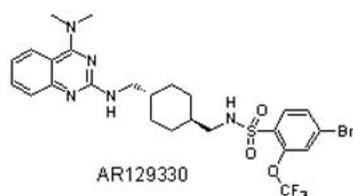


51.

DISCOVERY OF MCH-R1 ANTAGONISTS FROM GPCR-DIRECTED LIBRARIES.

Thuy Anh Tran¹, Nigel Beeley¹, Bill Thomsen¹, I Lin Lin¹, and Yoshinori Sekiguchi². (1) Arena Pharmaceuticals Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121, TTran@arenapharm.com, (2) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd

GPCR-directed libraries were designed and synthesized based on core structures selected from a range of known ligands for class 1 GPCRs. From within a sub-library built around quinazolines, we identified a number of compounds which were functional antagonists of the human MCH-R1 as demonstrated by their ability to inhibit MCH-induced calcium flux in cells transfected with a constitutively activated (CART) form of hMCH-R1. Initial hits for the receptor (e.g. AR129330) had IC₅₀ values in the 100nM range. Our “privileged structure” approach that resulted in interesting hits for hMCH-R1 as well as the physicochemical properties and *in vitro* PKprofiles of AR129330 and related compounds will be described.



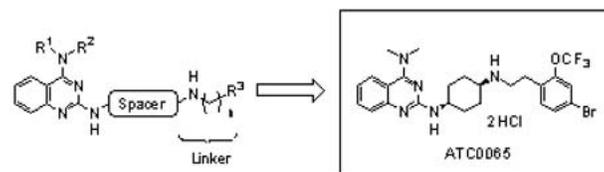
52.

IDENTIFICATION OF ATC0065 AS A POTENT ANTAGONIST OF HMCH-R1.

Kosuke Kanuma¹, Yoshinori Sekiguchi¹, Katsunori Omodera¹, Mariko Nishiguchi¹, Takeo Funakoshi¹, Shigeyuki Chaki¹, Bryan Kramer², Debbie Hsu², Martin Casper², Sonja Strah Pleyne², Graeme Semple², Nigel Beeley², Bill Thomsen², I Lin Lin², and Thuy Anh Tran². (1) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403 Yoshino-cho, Kita-ku, Saitama, Saitama 331-9530, Japan, k.kanuma@po.rd.taisho.co.jp, (2) Arena Pharmaceuticals Inc

In an effort to optimize our initial 4-(dimethylamino)quinazoline hMCH-R1 antagonist lead molecules, we focused our attention on different types of linker connecting the central spacer and right hand side portion with the aim of enhancing antagonist activity and improving the physicochemical and *in vitro* PKproperties. For this purpose we synthesized a series of amino-linked 4-(dimethylamino) quinazoline derivatives and identified ATC0065 as a potent

hMCH-R1 antagonist. Here, we highlight the synthesis and SAR of this series of derivatives including a detailed description of the properties of ATC0065.

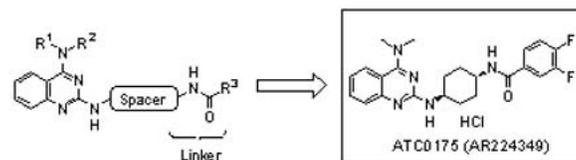


53.

IDENTIFICATION OF ATC0175 (AR224349) AS A POTENT ANTAGONIST OF

HMCH-R1. *Yoshinori Sekiguchi¹, Kosuke Kanuma¹, Katsunori Omodera¹, Mariko Nishiguchi¹, Takeo Funakoshi¹, Shigeyuki Chaki¹, Bryan Kramer², Debbie Hsu², Martin Casper², Sonja Strah Pleyne², Graeme Semple², Bill Thomsen², I Lin Lin², and Thuy Anh Tran².* (1) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403 Yoshino-cho, Kita-ku, Saitama, Saitama 331-9530, Japan, yoshi.sekiguchi@po.rd.taisho.co.jp, (2) Arena Pharmaceuticals Inc

During optimization of 4-(dimethylamino)quinazoline derivatives identified as hMCH-R1 antagonists from GPCR-directed screening libraries, we synthesized a series of amide-linked 4-(dimethylamino) quinazoline derivatives with the aim of enhancing biological activity and improving both the physicochemical properties and the *in vitro* PKprofile of our earlier lead series. From these efforts we identified ATC0175 (AR224349) as a potent antagonist of hMCH-R1. In this poster we will outline the synthesis and SAR of the amide-linked 4-(dimethylamino) quinazoline series including ATC0175.

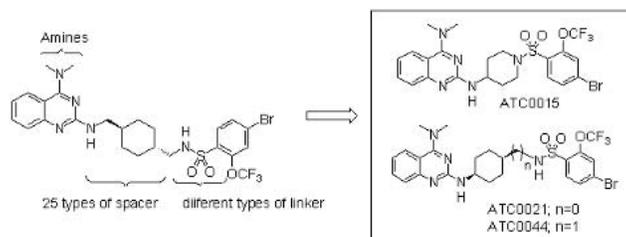


54.

SAR OF A SERIES OF 2-SUBSTITUTED 4-AMINO-QUINAZOLINES:

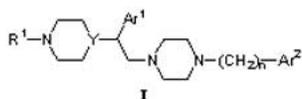
ANTAGONISTS OF HMCH-R1. *Bryan Kramer¹, Thuy Anh Tran¹, Debbie Hsu¹, Martin Casper¹, Sonja Strah Pleyne¹, Nigel Beeley¹, Bill Thomsen¹, I Lin Lin¹, Kosuke Kanuma², Katsunori Omodera², Mariko Nishiguchi², Takeo Funakoshi², Shigeyuki Chaki², and Yoshinori Sekiguchi².* (1) Arena Pharmaceuticals Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121, (2) Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd

A series of 4-(dimethylamino)quinazoline derivatives (e.g. AR129330) were identified as potential chemical starting points for our MCH-R1 discovery program from in-house libraries and a hit-to-lead program was initiated. We herein outline the development of the early SAR of these compounds including a detailed examination of the required spacing between the quinazoline portion and the terminal aromatic ring, the size and stereochemistry of the spacer group as well as a brief exploration of the substitution requirements around the terminal aromatic ring. These efforts resulted in the identification of compounds such as ATC0015, ATC0021, and ATC0044, and suggested that the length and stereochemistry of the spacer group is an important determinant of antagonist activity at hMCH-R1.



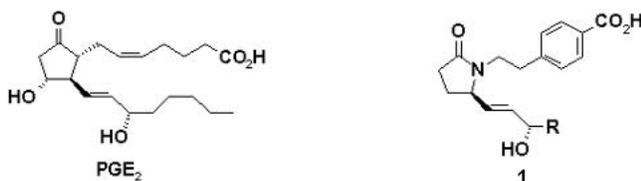
55. SYNTHESIS AND SARs OF NOVEL PIPERAZINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR ANTAGONISTS. *Atsuo Nakazato, Takaaki Ishii, Taketoshi Okubo, Dai Nozawa, Shigeyuki Chaki, Tomokazu Ueki, and Shigeru Okuyama, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403, Yoshino-cho, Kita-ku, Saitama-shi, Saitama 331-9530, Japan, Fax: +81-48-652-7254, atsuo.nakazato@po.rd.taisho.co.jp*

Melanocotin receptors (MC) consist of at least 5 different subtypes (1–5). Recently, some nonpeptide agonists of MC4 receptor have been investigated to discover drugs of feeding regulation. In contrast, we have presented that potent and selective MC4 receptor antagonist MCL0129, (-)-1-[2-(4-fluorophenyl)-2-(4-isopropylpiperazin-1-yl)ethyl]-4-[4-(2-methoxynaphthalen-1-yl)butyl]piperazine ($R^1 = i\text{-Pr}$, $Ar^1 = 4\text{-F-Ph}$, $Ar^2 = 2\text{-MeO-Nap}$, $n = 4$), exhibited anxiolytic-like and antidepressant-like activities. In this meeting, the synthesis and SARs of novel piperazine derivatives **1** as melanocortin-4 receptor antagonists will be presented.



56. DISCOVERY OF POTENT PROSTAGLANDIN EP₂ AND EP₄ RECEPTORS AGONISTS THAT INHIBIT BRONCHOMUSCLE CONSTRICTION IN GUINEA PIGS. *Zhong Zhao¹, Bagna Bao², Nadia Brugger¹, David Fischer³, Claudio Giachetti⁴, Lucia Golzio⁴, Srinivasa Karra¹, Paolo Marinelli⁴, Sean McKenna², Elizabeth Palmer², Adulla Reddy¹, Yufang Xiao¹, and Gian Luca Araldi¹.* (1) Biomedical Chemistry Group, Serono Reproductive Biology Institute, Rockland, MA 02370, zhong.zhao@serono.com, (2) Lead Discovery Group, Serono Reproductive Biology Institute, (3) Cellular and Biochemical Pharmacology Group, Serono Reproductive Biology Institute, (4) LCG-RBM, Discovery Serono International S.A

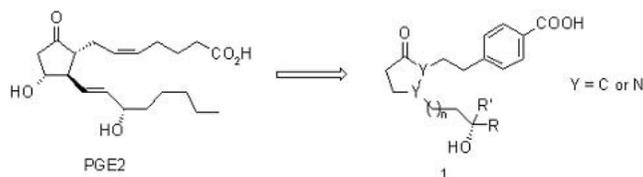
Analogues of PGE₂, wherein the hydroxyl cyclopentanone ring has been replaced with a γ -lactam ring and the alkenyl α -chain been replaced by the phenethyl chain (**1**) were found to exhibit potent and selective agonist activity at the prostaglandin E₂ and E₄ (EP₂ and EP₄) receptors. These compounds displayed improved *in vivo* pharmacokinetic profile. Receptor selectivity was modified by the appropriate selection of the ω -chain. The discovery of selective EP₂ or EP₄ receptor agonists is described, together with the finding of EP₂ and EP₄ dual agonists. These novel analogues resulted in an improved activity/duration profile compared to natural PGE₂. These analogues are shown to inhibit methacholine-induced bronchomuscle constriction in guinea pigs.



57. DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL AZA-PROSTAGLANDIN DERIVATIVES ANALOGS OF PGE₂ AS SELECTIVE EP₂ AND EP₄ RECEPTORS AGONISTS. *Gian Luca Araldi¹, Helena Majgier-Baranowska¹, Nadia Brugger¹, David Fischer², Yihua Liao¹, Elizabeth Palmer³, Yufang Xiao¹, and Zhong Zhao¹.* (1) Biomedical Chemistry Group, Serono Reproductive Biology Institute, One Technology Place, Rockland, MA 02370, Fax: 781-681-2939, gian.araldi@serono.com, (2) Cellular and Biochemical Pharmacology Group, Serono Reproductive Biology Institute, (3) Lead Discovery Group, Serono Reproductive Biology Institute

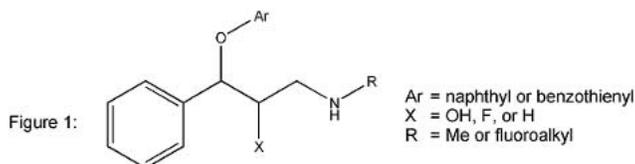
The preparation and assessment of biological activity of azaprostaglandin derivatives **1** analogues of the natural ligand for the prostaglandin receptors, PGE₂, is described. Replacement of the hydroxyl cyclopentanone ring with heterocyclic rings and substitution of the unsaturated α -alkenyl chain with a metabolically stable phenethyl chain led to the development of potent and selective analogs of PGE₂ with an improved pharmacokinetic profile. Receptor selectivity was achieved by the appropriate selection of the ω -chain. The discovery of selective EP₂, or EP₄ receptor agonists is described together with

the finding of novel EP₂ and EP₄ dual agonists. These analogues resulted in an improved activity/duration profile in comparison to PGE₂.



58. EFFECT OF HYDROXYLATION AND FLUORINATION OF ARYLOXY PHENYLPROPANAMINE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS ON CYP450 2D6 DEPENDANT METABOLISM. *Serge L. Boulet¹, Brian M. Mathes¹, Kevin J. Hudziak¹, John R. Boot², Anne Helene Clugery², Jeremy D. Findlay², Annie A. Lavis², Sivi Mahadevan³, Louise Wallace², and Sandra A. Filla¹.* (1) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-0715, boulet_serge@lilly.com, (2) Lilly Research Center, Eli Lilly and Company, UK, (3) Lilly Development Centre S. A, Eli Lilly and Company, Belgium

Stereoselective synthesis and evaluation of a series of 2-hydroxylated (Figure 1, X = OH), 2-fluorinated (X = F), and N-fluoroalkylated (R = fluoroalkyl) 3-aryloxy-3'-phenylpropanamines were undertaken to probe the effect of amine pKa modulation on CYP450 2D6 dependant metabolism. In general, lowering the pKa of the basic amine (range of -6.8-9.7) had the effect of decreasing the metabolism via CYP450 2D6. The modifications were also evaluated in terms of their binding affinities at the serotonin (5-HT) and norepinephrine (NE) transporters. The stereochemistry of the chain hydroxylated compounds (X = OH) was more important on binding affinities at 5-HT and NE than on their fluorinated counterparts (X = F) and, in general, N- fluoroalkylation (R = fluoroalkyl) was less tolerated.



59. SYNTHESIS AND DISCOVERY OF NOVEL SMALL MOLECULE INHIBITORS OF THE NOREPINEPHRINE RE-UPTAKE TRANSPORTER. *Manuel Cases¹, Gordon Campbell¹, Louise Haughton¹, John J. Masters², Magnus W. Walter¹, Peter T. Gallagher¹, David R. Dobson¹, Terry Finn¹, Benjamin Bonnier³, Craig White¹, Jeremy D. Findlay¹, Lorna Hayhurst¹, Ann Helene Kluge¹, Sivi Mahadevan³, Françoise J. Brunelle³, Claude L. Delatour³, Annie A. Lavis³, Nancy A. Dezutter³, Virginie N. Vervaeke³, Joël Y. Liénard³, and John R. Boot¹.* (1) Eli Lilly and Company Ltd, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU206PH, United Kingdom, (2) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, jjm@lilly.com, (3) Lilly Development Centre

Significant advances in the treatment of several neurological disorders have been realized by the clinical development and use of small molecule inhibitors of neurotransmitter re-uptake transporters. Small molecule inhibitors that are selective for the norepinephrine transporter (NET) have been shown to be effective for the treatment of both depression and attention hyperactivity disorders (ADHD). The laboratories have ongoing research efforts directed at the identification of selective and orally bioavailable antagonists of NET. In this poster, we present the structure activity relationships for a select group of novel and selective inhibitors of the NET. The synthetic routes, NET binding affinity, selectivity versus other biogenic amine transporters, and physicochemical properties of these molecules will be disclosed.

60.

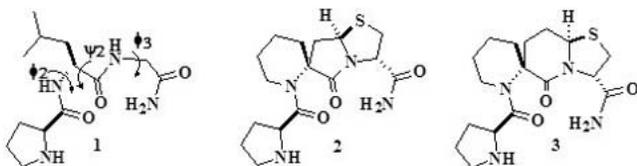
SYNTHESIS AND SELECTIVITY STUDIES OF YOHIMBINE AND ITS MONOMERIC ANALOGS ON α 2C-ADRENERGIC RECEPTORS. *Suni M. Mustafa¹, Supriya A. Bavadekar², Bob M. Moore¹, Stephen B. Liggett³, Dennis R. Feller², and Duane D. Miller¹.* (1) Department of Pharmaceutical Sciences, University of Tennessee, Health Science Center, 847 Monroe Avenue, Memphis, TN 38163, Fax: 901-448-6828, (2) Department of Pharmacology, University of Mississippi, (3) Department of Medicine and Pharmacology, College of Medicine, University of Cincinnati

It has been reported that α 2 adrenergic receptors play a modulatory role in the regulation of blood pressure. The relevance of α 2 adrenergic receptors for vascular tone regulation can be explored with yohimbine, a selective antagonist of these receptors. Yohimbine is one of the 32 isomers of indole alkaloids called yohimbanes and the selectivity of the various yohimbane alkaloids depends on the stereochemical configuration of the five carbon centers. The interaction of yohimbane compounds and the AR subtypes determine their use as pharmacological tools and therapeutic agents. To date drugs with high specificity for the α 2 adrenergic receptors show marginal selectivity. In order to develop selective α 2 subtype compounds, yohimbine dimers with methylene and methylene-diglycine spacer linkages were prepared and evaluated for receptor binding on human α 2-adrenoceptor subtypes expressed in Chinese hamster ovary cells. The in vitro results showed that such compounds are highly potent and selective α 2c-AR ligands. In continuation of these studies we have prepared several yohimbine monomers with different spacers and evaluated their selectivity on α 2c-AR ligands. The present poster describes the synthesis and selectivity studies of yohimbine and various monomeric analogs on α 2c- adrenergic receptors.

61.

SYNTHESIS OF PIPECOLIC ACID BASED SPIRO BICYCLIC PEPTIDOMIMETIC MODULATORS OF THE DOPAMINE RECEPTOR. *Ravindranadh V Somu and Rodney L. Johnson, Department of Medicinal Chemistry, University of Minnesota, 8-167 Weaver Densford Hall, 308 Harvard St. SE, Minneapolis, MN 55455, ravin002@umn.edu*

L-Prolyl-L-leucyl-glycinamide (PLG, **1**) has been found to exert an important modulatory effect on dopaminergic neurotransmission in the central nervous system. In an attempt to elucidate the bioactive conformation of PLG, several conformationally constrained spiro bicyclic analogs have been synthesized. The 5.5.5 analog was found to have activity comparable to PLG. Subsequent synthesis of the 5.5.6 and 5.6.5 analogs, with their high activity profile explicitly showed that even subtle changes in the torsional angles ϕ_2 and ψ_2 and ϕ_3 can result in significant changes in biological activity. The spiro bicyclic PLG analogs based upon the six-membered pipercolic acid residue were desired to explore the scope of these torsion angle changes further. However, lack of efficient methods for the asymmetric synthesis of 2-alkyl pipercolic acid makes this task chemically challenging. A versatile route was devised and the synthesis of six-membered analogs **2** (6.5.5) and **3** (6.6.5) was achieved successfully starting from racemic pipercolic acid.



62.

DESIGN, SYNTHESIS AND EVALUATION OF ENANTIOMERICALLY PURE SUBSTITUTED HEXAHYDROPIRAZINOQUINOLINES AS POTENT AND HIGHLY SELECTIVE DOPAMINE 3 RECEPTOR LIGANDS. *Ke Ding¹, Jianyong Chen¹, Min Ji¹, Xihan Wu¹, Judith Varady¹, Beth Levant², and Shaomeng Wang¹.* (1) The Department of Internal Medicine and the Department of Medicinal Chemistry, The University of Michigan, 1500 E. Med.Center Dr, Ann Arbor, MI 48109-0934, keding@med.umich.edu, (2) Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center

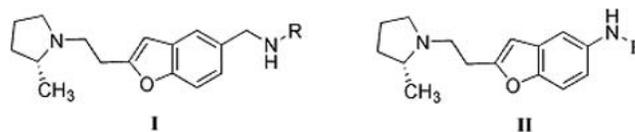
The D3 receptor has been proposed as a promising target for new therapies for treatment of addiction, dependence and abuse of cocaine and other psychostimu-

lants, schizophrenia, Parkinson's disease, depression and other neurological diseases. Through the structure- and computational pharmacophore-based database searching, we have identified hexahydropyrazinoquinolines as fairly potent D3 receptor ligands with moderate selectivity over other dopamine receptors. An efficient synthetic method was developed to prepare enantiomerically pure hexahydropyrazinoquinoline derivatives and to carry out structure-activity relationship studies, which led to new ligands with high-affinities for the D3 receptor and outstanding selectivity over the D1 and D2 receptors. For example, **15a** has a Ki value of 5.6 nM to the D3 receptor and selectivity greater than 10,000- and 1400-fold over the D1 and D2 receptors, respectively.

63.

SYNTHESIS AND SAR OF BENZOFURAN-BASED H3 RECEPTOR ANTAGONISTS. *Minghua Sun, Chen Zhao, Micheal Curtis, Ramin Faghieh, Gregory Gfesser, Thomas R. Miller, Kennen Marsh, Jill Wetter, Timothy A. Esbenshade, Arthur A Hancock, and Marlon Cowart, Neuroscience Research, R4MN, Abbott Laboratories, AP9A, 100 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-9379195, sun.minghua@abbott.com*

The histaminergic system modulates CNS physiology through H1, H2, and H3 receptors. H3 receptors play a role in the regulation of neurotransmitters such as histamine and acetylcholine, and H3 antagonists from a variety of chemical series demonstrate efficacy in rodent models of cognition and attention. Potent antagonists based on 5-aryl-substituted 2-aminoethylbenzofurans such as ABT-239 have been reported. In order to further improve potency and increase the diversity of this chemical series, two new sub-classes were investigated. Analogs with either a 5-aminomethyl (I) or a 5-amino (II) linkage were synthesized. Many compounds were found to have subnanomolar potency for rat and human H3 receptors. The synthesis and SAR of these new compounds, along with binding affinities and some pharmacokinetic properties will be described.



64.

PROBING THE LIGAND-BINDING POCKET OF THE CANNABINOID RECEPTORS: SYNTHESIS AND TESTING OF NOVEL PHENYL SUBSTITUTED SIDE-CHAIN ANALOGS OF Δ 8-THC. *Mathangi Krishnamurthy, Department of Pharmaceutical Sciences, University of Tennessee, Memphis, 847 Monroe Avenue, Rm 327, Memphis, TN 38163, Fax: 901-448-6828, mkrishna@utm.edu, Antonio M. Ferreira, Department of Chemistry, University of Memphis, and Bob M. Moore, Department of Pharmaceutical Sciences, University of Tennessee, Health Science Center*

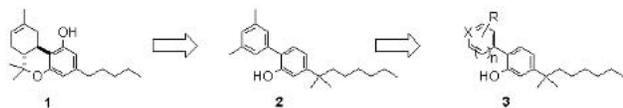
A novel series of phenyl substituted side-chain analogs of Δ 8-THC were synthesized to characterize the structural requirements of the ligand-binding pocket (LBP) of the CB-1 and CB-2 receptors. We hypothesized that the introduction of a phenyl side-chain would significantly alter the electronic properties of both the side-chain and ring A of Δ 8-THC while maintaining steric bulk and conformational restraint. We synthesized and tested a series of C1'-substituted phenyl derivatives with dimethyl (1), dithiolane (2), methylene (3) and ketone (4) substituents at the 1' position of the side-chain. Compounds (1) [CB-2 (Ki) – 0.91 nM, CB-1 (Ki) – 12.3 nM] and (2) [CB-2 (Ki) – 23.6 nM, CB-1 (Ki) – 297 nM] showed a 13-fold increase in selectivity for the CB-2 receptor in contrast to the lead compound Δ 8-THC [CB-1 (Ki)/CB-2 (Ki) – 1.14]. Here we report our efforts in optimizing the dimethyl phenyl lead (1) to further explore the SAR of this class of compounds.

65.

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIP OF BIARYL CANNABINOID MIMETICS. *Karin Worm¹, Q. Jean Zhou¹, Roland E. Dolle¹, Gabriel Stabley², and Robert N. DeHaven².* (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, kworm@adolor.com, (2) Department of Pharmacology, Adolor Corporation

Classical cannabinoids display a wide range of physiological effects including analgesic, anti-inflammatory, anticonvulsive and immunosuppressive activity. The tricyclic moiety in tetrahydrocannabinol (THC) **1** is not essential for binding to the cannabinoid receptors as demonstrated by the biaryl phenol **2**, a

previously reported cannabinoid mimetic. A solid phase synthesis approach and the commercial availability of a diverse set of aryl boronic acids allowed access to a large number of analogs **3**. Details of the synthesis including a comparison of microwave and conventional conditions, binding data to the CB1 and CB2 receptors and resulting SAR will be presented.



66.

SYNTHESIS AND BIOLOGICAL EVALUATION OF ADENOSINE A_{2A} RECEPTOR ANTAGONISTS. John Caldwell¹, Julius Matasi¹, Deen Tulshian¹, Leyla Arik², Ahmad Fawzi², Carolyn Foster², Lia Kwee Isaac², Jean Lachowicz², and Hongtao Zhang². (1) CV/CNS Department of Chemical Research, Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 908-740-7152, john.caldwell@spcorp.com, (2) CV/CNS Department of Biological Research, Schering Plough Research Institute

Parkinson's disease (PD) is a neurodegenerative motor disorder resulting from a deficiency of dopamine levels in the brain. Among existing therapies for Parkinson's disease are L-dopa and dopamine agonists which increase dopamine levels in the brain; yet, this therapy is limited by side effects and lack of efficacy over an extended time. Adenosine A_{2A} antagonists offer a potential effective treatment since they display an improvement in symptoms associated with Parkinson's disease in numerous animal models. A summary of the synthesis and SAR of a novel class of A_{2A} receptor antagonists will be presented.

67.

SYNTHESES OF NOVEL FLUORINATED PHENCYCLIDINE ANALOGS: VARIATION OF RING SIZES. Adebayo Adejare and Shengguo Sun, Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104-4495, Fax: 215-895-1161, a.adejar@usip.edu, ss0388@usip.edu

Selective non-competitive antagonists at the phencyclidine (PCP) binding sites on the N-methyl-D-aspartate (NMDA) receptor have potential as neuroprotective agents especially against neurodegeneration caused by over-stimulation of neurons during states of ischaemia such as stroke. The designed agents are expected to bind inside of and block the cation channel associated with NMDA receptors, preventing over-firing of the neurons even in the presence of excitants. The purpose of this study was to synthesize several designed compounds. All of the target compounds were synthesized in four steps, and the net yields varied from 5 to 41%. Each compound was characterized by obtaining ¹H, ¹³C, and ¹⁹F-NMR spectra as well as MS, all of which were consistent with the proposed structures. Pharmacological evaluations of the compounds on NMDA receptors are ongoing.

68.

SYNTHESIS AND EVALUATION OF POTENTIAL INHIBITORS AND INACTIVATORS OF γ -AMINO BUTYRIC ACID AMINOTRANSFERASE (GABA-AT). Zhiyong Wang and R. B. Silverman, Department of Chemistry, Northwestern University, 2145 Sheridan Rd, Evanston, IL 60208, Fax: 847-491-7713, wzyong@chem.northwestern.edu

γ -Aminobutyric acid aminotransferase (GABA-AT), a pyridoxal 5'-phosphate (PLP)-dependent enzyme, is responsible for the degradation of the inhibitory neurotransmitter γ -aminobutyric acid (GABA). Inhibition of this enzyme results in increased availability of GABA and could have therapeutic applications in treating neurological disorders such as epilepsy. Vigabatrin (4-aminohex-5-enoic acid; γ -vinyl GABA), an antiepileptic drug marketed in Europe, is a potent mechanism-based inactivator of GABA-AT. Inactivation has been shown to proceed by two divergent mechanisms: a Michael addition pathway and an enamine pathway. Four isosteres of vigabatrin in which a cyclopropane functionality is substituted for the alkene of vigabatrin were synthesized as potential inactivators of GABA-AT that can only inactivate the enzyme through the Michael addition pathway, but they were determined to be only reversible inhibitors of the enzyme.

The synthesis of all the four stereo isomers of 3-amino-5-oxocyclohexanecarboxylic acid as potential inhibitors of GABA-AT, and the synthesis of (2R,4S)-4-amino-6,6-dichlorobicyclo[3.1.0]hexane-2-carboxylic acid as a potential inactivator which might inactivate the enzyme through an aromatization mechanism, will also be discussed.

69.

1-(3-NITRO-PYRID-2-YL)-PIPERAZINE ANALOG AS POTENT METABOTROPIC GLUTAMATE RECEPTOR INHIBITOR. Ji Yang, Jiangchao Yao, Aniket Patel, Mohamed Hachicha, and Parviz Gharagozloo, Discovery Research, Purdue Pharma LP, 6 Cedar Brook Drive, Cranbury, NJ 08512, Fax: 609-409-6930, ji.yang@pharma.com

Neuropathic pain is caused by damage to the peripheral or central nervous system and is maintained by aberrant somatosensory processing. There is growing evidence relating the activity at Group I mGluRs (mGluR1 and mGluR5) to pain processing, and inhibiting these receptors reduces pain. We report in this poster that analogs with an ynone-linker between 1-(3-nitro-pyrid-2-yl)-piperazine and phenyl group exhibit superior potencies at mGluR5.

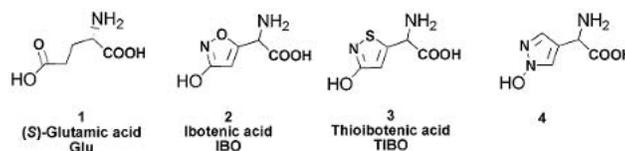
70.

SYNTHESIS OF NOVEL METABOTROPIC GLUTAMATE RECEPTOR LIGANDS.

Charlotte Grube Jørgensen¹, Jan Kehler², Hans Bräuner-Osborne¹, Povl Krosggaard-Larsen¹, and Ulf Madsen¹. (1) Department of Medicinal Chemistry, Danish University of Pharmaceutical Sciences, Universitetsparken 2, Copenhagen DK-2100, Denmark, chj@dfh.dk, (2) H. Lundbeck A/S

The Glu analogue and natural product Ibotenic acid (IBO, **2**), is an agonist at iGluRs and mGluRs and does not discriminate between Group I and II mGluRs. The sulphur analogue of IBO, thioibotenic acid (TIBO, **3**) and the pyrazole analogue (**4**) are agonists at Group I and Group II mGluRs but interestingly also at Group III mGluRs.

Analogues in the isothiazole and pyrazole series have been synthesized and the results will be presented. Introduction of substituents in compound **3** and **4** significantly changes the affinity for the different mGluRs, resulting in subtype-selective compounds.



71.

LIBRARY DESIGN AND SYNTHESIS OF IONOTROPIC GLUTAMATE RECEPTOR LIGANDS. Xiaohong Shou and A. Richard Chamberlin, Department of Chemistry, University of California, Irvine, Irvine, CA 92697, shoux@uci.edu

A new class of potential ligands for the kainate (KA) subclass of ionotropic glutamate receptors (iGluR) was designed and synthesized. Electrophysiological and pharmacological assays identified two reasonably potent molecules, the pharmacophore of which guides further library approach to the search for more active and selective iGluR ligands. Molecular modeling of the active ligands with iGluR2 suggested a core scaffold to generate the diversity of the library. Our screened ligands are intended to serve as pharmacological tools for iGluR characterization and provide novel insight into both structural and functional properties of iGluRs.

72.

ASYMMETRIC SYNTHESIS AND STUDY OF GLUTAMATE ANALOGUES. Jared K. Nelson¹, David J. Burkhart¹, Andrew R. McKenzie¹, Katherine I. Myers¹, Xue Zhao², Kathy R. Magnusson², and Nicholas R. Natale¹. (1) Department of Chemistry, University of Idaho, 301 Renfrew Hall, P.O. Box 442343, Moscow, ID 83844-2343, nels2437@uidaho.edu, (2) Biological Sciences Department, University of Idaho

Molecules that bind the glutamate receptor could potentially be useful as medicines to treat neurological disorders. We have prepared the glutamate sub-type selective ligand (S)-ACPA in high optical purity by an independent route which uses asymmetric catalysis. Our route compares very favorably to the previous resolution route: the literature yield was 0.2%, our overall yield is

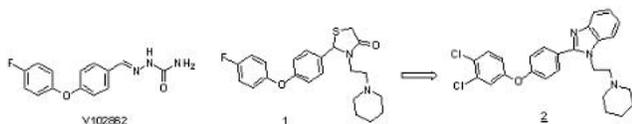
32%, approximately 160 times more efficient. Given that our synthesis can be performed routinely in 100 mg batches, and the literature path was reported on single mg scale, the overall improvement of efficiency for our synthetic route is four orders of magnitude. Additionally, our route is amenable to the development of structurally diverse analogues of ACPA. We have verified the biological efficacy of (S)-ACPA in a radioligand displacement study: our synthetic (S)-ACPA completely displaces AMPA from mouse brain within experimental error. Our current work involves the incorporation of novel functionality at the isoxazole C-5 position for synthesis of second-generation analogues, which may exhibit high-affinity, sub-type selective binding to the AMPA receptor.

73.

DESIGN AND SYNTHESIS OF NOVEL POTENT ARYL SUBSTITUTED

BENZIMIDAZOLES SODIUM CHANNEL BLOCKERS. Xiaoming Zhou, Qun Sun, Donald J. Kyle, Victor Ilyin, and Jim Limberis, Discovery Research, Purdue Pharma L.P., 6 Cedar Brook Drive, Cranbury, NJ 08512, Fax: 609-409-6930, xiaoming.zhou@pharma.com

V102862 is a state-dependent sodium channel blocker that is efficacious in animal models of neuropathic pain. However, an in vivo metabolism study in rats suggested that the semicarbazone moiety of V102862 could account for formation of toxic semicarbazide metabolites. In order to improve potency and pharmaceutical profile, a focused chemical library with various substituted thiazolidinones was prepared. The lead compound 1 was identified with a K_i of 90 nM for state-dependent inhibition of Nav1.2 (rBIIa Na) channels co-expressed with beta 1 subunit in *Xenopus* oocytes. Further modification of the thiazolidinone compound 1 led to a series of novel potent aryl substituted benzimidazoles (e.g. 2) as sodium channel blockers.



74.

DESIGN OF NOVEL SODIUM CHANNEL BLOCKERS BASED ON AN AMITRIPTYLINE SCAFFOLD, TOWARDS THE TREATMENT OF PAIN. Debjani P. Hudgens¹, Paulianda J. Griffith², Manoj K. Patel², and Milton L. Brown¹. (1) Department of Chemistry, University of Virginia, McCormick Road, P.O. Box 400319, Charlottesville, VA 22904, dp8p@virginia.edu, (2) Department of Anesthesiology, University of Virginia

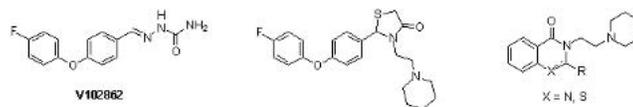
Sodium channel blockers may serve as a highly effective method for treating pain syndromes, such as neuropathic pain in the form of postherpetic neuralgia and diabetic neuropathy, as well as many other types of chronic pain. Recently literature precedence has shown that a known tricyclic antidepressant, amitriptyline, behaves as a potent sodium channel blocker with 73.8 (+/- 2.3) percent inhibition at 10 microM. This astonishingly high ability to block sodium channels is even much greater than the long-acting local anesthetic bupivacaine with 63.6(+/- 2.4) percent inhibition at 10 microM. Therefore amitriptyline would seem to serve as a highly effective scaffold from which numerous analogues could be derived. A series of compounds were then created utilizing traditional medicinal chemistry techniques, with modification of the scaffold at three major sites. Biological testing of these analogues by electrophysiological methods, along with direct displacement of [³H]-BTX, revealed these compounds to be potent channel inhibitors.

75.

QUINAZOLINONES AND BENZOTHIAZINONES AS NOVEL SODIUM CHANNEL BLOCKERS. Sam F. Victory, Qun Sun, Jim Limberis, and Donald J. Kyle, Discovery Research, Purdue Pharma, L.P., 6 Cedar Brook Drive, Cranbury, NJ 08512, sam.victory@pharma.com

V102862 is a potent state-dependent sodium channel blocker ($K_i = 370$ nM, rBIIa) that has been shown to be efficacious in the Chung model of neuropathic pain. Toward the discovery of a second-generation compound having an improved pharmaceutical profile, we embarked on a systematic structure-activity investigation aimed at replacing the semicarbazone moiety of V102862 with various heterocycles as a bioisosteric replacement. Our laboratories have reported on several series of high affinity sodium channel blockers as part of this effort, including a series of compounds containing a thiazolidinone ring

system as a replacement. Some of the most potent compounds in the thiazolidinone series possessed a hydrophobic aryl ether moiety, similar to V102862, and also a piperidinylethylamine moiety. To further explore the bioisosteric replacement of the semicarbazone moiety of V102862, several additional series of compounds were synthesized including those having a quinazolin-4(3H)-one or a 2,3-dihydro-benzothiazin-4-one core ring system. Within each of these new series, the optimized piperidinylethylamine group of the thiazolidinone series was held constant while the hydrophobic aryl ether moiety was varied, generating potent sodium channel blockers in each series. Details of the synthesis and SAR of analogues will be presented.



76.

CINNAOYLIMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS POTENT VOLTAGE-GATED POTASSIUM CHANNEL MODULATORS FOR USE AS

ANTICONSULSANTS. Callain Y. Kim¹, Wayne Childers², Magid Abou-Gharbia², Boyd Harrison², Donna Huryn², Kim Mason², Mark Bowlby³, Kenneth Rhodes⁴, Mike Monaghan³, Howard Zhang³, Flora Jow³, Steve Lin³, Qiang Wang³, and Tony Lee³. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, kimcy@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Department of Neuroscience, Wyeth Research, Princeton, (4) Johnson & Johnson Pharmaceutical, Raritan, NJ

Ion channels are transmembrane proteins that regulate the passage of various ions through the membrane. In excitable tissues, voltage-gated potassium (Kv) channels play an essential role in establishing the resting membrane potential and in modulating the frequency and duration of the action potential. Opening of Kv1.1-containing channels in response to depolarization induces an outward current that serves to re-polarize the membrane, preparing it for subsequent depolarization events. Association of the pore-forming Kv1.1 α -subunit with the cytoplasmic Kv β 1 subunit bestows rapid inactivation upon the ion channel. Currents resulting from the opening of Kv channel complexes possessing the Kv1.1/Kv β 1 complex are thought to play an important role in neuronal excitation and neurotransmitter release in excitatory glutamatergic pathways that are often implicated in epileptic seizure activity. Therefore, agents that activate Kv1.1 currents or, alternatively, inhibit the inactivation of Kv1.1 currents (disinactivators) in these seizure-sensitive brain regions would be expected to reduce neuronal excitability, raise seizure threshold and serve as efficacious anticonvulsant agents. Our investigations into this target have identified several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in a PTZ-induced seizure model. This presentation describes the design, synthesis and SAR of a series of cinnamoylimidazolidine-2,4-dione derivatives which possess anticonvulsant potency and a therapeutic index that are superior to that of the standard antiepileptic drug valproic acid.

77.

DESIGN, SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF 3-BENZOYLIMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS A KV1.1/ β 1 POTASSIUM CHANNEL DISINACTIVATOR. Callain Y. Kim¹, Wayne Childers², Magid Abou-Gharbia², Boyd Harrison², Donna Huryn², Mark Bowlby³, Kenneth Rhodes⁴, Mike Monaghan³, Howard Zhang³, Flora Jow³, Steve Lin³, Qiang Wang³, and Tony Lee³. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, kimcy@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, (3) Department of Neuroscience, Wyeth Research, Princeton, (4) Johnson & Johnson Pharmaceutical, Raritan, NJ

Voltage-gated (Kv) K⁺ channels are octameric membrane proteins found in all excitable cells. In neurons, these channels re-polarize the plasma membrane following excitatory synaptic events or action potentials, and thereby control neuronal excitability and neurotransmitter release. Accumulating evidence suggests that complexes containing the pore-forming Kv1.1 α -subunit and the cytoplasmic Kv β 1-subunit play a major role in action potential propagation and neurotransmitter release in excitatory glutamatergic pathways. These subunits coassociate to form Kv channels that activate upon membrane depolarization, but then rapidly inactivate, allowing these channels to set the interval between action potentials and control nerve terminal depolarization. Compounds that

inhibit this rapid inactivation (termed "disinactivators") would be expected to keep these channels open longer, resulting in hyperpolarization of the neuronal membrane, lengthening of the inter-spike interval and reduction in neurotransmitter release. Through these effects, disinactivators should raise seizure threshold and block the initiation of epileptic seizures. Our investigations have led to the identification of several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in vivo in a PTZ-induced seizure model. The design, synthesis and SAR of a series of 3-benzoylimidazolidine-2,4-dione derivatives will be described.

78.

FUSED BICYCLIC DIONE DERIVATIVES AS KV1.1/KV β 1 POTASSIUM CHANNEL DISINACTIVATORS WITH ANTICONVULSANT ACTIVITY. *Lynne Greenblatt¹, Jerome Wu¹, Boyd Harrison¹, Donna Huryn¹, Magid Abou-Gharbia¹, Alan Katz¹, Mark Bowlby², Flora Jow², Yan Lee², Steven Lin², Mike Monaghan², Kenneth Rhodes³, Qiang Wang², and Howard Zhang².* (1) Chemical and Screening Sciences, Wyeth Research, CN-8000, Princeton, NJ 08543, Fax: 732-274-4505, greenbl1@wyeth.com, (2) Department of Neuroscience, Wyeth Research, Princeton, (3) Johnson & Johnson Pharmaceutical, Raritan, NJ

Voltage-gated (Kv) K⁺ channels are octameric membrane proteins found in all excitable cells. In neurons, these channels re-polarize the plasma membrane following excitatory synaptic events or action potentials, and thereby control neuronal excitability and neurotransmitter release. Accumulating evidence suggests that complexes containing the pore-forming Kv1.1 α -subunit and the cytoplasmic Kv β 1-subunit play a major role in action potential propagation and neurotransmitter release in excitatory glutamatergic pathways. These subunits coassociate to form Kv channels that activate upon membrane depolarization, but then rapidly inactivate, allowing these channels to set the interval between action potentials and control nerve terminal depolarization. Compounds that inhibit this rapid inactivation (termed "disinactivators") would be expected to keep these channels open longer, resulting in hyperpolarization of the neuronal membrane, lengthening of the inter-spike interval and reduction in neurotransmitter release. Through these effects, disinactivators should raise seizure threshold and block the initiation of epileptic seizures. Our investigations into this target have led to the identification of several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in vivo in a PTZ-induced seizure model. The design, synthesis and SAR of a series of fused bicyclic dione derivatives will be described.

79.

SUBSTITUTED HETEROCYCLIC DIONE AMIDE DERIVATIVES AS POTENT VOLTAGE-GATED POTASSIUM CHANNEL DISINACTIVATORS. *Jerome Wu¹, Gan Zhang², Alan Katz¹, Wayne E. Childers Jr.¹, Boyd Harrison¹, Donna Huryn¹, Magid Abou-Gharbia¹, Mark Bowlby³, Flora Jow³, Yan Lee³, Steven Lin³, Mike Monaghan³, Kenneth Rhodes⁴, Qiang Wang³, and Howard Zhang³.* (1) Chemical and Screening Sciences, Wyeth Research, CN-8000, Princeton, NJ 08543, Fax: 732-274-4505, wuc@wyeth.com, (2) Array Biopharma, Inc, Longmont, CO, (3) Department of Neuroscience, Wyeth Research, Princeton, (4) Johnson & Johnson Pharmaceutical, Raritan, NJ

Ion channels are transmembrane proteins that regulate the passage of various ions through the membrane. Voltage-gated potassium (Kv) channels participate in several cellular processes. In excitable tissues, these ion channels play an essential role in establishing the resting membrane potential and in modulating the frequency and duration of the action potential. Opening of Kv1.1-containing channels in response to depolarization induces an outward current that serves to re-polarize the membrane, preparing it for subsequent depolarization events. Association of the pore-forming Kv1.1 α -subunit with the cytoplasmic Kv β 1 subunit bestows rapid inactivation upon the ion channel. Currents resulting from the opening of Kv channel complexes possessing the Kv1.1/Kv β 1 complex are thought to play an important role in neuronal excitation and neurotransmitter release in excitatory glutamatergic pathways that are often implicated in epileptic seizure activity. Therefore, agents that activate Kv1.1 currents or, alternatively, inhibit the inactivation of Kv1.1 currents (disinactivators) in these seizure-sensitive brain regions would be expected to reduce neuronal excitability, raise seizure threshold and serve as efficacious anticonvulsant agents. Our investigations into this target have identified several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in a PTZ-induced seizure model. In this poster, we present the synthesis and SAR of

a series of pyrrolidine- and pyrazolidine-3,5-dione analogs which possess potent Kv1.1/Kv β 1 disinactivating activity. Evidence for a potential binding site on the Kv β 1 subunit will be discussed.

80.

SYNTHESIS AND SAR OF A SERIES OF CYCLIC 1,3-DIONES AS KV1.1/KV β 1 POTASSIUM CHANNEL DISINACTIVATORS POSSESSING ANTICONVULSANT ACTIVITY. *James J. Bicksler¹, Dimitri Sarantakis¹, Jerome Wu¹, Wayne E. Childers Jr.¹, Boyd Harrison¹, Donna Huryn¹, Magid Abou-Gharbia¹, Alan H. Katz¹, Mark Bowlby², Flora Jow², Yan Lee², Steven Lin², Mike Monaghan², Kenneth Rhodes³, Qiang Wang², and Howard Zhang².* (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, bicksjl@wyeth.com, (2) Department of Neuroscience, Wyeth Research, Princeton, (3) Johnson & Johnson Pharmaceutical, Raritan, NJ

Voltage-gated (Kv) potassium channels are octameric membrane proteins found in all excitable cells. In neurons, these channels re-polarize the plasma membrane following excitatory synaptic events or action potentials, and thereby control neuronal excitability. Accumulating evidence suggests that complexes containing the pore-forming Kv1.1 α -subunit and the cytoplasmic Kv β 1-subunit play a major role in action potential propagation and neurotransmitter release in excitatory glutamatergic pathways. Co-association of these subunits within the ion channel complex results in an ion channel that activates upon membrane depolarization, but then rapidly inactivates, allowing these channels to set the interval between action potentials and control nerve terminal depolarization. Compounds that inhibit this rapid inactivation (termed "disinactivators") would be expected to keep these channels open longer, resulting in hyperpolarization of the neuronal membrane, lengthening of the inter-spike interval and reduction in neurotransmitter release. Through these effects, disinactivators should raise seizure threshold and block the initiation of epileptic seizures. Our investigations into this target have led to the identification of several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in vivo in a PTZ-induced seizure model. The design, synthesis and SAR of a series of cyclic-1,3-dione derivatives will be described.

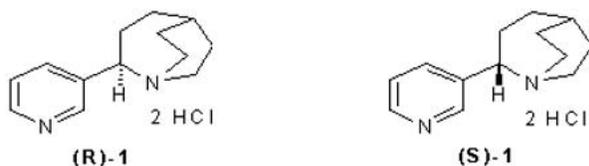
81.

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF BICYCLIC-1,3-DIONE DERIVATIVES AS KV1.1/KV β 1 POTASSIUM CHANNEL DISINACTIVATORS. *Wayne E. Childers Jr.¹, Jerome Wu¹, Callain Y. Kim², Edward Podlesny¹, Boyd Harrison¹, Donna Huryn¹, Magid Abou-Gharbia¹, Alan Katz¹, Mark Bowlby³, Flora Jow³, Yan Lee³, Steven Lin³, Mike Monaghan³, Kenneth Rhodes⁴, Qiang Wang³, and Howard Zhang³.* (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, childew@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA, (3) Department of Neuroscience, Wyeth Research, Princeton, (4) Johnson & Johnson Pharmaceutical, Raritan, NJ

Voltage-gated (Kv) K⁺ channels are octameric membrane proteins found in all excitable cells. In neurons, these channels re-polarize the plasma membrane following excitatory synaptic events or action potentials, and thereby control neuronal excitability and neurotransmitter release. Accumulating evidence suggests that complexes containing the pore-forming Kv1.1 α -subunit and the cytoplasmic Kv β 1-subunit play a major role in action potential propagation and neurotransmitter release in excitatory glutamatergic pathways. These subunits co-associate within the complex to form Kv channels that activate upon membrane depolarization, but then rapidly inactivate, allowing these channels to set the interval between action potentials and control nerve terminal depolarization. Compounds that inhibit this rapid inactivation (termed "disinactivators") would be expected to keep these channels open longer, resulting in hyperpolarization of the neuronal membrane, lengthening of the inter-spike interval and reduction in neurotransmitter release. Through these effects, disinactivators should raise seizure threshold and block the initiation of epileptic seizures. Our investigations into this target have led to the identification of several series of compounds that inhibit the inactivation of the Kv1.1/Kv β 1 complex and display anticonvulsant activity in vivo in a PTZ-induced seizure model. The design, synthesis and SAR of a series of bicyclic-1,3-dione derivatives will be described.

82. ENANTIOSPECIFIC SYNTHESIS OF NACHR LIGANDS, (R) AND (S)-2-(3-PYRIDYL)-1-AZABICYCLO[3.2.2]NONANE DIHYDROCHLORIDE. *B.S. Bhatti and Gregory D. Hawkins, Medicinal Chemistry, Targacept Inc, 200 East First Street, Suite 300, Winston-Salem, NC 27101-4165, Fax: 336-480-2113, bhattib@Targacept.com, greg.hawkins@targacept.com*

The synthesis and in vitro pharmacology of (R) and (S)-2-(3-pyridyl)-1-azabicyclo[3.2.2]nonane, (R)- and (S)-1, will be presented. The key step in the synthesis of the title compounds is the alkylation of the imine formed from 3-pyridylmethylamine and either (-) or (+)-2-hydroxy-3-pinane. These alkylations (using LDA and 4-(2-bromoethyl)oxane) occur in a complementary, stereospecific manner to yield intermediates which are readily transformed to (R)- and (S)-1. The enantiomeric purity of each of the title compounds was confirmed by chiral HPLC, and the absolute configurations were determined by X-Ray crystallographic analysis. While both (R)- and (S)-1 exhibit high affinity for CNS nAChRs, they differ in their activity at PNS nAChRs.



83. SELECTIVE $\alpha 7$ NICOTINIC RECEPTOR LIGANDS. *Anatoly Mazurov¹, Jozef Klucik², Lan Miao¹, Teresa Y. Phillips¹, Angela Seamans¹, Jeffrey D. Schmitt², and Craig Miller¹. (1) Department of Medicinal Chemistry, Targacept, Inc, 200 East First Street, Winston-Salem, NC 27410, Fax: 336-480-2113, anatoly.mazurov@targacept.com, (2) Molecular Design Group, Targacept, Inc*

The widely distributed and abundant $\alpha 7$ nicotinic acetylcholine receptors (nAChRs) have been reported to be involved in a number of processes, including cognition, neuroprotection, sensory gating, and inflammation. Selective modulators of the $\alpha 7$ subtype are thus potentially therapeutic in a variety of CNS disorders. Targacept's proprietary virtual library design methodologies were employed to guide iterative parallel optimization of an early lead. With minimal effort numerous highly potent and selective $\alpha 7$ ligands were developed, including a potent agonist ($K_i = 0.3$ nM; $EC_{50} = 33$ nM; $E_{max} = 100\%$). As a class, these compounds exhibit diminished activation of those receptor subtypes that are known to induce undesirable side effects (e.g., ganglionic and skeletal muscle nicotinic receptors as well as muscarinic receptors).

84. STRUCTURE ACTIVITY STUDIES OF MULTIPLE RING ANALOGUES OF METHYLLYCAONITINE: SYNTHESIS OF ANTAGONISTS TO THE NICOTINIC ACETYLCHOLINE RECEPTORS. *Stephen C. Bergmeier¹, Junfeng Huang¹, Damon D. Reed¹, Susan McKay², and Dennis B. McKay². (1) Department of Chemistry and Biochemistry, Ohio University, Athens, OH 45701, bergmeis@ohio.edu, (2) Division of Pharmacology, College of Pharmacy, Ohio State University*

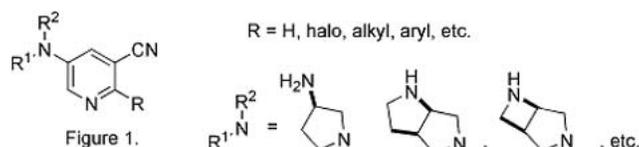
The development of agents for the differentiation of specific subtypes of neuronal nicotinic acetylcholine receptors (nAChRs) has significant implications for advancements in the treatment of a variety of pathological conditions. The goal of our research is to identify and understand molecular determinants of nAChR-small molecule interactions. Methylllycaconitine (MLA) is a diterpene alkaloid isolated from plants of the genera *Aconitum* and *Delphinium*. MLA is the most potent nonpeptide nAChR antagonist known with selectivity for $\alpha 7$ nAChRs, and moderate affinity for $\alpha 3\beta 4^*$ nAChRs. We have prepared analogues of MLA containing multiple rings of the norditerpenoid scaffold in order to provide compounds with enhanced potency and selectivity. We have prepared ring E/F, ring E/B, and ring B/F analogues of this complex alkaloid to understand the origins of these activities on multiple nAChRs subtypes. The synthesis and receptor affinity of these compounds will be presented.

85. STRUCTURE ACTIVITY STUDIES OF RING E ANALOGUES OF METHYLLYCAONITINE. SYNTHESIS OF ANTAGONISTS TO THE $\alpha 3\beta 4^*$ NICOTINIC ACETYLCHOLINE RECEPTORS. *Stephen C. Bergmeier¹, Junfeng Huang¹, Aravinda Pulipaka¹, Prasanna Pulanikat¹, Kristjan M. Arason¹, Khadiga Ismail², Darrell L. Bryant³, Susan McKay³, and Dennis B. McKay³. (1) Department of Chemistry and Biochemistry, Ohio University, Athens, OH 45701, bergmeis@ohio.edu, (2) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, (3) Division of Pharmacology, College of Pharmacy, Ohio State University*

The development of agents for the differentiation of specific subtypes of neuronal nicotinic acetylcholine receptors (nAChRs) has significant implications for advancements in the treatment of a variety of pathological conditions. The goal of our research is to identify and understand molecular determinants of nAChR-small molecule interactions. Methylllycaconitine (MLA) is a diterpene alkaloid isolated from plants of the genera *Aconitum* and *Delphinium*. MLA is the most potent nonpeptide nAChR antagonist known with selectivity for $\alpha 7$ nAChRs, and moderate affinity for $\alpha 3\beta 4^*$ nAChRs. We have prepared several series of ring E analogues in which both the succinimidoanthranilate ester and the piperidine nitrogen substituent have been extensively modified. The synthesis and receptor affinity of these compounds will be presented.

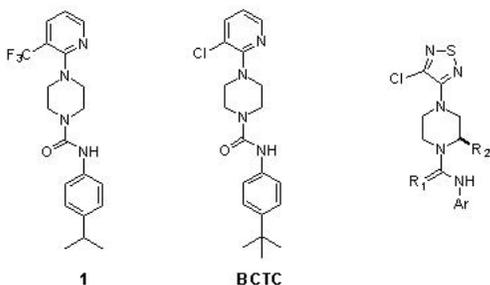
86. SYNTHESIS AND SAR EVALUATION OF 3-AMINO-5-CYANO PYRIDINES AS NOVEL $\alpha 4\beta 2$ NEURONAL NICOTINIC RECEPTOR (NNR) AGENTS. *Tao Li, David J. Anderson, Anwer Basha, William H. Bunnelle, Peter Curzon, Jianguo Ji, Jennifer M. Pace, Kevin Sippy, Michael R. Schrimpf, Karin Tietje, and Michael D. Meyer, R47W, Abbott Laboratories, AP9A-1, Abbott Park, IL 60064, Fax: 847-937-9195*

Neuronal nicotinic receptors (NNR) have been an important target for the treatment of central nervous system disorders. Among multiple NNR subtypes, the $\alpha 4\beta 2$ subtype is understood to be involved in the analgesic response of nicotinic compounds. Our team recently designed and synthesized a series of potent agonists built around the 5-cyanopyridine motif as shown in Figure 1. Various diamines at the 3-position, and a variety of substituents at the 6-position were investigated. The compounds are potent ligands for the $\alpha 4\beta 2$ NNR as evidenced by $K_i < 1$ nM for displacement of [³H](-)-cytisine from rat brain membranes and exhibit in vitro agonist efficacy in Ca^{++} flux experiments. In addition, several compounds have shown in vivo activity across a range of preclinical pain models. The synthesis and SAR of this series will be presented.



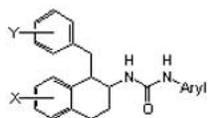
87. SYNTHESIS AND EVALUATION OF 1,2,5-THIA DIAZOLYLPIPERAZINES AS VANILLOID RECEPTOR 1 ANTAGONISTS. *Sam F. Victory, Laykea Tafesse, Bin Shao, Lori A. Schmid, Eugene Gross, Khondaker Islam, Qun Sun, Kenneth J. Valenzano, and Donald J. Kyle, Discovery Research, Purdue Pharma L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, sam.victory@pharma.com*

A series of 4-(2-pyridyl)piperazine-1-carboxamides were recently identified in our laboratory as highly potent vanilloid receptor 1 antagonists through a lead optimization process that began with the identification of compound 1 in an internal high-throughput screening effort. Results of this optimization process led to the identification of BCTC as a potent and orally available VR1 antagonist. To expand the SAR of the lead series, various heterocycles were utilized as a replacement for the pyridine ring. The 4-chloro-1,2,5-thiadiazole ring system was found to be one of the few effective replacements. Results of an SAR study that focused on modifications of the phenyl ring will be presented for a thiourea and urea series, as well as the results of introducing a methyl group onto the piperazine ring.



88. β -AMINOTETRALIN UREAS AS NOVEL VR1 ANTAGONISTS: SYNTHESIS, *IN VITRO* AND *IN VIVO* ACTIVITY. Michele C. Jetter¹, Mark A. Youngman¹, James J. McNally¹, Mark McDonnell¹, Scott L. Dax¹, Ellen E. Codd², Raymond W. Colburn², Dennis J. Stone², Sui Po Zhang², Christopher M. Flores², Nadia Nasser³, and Adrienne Dubin³. (1) Analgesics Chemistry, Johnson & Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Roads, Spring House, PA 19477, Fax: 215-628-4985, mjetter@prdu.s.jnj.com, (2) Analgesics Biology, Johnson & Johnson Pharmaceutical Research and Development, LLC, (3) Neurosciences, La Jolla CA, Johnson & Johnson Pharmaceutical Research and Development, LLC

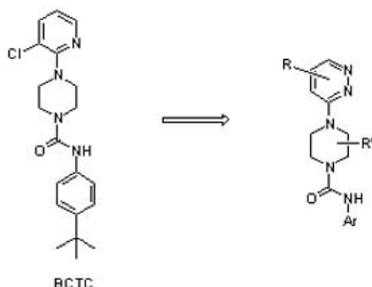
The human vanilloid receptor (VR1) is a cation-selective channel that is gated by nociceptive stimuli such as capsaicin (the pungent component of chili peppers), low pH, heat and endogenous ligands such as anandamide. These receptors are expressed by primary sensory neurons involved in nociception and neurogenic inflammation. The implication of the VR1 channel in pain and hyperalgesia make it an attractive therapeutic target for drug discovery. We have identified a novel series of VR1 antagonists that incorporates a β -aminotetralin scaffold as a key structural element. Compounds in this series exhibit low nanomolar activity in both VR1 binding and capsaicin-induced calcium flux functional assays. Many of these compounds have also been characterized in a rat carrageenan paw hot plate model where they possess oral activity in reversing inflammatory thermal hyperalgesia. This poster highlights the synthesis, chiral resolution and biological activity of several related series of aminotetralin ureas as potent VR1 antagonists.



Ar = 5-isoquinolinyl or 2-hydroxy-8-naphthyl

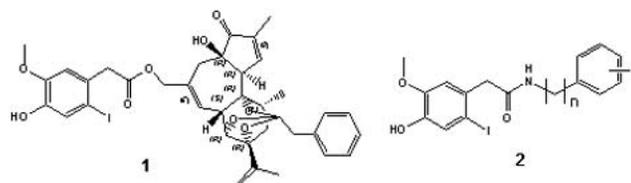
89. SYNTHESIS AND EVALUATION OF 4-(2-PYRIDAZINE)PIPERAZINE-1-CARBOXAMIDES AS VANILLOID RECEPTOR 1 ANTAGONISTS. Laykea Tafesse, Lori A. Schmid, Qun Sun, Yakov Rotshteyn, Kenneth J. Valenzano, and Donald J. Kyle, Discovery Research, Purdue Pharma L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, laykea.tafesse@pharma.com

A biased chemical library of 4-(pyridazine)piperazine-1-carboxamide analogs was prepared in an effort to improve the pharmaceutical and pharmacological profile of the lead compound BCTC. A library of approximately 50 analogs was prepared and evaluated for VR1 antagonist activity in capsaicin-induced (CAP) and pH (5.5)-induced (pH) FLIPR assays in a human VR1-expressing HEK293 cell line. The most potent VR1 antagonists were found to have IC₅₀'s in the range of 15-200 nM with improved pharmaceutical and pharmacological profile versus the lead BCTC. These compounds represent possible second generation BCTC analogs.



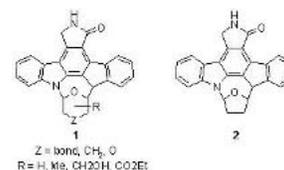
90. SYNTHESIS AND PHARMACOLOGY OF IODOHOMOVANILLIC AMIDES AS VANILLOID (VR1) ANTAGONISTS. Mark McDonnell¹, Scott L. Dax¹, Sui-Po Zhang¹, and Adrienne Dubin². (1) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Roads, Spring House, PA 19477, mmcdonne@prdu.s.jnj.com, (2) Johnson & Johnson Pharmaceutical Research and Development LLC

In our search for a more potent radioligand at the vanilloid (VR1) receptor, we discovered a novel iodinated resiniferatoxin (RTX) derivative, compound 1, with subnanomolar binding affinity. This finding, namely iodination at the C-2 center of the vanillyl moiety, was extended to lower molecular weight homovanillic acid derivatives, 2. The binding and functional activity of these compounds at VR1 is presented.



91. ANTI-TUMOR AND ANTI-ANGIOGENIC ACTIVITY OF HETEROCYCLE-BRIDGED FUSED PYRROLOINDENOCARBAZOLES. Ted L. Underiner¹, Bruce A. Ruggeri², Lisa Aimone³, Thelma S. Angeles³, George Gessner³, Edward Hellriegel⁴, Candy Robinson², Jasbir Singh⁵, and Shi X. Yang³. (1) Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: 610-344-0065, tunderin@cephalon.com, (2) Department of Oncology, Cephalon, Inc, (3) Department of Biochemistry, Cephalon, Inc, (4) Department of Drug Disposition and Safety, Cephalon, Inc, (5) Department of Medicinal Chemistry, MediChem

A series of heterocycle-bridged fused pyrroloindencarbazoles (1) were prepared and evaluated against a panel of kinases (e.g., trkA, VEGFR-2, PDGFR- β , PKC, and InRK). Preliminary pharmacokinetic properties of these carbazoles revealed that potent trkA inhibitor (2) possessed an oral bioavailability of 19% (rat). Compound 2 displayed significant growth inhibition of human and murine prostate carcinoma xenografts in nude mice, synergistic enhancement of survival in an orthotopic pancreatic tumor model when used in combination with gemcitabine and showed dose related anti-angiogenic activity when evaluated ex vivo (rat aortic ring explant model) as well as in vivo (PAEC-VEGF/bFGF Matrigel implant model).



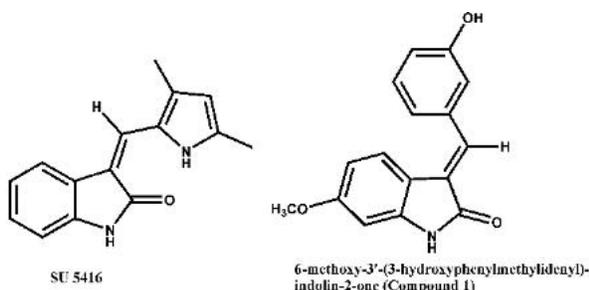
92. BENZENESULFONAMIDE DERIVATIVES AS NOVEL ANTIMICROTUBULE AGENTS. Ji Wang Chern, Grace Shiahuy Chen, Kuan Yu Chen, Pei Yu Chen, and Feng Yi Chen, College of Medicine, National Taiwan University, School of Pharmacy, No.1, Section 1, Jen-Ai Road, Taipei 100, Taiwan, Fax: 886-2-23934221, chern@jwc.mc.ntu.edu.tw

One of the major components of cancer progression is the loss of normal controls on cell growth. Antitumor agents which can alter the cancer cell cycle and induce apoptosis are the promising novel approaches. In the course of our study directed towards discovery of novel potential antitumor agents, the interesting antitumor activities of benzenesulfonamide derivatives prompted us to design a series of carbazolybenzenesulfonamides as potential cell cycle inhibitors. Two of our designed compounds, GM116 and GM119, exhibit potent antitumor activity and cause G2/M phase arrest against various cancer cell lines. Both compounds do not inhibit the cdk2/cyclin complex kinase activity and cause cyclin B protein accumulation. They were found to cause cell cycle arrest at M phase owing to its tubulin depolymerization ability and to induce apoptosis.

93.

SU-5416 ANALOGS WITH ANTI-PROLIFERATIVE, ANTI-MICROTUBULE AND APOPTOSIS INDUCING PROPERTIES. *Bulbul Pandit¹, Pui Kai Li¹, Zhigen Hu¹, Dan L. Sackett², Zili Xiao¹, and Christine Cheah¹.* (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) Laboratory of Integrative and Medical Biophysics, National Institute of Child Health and Human Development

Compounds that contain 2-indolinone moieties have been reported to exhibit diverse pharmacological activities. SU 5416 inhibits VEGF (FK-1) receptor tyrosine kinase activity and SU 6668, currently in phase III clinical trial, is a potent inhibitor of receptor tyrosine kinases. In our search for growth factor receptor kinase inhibitors, we discovered a group of 2-indolinone containing compounds with potent anti-proliferative activities (in submicromolar concentration) against PC-3 androgen-independent prostate cancer cell line. Cell cycle analyses indicated that our lead compound inhibits the growth of cancer cells by arresting the cells predominantly in G2/M phase. It also induces apoptosis and exhibits anti-microtubule activity similar to podophyllotoxin. Structure-activity-relationship studies indicate that the nature of the substituted group at the 3-position and the substitution patterns on the 2-indolinone moiety is critical to the anti-proliferative, anti-apoptotic and anti-microtubule activities. This is the first report that demonstrates anti-microtubule activity of 2-indolinone containing compounds.



94.

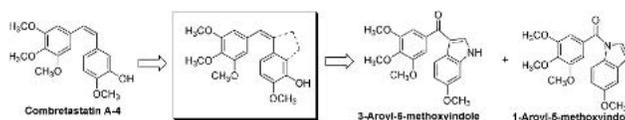
DISCOVERY OF STA-5312: A NOVEL MICROTUBULE INHIBITOR DEMONSTRATING POTENT IN VITRO AND IN VIVO ANTITUMOR ACTIVITIES AGAINST MDR CANCERS. *Lijun Sun, Keizo Koya, Hao Li, Teresa Przewloka, David James, Shoujun Chen, Zhiqiang Xia, Guiqing Liang, Noriaki Tatsuta, Yaming Wu, Dan Zhou, Timothy Korb, Zhenjian Du, and Mitsunori Ono, Synta Pharmaceuticals Corp, 45 Hartwell Avenue, Lexington, MA 02421, Fax: 781-274-8228*

The development of resistance to chemotherapy with existing anticancer drugs has challenged the pharmaceutical industry to rapidly identify and develop new chemical entities able to counteract this unmet medical needs. We report herein the detailed SAR studies that lead to the discovery of STA-5312, a novel indolizine microtubule inhibitor currently under phase-1 clinical trials. STA-5312 demonstrates substantial in vitro anti-proliferative activities against cancer cell lines, including multi-drug resistance (MDR) phenotypes, with IC50 values extending down into the nanomolar range. The in vitro cytotoxic effects have been demonstrated across a wide array of tumor types, including hematologic and solid tumor cell lines of various origins (e.g. leukemia, lymphoma, breast, colon, uterine). STA-5312 is as active against several tumor cell lines that express moderate to high levels of P-glycoprotein (Pgp), including cell lines insensitive to Paclitaxel, Vincristine, and Adriamycin in which Pgp activity is a major contributor to the MDR phenotype. STA-5312 also demonstrated in vivo activity in several murine tumors and human tumor xenograft models, including drug resistant tumors.

95.

CONCISE SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF COMBRETASTATIN A-4 ANALOGUES, 1-AROYLINDOLES AND 3-AROYLINDOLES, AS NOVEL CLASSES OF POTENT ANTITUBULIN AGENTS. *Hsing Pang Hsieh, Jing Ping Liou, Yi Ling Chang, and Shioh Ju Lee, Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, 9F, 161, Sec. 6, Min-Chuan East Road, Taipei, 114, Taiwan, Fax: 886-2-2792-9703, hphsieh@nhri.org.tw*

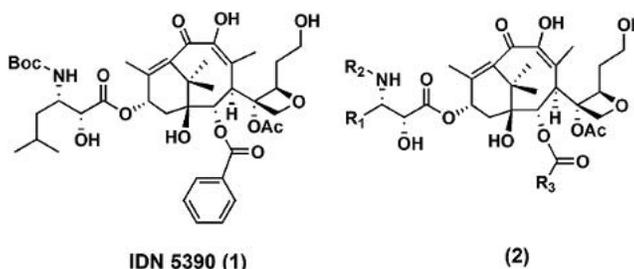
The synthesis and study of structure-activity relationship of two new classes of synthetic antitubulin compounds based on 1-aroilindole and 3-aroilindole skeleton are described. Lead compounds 3, 10 and 14 displayed potent cytotoxicity with IC50 = 0.9 to 22 nM against human NUGC3 stomach, MKN45 stomach, MESSA uterine, A549 lung, and MCF-7 breast carcinoma cell lines. The inhibition of proliferation correlated with in vitro polymerization inhibitory activities. Structure-activity relationships revealed that 6-methoxy substitution of 3-aroilindoles and 5-methoxy substitution of 1-aroilindoles contributes to a significant extent for maximal activity by mimicking the para substitution of the methoxy group to the carbonyl group in case of aminobenzophenones. Addition of a methyl group at the C-2 position on indole ring exerts increased potency. 3,4,5-Trimethoxybenzoyl moiety was necessary for better activity, but not essential and can be replaced by 3,5-dimethoxybenzoyl and 3,4,5-trimethoxybenzoyl moieties. We conclude that 1- and 3-aroilindoles constitute an interesting new class of antitubulin agents with the potential to be clinically developed for cancer treatment.



96.

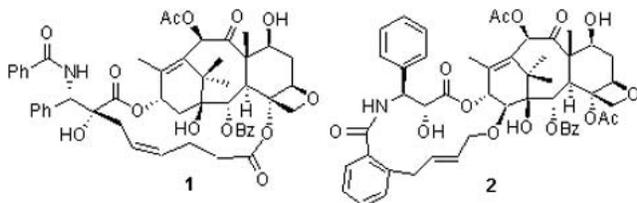
SYNTHESIS AND SAR STUDIES OF NOVEL C-SECO-TAXOIDS. *Antonella Pepe¹, Ilaria Zanardi¹, Paula J. Pera², Ralph Bernacki², Cristiano Ferlini³, Giovanni Scambia³, Gabriele Fontana⁴, Antonella Riva⁴, Ezio Bombardelli⁴, and I Ojima¹.* (1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, apepe@ic.sunysb.edu, (2) Grace Cancer Drug Center, Roswell Park Cancer Institute, (3) Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, (4) Indena S.p.A

SAR studies on paclitaxel over the last 15 years confirmed the importance of the baccatin core to the anticancer activity of this important drug. One of the few exceptions discovered so far is IDN 5390 (1), a novel taxoid with the C-ring of the taxane skeleton cleaved. This novel C-seco-taxoid is a promising drug candidate to deal with non-MDR based resistance to paclitaxel caused by the upregulation of the class III β -tubulin. It has been recently shown that some mammalian cells resistant to paclitaxel overexpress specific β -tubulin classes. In particular, in ovarian tumors from cancer patients the upregulation of class III β -tubulin confers this type of resistance to paclitaxel. Microtubules composed of the class III β -tubulin are by far more sensitive to IDN 5390 than to paclitaxel. These results led us to design a series of IDN 5390 analogs. The synthesis and SAR studies of these novel C-seco-taxoids (2) will be presented with a focus on their ability to bind to overexpressed class III β -tubulin.



97. RATIONAL DESIGN, SYNTHESIS AND EVALUATION OF CONFORMATIONALLY RESTRAINED NOVEL PACLITAXEL ANALOGS. *Liang Sun, Raphael Geney, Xudong Geng, and Iwao Ojima, Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, liasun@ic.sunysb.edu*

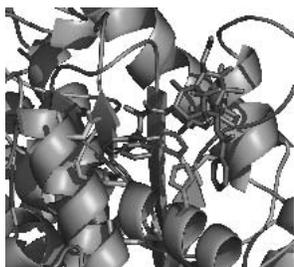
Conformationally restricted macrocyclic analogs are commonly used for the investigation of bioactive conformations of drugs in their interaction with proteins. In order to understand the interaction of paclitaxel with β -tubulin in detail, two types of novel macrocyclic paclitaxel analogs, represented by the structure 1 and 2, with rigid conformations were designed and synthesized. These taxoids were assayed for their tubulin-polymerization activity and cytotoxicity. Modeling studies, synthesis and biological evaluation of the macrocyclic taxoids will be presented.



98. TAXOL SPECIFICITY: YEAST VS. MAMMALIAN TUBULIN. *Pahk Thepchatri, James Nettles, James P Snyder, and Dennis Liotta, Department of Chemistry, Emory University, 1521 Pierce Drive, Atlanta, GA 30322, Fax: 404-727-6586, pthepch@emory.edu*

Taxol is a clinically important anticancer drug for the treatment of breast, ovarian, and lung cancers. However, Taxol is neurotoxic, and cancer develops resistance to the drug. In the wake of these disadvantages, several antimetabolic compounds are known. Many of these drugs share Taxol's binding site. Therefore, better understanding of the binding site could lead to the design of more effective microtubule stabilizers.

Yeast shares 75% sequence identity with mammalian tubulin (TB), but Taxol (Figure 1: Blue) is unable to polymerize yeast-TB to microtubules. Experimental studies by the Himes et al. showed that mutating five residues in yeast protein to the mammalian counterpart resulted in Taxol-driven polymerization of yeast-TB. Computational studies were performed to determine which of the residues contribute to important binding interactions in mammalian-TB that are not available in yeast. Results suggest that His229 (Figure 1: Red) provides the most important interactions to the binding of Taxol, while the other four residues (Figure 1: Green) contribute considerably less.



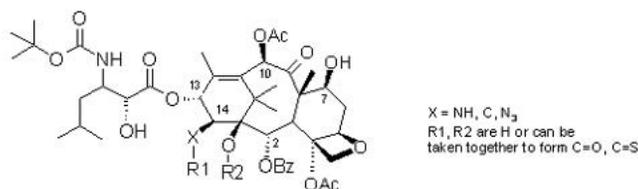
99. SAR OF 14-SUBSTITUTED TAXANES. *Gabriele Fontana¹, Arturo Battaglia², Maria Luisa Gelmi³, Eleonora Baldelli², Giacomo Carezzi³, Ezio Bombardelli¹, Carla Manzotti¹, and Ralph J. Bernacki⁴.* (1) Indena S.p.A, Viale Ortles, 12, Milan 20139, Italy, Fax: +39 02 57496 280, gabriele.fontana@indena.com, (2) Istituto CNR "I.S.O.F." - Area della Ricerca di Bologna, (3) Istituto di Chimica Organica, Università di Milano, (4) Grace Cancer Drug Center, Roswell Park Memorial Institute

The success of paclitaxel and docetaxel as anticancer agents stimulated the search of innovative analogues endowed with more favorable pharmacological profile. Ortataxel, lead of the class of 14-hydroxy taxoids, represents a milestone in such a research.

Although the 14-substitution plays an important rôle in the biology of Taxanes, an extensive SAR for this position was believed not possible due the

lacking of natural occurring 14-substituted taxoids and of chemical methodologies for the modification of position 14.

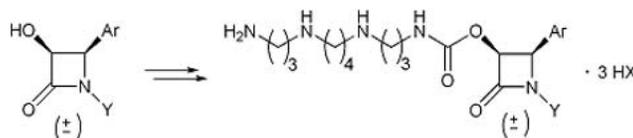
During our studies to solve the supply of 14-hydroxytaxoids we have developed the chemistry of the enolate of 13-oxo-7-protected baccatin. Such a chemistry gave us a powerful tool for modifying position 14, opening new perspectives in the Taxane chemistry. By quenching the enolate with different electrophiles, we have generated a wide number of 14-functionalized taxoids. *In vitro* and *in vivo* data confirmed the importance of 14-substitution and permitted the selection of new candidates.



X = NH, C, N₃
R1, R2 are H or can be taken together to form C=O, C=S

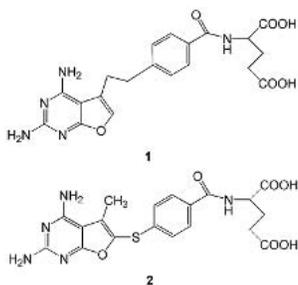
100. SYNTHESIS OF NEW POLYAMINE- β -LACTAM CONJUGATES AS POTENTIAL ANTI-CANCER AGENTS. *Ilaria Zanardi¹, Greta Varchi¹, Arturo Battaglia², and Iwao Ojima¹.* (1) Department of Chemistry, State University of New York, Stony Brook, NY 11794-3400, Fax: 631-632-7942, zanardi@isof.cnr.it, (2) Institute for the Organic Synthesis and Photo Reactivity, National Research Council

β -Lactams have been widely used as antibiotics due to their potent antibacterial activity. However, their anticancer activity has not been extensively investigated. We found that several cis-3-methoxy-4-aryl- β -lactams exhibited good cytotoxicity (IC₅₀ = 12-17 mM). N-thiolated β -lactams have also been shown to induce tumor specific apoptosis. Since many tumor types have been shown to contain elevated levels of polyamine as well as PAT (a cell surface protein) for importing exogenous polyamines, we reasoned that conjugates of spermine with cytotoxic β -lactams would provide a new class of specific anticancer agents. The design, synthesis and biological evaluation of novel β -lactam-spermine conjugates will be presented.



101. DESIGN AND SYNTHESIS OF N-[4-[(2,4-DIAMINO-5-METHYLFURO[2,3-D]PYRIMIDIN-6-YL)THIO]BENZOYL]-L-GLUTAMIC ACID AS A CLASSICAL DUAL INHIBITOR OF TS AND DHFR. *Aleem Gangjee¹, Hitesh Kumar D. Jain¹, Sherry F. Queener², and Roy L. Kisliuk³.* (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, hiteshjain_1978@yahoo.com, (2) Department of Pharmacology and Toxicology, Indiana University, (3) Department of Biochemistry, Tufts University School of Medicine

Gangjee et al. previously reported compound **1** as a moderate inhibitor (IC₅₀ = 1 μ M), of dihydrofolate reductase (DHFR). This compound was designed to be a dual inhibitor of both DHFR and thymidylate synthase (TS). However, compound **1** did not possess any significant TS inhibitory activity. One probable reason for this is that when it binds to TS in the "flipped" mode the side chain substituent lies between the 6- and 7- carbon atom of a 6-6 system and may account for its low TS inhibitory activity. As an extension of our ongoing work, compound **2**, was synthesized as a potential dual inhibitor of TS and DHFR. Compound **2** was designed to interact with DHFR using the normal 2,4-diamino binding mode and with TS using the "flipped" 2-amino-4-oxo binding mode in which the furo oxygen mimics the 4-oxygen of known 2-amino-4-oxopyrimidine TS inhibitors. The synthesis and biological activities of **2** against TS and DHFR will be reported.



102. DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SMALL-MOLECULE INHIBITORS OF BCL-2 AND BCL-XL PROTEINS BASED UPON GOSSYPOL. *Guozhi Tang¹, Zaneta Nikolovska-Coleska¹, Renxiao Wang¹, Liang Xu¹, Mei Lan Liu², Manchao Zhang², Dajun Yang², York Tomita³, and Shaomeng Wang².* (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, Fax: 734-647-9647, tangle@med.umich.edu, (2) Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, (3) Lombardi Cancer Center, Georgetown University

Anti-apoptotic B-cell lymphocyte/leukemia-2 (Bcl-2) and its homologous Bcl-xL proteins are overexpressed in many human cancers. Non-peptidic, cell-permeable, small molecules that mimic proapoptotic BH3 domains represent a highly attractive approach to inhibit the anti-apoptotic function of Bcl-2 and Bcl-xL proteins and to overcome the protective effects of Bcl-2 and Bcl-xL in cancer cells. Through computational structure-based database screening, we discovered that gossypol, a natural polyphenol from cotton seed, bind to Bcl-2 and Bcl-xL proteins. Based on the three-dimensional structure of gossypol in complex with Bcl-xL protein and molecular modeling, we have designed and synthesized new analogues. We wish to present the design, synthesis, and biochemical and cellular studies of these novel small-molecule inhibitors of Bcl-2 and Bcl-xL proteins.

103. DESIGN, SYNTHESIS AND TESTING OF NOVEL AND HIGHLY POTENT BCL-2 INHIBITORS AS NEW ANTI-CANCER AGENTS. *Guoping Wang¹, Zaneta Nikolovska-Coleska¹, Renxiao Wang¹, Liang Xu¹, Wen Hua Tang¹, Mei Lan Liu¹, Manchao Zhang¹, Dajun Yang¹, Marc E. Lippman¹, York Tomita², and Shaomeng Wang¹.* (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, guopingw@med.umich.edu, (2) Lombardi Cancer Center, Georgetown University

Through structure-based design, we have designed and synthesize novel small-molecule inhibitors of Bcl-2. Biochemical binding assay determines that the most potent inhibitor has a K_i value of approximately 4 nM binding to the Bcl-2 protein. They also potently inhibit cancer cell growth and induce apoptosis in cancer cells with high levels of Bcl-2 proteins and display a good selectivity to normal cells. Evaluation of one fairly potent inhibitor in human prostate cancer PC-3 xenograft model in nude mice shows that the inhibitor achieves a good in vivo antitumor activity in inhibition of tumor growth, alone and in combination with taxotere. Taken together, our in vitro and in vivo results suggest that highly potent small-molecule inhibitors of Bcl-2 may have a great therapeutic potential for the treatment of many different types of human cancer.

104. EXPLORATION OF ANALOGS OF RWJ-540973/JNJ-10198409: SEPARATION OF ANTI-ANGIOGENIC AND ANTI-PROLIFERATIVE ACTIVITIES. *Umar S. M. Maharoo¹, Chih Y. Ho, Donald W. Ludovici, Eric D. Strobel, Laura Andracka, Hong Lu, Rose Tominovich, Judith Baker, Jan Sechler, Candace Burns, Tom Garrabrant, Jay Mei, Robert Tuman, Dana L. Johnson, and Robert A. Galemno Jr.,* Oncology Research Team, Johnson & Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, P.O.Box 776, Spring House, PA 19477, Fax: 215-628-4985, umaharoo@prdus.jnj.com

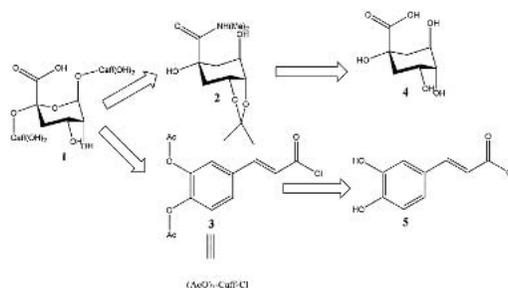
RWJ-540973/JNJ-10198409 is a novel, potent anti-cancer agent with both anti-angiogenesis and anti-proliferative activities. The anti-angiogenic activity is a result of its potent PDGF receptor tyrosine kinase inhibition ($IC_{50} = 2$ nM) as

demonstrated by both in vitro and in vivo experiments. This compound has anti-proliferative activity in 8 of 10 human tumor cell lines tested ($IC_{50} = 2$ to 30 nM) as well as in PDGF-BB driven human smooth muscle cell growth (HCASMC) ($IC_{50} = 3$ nM) while having little effect in LSGS stimulated HUVEC cells. The anti-proliferative effect upon tumor cells has been shown to be cytostatic rather than cytotoxic with the cells blocked in the G2/M transition of the cell cycle. Further exploration of the SAR of this series for improved pharmacokinetic profile resulted in separation of anti-angiogenic and anti-proliferation activity. The structural modifications defining each class will be discussed.

105. INTERFERENCE OF ECHINACEA ANGUSTIFOLIA WITH CANCER CHEMOTHERAPY. *Eric D Huntimer, Chemistry & Biochemistry, South Dakota State University, Shepard hall 121, Brookings, SD 57007, Eric.Huntimer@SDSTATE.EDU*

Echinacea angustifolia has significant anti-inflammatory activity. This activity was correlated with hyaluronidase inhibition from phenolic compounds and is associated with wound healing. Hyaluronidase also enhances the tumor-penetrating ability of doxorubicin. Because phenolic acids inhibit hyaluronidase, they may prove detrimental if taken with hyaluronidase-supplemented chemotherapy. This project was designed to examine the interference Echinacea compounds may possess with cancer cells treated with doxorubicin and hyaluronidase.

Our data on HeLa cells showed that the butyl acetate-soluble compounds, chioric acid, and the standardized extract interfered with chemotherapy, causing cell proliferation. Breast cancer cells showed significant proliferative activity under similar conditions as the HeLa cells. A structure-activity relationship will be conducted among several phenolic compounds. Chicoric acid was synthesized previously, while the synthesis of 1,3-O-dicaffeoylquinic acid (1) is in progress. The protected intermediates 2 and 3 are built from quinic acid (4) and caffeic acid (5). Further studies on these projects are in progress.



106. NOVEL ANTI-PROLIFERATIVES FOR INHIBITION OF ANGIOGENESIS AND CANCER. *Megumi Kawai¹, Nwe Y. BaMaung¹, Richard Craig², M. Katie Verzal³, Pingping Lou¹, Jieyi Wang¹, Paul Tapang¹, Daniel H. Albert¹, Zehan Chen¹, Ingrid Joseph¹, Michael R. Michaelides¹, Jack Henkin¹, George Sheppard¹, Yujia Dai¹, Anil Vasudevan³, Jennifer Bouska¹, Terry Magoc¹, Steven Anderson¹, Yi Chun Wang¹, David Frost¹, and Rick Lesniewski¹.* (1) Cancer Research, Global Pharmaceutical R & D, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, Fax: 847-937-8378, megumi.kawai@abbott.com, (2) Patent Liasons, Abbott Laboratories, (3) Medicinal Chemistry Technology, Abbott Laboratories

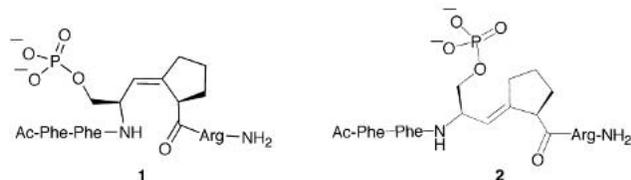
Tumor Growth and progression are believed to depend on new blood vessel formation, a process known as angiogenesis. Proliferation of endothelial cells (EC) is required in angiogenesis. Originally we identified 3-substituted indole hydrazones with good oral bioavailability. Chemistry efforts were initiated and the analogues were evaluated for EC proliferation. More than 10 compounds were found to have IC_{50} of 10 nM. These compounds were also active against a panel of tumor lines with IC_{50} of 10-200 nM. Mechanistic studies revealed that the indoles affected cellular microtubule structure and inhibited tubulin polymerization in vitro. They were further shown to affect tubulin binding to colchicine and vinblastine. The compounds were tested in vivo for angiogenesis and tumor inhibition and were found to inhibit mouse cornea angiogenesis and HT-1080 tumor growth in mice. In summary, we have identified 3-substituted indoles as

novel anti-mitotic compounds that are effective in inhibiting angiogenesis and tumor growth.

107.

PHOSPHOSER-CIS-PRO ISOSTERE INHIBITS PIN1 23-FOLD BETTER THAN THE TRANS-PRO ISOSTERE. Felicia A. Etkorn, Xiaodong J. Wang, Bailing Xu, Freda K. Neiler, and Ashley B. Mullins, Department of Chemistry, Virginia Tech, 107 Davidson Hall (0212), Blacksburg, VA 24061, Fax: 540-231-3255, fetzkorn@vt.edu, xiwang5@vt.edu

The cell cycle regulator, Pin1 (protein interacting with NIMA #1), is an essential peptidyl-prolyl isomerase. As a potential anti-cancer drug target, Pin1 regulates the activity of several cell cycle enzymes, including Cdc25, Wee1 and Plk1. Two stereoisomeric Pin1 substrate analogues were designed and synthesized. The central pSer-cis/trans-Pro core of the Pin1 substrate was replaced by Z- and E-alkene isosteres. Two other alkene isosteres were also synthesized. The protease-coupled assay demonstrated that all four compounds inhibit Pin1. Both **1** and **2** were competitive inhibitors and the cis isostere, **1**, was 23 times more potent ($K_{is} = 1.74 \pm 0.08 \mu\text{M}$) than its trans counterpart, **2** ($K_{is} = 39.8 \pm 2.4 \mu\text{M}$). This suggests that Pin1 binds cis substrate at the active site more tightly than trans substrate. Inhibition of the A2780 human ovarian cancer cell line by **1** and **2** correlates well with Pin1 inhibition.



108.

SMAC PEPTIDO-MIMETICS AS XIAP INHIBITORS. Jianyong Chen, Nikolovska Coleska Zaneta, Liang Xu, and Shaomeng Wang, Department of Internal Medicine, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48105, Fax: 734-647-9647, jjachen@umich.edu

Smac (second mitochondria-derived activator of caspases, or DIABLO) was recently identified as a protein released from mitochondria in response to apoptotic stimuli. Smac was shown to directly interact with XIAP and other IAPs and to promote apoptosis by antagonizing IAPs. Unlike most protein-protein interaction, the binding between XIAP and Smac is mediated by a well-defined small binding pocket in the XIAP BIR3 domain and only four amino acid residues (AVPI) at the N-terminus of Smac. Indeed, short Smac peptides, including the AVPI 4-residue Smac peptide, have the same binding affinity as the mature Smac protein with a K_d value approximately $0.4 \mu\text{M}$. Therefore, targeting the XIAP BIR3 domain where Smac binds may represent a highly promising therapeutic strategy for overcoming apoptotic resistance caused by XIAP in prostate cancer and other types of cancer. We wish to report the design, synthesis, biochemical and biological evaluations of novel and potent Smac peptide-mimetics. We showed that CJ-464 and CJ-467 bind to XIAP BIR3 domain with K_i values of 130 and 140 nM, respectively. Importantly, these Smac peptide-mimetics effectively sensitize cancer cells to apoptosis induced by chemotherapeutic agents.

109.

STRUCTURE-BASED DESIGN, SYNTHESIS AND EVALUATION OF CONFORMATIONALLY CONSTRAINED SMAC MIMETICS THAT TARGET XIAP/CASPASE-9 INTERACTION SITE. Haiying Sun¹, Zaneta

Nikolovska-Coleska², Chao Yie Yang², Liang Xu², York Tomita³, Krzysztof Krajewski⁴, Peter P. Roller⁴, and Shaomeng Wang¹. (1) Departments of Internal Medicine, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, haiyings@med.umich.edu, (2) Intel Med, The University of Michigan, (3) Georgetown University, (4) Laboratory of Medicinal Chemistry, NCI, National Institutes of Health

Smac/DIABLO (second mitochondria-derived activator of caspase or direct IAP binding protein with low pI) is a protein released from mitochondria in response to apoptotic stimuli. It can directly interact with the BIR3 domain of XIAP, cIAP-1 and cIAP-2 and a single BIR domain in ML-IAP and functions as a direct endogenous inhibitor of IAP proteins. In recent studies it has been found Smac peptides as short as 4-residues derived from Smac protein bind to the recombi-

nant XIAP BIR3 domain protein with the same affinities as the mature Smac protein. In order to overcome the intrinsic limitations of Smac peptides (e.g. poor in vivo stability and poor bioavailability), a series of conformationally constrained Smac mimetics were designed and synthesized. Their binding affinity was evaluated in FP-based binding assay. The two most potent compounds SH-102 and SH-109 are 15-folds more potent than Smac AVPI peptide. SH-102 was evaluated for its ability to potentiate cisplatin-induced apoptosis in the PC-3 human prostate cells with high levels of XIAP protein. Combination of cisplatin with 10 mM of SH-102 significantly increases the apoptosis from 30% to 60% in PC-3 cells.

110.

2-AMINO-O⁴-BENZYLPTERIDINES AND O⁴-BENZYLFOVIC ACID: POTENT INACTIVATORS OF O⁶-ALKYLGUANINE-DNA ALKYLTRANSFERASE AND POTENTIAL CHEMOTHERAPY ADJUVANTS. Michael E. Nelson¹, Natalia Loktionova², Anthony E. Pegg², and Robert C. Moschel¹. (1) Laboratory of Comparative Carcinogenesis, The National Cancer Institute at Frederick, P.O. Box B, Bldg 538, Rm 103, Frederick, MD 21702-1201, Fax: 301-846-6146, nelsonm@ncifcrf.gov, (2) The Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine

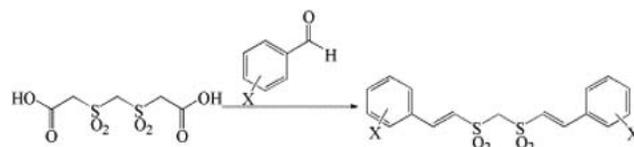
The human DNA repair protein, O⁶-alkylguanine-DNA alkyltransferase (alkyltransferase) is the primary source of resistance many tumor cells exhibit to chemotherapeutic agents that modify the O⁶-position of DNA guanine residues (temozolomide, BCNU, etc.). The inactivation of this protein can bring about a significant improvement in the therapeutic effectiveness of these chemotherapy drugs. O⁶-Benzylguanine, the prototype alkyltransferase inactivator is currently in clinical trials in combination with BCNU and temozolomide. Although O⁶-benzylguanine is a promising chemotherapy adjuvant, it is not an ideal drug since it is very insoluble in water and is not selective for alkyltransferase inactivation in tumors. Therefore, we have prepared a series of 2-amino-O⁴-benzylpteridine derivatives that can be functionalized to improve water solubility and tumor selectivity. All of these derivatives are very potent alkyltransferase inactivators. Furthermore, O⁴-benzylfolic acid is an extremely water soluble and potent alkyltransferase inactivator that appears to be selective for alkyltransferase inactivation in tumors that overexpress the α -folate receptor. Tumor selective alkyltransferase inactivation would be advantageous since it should greatly limit the clinical side effects associated with systemic alkyltransferase inactivation. Therefore, O⁴-benzylfolic acid may prove to be superior to O⁶-benzylguanine as a chemotherapy adjuvant.

111.

SYNTHESIS AND ANTICANCER ACTIVITY OF BIS(STYRYLSULFONYL)METHANES. Venkat R Pallela¹, Muralidhar Reddy Mallireddigari¹, Stanley C Bell², Stephen Cosenza³, E. Premkumar Reddy¹, and M.V. Ramana Reddy¹. (1) Fels Institute for Cancer Research, Temple University School of Medicine, 3307, North Broad Street, Philadelphia, PA 19140-5101, pallela@yahoo.com, (2) Department of Medicinal Chemistry, Onconova Therapeutics, Inc, (3) Fels Institute for Cancer Research

Several vinyl sulfones and ketones have recently been shown to be potent inhibitor of HIV-1 integrase and human rhinovirus protease. They are also shown to inhibit disease associated cysteine proteases such as cathepsins and calpains that are involved in progressive cartilage and bone degradation associated arthritis. Curcumin, a member of bis(styryl) ketones, is an active ingredient in turmeric, was recently reported as potent inhibitor of tumor invasiveness and angiogenesis and is in phase 1 clinical trials for colon cancer.

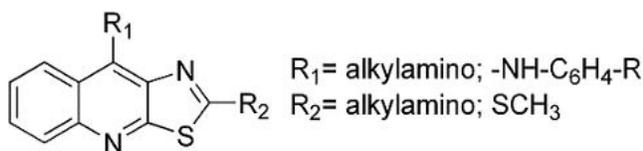
In pursuit of developing more potent sulfonyl analogues of curcumin, we designed and synthesized a series of novel bis(styrylsulfonyl) methanes and studied the biological activity of these compounds on various types of cancer cell lines. The nature of substituents on aromatic rings and geometry at the double bond determines the activity of these compounds in their ability to kill cancer cells. In this presentation, synthesis, structure function analysis and biological activity of bis(substituted-styrylsulfonyl) methanes is discussed.



112. SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL CYTOTOXIC THIAZOLO[5,4-B]QUINOLINES DERIVATIVES.

Marco A. Loza-Mejía, Angelina Quintero, José D. Solano, Susana Olvera-Vázquez, and Alfonso Lira-Rocha, Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Cd. Universitaria, Coyoacán, Mexico 04510, Mexico, Fax: 5556225329, lira@servidor.unam.mx

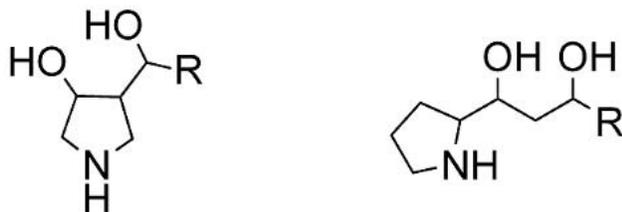
A series of 9-anilinothiazolo[5,4-b]quinolines, of the general structure showed below, have been synthesized and tested in vitro for antitumoral activity. The compounds were obtained by a divergent synthesis. Electron-releasing and electron-withdrawn groups were incorporated at the anilino ring as well as alkylamino groups. In general, the compounds with an alkylamino residue showed very good cytotoxic activity on the tumoral cell lines (MCF-7), HeLa, SW-480, SW-620, C-33, Calo, CHO, K-562). The synthetic and biological assays results will be presented.



113. SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SPHINGOSINE ANALOGS.

Rhonda L. Moore¹, Ann M. Dougherty¹, Dennis C. Liotta¹, Frank E. McDonald¹, and Alfred H. Merrill Jr.². (1) Department of Chemistry, Emory University, 1515 Dickey Dr, Atlanta, GA 30322, rmoore4@emory.edu, (2) Department of Biology, Georgia Institute of Technology

Sphingolipids are a ubiquitous class of molecules that play major roles in an organism's growth, differentiation, intracellular signaling and cell death. They are found in cell membranes and other lipid rich structures. Experimental data has shown that in CF1 mice treated with a colon carcinogen dietary sphingolipids reduced the appearance of colonic crypt foci and number of tumors formed. Novel synthetic analogs have been prepared to further investigate the mechanism of action of these compounds and to enhance their activity relative to naturally occurring sphingolipids. These analogs possess a long chain backbone where the traditional 2-amino-1,3-diol headgroups has been transposed to its 2-amino-3,5-diol counterpart. In addition, rigidity was introduced into the structure by incorporating the amino group within various pyrrolidine rings. In this poster we discuss our syntheses of these analogs as well as their biological activity.



114. SYNTHESIS AND BIOLOGICAL EVALUATION OF PHOSPHATE ISOSTERES AS METABOLICALLY STABLE AGONISTS OR ANTAGONISTS OF S1P RECEPTORS.

Frank W. Foss Jr.¹, Jeremy J. Clemens¹, Michael D. Davis², Kevin R. Lynch², and Timothy L Macdonald¹. (1) Department of Chemistry, University of Virginia, McCormick Rd, P.O. Box 400319, Charlottesville, VA 22904-4319, Fax: 434-982-2302, fwf4b@virginia.edu, (2) Department of Pharmacology, University of Virginia

In vitro studies of sphingosine-1-phosphate (S1P) analogues have demonstrated significant activity as selective agonists or antagonists at one or more of the five S1P receptors. While some compounds had activity profiles similar to phospho-FTY720 (a novel immunomodulator and S1P receptor ligand), in vivo studies did not show similar biological activity. From these results we hypothesized that one or more lipid phosphatases played a critical role in the inactivation of our S1P

receptor ligands. This present study demonstrates the synthesis and biological activity of a variety of metabolically stable phosphate mimics.

115. PEPTIDE BEACONS AS NOVEL PHOTODYNAMIC THERAPY (PDT) AGENTS.

Juan Chen¹, Klara Stefflova², Soungkyoo Kim¹, Mark Niedre³, Brian Wilson³, Jerry Glickson¹, and Gang Zheng¹. (1) Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, Fax: 215-746-8764, jchen@rad.upenn.edu, (2) Department of Chemistry, University of Pennsylvania, (3) Medical Biophysics and Ontario cancer Institute, University of Toronto

We have designed and synthesized a peptide beacon consisting of a sequence that is specific to a cleavage enzyme overexpressed in tumor cells. A dye and a quencher are conjugated to the ends of this sequence respectively. Proximity of the dye to the quencher quenches fluorescence and photoreactivity of the dye through energy transfer. In the presence of the tumor-specific enzyme, the beacon sequence is cleaved and the quencher departs from the dye. Upon irradiation with light, the dye is no longer in vicinity of the quencher thus emits fluorescence and generates cytotoxic singlet oxygen. Using a caspase-3 substrate as a model, we have validated our concept of the singlet oxygen quenching and the subsequent activation of singlet oxygen production upon caspase-3 cleavage. So the beacon serves both as a directed PDT agent and as a tumor specific diagnostic agent.

116. PHOTODYNAMIC THERAPY (PDT) AGENT WITH A BUILT-IN APOPTOSIS SENSOR.

Klara Stefflova¹, Juan Chen², and Gang Zheng². (1) Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, Fax: 215-746-8764, stefflok@sas.upenn.edu, (2) Department of Radiology, University of Pennsylvania

For any sophisticated disease treatment, it is necessary to develop not only the active agent but also the tool that will assess the efficacy of this treatment. We have synthesized a novel PDT agent that can detect early apoptosis. This molecule contains a photosensitizer that is also a fluorophore (pyropheophorbide) connected to a fluorescence quencher (BHQ) by a nine-amino acid caspase-3 substrate (GDEVDSGSK). This agent produces singlet oxygen upon light activation, which induces the cascade of apoptosis events. Caspase-3, an enzyme activated in the early stages of apoptosis, cleaves the substrate between pyropheophorbide and BHQ and restores fluorescence of the cell. Therefore, cancer cells that are successfully treated by this agent will "light up," indicating a therapeutic outcome. We have quantified the efficiency of quenching by the caspase-3 cleavage in vitro. The results show 7-fold increase in fluorescence for the molecules that are in the presence of caspase-3.

117. PHTHALOCYANINE-BASED TUMOR IMAGING AND PHOTODYNAMIC THERAPY AGENTS TARGETING LDL RECEPTORS.

Hui Li¹, Soungkyoo Kim¹, Diane Marotta¹, Ulas Sunar², Theresa Busch³, Britton Chance⁴, Jerry Glickson¹, and Gang Zheng¹. (1) Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, Fax: 215-746-8764, hui@rad.upenn.edu, (2) Physics Dept, University of Pennsylvania, (3) Radiation Oncology, University of Pennsylvania, (4) Biochemistry & Biophysics, University of Pennsylvania

Overexpression of LDL receptors (LDLr) in cancer cells provides the rationale to deliver imaging and therapeutic agents to tumors via LDLr pathway. Short recycling time of LDLr offers an amplification mechanism for probes to be accumulated in tumor. Novel probe - Phthalocyanine (Pc) was synthesized with two oleate moieties incorporated into the Pc ring through silicon coordination to prevent the dyes from aggregation and to provide anchors for tight binding. Effective LDL reconstitution yields a high protein recovery (55%) and a high probe/protein molar ratio (500:1). In vitro PDT was carried out on LDLr overexpressing HepG2 cells (5mW/cm², 5J/cm²), substantial decrease of cell colonies was observed upon PDT treatment. In vivo absorption of Pc-LDL by HepG2 tumor using two channel I&Q spectrometer demonstrated preferential accumulation of the probe in tumor tissue. In conclusion, preliminary in vitro and in vivo data indicated Pc can be used for targeted tumor imaging and PDT.

118. SYNTHESIS AND UTILIZATION OF LDL RECEPTOR-TARGETED MRI CONTRAST AGENT. *Ian Corbin, Hui Li, Juan Chen, Jerry D Glickson, and Gang Zheng, Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, Fax: 215-746-8764, corbin@rad.upenn.edu*

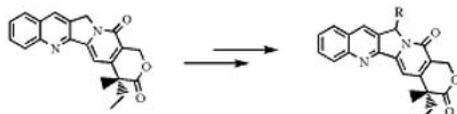
Low-density lipoproteins (LDL) are an endogenous transport vehicle in mammalian systems. These liposomal-like particles consist of a phospholipid monolayer encapsulating a hydrophobic core. Spanning the lipid monolayer is the apolipoprotein B-100 which is a recognition protein for targeting LDL to cells expressing the LDL receptor. LDL can be modified to incorporate contrast agents for imaging. Magnetic resonance imaging (MRI) is an attractive imaging modality offering tomographic imaging with excellent spatial resolution. However, the inherent low sensitivity of MRI makes the design of targeted contrast agents a challenging task. In our design, two mechanisms contribute to the contrast enhancement. First, a high ratio of lipophilic gadolinium (Gd) chelate (Gd-DTPA-Bis(stearylamide)) was synthesized and incorporated into the lipid monolayer of LDL (200:1) to provide a high payload. Secondly, the LDL receptor-mediated endocytosis provides means to amplify the signal enhancement. Preliminary animal experiments indicate that Gd-labeled LDL is a promising targeting MRI contrast agent.

119. SYNTHESIS OF NOVEL BACTERIOCHLOROPHYLL ANALOGS AS TARGETED CONTRAST AGENTS FOR CANCER DETECTION AND TREATMENT. *Soungkyoo Kim¹, Chenze Qi¹, Yu Chen², Hui Li¹, Britton Chance², Jerry Glickson¹, and Gang Zheng¹. (1) Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, Fax: 215-746-8764, skim@rad.upenn.edu, (2) Biochemistry & Biophysics, University of Pennsylvania*

Near-infrared (NIR) dyes are presently attracting considerable interest as fluorescence probes for detection of cancer and as photosensitizers for cancer treatment by photodynamic therapy (PDT). Bacteriochlorophyll (BChl), has several photophysical and chemical characteristics that make it an ideal NIR dye for PDT and imaging. However due to the instability of this pigment, preparation of stable and biocompatible BChl analogs is a synthetic challenge. Here we describe efficient syntheses of isothiocyanate-containing BChl analogs. The introduction of isothiocyanate into the BChl macrocycle permits the bioconjugation of these NIR dyes with a number of biologically important ligands. To illustrate this point we covalently linked 2-deoxyglucose to our BChl analogs. The 2-deoxyglucose moiety permits specific targeting of our NIR dyes to cancer cells which overexpress glucose transporters. We report that in vivo fluorescence imaging in tumor bearing mice demonstrates that these novel optical agents are useful for the detection and treatment of subsurface tumors.

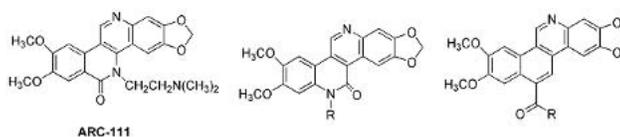
120. SYNTHESIS AND TOPO I INHIBITION OF 5-SUBSTITUTED CAMPTOTHECINS. *Li Ming Zhou, Yasheen Zhou, Alex Burgin, Xuesheng Mo, David Zembower, and Yongping Xie, deCODE genetics, 2501 Davey Road, Woodridge, IL 60517, lzhou@decode.com*

We have designed and synthesized a series of 5-substituted camptothecin analogs. Several molecules inhibited Topoisomerase I mediated relaxation with potencies compatible to Topotecan. Aided by molecular modeling analysis, we hypothesized that camptothecin binds to DNA-Topoisomerase I complex in a similar mode as indolocarbazoles, a different series of Topo I inhibitors with DNA binding activity. By mimicking indolocarbazole, we proposed that the introduction of side chains at position 5 of camptothecin, a potential DNA groove binding moiety, may improve its weak DNA binding affinity. Details of the synthesis and the biological activity will be presented. Acknowledgment. This research was funded by SBIR Grant IR43 CA93187-01 awarded by the National Institutes of Health.



121. BENZO[*l*]PHENANTHRIDINES AND 6H-DIBENZO[*c,h*][2,6]NAPHTHYRIDIN-5-ONES WITH POTENT TOPOISOMERASE I-TARGETING ACTIVITY AND CYTOTOXICITY. *Alexander L. Ruchelma¹, Shejin Zhu¹, Nai Zhou², Angelia Liu², Leroy F. Liu³, and Edmond J. LaVoie⁴. (1) Department of Pharmaceutical Chemistry, Rutgers University, 160 Frelinghuysen Road, Piscataway, NJ 08854, Fax: 732-445-6312, ruchelma@hotmail.com, elavoie@rci.rutgers.edu, (2) Dept. of Pharmacology, University of Medicine and Dentistry of New Jersey, (3) Dept. of Pharmacology, University of Medicine and Dentistry of New Jersey and the Cancer Institute of New Jersey, New Brunswick, New Jersey, (4) Department of Pharmaceutical Chemistry, Rutgers University and Cancer Institute of New Jersey, New Brunswick, New Jersey*

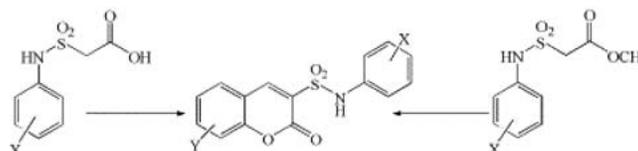
6H-Dibenzo[*c,h*][1,6]naphthyridin-6-one derivatives, such as ARC-111, have recently been shown to have exceptional topoisomerase I (TOP1)-targeting activity and to be efficacious by either oral or parenteral administration as anticancer agents in tumor-bearing mice. Studies have been extended to include 6H-dibenzo[*c,h*][2,6]naphthyridin-5-ones, which represent "reversed lactam" analogues, as well as structurally-related 12-carboxy derivatives of benzo[*l*]phenanthridine. Within both of these new genera of compounds that are related to the family of ARC-111 TOP1-targeting agents, several analogues have exhibited activity with IC₅₀ values ranging from 3 to 0.150 nM. The influence of structural modification on relative TOP1-targeting activity and cytotoxicity was evaluated. Cytotoxicity was assessed in RPMI8402 and P388 cells, as well as in their camptothecin-resistant variants.



122. SYNTHESIS OF NEW COUMARIN 3-(N-PHENYL) SULFONAMIDES AND THEIR ANTICANCER ACTIVITY. *N. Srinivasa Reddy¹, Muralidhar Reddy Mallireddigari¹, Stanley C Bell², E. Premkumar Reddy¹, and M.V. Ramana Reddy¹. (1) Fels Institute for Cancer Research, Temple University School of Medicine, 3307, North Broad Street, Philadelphia, PA 19140, Fax: 215-707-7336, nsreddy@temple.edu, (2) Department of Medicinal Chemistry, Onconova Therapeutics, Inc*

The diverse biological activities of natural and synthetic coumarin derivatives as anticoagulants and antithrombotics are well known. Some of the coumarin derivatives are also reported as triplet sensitizers, anti-HIV agents, lipid-lowering agents and antioxidants. They have also been found to inhibit lipid peroxidation and to possess vasorelaxant and anti-inflammatory activity. Many coumarin derivatives are also known as free radical scavengers and two naturally occurring coumarins have been found to exhibit cytotoxicity against a panel of mammalian cancer cell lines. Some coumarin-3-carboxamides were reported as potent inhibitors of proteases such as α -chymotrypsin (CT) and human leukocyte elastase (HLE). Recently a series of arylsulfonamides have been reported as potent inhibitors of various cancer cells at a very low concentration. Based on the diverse biological activities of the coumarins and aryl sulfonamides, we have designed and synthesized a series of novel compounds that have both coumarin and sulfonamide entities in one molecule and have evaluated them for their anti-tumor activity.

Here we wish to present a simple and convenient synthesis of coumarin-3-(N-phenyl) sulfonamides in one step. Synthesis of Coumarin 3-(N-phenyl) sulfonamides was accomplished by Knoevenagel condensation of 3-oxo 3-(N-phenyl) propionic acids with suitable salicylaldehydes in acetic acid with catalytic base with good yields. All the compounds obtained were tested for their anticancer activity against various tumor cell lines.



123.

3-AMINOPHENYLDIHYDROINDENOPYRAZOLE ANTI-TUMOR AGENTS WITH A DUAL MODE OF ACTION. *Chih Y. Ho, Donald Ludovici, Umar Maharoo, Eric Strobel, Laura Andraka, Jack Yen, Robert W. Tuman, Jay Mei, Ann DeVine, Rose Tominovich, Hong Lu, Judith Baker, Candace Burns, Jan Sechler, Dana Johnson, and Robert A. Gallema, Oncology Research Team, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-4985, Cho@prdu.s.jnj.com*

It has become increasingly clear in recent years that angiogenesis plays a major role in uncontrolled tumor growth and metastasis. Several pro-angiogenic growth factors and families of receptor tyrosine kinases have been identified to be important in the process of angiogenesis, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) and interaction with their respective tyrosine kinase receptors. Our interest is to develop anti-angiogenic compounds with an additional dual tumor cell anti-proliferative activity capable of inhibiting tumor progression by overlapping mechanisms. Tumors can be regarded as a two-compartment system consisting of the neovasculature supporting tumor growth composed of 'normal' homogeneous vascular endothelial cells, smooth muscle cells and pericytes surrounded by colonies of poorly differentiated, heterogeneous cancer cells. To find molecules that would affect both the vascular and tumor cell compartments, we identified several chemical series with the potential to inhibit the PDGFR- β kinase-mediated angiogenic effect then assayed these series for dual anti-proliferative activity against an extensive panel of human tumor cell lines. This presentation will center on the parallel optimization of a series of compounds for both the PDGF RTK mediated anti-angiogenic activity and tumor cell selective anti-proliferative activity, culminating in the inhibitor RWJ 540973 (JNJ 10198409). A model for the docking of this compound in the kinase ATP binding site and in vivo anti-tumor activity will also be discussed.

124.

SYNTHESIS OF NOVEL CHLOROMETHYLPHENYL PURINE NUCLEOSIDE ANALOGUES AND RELATED COMPOUNDS. *Nageswara R. Kode, Aduwami Dare, and Shashikant Phadtare, College of Pharmacy, Xavier University of Louisiana, 1 Drexel drive, New Orleans, LA 70125*

Synthesis of nucleoside analogues of purine, pyrimidine and related nucleic acid bases for potential chemotherapeutic agents is the on going research in medicinal chemistry at our Laboratory. In the present study 6-Chloropurine was reacted with p-dichloroxyline in dimethyl formamide and potassium carbonate medium to furnish N9- [(Chloromethyl)Phenylmethyl]-6-Chloropurine and the N7- [(Chloromethyl)Phenylmethyl]-6-Chloropurine. By changing the molar ratios of the reagents, the reaction time and temperature we have succeeded to isolate the N-9 linked Phenylmethyl-6-Chloropurine dimer. Structure elucidation was done with the application of high field proton NMR and the details will be presented.

125.

SYNTHESIS OF NOVEL CYCLOBUTYL NUCLEOSIDES. *Shuli Mao, Michael W Hager, and Dennis C. Liotta, Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, Fax: 404-712-8679, smao@emory.edu*

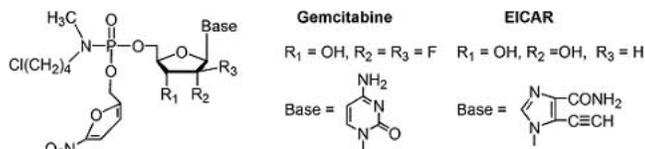
Several carbocyclic nucleoside analogues exhibit good biological activity as well as resistance to degradation by phosphorylases. Among them, several fluorinated carbocyclic nucleosides have been reported recently that show promising antiviral activity. In this poster, we present details about the synthesis and biological activity of several novel cyclobutyl nucleosides, some of which exhibit potentially useful resistance profiles.

126.

SYNTHESIS OF PHOSPHORAMIDATE PRODRUGS OF ANTITUMOR AND ANTIVIRAL NUCLEOSIDE ANALOGUES. *Weidong Wu and Richard F. Borch, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue Cancer Center, Purdue University, 201 South University St, West Lafayette, IN 47907, Fax: 765-496-1496, wdwu@pharmacy.purdue.edu*

Nucleoside analogues represent an important class of anticancer and antiviral drugs. The biological activity of these agents requires initial intracellular

conversion to nucleoside 5-monophosphates by kinase-mediated phosphorylation. However, inefficient intracellular phosphorylation of these nucleoside agents, resulting from decreased nucleoside kinase activity by development of drug resistance, has reduced the efficacy of these agents. One approach to solve this problem consists of developing nucleoside phosphoramidate prodrugs that would deliver nucleoside 5-monophosphates intracellularly. These phosphoramidate prodrugs contain an ester group that undergoes intracellular activation and cleavage, generating phosphoramidate anion. This intermediate undergoes spontaneous cyclization and P-N bond cleavage by water to liberate the nucleoside monophosphate quantitatively. Synthesis of phosphoramidate prodrugs of a variety of anticancer and antiviral nucleoside analogues, including gemcitabine (2,2-difluorodeoxycytidine) and EICAR (5-ethynyl-1- β -D-ribofuranosylimidazole-4-carboxamide), will be reported.

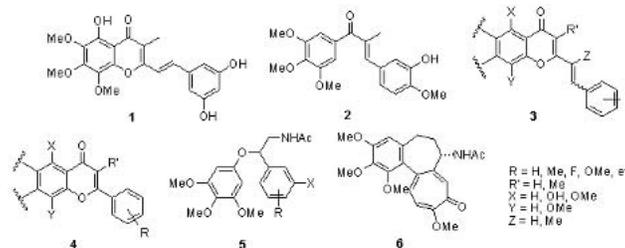


127.

SYNTHESIS OF POTENTIAL TUMOR VASCULATURE TARGETING AGENTS.

Abdul Hannan¹, Nicholas J. Lawrence², Alan T. McGown³, and Sylvie Ducki³. (1) Department of Chemistry, CARDIFF UNIVERSITY, PO Box 912, Cardiff CF10 3TB, United Kingdom, HANNANA@cf.ac.uk, (2) Department of Chemistry, Cardiff University, (3) Centre for Molecular Drug Design, University of Salford

A series of analogues of hormothamnione (1), a potent cytotoxin isolated from the marine cryptophyte *Chrysothamnium taylori*, and of chalcone (2), a potent antimitotic agent with excellent cell growth inhibitory properties, were synthesised. The styrylchromones (3) were obtained by the Claisen-like condensation of the corresponding chromones and substituted benzaldehydes. Flavones (4) were synthesised from the corresponding aroyl chlorides and Khellinone. Furthermore, the class of ethers (5) were synthesised. These are hybrids of colchicine (6), a well known antimitotic agent possessing an *N*-acetyl side chain and combretastatin A-4.



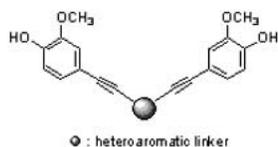
The above compounds were tested for inhibition of cancer cell growth, and the cytotoxicity to K562 cells (expressed as the IC_{50}) ranged from 50 μM to $<1 \mu\text{M}$. The highest potency (0.46 μM) was exhibited by a trimethoxy styrylchromone based on the scaffold of Khellin.

128.

SYNTHESIS OF SYMMETRICAL BIS-ALKYNYL OR ALKYL PYRIDINE AND THIOPHENE DERIVATIVES AND THEIR ANTIANGIOGENIC ACTIVITIES. *Chan Mug Ahn¹, Woon Seob Shin², Seokjoon Lee³, Hyeon-Woo Lee⁴, and Ho Bum Woo¹. (1) Department of Basic Sciences, Wonju College of Medicine, Yonsei University, 162 IL SAN-DONG, Wonju 220-701, South Korea, Fax: +82-33-745-2170, ahn0707@wonju.yonsei.ac.kr, (2) Department of Microbiology, Kwandong University College of Medicine, (3) Department of Premedical Science, Kwandong University College of Medicine, (4) Department of Biochemistry, Wonju College of Medicine, Yonsei University*

Fourteen symmetrical bis-alkynyl or alkyl pyridine and thiophene derivatives were synthesised and their antiangiogenic activity was evaluated with the

proliferation and tube formation inhibitory activity on the human umbilical vein endothelial cells (HUVEC). Compound 6, 8 and 10, rigid mimetic structure of curcumin, showed the potent growth inhibitory activity and the potent tube formation inhibitory activity. The synthesis and biological activity as well as the structure-activity relationships of these compounds will be discussed.

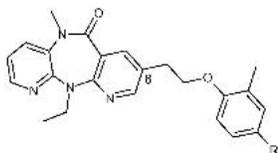


129.

NOVEL 8-SUBSTITUTED DIPYRIDODIAZEPINONE INHIBITORS WITH BROAD-SPECTRUM OF ACTIVITY AGAINST NNRTI-RESISTANT HIV-1.

Christiane Yoakim¹, Pierre R Bonneau², Robert Déziel¹, Louise Doyon², Jianmin Duan², Ingrid Guse¹, Bruno Haché¹, Serge Landry¹, Eric Malenfant¹, Julie Naud¹, William W. Ogilvie¹, Jeff A. O'Meara¹, Raymond Plante¹, **Bounkham Thavonekham**¹, Bruno Simoneau¹, Michael Boes¹, and Michael G. Cordingley². (1) Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, bthavonekham@lav.boehringer-ingelheim.com, (2) Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Research & Development

HIV-1 reverse transcriptase is a key target for the inhibition of viral replication. However, treatment with regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTI), often lead to resistance due to drug-specific mutations, leaving patients with no further NNRTI options. Advanced 8-substituted dipyridodiazepinone derivatives were used as a starting point for the identification of new inhibitors with a broader antiviral profile and promising pharmacokinetic parameters. The cellular activity, biopharmaceutical and pharmacokinetic profiles of these novel analogues will be described.

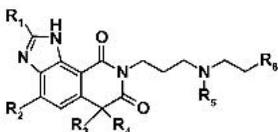


130.

NOVEL INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS RNA-DEPENDENT RNA POLYMERASE.

Josée Bordeleau¹, Michel Liuzzi², Stephen Mason², Gordon Bolger², Nathalie Dansereau², Gulrez Fazal¹, Yvon Gaudette², Lisette Lagacé², Serge Landry¹, Jean Rancourt¹, and Bruno Simoneau¹. (1) Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, jbordeleau@lav.boehringer-ingelheim.com, (2) Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Research & Development

The respiratory syncytial virus (RSV) is the leading cause of severe respiratory tract infection in infants and a major cause of morbidity and mortality in elderly and immunocompromised adults. We have targeted the viral RNA-dependent RNA polymerase activity in order to find potential inhibitors of RSV. Through screening of a novel assay format, we have identified a specific inhibitor of RSV polymerase. Optimization of this initial hit has led to the identification of potent inhibitors of RSV replication. The biological activities, profile and synthesis of this new series of inhibitors will be described.

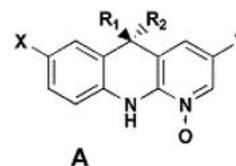


131.

SAR OF 5,10-DIHYDROBENZO[b][1,8]NAPHTHYRIDINE N-OXIDES AS NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS OF HIV-1 WITH HIGH POTENCY AGAINST CLINICALLY RELEVANT MUTANTS VARIANTS.

Barry L. Johnson¹, Christine M. Tarby², Anthony J. Cocuzza², Anurag Srivastava², Donna M. Bilder², Rajagopal Bakthavatchalam³, Qiyang Lin², James D. Rodgers², George L. Trainor², Paul S. Anderson², Lee T. Bachelor³, Sharon Diamond², Ronald M. Klabe³, Beverly C. Cordova³, Sena Garber³, Kelly Logue³, Susan Jeffrey³, and Susan Erickson-Viitanen³. (1) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702, barry.johnson@bms.com, (2) Pharmaceutical Research Institute, Bristol-Myers Squibb Company, (3) DuPont Pharmaceuticals Company

The SAR of 5,10-dihydrobenzo[b][1,8]-naphthyridine N-oxides (A) as potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) of human immunodeficiency virus type one (HIV-1) are described. The SAR was followed to optimize a number of parameters; wild type RT activity, activity against clinically relevant mutant RTs, protein binding free fraction and pharmacokinetic properties. The most advantageous blend of these properties was sought in order to advance compounds. These anti-virals have superior resistance profiles over efavirenz and other currently marketed NNRTIs. The new compounds were designed for use as durable components of HIV combination therapies and may function as constituents of salvage therapy for antiretroviral-experienced patients failing their current regimens.

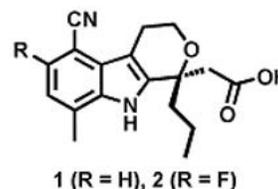


132.

SYNTHESIS OF PYRANOINDOLE DERIVATIVES AS HCV POLYMERASE

Inhibitors. **Kaapjoo Park**¹, Ariamala Gopalsamy¹, John W. Ellingboe¹, Anita Howe², and Mark Orłowski². (1) Department of Exploratory Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, Fax: 845-602-3045, ParkK3@wyeth.com, (2) Department of Infectious Disease, Wyeth Research

Potent HCV (Hepatitis C Virus) polymerase inhibitors (R)-(5-cyano-8-methyl-1-propyl-1,3,4,9-tetrahydro-pyrano[3,4-b]indol-1-yl)-acetic acid (**1**) and (R)-(5-cyano-6-fluoro-8-methyl-1-propyl-1,3,4,9-tetrahydro-pyrano[3,4-b]indol-1-yl)-acetic acid (**2**) were synthesized by employing a Fisher indole synthesis, Friedel-Crafts alkylation, and chiral resolution (IC₅₀ = 210 nM and 70 nM, respectively). The stereochemistry of the more active enantiomers of pyranoindoles **1** and **2** was assigned R based on X-ray crystallographic analysis of their 4-bromobenzyl amide derivatives. Additional pyranoindole derivatives were synthesized by varying the 5-CN group and substituents in the pyran ring. However, most of the pyranoindole derivatives were found to be less active as HCV polymerase inhibitors. In conclusion, it was found that the 5-CN and 1-propyl moieties of the pyranoindole are crucial to HCV polymerase inhibition, and 6-F or 6-H, 8-methyl or 8-F are tolerated, and that activity resides in the R enantiomer.



139.

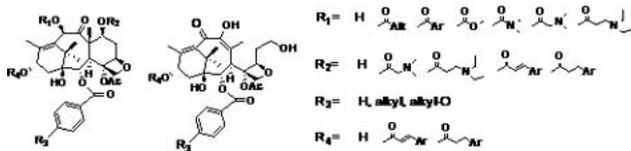
STUDIES OF L-PYRANOSSES ON RING III OF PYRANMYCINS. *Jinhua Wang, Jie Li, and Cheng Wei T. Chang*, Department of Chemistry and Biochemistry, Utah State University, 0300 Old Main Hill, Logan, UT 84322, Fax: 435-797-3390, jinhuaawang@cc.usu.edu, jieli@cc.usu.edu, chang@cc.usu.edu

L-pyranoses are commonly observed on naturally occurring antibiotics, such as neomycin. As more interest was devoted into the studies of biological function of these L-sugars, the need for the preparation of these sugars increases. However, most synthetic methodologies of L-sugars involve multiple steps processes that cannot be utilized conveniently. Pyranmycins, a novel class of aminoglycosides synthesized in our laboratory, are neomycin derivatives in which the neobiosamine is substituted with a glycopyranose. An efficient synthesis of L-pyranoses is reported here. The synthesis and antibacterial activity studies of pyranmycins with these L-pyranoses on ring III have been carried out. One compound shows prominent antibacterial activity against both gram-positive and gram-negative bacteria. The revealed structure-activity relationship information will lead to the future designs of pyranmycin against drug resistant bacteria.

140.

DESIGN, SYNTHESIS AND SAR OF TAXANE-BASED ANTI-TUBERCULOSIS AGENTS. *Qing Huang¹, Ilaria Zanardi², Antonella Pepe³, Pravin A. Nair³, Peter J Tonge², Teruo Kirikae⁴, Fumiko Kirikae⁴, and Iwao Ojima³*. (1) Department of Chemistry, State Univ. of New York at Stony Brook, Stony Brook, NY 11794-3400, Fax: 631-632-7942, qinhuang@ic.sunysb.edu, (2) Department of Chemistry, State University of New York, (3) Department of Chemistry, State University of New York at Stony Brook, (4) Department of Infectious Diseases and Tropical Medicine, International Medical Center of Japan

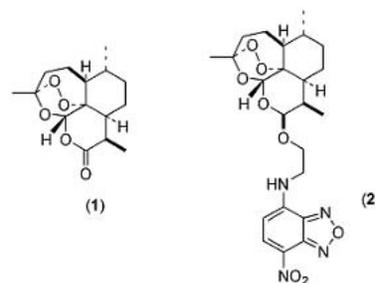
The emergence of multi-drug resistant Mycobacterium tuberculosis strains has made many of the currently available anti-TB drugs ineffective. Our preliminary studies indicate that some taxanes are potent anti-TB agents, which do not have cross-resistance with currently used chemotherapeutics. We believe that taxane is a good pharmacophore for the development of novel anti-TB drugs. Based on the structural and functional homology between FtsZ and tubulin, we hypothesized that taxanes might possess anti-TB activity by inhibiting the (de)polymerization of FtsZ in M. tuberculosis. We will present the design, synthesis and SAR of new non-cytotoxic taxane-based anti-TB agents as well as possible mechanism of action.



141.

EFFORTS TO UNDERSTAND THE UPTAKE, LOCALIZATION AND TARGETS OF ARTEMISININ ACTION USING FLUORESCENT PROBES. *Kannoth M. Muraleedharan¹, Anuradha Srivastava², Babu L. Tekwani², and Mitchell A. Avery¹*. (1) Department of Medicinal Chemistry, The University of Mississippi, University, MS 38677, murali@olemiss.edu, (2) National Center for Natural Products Research, The University of Mississippi

Artemisinin (1) and its analogs have received significant attention because of their noticeable activities against drug-resistant strains of *P. falciparum*. Previous efforts from our laboratory to explore broad-spectrum anti-infective properties of artemisinin analogs have shown that this class of molecules can be structurally modified to exhibit promising anti-leishmanial activity in addition to their anti-malarial action. Here we present the results of our efforts to understand the uptake, localization and possible targets of artemisinin action against leishmania and malaria parasites using molecular probes where the core artemisinin is attached to fluorescent groups (eg. 2).



142.

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF PSEUDOLARIC ACID B: A NOVEL ANTIPNEUMOCYSTIC AND ANTIFUNGAL NATURAL PRODUCT. *Kimberly K. Vines¹, Blake E. Watkins¹, Mitchell A. Avery¹, and Dennis R. Feller²*. (1) Department of Medicinal Chemistry, University of Mississippi, 417 Faser Hall, University, MS 38677, kvines@earthlink.net, watkins@olemiss.edu, (2) Department of Pharmacology, University of Mississippi

Pseudolaric Acid B (PLAB), a diterpene acid isolated from the bark of *Pseudolarix kaempferi*, is a promising lead compound for the development of a new class of antipneumocystic and antifungal agents. We speculate that PLAB exerts its antipneumocystic and antifungal activity by a novel mechanism of action. A principal action in human cell lines is activation of Peroxisome Proliferating-Activated Receptor (PPAR), a previously unrecognized therapeutic molecular target in pathogens. A synthesis using a model substrate has been completed. Key steps of this approach include an acrylate Diels Alder cycloaddition to give a bicyclo[2.2.2] acid, epoxidation, a tandem ring-opening-ring closing event, decarboxylation, and an enhanced Wagner-Meerwein rearrangement to afford the bicyclo[3.2.1] core of the tetracyclic lactone. Results from the application of this synthetic route to the actual substrate will be presented.

143.

SYNTHESIS OF TWO STEROL HYDRAZONE DERIVATIVES FROM 2-HYDRAZINE-2-IMIDAZOLINE AND THEIR ANTIPROLIFERATIVE EVALUATION AGAINST LEISHMANIA MEXICANA. *Gonzalo G. Visbal¹, Alvaro Alvarez-Aular¹, Roxy Luna², Dwight Arrieche², and Edgar Marchan²*. (1) Centro de Química, Instituto Venezolano de Investigaciones Científicas, Carretera Panamericana Km11, Altos de Pipe, Caracas-1020A, Venezuela, Fax: 58-212-5041350, gvisbal@ivic.ve, (2) Instituto de Investigaciones en Biomedicina y Ciencias Aplicadas, Universidad de Oriente

Two sterol hydrazone derivatives, the 20-hydrazone-imidazol-2-yl-5 α -pregnan-3 β -ol (1) and 22-hydrazone-imidazol-2-yl-cholesterol (2), were prepared by reaction of 2-hydrazone-imidazoline with 5 α -pregnan-3 β -ol-20-one and 3 β -tetrahydropiraniloxi-23-nor-cholesterol-5-en-23-al with catalytic amount of p-Ts acid in methanol under reflux for 24h afforded the compounds 1 and 2 respectively in good yield (80-90 %), these sterol hydrazone derivatives were characterized by IR, ¹H NMR spectroscopy and Elemental analyses. The compounds 1 and 2 were tested for in vitro activity against cultured promastigotes of *Leishmania mexicana* to determine the effects on cell proliferation. Concentrations of 10 μ M the compound 1 shown inhibition of growth in 78% in 40h while the compound 2 was lethal in 30 min, at low concentrations a dose-dependent reduction of the growth rate was the only observable effect. These results shown as, that the 22-hydrazone-imidazol-2-yl-cholesterol (2) exhibited potent inhibition against cultured extracellular promastigotes of *Leishmania mexicana*.

144.

SYNTHESIS AND ANTIGARDIAL ACTIVITY OF 2-(TRIFLUOROMETHYL)BENZIMIDAZOLE DERIVATIVES. *Francisco Hernandez-Luis¹, Miguel Angel Vilchis-Reyes¹, Lilian Yépez-Mulia², Alicia Hernandez-Campos¹, Rafael Castillo¹, and Amparo Tapia²*. (1) Departamento de Farmacia, Universidad Nacional Autónoma de México, Lab 122, Edificio E, Facultad de Química, Mexico City 04510, Mexico, Fax: +525-622-5329, franher@servidor.unam.mx, (2) Unidad de Investigación Médica en Enfermedades Infecciosas y Parasitarias, Centro Médico Nacional Siglo XXI, IMSS

Benzimidazole-2-carbamate derivatives, such as Albendazole and Mebendazole, used mainly as anthelmintics, have been found to possess in vitro activity

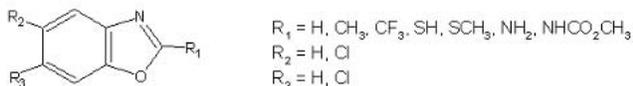
against *Giardia intestinalis*. Considering the poor solubility and passive permeability of these drugs, we have initiated a research program to have information about the structural requirements for antigiardial activity and physicochemical properties for optimal pharmacokinetics profile. We now report the synthesis and in vitro evaluation of twelve derivatives of 2-(Trifluoromethyl)benzimidazole against *Giardia intestinalis*. The aqueous solubility, partition coefficient (log P) and permeability will also be presented.

145.

SYNTHESIS AND GIARDICIDAL ACTIVITY OF SUBSTITUTED BENZOXAZOLE

DERIVATIVES. *Rafael Castillo*¹, *Victor Arroyo-Sánchez*¹, *Alejandro Luna-González*², *José González-Aguilar*¹, *Alicia Hernández-Campos*¹, *Francisco Hernández-Luis*¹, *Lilian Yépez-Mulia*³, and *Amparo Tapia*³. (1) Departamento de Farmacia, Universidad Nacional Autónoma de México, Lab 122, Edificio E, Facultad de Química, Mexico City 04510, Mexico, Fax: +525-622-5329, rafaelc@servidor.unam.mx, (2) Facultad de Química, Departamento de Farmacia, Universidad Autónoma de Guanajuato, (3) Unidad de Investigación Médica en Enfermedades Infecciosas y Parasitarias, Centro Médico Nacional Siglo XXI, IMSS

During the last decade we have been working on the synthesis and antiparasitic activity of 1-H and 1-methylbenzimidazole derivatives. We have found that 1-methyl derivatives are more active than their 1-H analogs. In order to have more information about the structural requirements for antiprotozoal activity, a series of benzoxazole derivatives of the general formula below have been synthesized and tested in vitro against *Giardia intestinalis*. The synthesis and antigiardial activity of these compounds will be presented and compared with their 1-H and 1-methylbenzimidazole analogs.

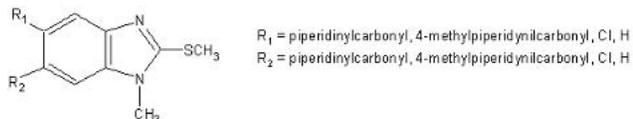


146.

SYNTHESIS AND ANTIPARASITIC ACTIVITY OF NOVEL 2-

(METHYLTHIO)BENZIMIDAZOLE DERIVATIVES. *Alicia Hernández-Campos*¹, *Rafael Castillo*¹, *Francisco Hernández-Luis*¹, *Nayeli López-Balbiaux*¹, *Yeni Islas-Fonseca*¹, *Eduardo Sandoval-Rivera*¹, *Lilian Yépez-Mulia*², and *Amparo Tapia*². (1) Departamento de Farmacia, Universidad Nacional Autónoma de México, Lab 122, Edificio E, Facultad de Química, Mexico City 04510, Mexico, Fax: +525-622-5287, hercam@servidor.unam.mx, (2) Unidad de Investigación Médica en Enfermedades Infecciosas y Parasitarias, Centro Médico Nacional Siglo XXI, IMSS

As part of our search for new antiparasitic agents, a new series of benzimidazole derivatives, of the general formula shown below, have been synthesized and tested in vitro against *Trichinella spiralis* and *Giardia intestinalis*. Results indicate that these compounds were active against *G. intestinalis* but not against *T. spiralis*. Compounds which have the amino carbonyl group at position 6 were more active than those with this group at position 5. These results indicate that the hydrogen at position 1 is not required for antiprotozoal activity.



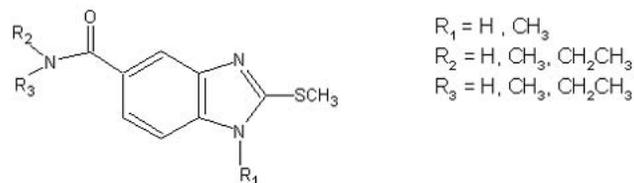
147.

SYNTHESIS AND ANTIPROTOZOAL ACTIVITY OF 1-H AND 1-

METHYLBENZIMIDAZOLE 5(6)-CARBOXAMIDES. *Nayeli López-Balbiaux*¹, *Patricia Vargas-Benítez*¹, *Alicia Hernández-Campos*¹, *Francisco Hernández-Luis*¹, *Lilian Yépez-Mulia*², *Amparo Tapia*², and *Rafael Castillo*¹. (1) Departamento de Farmacia, Universidad Nacional Autónoma de México, Lab 122, Edificio E, Facultad de Química, Mexico City 04510, Mexico, balbiaux@correo.unam.mx, (2) Unidad de Investigación Médica en Enfermedades Infecciosas y Parasitarias, Centro Médico Nacional Siglo XXI, IMSS

A series of 1-H and 1-methyl-2-(methylthio)benzimidazole 5(6)-carboxamides, of the general formula shown below, have been synthesized and tested in vitro against *Giardia intestinalis* and *Trichomonas vaginalis*. Metronidazole,

Nitazoxanide and Albendazole were also tested in the assay. The synthesis and antiprotozoal activity of these compounds will be presented.



148.

NOVEL DICATIONIC FUSED RING SYSTEM DNA-MINOR GROOVE BINDERS AND

ANTIPARASITIC AGENTS. *Reem K. Arafa*¹, *Brun Reto*², *Fariat A. Tanius*¹, *W. David Wilson*¹, and *David W. Boykin*¹. (1) Department of Chemistry, Georgia State University, Atlanta, GA 30303, Fax: 404-651-1416, (2) Swiss Tropical Institute

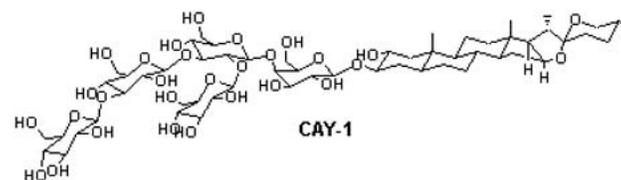
Dicationic DNA minor groove binders have displayed useful antiparasitic activities. One such molecule is the diamidine pentamidine, which is currently in clinical use for management of trypanosomiasis, antimony-resistant leishmaniasis, and *Pneumocystis carinii* pneumonia. Dicationic carbazoles, dibenzofurans and dibenzothiophenes were reported as minor groove binders with antiprotozoan activity. We have developed a series of bis-guanidino, *N*-alkyl substituted bis-guanidino and bis-reversed amidino derivatives of some fused ring systems (9*H*-fluorene, fluorene-9-one, anthraquinone, acridine). These molecules were prepared from diamino analogs and synthetic details will be provided. Carbamate and *N*-alkoxy potential prodrugs of selected dications were prepared to potentiate their oral bioavailability. The synthesized compounds gave promising *in vitro* results against *Trypanosoma brucei rhodesiense*, *Plasmodium falciparum* (some more active than reference drugs). Similar results were obtained from *in vivo* testing against *Trypanosoma brucei rhodesiense*. We report the first fused ring system dicationic derivative, 2,7-bis-*N*-isopropylguanidinofluorene, to give total cures in a trypanosomiasis mouse model.

149.

SYNTHESIS OF CAY-1, AN ANTIFUNGAL STEROIDAL SAPONIN.

Katharine L. Bowdy and *Branko S. Jursic*, Department of Chemistry, University of New Orleans, 2000 Lakeshore Dr, New Orleans, LA 70148, Fax: 504-280-6860, kbowdy@yahoo.com

The mortality rates associated with immuno-compromised individuals suffering from invasive fungal infections (IFI) can be as high as 80%, with many strains of fungi responsible for IFIs showing resistance to common broad-spectrum antifungal treatments. Saponins, steroidal glycosidic compounds abundant in the plant kingdom, are well known for their potent antimicrobial activities against multiple strains of fungi, including fungal strains that have medically been deemed resistant to currently used treatments. One saponin of particular interest, CAY-1, recently isolated from the cayenne pepper plant, has shown a broad spectrum of antifungal activity. In order to further explore and utilize the antimicrobial properties of CAY-1 against IFIs, it is necessary to develop a reliable and relatively simple synthetic method for the preparation of CAY-1 on the gram scale. Efforts towards the synthesis of CAY-1 will be presented.



150.

SYNTHESIS OF PROTEIN FARNESYLTRANSFERASE INHIBITORS AS

ANTI-MALARIAL DRUGS. *Laxman Nallan*, Department of chemistry, University of Washington, Box; 351700, Seattle, WA 98195-1700, Fax: 206-685-8665, nallan@u.washington.edu, *Michael H Gelb*, Department of Chemistry, University of Washington, and *Wesley C Van Voorhis*, Infectious Diseases, University of Washington

Protein prenylation, a novel post translational modification, involves the covalent attachment of either a 15-carbon farnesyl or a 20-carbon geranylgeranyl

isoprenoid to the carboxy terminal cystine residue via a thioether bond. The enzymes responsible for isoprenoid addition to proteins are termed protein prenyltransferases and the CaaX prenyltransferases, classified by their lipid substrate and termed protein farnesyltransferase (FTase) and protein geranylgeranyltransferase type I (GGTase I) and protein geranylgeranyltransferase type II (GGTase II).

Protein prenylation occurs in protozoan parasites. Gelb et al. reported that protein farnesylation occurs in the trypanosomatids, *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania mexicana amazonensis*. Malaria is one of the most widespread infectious diseases in the tropics. Over 300 million persons are infected each year, resulting in more than one million deaths annually. The fatal cases are generally caused by the most virulent human malaria parasite, *Plasmodium falciparum*. Current clinical treatment involves the use of inexpensive drugs such as chloroquine. However, resistance has rendered many of these drugs ineffective. Chakrabarti et al. reported that an FTase inhibitor showed inhibition activity against the growth of *P. falciparum* in human red blood cells.

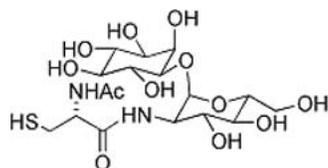
Our specific aim is to synthesize inhibitors of *P. falciparum* protein farnesyltransferase (Pf-PFT) as drugs against malaria. We have synthesized a variety of PFTIs that have been patented and found that Bristol Myers Squibb (BMS) PFTIs are far superior at killing *P. falciparum*.

151.

SYNTHESIS OF SUBSTRATE-MIMIC ANALOGUES OF MYCOTHIOI AS INHIBITORS OF RV1170 AND RV1082 OF MYCOBACTERIUM TUBERCULOSIS.

Belhu B. Metaferia and **Carole A. Bewley**, NIDDK/Laboratory of Bioorganic Chemistry, National Institutes of Health, 9000 Rockville Pike, Bldg 8-1A02, Bethesda, MD 20892, belhum@intra.nidk.nih.gov

Mycobacterium tuberculosis, the causative agent of tuberculosis, has infected about two billion people worldwide and is a cause for more than two million deaths per year. The need for potent therapeutic agents has increased because of multi-drug resistance (MDR) and the serious complications in patients who are immunocompromised due to diseases such as HIV/AIDS. One of the promising strategies in developing new antitubercular drugs is to target the biosynthetic machinery that produces mycothiol (MSH, 1). Mycothiol is a low molecular weight thiol found in actinomycetes, such as *Mycobacterium tuberculosis* which plays an important role as a detoxification agent and providing the organism with a reducing cellular environment; hence resistance to drugs and protection from oxidative stress. As part of our ongoing effort to discover potent inhibitors of the biosynthesis of mycothiol, we present the synthesis and preliminary biological evaluations of new analogues that structurally mimic mycothiol as potential inhibitors of mycothiol amidase (Rv1082) and the deacetylase (Rv1170) enzymes.



1. MSH, (Mycothiol)

152.

SYNTHESIS OF TWO NEW INHIBITORS OF THE STEROL 24-METHYLTRANSFERASE AND ACTIVITY AGAINST PARACOCCIDIODES BRASILIENSIS.

Gonzalo G Visbal¹, **Gioconda San-Blas**², **Alvaro Alvarez-Aular**¹, and **Belisario Moreno**². (1) Centro de Quimica, Instituto Venezolano de Investigaciones Cientificas, Carretera Panamericana Km11, Altos de Pipe, Caracas-1020A, Venezuela, Fax: 58-212-5041350, gvisbal@ivic.ve, (2) Centro de Microbiologia y Biologia Celular, Instituto Venezolano de Investigaciones Cientificas

We report the synthesis of two new sterols: 22-piperidin-2-yl-pregnan-3 β ,22(S)-diol (**aza-2**) and 22-piperidin-3-yl-pregnan-3 β , 22(S)-ol (**aza-3**), as inhibitors of the (S)-adenosyl-L-methionine: δ 24(25) sterol methyl transferase (SMT) an important enzyme that regulates carbon flow in the sterol pathway of plants, fungi and protozoa. As such, SMT may work as an attractive therapeutic target. Therefore, we studied growth inhibition and modification of sterol composition

of the pathogenic yeastlike phase of the dimorphic fungus *Paracoccidioides brasiliensis*, by means of 22,26-azasterol (**aza-1**) and their analogs **aza-2** and **aza-3**. Inhibition was 100% for **aza-1** at 5 μ M, 62% for **aza-2** at 10 μ M, and 100% for **aza-3** at 0.5 μ M. GC-MS detailed analysis of the endogenous sterols of *P. brasiliensis* with and without either (**aza-1**, **aza-2**, or **aza-3**) showed that their antiproliferative action is associated with the depletion of 24-methyl sterols.

153.

ORALLY EFFICACIOUS RENIN INHIBITORS: NEW PERSPECTIVES IN A CHALLENGING FIELD.

Juergen Maibaum, *Novartis Institute for Biomedical Research Basel, Novartis Pharma AG, Klybeckstrasse 220, WKL-136.683, 4002 Basel, Switzerland, Fax: 041-61-69-61163, juergen_klaus.maibaum@pharma.novartis.com*

The renin-angiotensin-aldosterone (RAAS) cascade plays a central role in the regulation of blood pressure and the homeostasis of body fluid volume, and there is strong evidence for its major pathophysiological role in tissue damage (heart, kidney, vasculature) via angiotensin II induced pro-inflammatory, cell-proliferative and fibrogenic pathways. Selective blockade of the RAAS at its source by inhibition of the rate-limiting, specific aspartyl peptidase renin has been recognized as a highly attractive paradigm to treat hypertension and protect from end-organ damage. However, the successful development of orally efficacious renin inhibitors has remained a challenge for more than 25 years in drug research. Aliskiren is a first-in-class, small-molecule renin inhibitor which resulted from a topographical X-ray structure-based design concept, leading to a beneficial physicochemical profile distinct from previous peptide-like inhibitors. This novel transition-state mimetic inhibitor has been demonstrated to be a highly selective, potent and long-lasting anti-hypertensive agent after oral administration in various animal models and in humans (currently in Phase III). Major aspects of the structural design approach, as it evolved during lead optimization within related compound classes, and pre-clinical pharmacology of aliskiren in SHR, double-transgenic rats and marmosets will be reviewed. Clinical data from hypertensive patients support the potential for aliskiren as a safe and effective once-daily oral treatment for hypertension.

154.

PPARPAN™ AGONISTS: THE NEXT GENERATION OF PPAR LIGANDS.

Paul L. Feldman, *GlaxoSmithKline, Research Triangle Park, NC 27709*

We have previously shown that activation of the PPAR subtypes by simultaneous administration of combinations of selective PPAR agonists produces synergistic effects in animal models of type 2 diabetes. These effects include normalization of post-prandial glucose and lowering of serum triglycerides and NEFAs without weight gain and less hemodilution. We now show that a single molecule that has agonist activity on PPAR alpha, PPAR gamma and PPAR delta exhibits the same synergy as that reported for the combination of individual selective PPAR agonist molecules. The agents offer promise for the treatment of metabolic syndrome and type 2 diabetes.

155.

ZETIA MECHANISM OF ACTION.

Scott W. Altmann, *Cardiovascular/Metabolic Disease Discovery Research, Schering-Plough Research Institute, K15-3-3600-C330, 2015 Galloping Hill Rd., Kenilworth, NJ 07033, Fax: 908-740-2383, scott.altmann@spcorp.com*

The discovery of ezetimibe (Zetia™), the first marketed cholesterol absorption inhibitor, has provided a new approach to reduction of elevated cholesterol, an important risk factor for cardiovascular disease. Combination of ezetimibe with a statin (e.g. Zocor™) blocks both sources of cholesterol (synthesis, dietary), and provides a significant reduction in total cholesterol levels. Elucidation of the molecular mechanism of ezetimibe has been of high interest, and a number of proteins have been studied as potential targets of ezetimibe. Identification and characterization of Niemann-Pick C1 Like 1 (NPC1L1) has established NPC1L1 as an essential protein in the cholesterol absorption process. While otherwise phenotypically normal, NPC1L1-deficient mice exhibit a significant reduction in absorbed cholesterol. Ezetimibe had no effect in the NPC1L1 knock-out mice,

indicating that NPC1L1 resides in an ezetimibe-sensitive pathway responsible for intestinal cholesterol absorption. Further characterization of this pathway may lead to discovery of new chemotypes active in blocking cholesterol absorption.

156.

DISCOVERY OF THE NOVEL ANTITHROMBOTIC AGENT BAY 59-7939, AN ORALLY ACTIVE, DIRECT FACTOR XA INHIBITOR. *Susanne Roehrig*¹, *Alexander Straub*¹, *Jens Pohlmann*¹, *Thomas Lampe*¹, *Josef Pernerstorfer*¹, *Karl Heinz Schlemmer*², and *Elisabeth Perzborn*³. (1) *Chemical Research, Bayer HealthCare AG, Aprather Weg 18a, 42096 Wuppertal, Germany, susanne.roehrig@bayerhealthcare.com*, (2) *Preclinical Pharmacokinetics, Bayer HealthCare AG*, (3) *Cardiovascular Research, Bayer HealthCare AG*

Despite recent progress in antithrombotic therapy, there is still an unmet medical need for safe and orally available anticoagulants. The coagulation enzyme Factor Xa (FXa) is a particularly promising target, and recent efforts in this field have focused on the identification of small-molecule inhibitors with good oral bioavailability. We identified oxazolidinone derivatives as a new class of potent FXa inhibitors. Lead optimization led to the discovery of BAY 59-7939, a highly potent and selective direct FXa inhibitor with excellent in vivo antithrombotic activity and high oral bioavailability. The X-ray crystal structure of BAY 59-7939 in complex with human FXa clarified the binding mode and the stringent requirements for high affinity. BAY 59-7939 was selected for clinical development for the prevention and treatment of thromboembolic diseases.

157.

DESIGN AND SYNTHESIS OF THROMBIN RECEPTOR (PAR-1) ANTAGONISTS - AWARD ADDRESS. *William J. Greenlee*, *CNS and Cardiovascular Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, william.greenlee@spcorp.com*

Cardiovascular disease, especially heart attack and stroke, remains a major cause of mortality in the United States and Western Europe. In most cases, the cause of death is the presence of a thrombus in a major artery, a result of inappropriate activation of the coagulation pathway. The enzyme thrombin plays a central role in this process by cleaving fibrinogen to fibrin, and by activating platelets, which contribute to arterial thrombus formation. In a process unique to the protease-activated receptor (PAR) family, thrombin cleaves the N-terminus of the thrombin receptor (PAR-1) present on these cells, creating a tethered ligand which activates the receptor. Antagonists of PAR-1 are of high interest as potential agents for the prevention of arterial thrombosis, especially since they may have less bleeding liability than other antithrombotic drugs (e.g. thrombin and factor Xa inhibitors). Starting from a modestly-potent lead derived from the natural product himbacine, we have discovered potent orally bioavailable PAR-1 receptor antagonists which block thrombin-induced activation of platelets and are active in a primate model of thrombosis. The design, synthesis and structure-activity relationships of this series of antagonists will be discussed.

158.

EXPANDING CHEMICAL DIVERSITY USING STEREOCONTROLLED SYNTHESIS. *John A. Porco Jr.*, *Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, MA 02215, Fax: 617-353-6466, porco@chem.bu.edu*

Complex molecules often provide opportunities for the preparation of new structures ("diversity exploration") with a goal to increase the structural diversity available from Nature and prepare molecules with novel chemical or biological properties. This presentation will outline examples from our research program illustrating our overall interest in expanding chemical diversity, including examples of projects being conducted at the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU). Projects involving the synthesis of chemical libraries utilizing stereochemical and positional variation within the molecular framework, as well as new methodologies to enable parallel synthesis of new scaffold architectures, will be described.

159.

POTENTIATION OF APOPTOSIS: REMARKABLY POTENT SMALL MOLECULE SMAC REPLACEMENTS. *Jef K. De Brabander*¹, *R. Mathew Thomas*¹, *Hidetaka Suzuki*¹, *Lin Li*¹, *Xiaodong Wang*², and *Patrick G. Harran*¹. (1) *Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, Fax: 214-648-6455, jdebra@biochem.swmed.edu*, (2) *Department of Biochemistry and Howard Hughes Medical Institute, The University of Texas Southwestern Medical Center at Dallas*

In this presentation, I will describe a joint effort between the Harran, Wang, and De Brabander groups related to the design, synthesis and evaluation of small molecules that mimic the function of Smac (second mitochondrial activator of caspases) by neutralizing the anti-apoptotic effects of IAPs (Inhibitor of Apoptosis Proteins) and potentiate TRAIL and TNF α mediated cell death.

160.

IDENTIFICATION OF POTENT, SELECTIVE VLA-4 ANTAGONISTS AS CHEMICAL TOOLS TO ANSWER BIOLOGICAL QUESTIONS. *Donna M. Hurynd*¹, *Susan Ashwell*¹, *Reinhardt B. Baudy*¹, *Darren B. Dressen*², *Stephen B. Freedman*², *Francine S. Grant*², *Jeffrey Kennedy*³, *Andrei W. Konradi*², *Anthony Kreft*¹, *Louis J. Lombardo*¹, *Michael A. Pleiss*², *Dimitri Sarantakis*⁴, and *Ted Yednock*⁵. (1) *Chemical Sciences, Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543, hurynd@wyeth.com*, (2) *Chemistry, Elan Pharmaceuticals*, (3) *Neuroscience, Wyeth Research*, (4) *Chemical and Screening Sciences, Wyeth Research*, (5) *Cell Biology, Elan Pharmaceuticals*

Through a series of iterative optimizations, highly potent, selective and orally efficacious VLA-4 antagonists were developed. Optimization activities focused not only on potency, but also reduction of protein binding, enhancements in metabolic stability and improved oral absorption. The resultant compounds were used as tools to evaluate the effect of VLA-4 antagonism in a variety of disease models in which integrin-mediated adhesion has been implicated. A description of the process to develop small molecule VLA-4 antagonists, and the effects of these molecules in a number of animal models of inflammatory diseases will be described.

161.

USING SMALL MOLECULE LIBRARIES TO PROBE PHARMACOLOGICAL SPACE. *John S. Lazo*, *Department of Pharmacology, University of Pittsburgh School of Medicine, E1340 Biomedical Science Tower, University of Pittsburgh, Pittsburgh, PA 15261, Fax: 412-648-2229, lazo@pitt.edu*

The identification of novel small molecules with clinically useful pharmacological attributes requires the concerted efforts of chemists, biologists and clinicians. Time-honored processes of forward pharmacology have recently been supplanted by target-oriented reverse pharmacology strategies. In this lecture, I will outline the advantages and limitations of both approaches, using examples from both academia and industry. Moreover, I will address issues of pharmacological space and novel strategies to identify new therapeutic agents for human diseases including cancer and neurodegeneration. These will include methods to detect alterations in the spatial location of drug targets, disrupters of protein-protein interactions, inhibitors of enzyme activity, and modifiers of ion channel functionality. Preclinical hurdles for identified molecules will also be discussed.

162.

DIVERSITY-ORIENTED SYNTHESIS AND CHEMBANK. *Stuart L. Schreiber*, *Department of Chemistry & Chemical Biology, Howard Hughes Medical Institute, Harvard Institute of Chemistry & Cell Biology, Molecular Target Laboratory, Harvard University, 12 Oxford Street, Cambridge, MA 02138, Fax: 617-495-0751*

Pharmaceutical companies develop small molecule therapeutic drugs in part by drawing upon government-sponsored research performed in universities and other non-profit institutions. Academic labs have recently transitioned towards the integration of small molecule synthesis, small molecule screens, and informatics with the primary goal of illuminating principles that underlie biology and disease. My lecture aims to provide insight into the development of one such example of the latter, specifically discussing advances in diversity-oriented synthesis and the public database ChemBank.

For the academic chemistry community to succeed in such efforts, it will be important for us to use a well-considered set of small molecules. Achieving success also requires addressing the cultural issues that distinguish academic and private sector research. Our experience has taught us that commercial

compounds, although valuable for providing coverage of traditional drug space, are limited in other respects, and that synthetic compounds produced by academic chemists offer many important advantages. These advantages include:

1. Valuable properties of small molecules not seen in commercial compounds such as the ability to disrupt protein-protein interactions, to enhance binding specificity, and to modulate targets previously thought to be "non-druggable". These properties are achieved through new kinds of chemistry, including asymmetric synthesis, combinatorial chemistry and diversity-oriented synthesis.
2. The distribution of these small molecules in a more extensive chemical space through the use of computational methods. Commercial compounds tend to lack stereochemical and skeletal diversity.
3. The participation of chemists prior to the start of the screening process develops an environment in which the chemists are extremely excited to participate with biologists in efforts to optimize the properties of the hits discovered in screens, thereby moving them towards more effective disease probes or drugs.

163.

ZEBULARINE INDUCES AND SUSTAINS DNA CYTOSINE DEMETHYLATION IN HUMAN CANCER CELLS. Peter A. Jones¹, Jonathan C. Cheng¹, Christine Yoo¹, Gangning Liang¹, and Victor E. Marquez². (1) Department of Biochemistry & Molecular Biology, University of Southern California Keck School of Medicine, 1441 Eastlake Avenue, Room 8302L, Mail Stop #83, Los Angeles, CA 90089-9181, Fax: 323-865-0102, jones_p@ccnt.hsc.usc.edu, (2) Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute at Frederick

Demethylating agents have great potential clinical promise in reversing the DNA hypermethylation evident in human cancers. However, the use of these agents is often limited by their cytotoxicities, non-specific effects on both normal and cancer cells, as well as their inability to permanently reverse methylation. Zebularine (1-(beta-D-ribofuranosyl)-1,2-dihydropyrimidin-2-one), a stable DNA methylation inhibitor, effectively sustains DNA demethylation and prevents gene resiliencing when administered in a continuous fashion to cultured cancer cells. This is associated with a specific and complete depletion of DNA methyltransferase 1 (DNMT1). Zebularine minimally affects the methylation, gene expression and the growth rate of a normal fibroblast cell line. The drug is selective towards cancer cells and may represent a strong candidate for epigenetic therapy.

164.

NUCLEOSIDE ANALOGUES AS AGENTS FOR THE TREATMENT OF HEPATITIS B AND C. Richard Storer, Antiviral R & D, Idenix Pharmaceuticals, Inc, 60 Hampshire Street, Cambridge, MA 02139, Fax: 617-665-9801, Storer.Dick@idenix.com

Novel nucleoside analogues continue to occupy a prominent position in the search for antiviral agents both to replace or augment existing therapies and to provide initial therapies for emerging pathogens. For the treatment of hepatitis B, the use of lamivudine is now well established and other nucleoside analogues are in advanced clinical development. The search for novel agents for the treatment of hepatitis C has been responsible for a resurgence in nucleoside chemistry over the past three years. Novel ribonucleoside analogues having modifications in either or both of the base and sugar moieties have been identified as potential candidates for development. Some important advances in synthetic approaches have been developed to gain access to the new structural classes. A review of important developments in the field will be presented.

165.

NOVEL FLUORINATED ANTIVIRAL NUCLEOSIDES: SYNTHESIS, MOLECULAR MECHANISM AND RESISTANCE. C. K. Chu, College of Pharmacy, The University of Georgia, Brooks Drive, Athens, GA 30602, Fax: 706-542-5381, dchu@rx.uga.edu

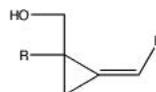
A number of fluorinated nucleosides, either at the heterocyclic and/or carbohydrate moiety, have been synthesized and found to exhibit interesting antiviral activities. A fluorine atom is considered to be isosteric with both hydroxyl group as well as hydrogen atom. Furthermore, a series of 2',3'-unsaturated nucleosides have demonstrated potent antiviral activity against HIV. In view of the interesting biological activity of these nucleosides having a fluorine atom or an

unsaturated moiety, it was of interest to synthesize the nucleosides possessing both fluorine and 2',3'-unsaturation as potential antiviral agents. Thus, we synthesized a number of 2'- or 3'-fluorinated 2',3'-unsaturated nucleosides as potential anti-HIV/HBV agents for the studies of structure-activity relationships. From the studies, we found that although a number of L-nucleosides are active against HIV, they are in general cross-resistant with 3TC, and the effect is particularly more pronounced in 4'-S nucleosides. However, this general statement does not apply to the situation in HBV, and we can explain their mechanism of resistance by molecular modeling of these agents along with the HIV/HBV polymerases (supported by NIH AI 32351 and AI25899).

166.

METHYLENECYCLOPROPANE ANALOGUES OF PURINE NUCLEOSIDES AS AGENTS AGAINST DRUG-RESISTANT CYTOMEGALOVIRUS. Jiri Zemlicka, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201-1379, 110 E. Warren Ave., Detroit, MI 48201-1379, Fax: 313-832-7294, zemlicka@kci.wayne.edu, and John C. Drach, Department of Biologic and Materials Science, University of Michigan, Ann Arbor, MI 48019-1078, Fax: 734-764-4497, jcdrach@umich.edu

Recently, we described a series of nucleoside analogues (**1**) where the ribo- or deoxyribofuranose moiety was replaced by a methylenecyclopropane template. A number of purine derivatives are potent antiviral agents effective particularly against human cytomegalovirus (HCMV). Thus, compounds **1a** and **1b** were selected for preclinical studies. Relevant examples of syntheses of biologically active analogues will be discussed. SAR studies established certain guanine analogues were the most active and least cytotoxic. The compounds acted late in the viral replication cycle consistent with inhibition of viral DNA synthesis. HCMV clinical isolates resistant to ganciclovir (GCV) due to mutations in gene UL97 were not resistant to the new analogues; resistant HCMV was selected by serial passage in the new drugs. Preliminary results suggest that more than one mutation in UL97 is required for resistance. These and related animal studies established that the new compounds are excellent candidates for further preclinical development. Supported by NIH grants CA32779, U19-AI31718, and P01-AI46390.



1a: B = 2-amino-6-cyclopropylaminopurine, R = H (S-enantiomer)
1b: B = Gua, R = CH₂OH

167.

FIXED CONFORMATION NUCLEOSIDE ANALOGS ARE EFFECTIVE AGAINST EXCISION-PROFICIENT HIV-1 RTs. P.L. Boyer, Retroviral Replication Laboratory, NIH-NCI HIV Drug Resistance Program, P.O. Box B, Bldg. 539, Frederick, MD 21702-1201, Fax: 301-846-6966, boyerp@ncifcrf.gov, V. E. Marquez, Laboratory of Medicinal Chemistry, National Cancer Institute, NIH, John G. Julius, Basic Research Program, SAIC-Frederick, Inc, and Stephen H. Hughes, Retroviral Replication Laboratory, NCI/HIV Drug Resistance Program, NCI-FCRDC, Frederick, MD 21702, Frederick, MD 21702, Fax: 301-846-6966, hughes@ncifcrf.gov

For HIV-1 RT, selective excision is an important mechanism of resistance to nucleoside analogs. To circumvent this mechanism, we are trying to develop nucleoside analogs that do not block DNA synthesis at the point of incorporation, but only after additional normal nucleotides have been added to the DNA. We tested a class of nucleoside analogs in which the sugar ring is locked in either the North or the South conformation. These analogs have a 3' OH present on the pseudosugar ring. HIV-1 RT did not effectively incorporate the analogs in which the sugar is in the South conformation. The North conformation analogs are readily incorporated into DNA; the primer is extended for two additional nucleotides before extension is inhibited. The North conformation analogs are relatively effective inhibitors of excision proficient HIV-1 RT mutants both in vitro RT assays and in the HIV viral infections in cultured cells.

168.

ENVELOPE SPECIFIC ANTI-HEPATITIS C AGENTS. *Michael L. Mohler¹, Carl E. Wagner², Gyong Suk Kang¹, Yu An Chang³, Everly B. Fleischer², Kenneth J. Shea², Hideki Tani⁴, Eldon E. Geisert Jr.⁴, Michael A. Whitt⁴, and Duane D. Miller¹. (1) Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, 847 Monroe, Suite 327, Memphis, TN 38163, mmohler@utm.edu, (2) Department of Chemistry, University of California at Irvine, (3) RIC Biotech & Trading, Inc, (4) College of Medicine, University of Tennessee Health Science Center*

Hepatitis C virus (HCV) infection is currently a global pandemic. Estimates of 150-200 million people worldwide and four million in the U.S. are chronically infected. The long-term sequelae of infection include chronic hepatitis (65%), cirrhosis and end-stage liver disease (25%), and hepatocellular carcinoma (10%). The current therapy, ribavirin and/or alpha-interferons is woefully inadequate due to low response rates, high relapse rates, and poor risk-benefit and expense-benefit ratios. The discovery of multiple putative HCV receptors [CD81 and Scavenger Receptor-Class B Type I (SR-BI)] has provided novel targets for therapy or prevention. Reconstitution of these interactions in vitro has shown that the large extracellular loops (LEL) of CD81 and SR-BI bind to the HCV E2 envelope glycoprotein. The significance of these interactions is not known however, hypothesized significances include viral mechanisms for cell entry or immune evasion. Ligand discovery strategies by screening and rational ligand design for inhibitors of the LEL-E2 interaction will be discussed.

169.

THALIDOMIDE ANALOGUES: DUAL INHIBITORS OF BOTH ANGIOGENESIS AND HUMAN CANCER CELL PROLIFERATION. *Scott M. Capitosti and Milton L. Brown,* Department of Chemistry, University of Virginia, McCormick Road, P.O. Box 400319, Charlottesville, VA 22904, Fax: 434-924-0798, smc4m@virginia.edu

The identification of agents with antiproliferative activity against endothelial cells has significant value for the treatment of many angiogenesis-dependent pathologies. Herein, we describe the discovery of a series of thalidomide analogues possessing inhibitory effects against both endothelial cells and human cancer cells. More specifically, two classes of thalidomide analogues were synthesized, including a phthalimide and quinazolinone class. Several analogues exhibited low micromolar potency in the inhibition of human microvascular endothelial cell (HMEC) proliferation, both in the presence and absence of vascular endothelial growth factor (VEGF). Several analogues in the quinazolinone class proved to inhibit microvessel outgrowth in a chicken chorioallantoic membrane assay. Additionally, several compounds were low micromolar to nanomolar inhibitors of various human tumor cell lines of breast, prostate, and colon cancers. Altogether, this data suggests these analogues as promising leads for the development of agents to treat cancers in which poor prognosis is correlated to increased microvessel density.

170.

BICYCLOMYCIN FLUORESCENT PROBES: SYNTHESIS AND BIOCHEMICAL, BIOPHYSICAL, AND BIOLOGICAL PROPERTIES. *Andrew P. Brogan¹, William R. Widge², and Harold Kohn¹.* (1) Division of Medicinal Chemistry and Natural Products, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, Fax: 919-843-7835, abrogan@unc.edu, (2) Department of Biology and Biochemistry, University of Houston

Bicyclomycin (BCM) is a commercially available antibiotic whose primary site of action in *Escherichia coli* is the transcription termination factor rho. Key aspects of the BCM-rho interaction—Kd, stoichiometry for BCM-rho binding, and whether BCM and ATP binding induce conformational changes in rho—remain unknown. In this study, the design, synthesis, and characterization of a series of bicyclomycin fluorescent probes (BFP) constructed to sense the BCM-rho interaction are described and their use documented. We show that dihydrobicyclomycins with medium-to-large C(5a)-substituents afforded excellent inhibitory activities exceeding those of BCM in the poly(C)-dependent ATPase assay. The utility of BFP in bicyclomycin-rho binding studies was documented through the use of 5a-(phenazin-2-ylmethylsulfanyl)-dihydrobicyclomycin. Excitation (290 nm) of W381 in wild-type rho in the presence of BFP and ATP led to fluorescence resonance energy transfer (FRET) and gave a Kd (BFP) of 9.9 μM. Using ADP in place of ATP or excluding nucleotide did not result in energy transfer,

which suggests that ATP binding induced a conformational change in rho. FRET measurements provided an approximate weighted average distance (23 Å) between W381 and BFP in the presence of bound ATP. The Kd value for BFP-rho was correlated with ATP binding at the 3 tight ATP binding (Kd (ATP) = 95 nM) sites in wild-type rho.

171.

DISCOVERY OF POTENT, NON-STEROIDAL FXR AGONISTS ORIGINATING FROM NATURAL PRODUCT-LIKE LIBRARIES. *K.C. Nicolaou¹, Ronald M Evans², A. J. Roecker¹, Robert Hughes¹, M. Downes³, and Jeffrey A. Pfefferkorn¹.* (1) Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Rd, La Jolla, CA 92037, kcn@scripps.edu, arock@scripps.edu, (2) Howard Hughes Medical Institute, The Salk Institute, (3) The Salk Institute of Biological Sciences

The efficient regulation of cholesterol synthesis, metabolism, acquisition, and transport is an essential component of lipid homeostasis. The farnesoid X receptor (FXR) is a transcriptional sensor for bile acids, the primary product of cholesterol metabolism. Accordingly, the development of potent, selective, small molecule agonists, partial agonists, and antagonists of FXR would be an important step in further deconvoluting FXR physiology. Herein, we describe the development of four novel classes of potent FXR activators originating from natural product-like libraries. Initial screening of a 10,000-membered, diversity-orientated library of benzopyran containing small molecules for FXR activation utilizing a cell-based reporter assay led to the identification of several lead compounds owning low micromolar activity (EC50's = 5 - 10 micromolar). These compounds were systematically optimized employing parallel solution-phase synthesis and solid-phase synthesis to provide four classes of compounds that potently activate FXR. Two series of compounds, bearing stilbene or biaryl moieties, contain members that are the most potent FXR agonists reported to date in cell-based assays. These compounds will find future utility as chemical tools to further define the physiological role of FXR as well as potential therapeutic leads for the treatment of diseases linked to cholesterol and bile acid metabolism and homeostasis.

172.

PROGRESS TOWARD THE TOTAL SYNTHESIS OF AMPHIDINOLIDE B1. *John S. Schneckloth Jr.,* Department of Chemistry, Yale University, New Haven, CT 06520, john.schneckloth@yale.edu, *Amit Mandal,* Department of Molecular, Cellular, and Developmental Biology, Yale University, and *Craig M. Crews,* Departments of Chemistry, Pharmacology and Molecular, Cellular, and Developmental Biology, Yale University

The amphinolides are a structurally diverse group of cytotoxic macrolides isolated from dinoflagellates of the genus *Amphidinium*. Amphidinolide B1 is the most studied of all amphinolides reported, as well as among the most potent and structurally complex. Despite significant interest from the synthetic and biological communities, no total synthesis of amphinolide B1 has been reported to date. We have developed a novel, convergent synthetic approach which involves construction of the diene moiety via a diastereoselective hydroboration/Suzuki-Miyaura cross coupling reaction. Progress towards completion of the total synthesis and plans for subsequent biological evaluation will be reported.

173.

COMBINATORIAL BIOSYNTHESIS OF NOVEL MTOR INHIBITORS. *Barrie Wilkinson¹, Matthew A. Gregory², Sabine Gaisser², Rachel E Lill¹, Rose M Sheridan³, Hrovje Petkovic⁴, Alison J. Weston¹, Isabelle Carletti¹, James Staunton⁵, Peter F. Leadlay⁶, and Ming Q. Zhang⁷.* (1) Department of Natural Products Chemistry, Biotica Technology Ltd, Chesterford Research Park, Little Chesterford, Nr Saffron Walden CB10 1XL, United Kingdom, Fax: +44-1799-532925, barrie.wilkinson@biotica.co.uk, (2) Department of Molecular Biology, Biotica Technology Ltd, (3) Department of Microbiology, Biotica Technology Ltd, (4) Department of Microbiology, Biotica Technology Limited, (5) Chairman of the Scientific Advisory Board, Biotica Technology Ltd, (6) Chief Scientific Officer, Biotica Technology Ltd, (7) Research Director, Biotica Technology Ltd

Rapamycin and its derivatives are the most selective kinase inhibitors known and represent the only established inhibitors of the serine/threonine kinase

mTOR. This ability to selectively target mTOR disrupts Akt mediated signalling and has been shown to reverse chemoresistance in lymphomas expressing Akt. The potential of rapamycin and analogues (rapalogues) is exemplified by the Wyeth compound CCI-779 which is designated for fast-track development for renal therapy after failure of initial therapy. We report the use of combinatorial biosynthetic approaches for the production of novel rapalogues. Deletion of a portion of the rapamycin biosynthetic gene cluster in *Streptomyces hygroscopicus* generated a rapamycin non-producing mutant. Complementation with gene cassettes carrying combinations of the deleted genes allowed the production of a library of rapalogues bearing altered oxidation and alkylation patterns. The feeding of exogenous carboxylic acids to specific mutants provided an orthogonal approach for increasing diversity through mutasynthesis in these engineered strains.

174.

RAPID ASSEMBLY OF DIVERSE AND POTENT AKT INHIBITORS. *Zhicai Wu*¹, John C. Hartnett², Lou Anne Neilson², Mark T. Bilodeau², George D. Hartman³, Stanley F. Barnett⁴, Deborah Defeo-Jones⁴, Sheng Fu⁴, Ronald Robinson⁵, and Hans E. Huber⁵. (1) Medicinal Chemistry, Merck & Co., Inc, WP14-2, P.O. Box 4, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-7310, zhicai_wu@merck.com, (2) Department of Medicinal Chemistry, Merck Research Laboratories, (3) Department of Medicinal Chemistry, Merck & Co., Inc, (4) Department of Cancer Research, Merck & Co., Inc, (5) Department of Cancer Research, Merck Research Laboratories

Akt is a serine/threonine kinase that is a key regulator of apoptosis and directly phosphorylates a number of proteins which are part of the cell survival machinery. Cells with activated Akt are less sensitive to apoptotic stimuli. Due to its role as a regulator of the cell's apoptotic machinery, Akt activation likely plays a critical role in tumorigenesis and Akt kinase has garnered a great deal of attention as a promising molecular target for cancer therapy. The inhibitors of Akt kinases might induce apoptosis alone or in combination with standard cancer chemotherapeutics. In this talk, we will present a rapid assembly of potent Akt1 and Akt2 inhibitors with diversified core structures from a common intermediate and their further modifications leading to compounds with excellent intrinsic potency, good cell potency, improved physical properties and PK profile.

175.

BISARYLMALEIMIDES AS INHIBITORS OF PROTEIN KINASE C AND GLYCOGEN SYNTHASE KINASE-3. *Han Cheng Zhang*, Hong Ye, Kimberly B. White, David F. McComsey, Claudia K. Derian, Bruce R. Conway, Michael F. Addo, Annette J. Eckardt, Diane R. Croll, Jian Li, Leonard R. Hecker, Lori Westover, Jun Z. Xu, Richard Look, Stuart Emanuel, Patricia Andrade-Gordon, Bruce P. Damiano, Keith T. Demarest, Gee Hong Kuo, and Bruce E. Maryanoff, Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477, Fax: 215-628-4985, hzhang@prds.jnj.com

Protein kinase C (PKC) enzymes regulate vascular tone, permeability, and proliferation, and they are involved in cardiovascular disease, cancer, ischemia, inflammation, and CNS disorders. The PKC- β isoform is induced in response to hyperglycemia in cardiac, aortic, renal, and retinal tissues, and therefore its inhibitors would have therapeutic potential for treatment of diabetic complications. Glycogen synthase kinase-3 (GSK-3) plays an important role in glucose homeostasis, CNS function, and cancer. Inhibition of GSK-3 β -dependent phosphorylation should activate insulin-dependent glycogen synthesis, affording a novel mode of treating type II diabetes. We have identified two distinct, novel series of maleimide-based compounds, macrocyclic bisindolylmaleimides and 3-(7-azaindoly)4-arylmaleimides, that provided interesting *dual inhibitors* of PKC- β and GSK-3 β and highly selective inhibitors of GSK-3 β , respectively. Details on the synthesis, structure and activity relationships, kinase selectivity, and cellular activity of the series will be presented.

176.

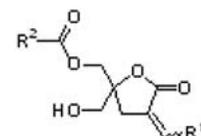
DISCOVERY AND PROGRESSION OF A NOVEL SERIES OF ORALLY ACTIVE P38 KINASE INHIBITORS. *Katerina Leftheris*¹, Gulzar Ahmed², Ray Chan², Alaric Dyckman¹, John Hynes¹, Shuqun Lin¹, Axel Metzger², Kevin Moriarty², Yvonne Shimshock², James Wen², John Wityak¹, Stephen Wroblewski¹, Hong Wu¹, Junjun Wu², Kamelia Behnia³, Arthur M. Doweiko⁴, Kathleen Gillooly⁵, Tsung Lin⁶, Derek Loo⁵, Kim McIntyre⁵, Sidney Pitt⁵, Ding Ren Shen⁵, David Shuster⁵, Hongjian Zhang³, Rosemary Zhang⁵, Joel Barrish¹, John Dodd¹, Ian Henderson², Gary Schieven⁵, and Maria Webb⁶. (1) Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, P. O. Box 4000, Princeton, NJ 08543-4000, katerina.leftheris@bms.com, (2) Department of Chemistry, Pharmacopeia, (3) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, (4) CADD, Pharmaceutical Research Institute, Bristol-Myers Squibb, (5) Discovery Biology, Pharmaceutical Research Institute, Bristol-Myers Squibb, (6) Department of Biology, Pharmacopeia

Overproduction of cytokines such as TNF- α and IL-1 β are implicated in a wide variety of inflammatory diseases, including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease and endotoxic shock, among others. There is convincing clinical evidence that protein antagonists of cytokines such as the soluble TNF- α receptor Fc fusion protein (etanercept), anti-TNF antibody (infliximab) and the IL-1 receptor antagonist (anakinra) can effectively treat chronic inflammatory diseases. The stress-activated signal transduction pathway leading to inflammatory cytokine production in stimulated immune cells is known to be regulated in part by p38 α mitogen activated protein (MAP) kinase. To this end, we and others have searched for inhibitors of p38 α as a means to inhibit inflammatory cytokine production. Herein, we describe our initial efforts in developing potent, selective triaminotriazine amides as inhibitors of p38 α MAP kinase. Our initial hit was identified through screening the Pharmacopeia compound collection. The lead compound possesses oral activity in *in vivo* models of acute and chronic inflammatory disease and represents a unique structural class compared to known p38 inhibitors. X-ray crystallography demonstrates that this compound accesses the ATP binding pocket of p38 α , forming a key hydrogen bond through a water molecule. A description of SAR progression, *in vivo* activity, profiling and X-ray crystallography will be discussed.

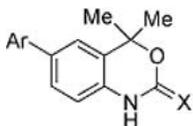
177.

THE DISCOVERY OF PROTEIN KINASE C (PK-C) ISOZYME: SPECIFIC LIGANDS DRIVEN BY A SOLID-PHASE COMBINATORIAL SYNTHESIS OF DIACYLGLYCEROL-LACTONES (DAG-LACTONES). *Dehui Duan*¹, Megan L. Peach², Christopher C. Lai³, Nancy E. Lewin⁴, James A. Kelley³, Peter M. Blumberg⁴, and Victor E. Marquez⁵. (1) Laboratory of Medicinal Chemistry, NCI-Frederick, NIH, 376 Boyles St., Bldg. 376, Rm 218, Frederick, MD 21702, Fax: 301-846-6033, duand@ncifcrf.gov, (2) Laboratory of Medicinal Chemistry, National Institutes of Health, (3) Laboratory of Medicinal Chemistry, National Cancer Institute, (4) Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Institutes of Health, (5) Laboratory of Medicinal Chemistry

The central role of the protein kinase C (PKC) in mediating cellular signal transduction makes it an important therapeutic target for cancer and other diseases. Diacylglycerol lactones (DAG-lactones) targeting the C1 domain of PKC have been identified as potent enzyme activators. A solid-phase combinatorial strategy utilizing IRORI's "direct sorting" technology has been implemented to accelerate the discovery process. Batches of 96-member libraries of DAG-lactones have been constructed with diverse combinations of commercially available aldehydes (R1CHO) and acid chlorides (R2COCl). Initial biological experiments are encouraging as various compounds show specificity towards PKC isozymes and other non-kinase C1 domain-containing targets. Secondary screens to search for the enhancement of specific PKC-mediated downstream pathways and specific translocations of the protein to different cellular compartments are being implemented. The chemistry and the biology will be reported in full.



178. SYNTHESIS AND SAR OF NOVEL, 6-ARYL-1,4-DIHYDROBENZO[D][1,3]OXAZINE-2-THIONES AS PROGESTERONE RECEPTOR MODULATORS LEADING TO THE POTENT AND SELECTIVE NON-STEROIDAL PR AGONIST TANAPROGET. *Andrew Fensome¹, Rajiv Chopra¹, Jeff Cohen², Mark A. Collins¹, Valerie Hudak¹, Karl Malakian¹, Andrea Olland¹, Kristine Svenson¹, Eugene A. Terefenko¹, Ray J Unwalla¹, James, M. Wilhelm¹, Scott Wolfrom¹, Yuan Zhu², Zhiming Zhang², Puwen Zhang¹, Richard C. Winneker², and Jay Wrobel¹.* (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, fensoma@wyeth.com, (2) Women's Health and Bone, Wyeth Research



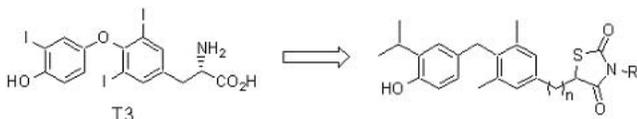
- 1, Ar = 3'-chlorophenyl, X = O
- 2, Ar = 2'-cyano-4-thiophene, X = S
- 3, Ar = 1'-methyl-5'-cyano-2-pyrrole, X = O
- 4, Ar = 1'-methyl-5'-cyano-2-pyrrole, X = S

Previously, we described the synthesis and SAR of a novel series of progesterone receptor (PR) antagonists based upon the 6-aryl-1,4-dihydro-benzo[d][1,3]oxazine-2-one ring system (e.g. **1**, IC₅₀ = 30 nM). More recently, we described the conversion of this class into potent PR agonists by the incorporation of sulfur to give 6-aryl-1,4-dihydro-benzo[d][1,3]oxazine-2-thiones (e.g. **2**, EC₅₀ = 0.4 nM). We also found in the antagonist series that we could make functional agonists by changing the 6-aryl group to a 2-cyanopyrrole (e.g. **3**, EC₅₀ = 1.1 nM).

It was then apparent that combining these features would increase potency. Incorporation of the 5'-cyano-2'-pyrrole moiety onto the 1,4-dihydrobenzo[d][1,3]oxazine-2-thione core produced the highly potent and selective non-steroidal PR receptor agonist **4**, tanaproget (EC₅₀ = 0.12 nM). In this presentation, we will demonstrate that tanaproget represents a potential first-in-class nonsteroidal PR agonist for contraception. Additional SAR, biological activity and structural information from a tanaproget/hPR-LBD co-crystal structure will be presented.

179. DESIGN AND SYNTHESIS OF LIGANDS FOR MUTATED THYROID HORMONE RECEPTOR (R320H): TAILOR-MADE APPROACH TOWARD THE GENETIC DISEASE. *Atsushi Hashimoto, Youheng Shi, and John T. Koh, Department of Chemistry and Biochemistry, University of Delaware, Brown Laboratory, Newark, DE 19716, Fax: 302-831-6335, atshashimo@aol.com*

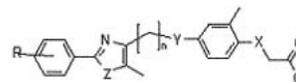
Resistance to thyroid hormone (RTH) is a genetic disease caused by mutations to the ligand-binding domain of the thyroid hormone receptor, TR β , that impair normal thyroid hormone (T₃) responsiveness. RTH mutations lead to a disruption to the normal hypothalamic pituitary axis leading to developmental and metabolic disorders. Our research group has shown that appropriately designed ligands can selectively rescue activity to receptors impaired by RTH mutations. This strategy represents a new and powerful approach to the potential treatment of genetic disease with small molecules. Among the TR mutations that have been found in RTH patients, Arg320→His is one of the most common. Using structural information of the wild-type TR-T₃ co-crystal structure, our group has recently developed new thyroid hormone analogs that can activate TR (R320H) with greater potency than in wild-type TR. In this session, our approach for design and synthesis of ligands and their SAR will be presented.



180. DESIGN AND SYNTHESIS OF NOVEL, POTENT, AND SELECTIVE PPAR DELTA AGONISTS. *Scott E. Conner, Guoxin Zhu, Chahrzad Montrose-Rafizadeh, Robert J Barr, Don Jett, Richard W Zink, Nathan Yumibe, and Nathan B Mantlo, Lilly Research Laboratories, Eli Lilly and Company, Discovery Chemistry Research and Technology, MC93A, DC1523, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-277-2035, conner_scott_e@lilly.com*

The peroxisome proliferator-activated receptors (PPARs) play an essential role in the processes of lipid homeostasis. Recent studies have found that the PPAR

delta isoform is a regulator of serum lipids, and selective agonists have been shown to dramatically lower serum triglyceride (TG) and low-density lipoprotein (LDL) levels, while increasing high-density lipoprotein (HDL) levels. There are currently no drugs in clinical use that selectively activate this receptor, although selective PPAR delta agonists have been shown to affect marked changes in the lipid profile in an obese rhesus monkey model. Dyslipidemia is a major risk factor in the development of atherosclerosis, and may be a suitable indication for this pleiotropic modulator of lipid metabolism. In this presentation, the design and synthesis of potent and selective PPAR delta agonists featuring 2,4,5-substituted thiazoles will be discussed. This presentation demonstrates the chemistry and SAR for the representative compound below.



181. DISCOVERY OF A NOVEL SERM THAT BEHAVES AS A POTENT ESTROGEN IN CNS NEURONS BUT LACKS NUCLEAR ER ACTIVITY. *Sandra C. Tobias¹, Jian Qiu², Martin J. Kelly², and Thomas S. Scanlan¹.* (1) Department of Pharmaceutical Chemistry, University of California San Francisco, 600 16th Street, Box 2280, San Francisco, CA 94143, Fax: 415-502-7220, stobias@itsa.ucsf.edu, (2) Department of Physiology and Pharmacology, Oregon Health and Science University

We have synthesized a novel SERM (STX) that activates rapid response in CNS neurons. STX is an analogue of 4-hydroxytamoxifen, but unlike 4-hydroxytamoxifen STX does not exist as a mixture of E/Z isomers. STX contains a carboxamide insertion between the olefin and basic side chain phenyl which confers stability of the olefin isomers. Most importantly, this amide insertion eliminates the ability of STX to bind to the nuclear estrogen receptors (ER α and ER β) and is unable to modulate ER-mediated gene transcription as other estrogens and SERMs. We have shown that STX has a potent estrogenic response in the CNS by rapidly inhibiting GIRK activation in hypothalamic GABA, proopiomelanocortin (POMC) and dopamine neurons. Thus far, STX is the only SERM that we know attenuates rapid responses, but lacks nuclear ER activity.

182. IDENTIFICATION OF A NOVEL THYROID HORMONE METABOLITE WITH POTENT PHYSIOLOGICAL EFFECTS. *Matthew E. Hart¹, Katherine L. Suchland², James Bunzow², Paul Kruzich², David Grandy², Grazia Chiellini³, Riccardo Zucchi³, Yong Huang⁴, Emil Lim⁴, and Thomas S. Scanlan¹.* (1) Department of Pharmaceutical Chemistry, University of California at San Francisco, 600 16th St, San Francisco, CA 94143, mhar4425@itsa.ucsf.edu, (2) Department of Physiology and Pharmacology, Oregon Health and Sciences University, (3) Dipartimento di Scienze dell'Uomo e dell'Ambiente, Sezione di Chimica e Biochimica Medica, (4) Department of Biopharmaceutical Sciences, University of California at San Francisco

Thyroid hormone action (TH) is mediated through the action of TH on its cognate nuclear receptors, TR. However, some effects of the TH occur within seconds of administration. In an effort to explain these rapid effects of the TH, we have identified a novel thyroid hormone metabolite that does not act on TR. This metabolite potently stimulates the production of cAMP in cultured cells expressing an orphan G-protein coupled receptor. In vivo experiments demonstrate that this metabolite also has significant physiological effects on thermoregulation and cardiac output. These data suggest an alternative pathway of TH action that is independent of TR.

183. CHEMICAL TAG FOR THE ESTROGEN RECEPTOR: AFFINITY LABELS AND THE GRADUATE WORK OF DAVID ROBERTSON. *John A. Katzenellenbogen, Department of Chemistry, University of Illinois at Urbana-Champaign, 600 S. Matthews Ave., Urbana, IL 61801, Fax: 217-333-7325, jkatzene@uiuc.edu*

When Dave Robertson was a graduate student at the University of Illinois (1977-1981), the estrogen receptor (ER) was still an elusive biochemical species that could only be characterized by the reversible binding of high specific activity tritium-labeled ligands like estradiol. Robertson conceived of and prepared the first effective affinity labeling agent for the ER, tamoxifen aziridine,

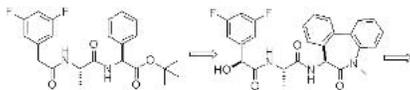
a simple aziridine analog of tamoxifen, and he showed that this agent reacted with ER with remarkable selectivity and efficiency. Subsequently, tamoxifen aziridine (and its tritium-labeled analog that was made available commercially) became chemical probes that were widely used in studies of ER structure and function. Robertson's work in this area set the standard for selective chemical tools to study receptor systems, and it presaged the molecular biology era that has revolutionized the studies of nuclear receptors, such as ER.

184.

TESTING THE AMYLOID HYPOTHESIS: OPTIMIZATION AND CHARACTERIZATION OF A NOVEL SMALL MOLECULE FUNCTIONAL G-SECRETASE INHIBITOR.

James E Audia¹, Jeffrey S Nissen¹, Thomas E. Mabry¹, Stacey McDaniel¹, Warren J. Porter¹, Steven S Henry¹, Thomas C. Britton¹, Jon K. Reel¹, James J. Droste¹, David Mitchell², Lynne A Hay², Qing Shi¹, Mark H Bender³, Leonard N Boggs³, Jeffrey W Cramer³, Dan Czilli⁴, Donna K. Dieckman³, Carlos O Garner³, Bruce Gitter⁴, Paul A. Hyslop⁴, Edward M Johnstone⁴, Wei Ying Li⁴, Sheila P. Little⁴, Carl McMillian³, F Dean Miller⁴, Tingui Yin⁴, Patrick May⁴, Eugene D. Thorsett⁵, Lee H Lattimer⁵, Jay S. Tung⁵, Beverly K Folmer⁵, Larry Y. Fang⁵, Jeffrey Neitz⁵, Jing Wu⁵, Harry F. Dovey⁵, Stephen B. Freedman⁵, and Dale B. Schenk⁵. (1) Discovery Chemistry Research & Technology, Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, (2) Chemical Process R&D, Eli Lilly and Company, (3) Lilly Research Laboratories, Eli Lilly and Company, (4) Neuroscience Discovery Research, Eli Lilly and Company, (5) Elan Pharmaceuticals

Overproduction and/or reduced clearance of beta-amyloid peptide play a critical role in the disease pathogenesis, according to the "Amyloid Hypothesis" of Alzheimer's Disease (AD). Among the modes of intervention suggested by this approach to AD are inhibition of beta- and gamma-secretases, the proteolytic enzymes implicated in the formation of beta-amyloid from its precursor molecule. We have previously described dipeptide functional gamma-secretase inhibitors capable of reducing beta-amyloid peptide levels in the brains of transgenic (PDAPP) mice and their subsequent optimization into highly potent dibenzocaprolactam inhibitors suitable for chronic in vivo experimentation. Herein we describe our further optimization of this series to identify and characterize, in transgenic and non-transgenic animal models, inhibitors appropriate for challenging the Amyloid Hypothesis in a clinical setting.



185.

NUCLEAR RECEPTORS AS DRUG TARGETS FOR THE TREATMENT OF METABOLIC DISEASE.

Richard A. Heyman, X-Cepto Therapeutics, Inc, 4757 Nexus Centre Drive, Suite 200, San Diego, CA 92121, RHeyman@x-ceptor.com

The orphan nuclear receptors LXR, FXR and ERR function as ligand dependent transcription factors and serve as sensors for the regulation of lipid and energy metabolism. To elucidate the role of these receptors, we have identified potent, synthetic ligands in conjunction with transgenic and knockout animals to identify target genes for these receptors. The LXR modulators regulate key genes involved in the macrophage and the foam cell that control reverse cholesterol transport, as well as genes involved in inflammation. In animal models of atherosclerosis, LXR modulators increase reverse cholesterol transport and cause regression of atherosclerotic plaques. The regulation of LXR provides a novel approach to the treatment of atherosclerosis. Similar approaches have been employed for FXR and the ERRs in order to characterize their role as drug targets in cardiovascular and metabolic disorders.

186.

ORALLY ACTIVE γ -SECRETASE INHIBITORS. **Richard E. Olson, Discovery Chemistry, Bristol-Myers Squibb Co, 5 Research Parkway, Wallingford, CT 06492-7660, Fax: 203-677-7884, richard.olson@bms.com**

The search for A β secretase inhibitors as potential Alzheimers therapeutics was one of several neuroscience initiatives which Dave Robertson helped launch during his years at DuPont-Merck Pharmaceuticals. Initial screening of protease inhibitor libraries identified a series of succinoylhydroxamates with sub-micromolar potency vs. γ -secretase, one of two enzymes involved in the

production of A β peptide from amyloid precursor protein. Optimization of this series provided selectivity vs. γ -secretase and improved pharmacokinetic properties. Efforts to improve CNS penetration led to the design of a related series of alcohol-based inhibitors with central A β efficacy in dog. Sub-chronic dosing caused duodenal lesions, believed to result from inhibition of presenilin-mediated Notch signaling. A perspective on the development of γ -secretase inhibitors in the light of effects on Notch processing will be discussed.

187.

STRUCTURE-ACTIVITY RELATIONSHIPS OF AMINO ACIDS THAT TARGET THE $\alpha 2\delta$ PROTEIN. **Andrew J Thorpe¹, Thomas Belliotti¹, I. Victor Ekhatov¹, Thomas Capiris¹, Jacob Schwarz¹, Jack Kinsora¹, Mark Vartanian¹, Leonard Meltzer¹, Charles Taylor¹, Ti Zhi Su¹, Mark Weber¹, David Wustrow¹, Mark Field², Mel Dickerson¹, Sean Donevan¹, and Zheng Li¹.** (1) Michigan Laboratories, Ann Arbor Campus, Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48185, (2) Sandwich Laboratories, Pfizer Global Research and Development

Pregabalin ((S)-3-Aminomethyl-5-methyl-hexanoic acid) exhibits robust activity in preclinical assays indicative of potential antiepileptic, anxiolytic and antihyperalgesic clinical efficacy. It binds with high affinity to the $\alpha 2\delta$ subunit of voltage gated calcium channels and is a substrate of the system L neutral amino acid transporter. A series of pregabalin analogs were synthesized and evaluated for their $\alpha 2\delta$ binding and for their affinity for the system L transporter. Compounds were also assessed in vivo for their ability to promote anxiolytic, analgesic and anticonvulsant actions. These studies suggest that distinct structure activity relationships exist for $\alpha 2\delta$ binding and system L transport inhibition and both interactions appear to play an important role in the in vivo profile of these compounds.

188.

INFLAMMATION AND THE REVOLUTION IN THE TREATMENT OF RHEUMATOID ARTHRITIS.

Steven B. Abramson, New York University School of Medicine and the New York University-Hospital for Joint Diseases, 301 East 17th Street, New York, NY 10003, StevenB.Abramson@msnyuhealth.org

The past two decades have witnessed remarkable changes in the management of RA as more aggressive treatment with disease-modifying agents is now the standard of care. This fundamental change in the clinical management of RA was motivated by two key insights: 1) that RA in most patients is a progressively disabling disease with increased mortality compared with the non-RA population; and 2) that radiographs can show progressive destructive changes despite apparent clinical improvement. Treatment with in the last five years has changed substantially with the introduction of biologic response modifiers, most notably TNF antagonists, such as infliximab, etanercept and adalimumab. Additional biologic agents that may modify the course of RA include IL-1 antagonists (e.g., anakinra), rituximab, CTLA4-Ig, anti-IL-6R, and anti-C5, among others. This presentation will focus on the acute and chronic inflammatory processes that drive rheumatoid arthritis, and provide an analysis of potential targets for disease modifying therapy.

189.

"P-38, MAP- KINASE: AN EXCITING TARGET FOR THE TREATMENT OF INFLAMMATORY DISEASES"

Celia Dominguez¹, Longbin Liu¹, Dawei Zhang¹, Nuria Tamayo¹, David Powers², Wong Min³, Feige Feige⁴, Robert Harris⁵, Stacie Wild⁶, Seshadri Neervannan⁷, Syed Rashid⁸, and Timothy Harvey⁸. (1) Chemistry, Research & Discovery, Amgen Inc, One Amgen Center Drive, M/S B29-1B, Thousand Oaks, CA 91320-1799, Fax: 805-480-1337, celiad@amgen.com, (2) HTS & Molecular Pharmacology, Amgen Inc, (3) Inflammation Research, Amgen Inc, (4) Inflammation Pharmacology, Amgen Inc, (5) Pharmacokinetics and Drug Metabolism, Amgen Inc, (6) Toxicology, Amgen Inc, (7) Pharmaceuticals, Amgen Inc, (8) Molecular Structure, Amgen Inc

The chronic inflammation and joint destruction that characterize RA are mediated by proinflammatory cytokines. In particular, TNF α and IL-1 β play key roles in the activities that lead to the initiation and progression of RA and other autoimmune inflammatory diseases. The inhibition of TNF α and IL-1 β presents a useful therapeutic strategy to suppress the inflammation and prevent joint damage caused by RA, as shown by the newer biologic therapies for RA (etanercept, infliximab, adalimumab, anakinra) that target these cytokines. p38 is a member of the MAPK family. MAPKs play an important role in intracellular

signaling by mediating a cascade of phosphorylation of kinases and transcription factors that regulate cell survival, apoptosis, and inflammatory cytokine production. p38 kinase is a serine/threonine kinase originally identified as an enzyme that was phosphorylated and activated by lipopolysaccharide (LPS) stimulation of monocytes. Subsequently, p38 kinase has been shown to be involved in the biosynthesis of TNF α and IL-1 β at the translational and transcriptional level. Herein we report potent, selective and efficacious p38 inhibitors and the progression to the clinical candidate and its pharmacodynamic effects in a First in Human Study.

190. SELECTIVE ESTROGEN RECEPTOR-BETA AGONISTS ARE POTENT ANTIINFLAMMATORY AGENTS.

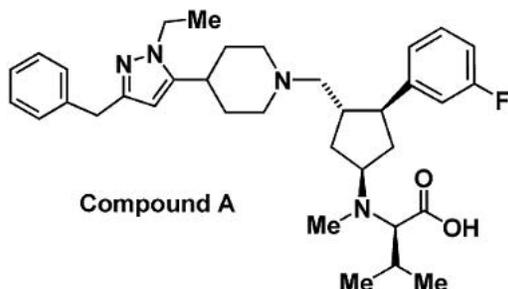
Ronald L. Magolda¹, Michael S. Malamas², Richard E. Mewshaw³, Heather A Harris⁴, James C. Keith Jr.⁵, Bob McDevitt⁶, Iwan Gunawan⁶, Christopher P Miller³, Leo M. Albert⁵, Yelena Leathurby⁷, and Eric S. Manas⁸. (1) Woman's Health, Wyeth Research, Collegeville, PA 19426, (2) Medicinal Chemistry, Wyeth Research, (3) Department of Medicinal Chemistry, Wyeth Research, (4) Women's Health Research Institute, Wyeth Research, (5) Department of Cardiovascular and Metabolic Diseases, Wyeth Research, (6) Department of Chemical Sciences, Wyeth Research, (7) Women's Health Institute, Wyeth Research, (8) Chemical and Screening Sciences, Wyeth Research

The discovery of a second subtype of the estrogen receptor (ER β) in 1996 provided the impetus to identify its physiological role in mediating estrogen action. The lack of ER β selective agonists tools have prevented characterization of this receptor. Employing a structure-based approach (X-ray crystallography data, molecular modeling) where we were able to exploit a single amino acid difference between the two ERs (ER β Ile421 to ER α Met373), we have designed a series of highly potent and selective agonists for ER β . We have also characterized their activity in several clinically relevant rodent models. This presentation will describe the design and synthesis of a several highly selective ER β agonists along with their novel pharmacological profile that offers new insights into the role of ER β .

191. DEVELOPMENT OF A POTENT, ORALLY ACTIVE ANTAGONIST OF THE HUMAN CCR5 RECEPTOR.

Paul E Finke, Department of Medicinal Chemistry, Merck Research Laboratories, RY 123-132, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-5790, paul_finke@merck.com

Since the discovery that the G-protein coupled beta-chemokine receptor CCR5 can function as a primary co-receptor with CD4 for host cell entry of macrophage-tropic HIV-1 strains, there has been an intense search for suitable CCR5 antagonists for use as HIV-1 infection preventatives and/or therapeutic agents. In addition, the entire chemokine field has seen an exponential increase in interest targeting other therapeutic areas. This laboratory has previously disclosed the identification of N-[(1R,3S,4S)-3-((4-(3-benzyl-1-ethylpyrazol-5-yl)piperidin-1-yl)methyl)-4-(3-fluorophenyl)cyclopentan-1-yl]-N-methyl-D-valine (Merck Compound A) which features a human CCR5 IC₅₀ = 1.0 nM, excellent selectivity vs other chemokine and off-target receptors, an IC₉₅ < 0.14 nM in a PBMC antiviral assay, and good oral absorption in three species. Based on these and other results, Compound A was selected for further evaluation as a pre-clinical development candidate. In conjunction with its evaluation as an anti-HIV-1 agent, its possible utility in other therapeutic areas has also been investigated. Some of these results will also be discussed, in particular, its possible role in the prevention of allograft transplant rejection.



192. SMALL MOLECULE ANTAGONISTS FOR THE CXCR2 CHEMOKINE RECEPTOR: N,N'-DIARYLUREAS AND RELATED SERIES.

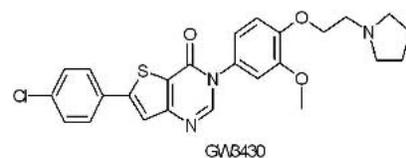
Jakob Busch-Petersen¹, Qi Jin¹, Brent W. McClelland¹, Hong Nie¹, Michael R. Palovich¹, Roderick S. Davis¹, Wei Fu¹, John D. Elliott², Miriam Burman³, James J. Foley³, Dulcie B. Schmidt³, Patty Podolin³, Brian J. Bolognese³, David C. Underwood³, Ruth R. Osborn³, Chris J. Dehaas³, Michael Salmon³, Donald C. Carpenter³, David J. Killian³, Henry M. Sarau³, and Katherine L. Widdowson¹. (1) Medicinal Chemistry, Respiratory and Inflammation CEDD, GlaxoSmithKline, 709 Swedeland Rd, King of Prussia, PA 19406, Fax: 610-270-4451, Jakob.2.Busch-Petersen@gsk.com, (2) Medicinal Chemistry, MMPD CEDD, GlaxoSmithKline, (3) COPD Biology, Respiratory and Inflammation CEDD, GlaxoSmithKline

Interleukin-8 (IL-8) and related C-X-C chemokines (GRO α , GRO β , and GRO γ) play an important role in the recruitment of leukocytes to the site of inflammation. To date, two receptor subtypes (CXCR1 and CXCR2) which bind these ELR+ C-X-C chemokines have been identified. The CXCR1 receptor appears to be selectively activated only by IL-8, while IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 bind with almost equal affinity to CXCR2. The discovery, SAR and in vivo activity of small molecule antagonists belonging to the N,N'-diarylurea and related series will be discussed.

193. DISCOVERY OF POTENT AND SELECTIVE MCH RECEPTOR-1 ANTAGONISTS FOR THE TREATMENT OF OBESITY.

Anthony L. Handlon, Kamal A Al-Barazanji, Kevin K. Barvian, Eric C Bigham, David L Carlton, Andrew J Carpenter, Joel P Cooper, Alex J Daniels, Deanna T Garrison, Aaron S Goetz, Gary M Green, Mary K Grizzle, Yu C Guo, Donald L Hertzog, Clifton E Hyman, Diane M Ignar, Gregory E Peckham, Jason D Speake, Christy Britt, and Will R Swain, Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709-3398, Fax: 919-315-0430, tony.l.handlon@gsk.com

Melanin concentrating hormone (MCH), a hypothalamic neuropeptide commonly found in vertebrates, plays a role in the central control of feeding behavior and energy balance in mammals. For example, when injected ICV into rat brain, MCH potently stimulates food intake. Furthermore, genetically altered mice that lack MCH consume less food and have reduced body weight whereas over-expressers are hyperphagic and obese. We have discovered a series of benzopyrimidines that are antagonists of the MCH receptor-1. This talk will focus on optimizing the bicyclic core of the lead series for potency, selectivity and solubility. Out of this work came GW3430, a functional antagonist with pIC₅₀ = 9.2, that causes significant weight loss in diet induced obese mice.



194. DESIGN AND SYNTHESIS OF POTENT, SELECTIVE MELANOCORTIN SUBTYPE-4 RECEPTOR AGONISTS FOR THE TREATMENT OF OBESITY.

Ning Xi¹, Jeffrey Adams¹, Yunxin Bo¹, Ning Chen¹, Michael Croghan¹, Elizabeth Doherty¹, Nianhe Han¹, Hongyu Liao¹, Qingyan Liu¹, Michael Kelly¹, Mark Norman¹, Markian Stec¹, Nuria Tamayo¹, Shimin Xu¹, Janet Cheetham¹, Duncan Smith¹, Faye Hsieh², Tony Bannon³, Clarence Hale³, Jamie Baumgartner³, and Christopher Fotsch¹. (1) Department of Chemistry Research & Discovery, Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, Fax: 805-480-3016, nxi@amgen.com, (2) Department of Pharmacokinetics & Drug Metabolism, Amgen Inc, (3) Department of Metabolic Disorders, Amgen Inc

Melanocortin receptors belong to the superfamily of G-protein-coupled receptors (GPCRs). They interact with bioactive peptides derived from the prohormone proopiomelanocortin (POMC), such as α , β , and γ -melanocyte-stimulating hormones (MSH) and adrenocorticotropic hormone (ACTH). One of the melanocortin subtype receptor, MC4R, is expressed in the hypothalamus and plays a critical role in controlling food intake and energy homeostasis. In this presentation we will discuss the design, synthesis and evaluation of potent, selective MC4R agonists for the treatment of obesity.

195.

OPIOID RECEPTOR ANTAGONISTS AND OBESITY: NON-CLINICAL STUDIES WITH ANTAGONISTS OF THE PHENYLPIPERIDINE STRUCTURAL CLASS.

Charles H. Mitch¹, Mark L. Heiman², Frank C. Tinsley², Paul J. Emmerson², Dana K. Sindelar², and Michael A. Statnick². (1) Discovery Chemistry Research and Technologies, Eli Lilly and Company, Lilly Corporate Center, Drop Code 0510, Indianapolis, IN 46285-0510, Fax: 276-7600, mitch@lilly.com, (2) Endocrine Research, Eli Lilly and Company

The opioid receptor system modulates many pathways known to be important in the regulation of appetite and body weight. Opioid agonists will stimulate food consumption while antagonists will reduce food intake. Potentiation of anti-obesity activity has also been observed on combination of opioid antagonists with appetite suppressing agents, such as cannabinoid antagonists. LY255582 is a potent opioid receptor antagonist that shows functional inverse agonist efficacy in cell lines expressing the cloned human delta opioid receptor. Using dietary-induced obese rats, LY255582 reduced 24-hour food intake and Respiratory Quotient (RQ). Inhibitory effects on food consumption correlated with ex vivo binding affinity for opioid receptors in brain. Chronic treatment with LY255582 resulted in a decrease in total body mass, decreased fat mass, and no change in lean mass. Blockade of central opioid receptors using an opioid antagonist like LY255582 may have clinical potential for the treatment of obesity.

196.

CB1 ANTAGONISTS. Jochen Antel, Discovery Management, Solvay Pharmaceuticals GmbH, Hans-Boeckler Allee 20, Hannover D-30173, Germany, Fax: 0-049-511-857-2786, jochen.antel@solvay.com

The discovery of cannabinoid receptors and their endogenous ligands in feeding-associated brain regions together with clinical observations about appetite stimulation caused by psychoactive products from Cannabis sativa, initiated considerable research efforts.

Central cannabinoid CB1 receptors play a role in the control of food consumption, especially via influencing the „food-seeking“ phase. CB1 receptors are also involved in several phenomena of cognition, dependence and habituation, which significantly widen the potential for drugs acting as antagonists via this mechanism.

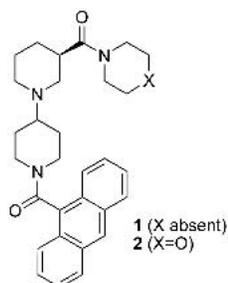
The clinical efficacy of CB1 receptor antagonists in the treatment of obesity as well as for smoking cessation has recently been demonstrated by Rimonabant (Sanofi-Synthelabo) being now in phase III clinical studies.

Solvay Pharmaceuticals discovered SLV319, a novel, potent and selective CB1 receptor antagonists and selected this compound for further clinical development. The talk will summarize recent results from mechanistic investigations and shed some light on the chemistry and pharmacology of CB1 receptor antagonists.

197.

NIPECOTIC ACID DERIVATIVES AS POTENT, NONSELECTIVE ACETYL-COA CARBOXYLASE INHIBITORS: A NOVEL APPROACH FOR OBESITY. David A.

Perry¹, H. James Harwood Jr.¹, Michael R. Makowski¹, Christopher J. Coletta¹, Justin Pyrke-Fairchild¹, Stephen F. Petras¹, Lorraine D. Shelly¹, Lawrence M. Zaccaro¹, Diane M. Hargrove¹, Kelly A. Martin¹, Deepak Dalvie², Victor Soliman², Christian J. Mularski¹, Ronald T. Wester¹, and Shane A. Eisenbeis³. (1) Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, Fax: 860-441-1128, David_A.Perry@groton.pfizer.com, (2) Pharmacokinetics, Dynamics and Metabolism, Pfizer Global Research and Development, (3) Pharmaceutical Sciences, Pfizer Global Research and Development



The rate-limiting step for *de novo* fatty acid biosynthesis is malonyl CoA production catalysed by acetyl CoA carboxylase isoform 1 (ACC-1) found in liver and adipose tissue. A second isoform (ACC-2) is found in the heart and skeletal muscle where malonyl CoA is a potent inhibitor of fatty acid oxidation. Inhibition of both isoforms is therefore an attractive target for lowering triglycerides and a potential treatment for obesity. The nipecotic acid derivative **1** was identified in a high throughput screen and found to inhibit both isoforms of ACC with equivalent potency (IC₅₀ ~50nM, rat enzyme). The close analog **2** exhibited significantly reduced clearance *in vivo* and demonstrated reduction of fatty acid synthesis and stimulation of whole body fatty acid oxidation in rodent models. The development of the SAR around this hit and our progress toward improving metabolic stability and removal of the undesirable anthracene moiety will be described.

198.

CANNABINOID RECEPTORS AS POTENTIAL THERAPEUTIC TARGETS FOR INFLAMMATION. Alexandros Makriyannis, Center for Drug Discovery,

Departments of Pharmaceutical Sciences and Molecular and Cell Biology, University of Connecticut, University of Connecticut, Storrs, CT 06269, Fax: 860-486-3089, makriyan@uconnvm.uconn.edu

Although the pharmacological properties of cannabis and some of its key ingredients including their analgesic and anti inflammatory effects have been studied over the past several decades, the biochemical basis of these effects are only now being understood. The two known cannabinoid receptors CB1 and CB2 were discovered only approximately fifteen years ago and shown to belong to the super family of G-protein coupled receptors. CB1, was identified in the mammalian brain but later also found in numerous other tissues including lung, heart, blood vessels and the reproductive system. Conversely, the CB2 receptor is believed to be associated primarily with the immune system. Two families of endogenous ligands represented by anandamide and 2-arachidonoyl glycerol appear to activate both of these receptors. The physiological functions of these endocannabinoids are terminated by action of two enzymes, fatty acid amidohydrolase and monoarachidonoyl glycerol lipase as well as by an endocannabinoid transporter involved in the movement of the endogenous ligands into the cell. The above mentioned proteins as well as others involved in the biosynthesis of endocannabinoids are excellent potential targets for the development of new medications for pain and inflammation. Recently, we have shown that activation of the CB2 receptors can lead to substantial effects in animal models for neuropathy and inflammation. Efforts to develop CB2-selective ligands as potential medications for inflammation and neuropathic pain are underway.

199.

ALLOSTERIC INHIBITION OF BETA 2 INTEGRINS BY LOW MOLECULAR WEIGHT COMPOUNDS: THE MOLECULAR BASIS. Gabriele Weitz-Schmidt, Karl

Welzenbach, Janet Dawson, Sylvain Cottens, Rainer Albert, Sompong Wattanasin, Ulrich Hommel, and Joerg Kallen, Department of Autoimmunity and Transplantation, Novartis Institutes of Biomedical Research, Basel CH-4002, Switzerland, Fax: ++41-61-3247534, gabriele.weitz@pharma.novartis.com

Beta 2 integrins are a family of alpha/beta cell surface receptors which control leukocyte recruitment to sites of inflammation. Therefore, they are promising therapeutic targets. All beta 2 integrins contain an inserted (I) domain on the alpha chain directly involved in ligand binding and an I-like domain on the beta 2 chain with a regulatory function. Beta 2 integrins need intracellular or cation activation to change their conformation from a low affinity to a ligand-binding competent state.

Various low molecular weight inhibitors of beta 2 integrins have been identified, in particular inhibitors of lymphocyte function associated antigen-1 (LFA-1). These inhibitors are of different chemical structures and differentially affect the conformational status of LFA-1. Based on their mode of action they can be classified into two major groups. The 'alpha I allosteric inhibitors' bind to the lovastatin (L)-site of the I domain distant from the ligand binding site thereby stabilizing the low affinity state of LFA-1. The 'alpha/beta I-like allosteric inhibitors' are thought to interact with the I-like domain thereby disrupting signal transmission between the LFA-1 I domains crucial for ligand binding.

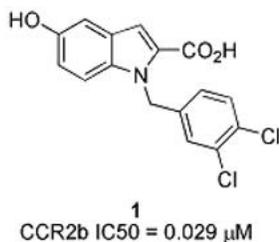
Our recent data demonstrate that the LFA-1 L-site allows structure-based optimization of statin-derived compounds towards LFA-1 inhibition. They strongly support the notion that allosteric inhibition of beta 2 integrins via their I domains may be of therapeutic value in treating inflammatory conditions.

200. ORALLY-ACTIVE ICE INHIBITORS FOR THE TREATMENT OF INFLAMMATORY AND AUTOIMMUNE DISEASES. *John C.R. Randle, Strategic Development, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02319-4242, Fax: 617-444-6570, randle@vrtx.com*

The interleukin converting enzyme (ICE, caspase-1) processes the inactive precursors of IL-1 β and IL-18 to the biologically active, pro-inflammatory cytokines. We have developed potent, selective, orally active ICE inhibitors that reduce cytokine production in vitro, at concentrations that do not inhibit apoptosis. Two lead clinical candidates, pralnacasan (HMR3480/VX-740) and VX-765, are orally active in a variety of animal models of inflammatory and autoimmune disorders. Pralnacasan and VX-765 have been well tolerated in the clinic at doses that reduce the production of IL-1 β ex vivo and, for VX-765, significantly decrease serum IL-18 in vivo. A PhIIa trial of pralnacasan in rheumatoid arthritis patients provided preliminary proof-of-concept, with reductions in serum inflammatory biomarkers, increased ACR20 response and corticosteroid sparing. In a PhIII trial in knee osteoarthritis patients, pralnacasan had dose-dependent effects on serum/urinary markers of cartilage and bone collagen turnover. Oral ICE inhibition is a promising therapeutic strategy for the treatment of inflammatory and autoimmune disorders.

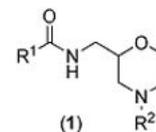
201. DISCOVERY AND OPTIMIZATION OF SMALL MOLECULE CCR2B ANTAGONISTS. *Jason G. Kettle, D. Huw Davies, Alan W. Faull, and Michael A. Stone, Astra Zeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom*

The recruitment and activation of select populations of leukocytes is a key feature of a variety of inflammatory conditions. Whilst this response is crucial for host defense during inflammation, the secretory products of white blood cells may increase injury by damaging surrounding healthy tissue. Monocyte Chemoattractant Protein-1 (MCP-1 or CCL2) is a member of the pro-inflammatory cytokines that mediate leukocyte chemotaxis and activation. These effects are mediated principally through activation of intracellular signalling pathways following binding of MCP-1 to the chemokine receptor CCR2b. MCP-1 is a potent chemotactic and activating factor for monocytes and memory T-cells and has been shown to regulate adhesion molecule expression and cytokine production. MCP-1 has been implicated in the pathophysiology of a wide range of both acute and chronic inflammatory conditions including rheumatoid arthritis and atherosclerosis. A CCR2b antagonist thus represents an attractive target for drug discovery, and screening of the corporate compound collection for inhibitors led to discover of a low molecular weight indole acid hit. The SAR and optimisation of this hit into candidate drug 1 will be presented, and discussion made of species selectivity issues, DMPK and pre-clinical toxicology.



202. CCR3 ANTAGONISTS: LEAD OPTIMIZATION AND IDENTIFICATION OF A CLINICAL CANDIDATE. *S. Hodgson, C. Eldred, L. Harrison, P. Gore, C. Cook, S. Keeling, S. Swanson, M. Dowle, M. Johnson, E. Robinson, N. Trevedi, and T. Redfern, Research & Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom*

CCR3 receptors are expressed on a number of inflammatory cells (eosinophils, basophils, and mast cells), and in response to certain chemokines (e.g. eotaxin) may control cell recruitment and activation. A CCR3 antagonist could have potential in diseases where allergic inflammatory cells are believed to play a role, such as allergic rhinitis and asthma. A lead series of morpholine derivatives (1) was shown to be potent and selective antagonists at the human CCR3 receptor, and was optimized to give a candidate for progression to clinical development.



203. SELECTIVE GLUCOCORTICOID RECEPTOR AGONISTS (SEGRAS). *Hartmut Rehwinkel, Heike Schaecke, Khusru Asadullah, Stefan Baeurle, Markus Berger, Hartwig Hennekes, Stefan Jaroch, Konrad Krolikiewicz, Manfred Lehmann, Anne Mengel, Duy Nguyen, Andreas Reichel, Andrea Rotgeri, Norbert Schmees, Arndt Schottelius, Werner Skuballa, and Peter Strehlke, Corporate Research, Schering AG, D-13342, Berlin, Germany, hartmut.rehwinkel@schering.de*

Glucocorticoids (GC) represent the most effective therapy for acute and chronic inflammatory disorders including allergic diseases. Their outstanding therapeutic effects, however, are often accompanied by severe and sometimes irreversible side effects, such as diabetes mellitus. Thus, there is a real need for "better" GCs, i.e. GCs with a reduced side effect profile which retain the anti-inflammatory and immunosuppressive properties of classical GCs. GCs modulate gene expression by either transactivation or transrepression mechanisms. The anti-inflammatory effects are mainly mediated via transrepression while many side effects are dependent on GC-mediated transactivation. Therefore, our aim was to identify glucocorticoid receptor (GR) ligands which preferentially induce transrepression with little transactivation. Here we show representatives of a novel class of non-steroidal compounds, selective glucocorticoid receptor agonists (SEGRAs), with a significant dissociation of transactivation from transrepression activity in vitro and in vivo. The selective GR-agonists represent promising new drug candidates with an improved efficacy/tolerability profile.

204. DIPEPTIDYL PEPTIDASE 4 (DPP-4) AS A TARGET FOR TYPE 2 DIABETES. *Thomas E. Hughes, Diabetes Research, Novartis Institute for Biomedical Research, 400 Technology Square, Cambridge, MA 02139*

The incretin peptide hormones GLP-1 and GIP have emerged as important modifiers of insulin secretion, glucagon secretion, and other endocrine responses to food intake. Treatment of patients with type 2 diabetes with GLP-1 or GLP-1 analogs leads to rapid improvements in plasma glucose. Unfortunately due to rapid clearance and a narrow therapeutic window, optimizing use of these peptides has been difficult. Further, both GLP-1 and GIP are inactivated rapidly in circulation by N-terminal digestion leading to a circulating half-life in man of only 1-2 minutes for these hormones. Through a series of efforts by independent laboratories, DPP-4 (CD-26, AN P27487) has been identified as the enzyme responsible for rapid inactivation of these peptides by cleavage of their N-terminal amino dipeptides. DPP4 inhibitors, therefore, have potential to improve glucose metabolism in patients with diabetes by increasing the concentration of circulating intact and active GLP-1 and GIP peptides. As a proline-specific dipeptidyl aminopeptidase, DPP4 displays key structural features allowing design of potent and selective inhibitors. Characteristics of the target and its utility in the treatment of diabetes will be highlighted using two N-substituted glycyl 2-cyanopyrrolidide inhibitors NVP-LAF237 and NVP-DPP728 as examples.

205. SYNTHESIS AND BIOLOGICAL EVALUATION OF POTENT, SELECTIVE, ORALLY ACTIVE 4-FLUORO-2-CYANOPYRROLIDINE INHIBITORS OF DPP-IV. *Curt D. Haffner¹, Darryl L. McDougald¹, Steven M. Reister¹, Kate A. Dwornik¹, Sab A. Randhawa¹, Brian D. Thompson¹, David J. Cowan¹, Brad R. Henke¹, Richard D. Caldwell¹, Istvan W. Kaldor¹, James M. Lenhard², Dallas K. Croom², Daphne Clancy², Donovan J. McConn³, Kevin M. Hedeem³, Kevin J. Wells-Knecht³, Melissa Secosky⁴, and Wenhai Zhang⁴.* (1) MV CEDD Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Five Moore Drive, Research Triangle Park, NC 27709, Fax: 919-315-0430, curt.d.haffner@gsk.com, (2) Metabolic Diseases, GlaxoSmithKline, (3) DMPK, GlaxoSmithKline, (4) Assay Development & Compound Profiling Discovery Research, GlaxoSmithKline

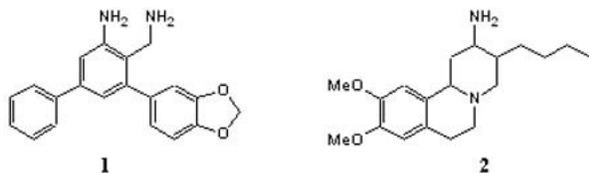
Dipeptidyl peptidase IV (DPP-IV) also known as T-cell antigen CD26, first identified in 1966, is a widely expressed serine exopeptidase. It has been shown to have several functions in humans. First, it contributes to extracellular matrix binding, second it functions as an adenosine deaminase (ADA)-binding protein,

and third exhibits post proline or alanine cleaving properties from oligo or polypeptides at the N-terminus. Incretins such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have been shown to be inactivated by DPP-IV. Both of these incretins play a major role in glucose homeostasis. GLP-1 agonists are currently being progressed clinically and have shown antidiabetic efficacy, however due to their large peptide structures cannot be administered orally. Recently, orally bioavailable small molecule DPP-IV inhibitors have shown clinical efficacy in type II diabetic patients. We describe the synthesis and biological evaluation of a series of potent, selective and orally active DPP-IV inhibitors containing a 4-fluoro-2-cyanopyrrolidine nucleus.

206.

NOVEL INHIBITORS OF DIPEPTIDYL-PEPTIDASE IV. *Markus P. Boehringer, Michael Hennig, Bernd Kuhn, Bernd M. Loeffler, Thomas Luebbers, Patrizio Mattei, Robert Narquizian, Jens Uwe Peters, Hans P. Wessel, and Pierre Wyss, Pharma Division, Preclinical Research PRBD, F. Hoffmann-La Roche Ltd, Basel CH-4070, Switzerland, Fax: ++41 61 688 8367, markus.boehringer@roche.com*

DPP-IV inhibition has recently attracted attention as a potential new treatment of type 2 diabetes, and several series of DPP-IV inhibitors have been evaluated in drug discovery programs. Most of these inhibitors are peptidomimetic structures derived from the endogenous substrate. In our search for novel structures, we have identified in a high-throughput screening campaign the aminopyrimidine 1 and the benzoquinolizine 2 as micromolar DPP-IV inhibitors. In a first hit exploration effort we were able to convert these hit clusters into nanomolar lead series. Multidimensional optimization led finally to compounds with highly promising characteristics. Various crystal structures of protein inhibitor complexes were used to rationalize the observed SAR and to guide the optimization of our lead structures.



207.

DESIGN, SYNTHESIS, AND PHARMACOLOGY OF BMS-477118: A LONG-ACTING, ORALLY ACTIVE DIPEPTIDYL PEPTIDASE IV INHIBITOR FOR THE TREATMENT OF TYPE II DIABETES. *Lawrence G. Hamann¹, David J. Augeri¹, David A. Betebner¹, Jeff Robl¹, David Magnin¹, Ashish Khanna², James G. Robertson³, Ligaya M. Simpkins¹, Prakash Taunk¹, Doree Sitkoff⁴, Carolyn Weigelt⁴, Qi Huang³, Song Ping Han³, Benoni Abboa-Offei³, Aiyang Wang³, Michael Cap³, Li Xin³, Li Tao⁵, Charles R Dorso⁶, Mark S Kirby⁶, and Rex A Parker³.* (1) *Discovery Chemistry, Bristol-Myers Squibb Company, P. O. Box 5400, Princeton, NJ 08543-5400, Lawrence.hamann@bms.com,* (2) *Department of Preclinical Candidate Optimization, Bristol-Myers Squibb Company,* (3) *Department of Metabolic Research, Bristol-Myers Squibb Company,* (4) *Department of Computer Aided Drug Design, Bristol-Myers Squibb Company,* (5) *Department of Exploratory Pharmaceuticals, Bristol-Myers Squibb Company,* (6) *Department of Metabolic and CV Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute*

Efforts to further elucidate structure-activity relationships within our previously disclosed series of β -quaternary amino acid linked L-*cis*-4,5-methanoproline-trile dipeptidyl peptidase IV (DPP-IV) inhibitors led to the exploration of vinyl substitution at the β -position of α -cycloalkyl substituted glycines. Despite poor systemic exposure, vinyl-substituted compounds showed extended duration of action in an acute rat *ex vivo* plasma DPP-IV inhibition model. Putative oxygenated metabolites were prepared and these compounds exhibited the potency and extended duration of action of their precursors in efficacy models measuring glucose clearance in Zucker^{fa/fa} rats. Extension of this approach to other β -quaternary derived inhibitors led to the discovery of additional analogues that are highly efficacious, stable, and long-acting DPP-IV inhibitors. This talk will outline the design, synthesis and pharmacology of compounds within this series leading to the identification of the clinical candidate BMS-477118.

208.

MK-0431: A POTENT, ORALLY ACTIVE DP-IV INHIBITOR FOR THE TREATMENT OF TYPE 2 DIABETES. *Dooseop Kim¹, Liping Wang¹, Jennifer Kowalchick¹, Emma R. Parmee¹, Linda L. Brockunier¹, Jiafang He¹, Jinyou Xu¹, Scott Edmondson¹, Maria Beconi², Lawrence F. Colwell Jr.¹, Bahanu Habulihaz¹, Huaibing He¹, Barbara Leiting³, Kathryn A. Lyons¹, Frank Marsilio³, Reshma A. Patel³, Ranabir Sinha Roy³, Yohannes Tefera², George Eiermann⁴, Joseph K. Wu³, Mathew J. Wyvratt¹, Michael H. Fisher¹, Bei B. Zhang³, Nancy A. Thornberry³, and Ann E. Weber¹.* (1) *Department of Medicinal Chemistry, Merck & Co., Inc, P.O. Box 2000, Rahway, NJ 07065,* (2) *Preclinical Drug Metabolism, Merck & Co., Inc,* (3) *Department of Metabolic Disorders, Merck & Co., Inc,* (4) *Department of Pharmacology, Merck & Co., Inc*

The incretin hormone glucagon-like peptide 1 (GLP-1) has been the subject of recent intense research efforts related to the treatment of type 2 diabetes. This hormone is released in the gut in response to food intake. GLP-1, in turn, stimulates the pancreas to synthesize and secrete insulin, while inhibiting the release of glucagon. Importantly, GLP-1 regulates insulin in a strictly glucose-dependent manner. Thus, there may be little or no risk of hypoglycemia. Other beneficial effects of GLP-1 therapy include slowing gastric emptying, reduction of appetite, and potential restoration of β -cell function. However, GLP-1 is rapidly degraded *in vivo* through the action of dipeptidyl peptidase IV (DP-IV), a serine protease which cleaves a dipeptide from the N-terminus to give the inactive GLP-1[9-36]amide. A small-molecule inhibitor of DP-IV would increase the half-life of GLP-1 and prolong the beneficial effects of this incretin hormone. Thus, inhibition of DP-IV is emerging as a new potential therapeutic approach to the treatment of type 2 diabetes. An intriguing possibility is that this mechanism might actually stabilize or even reverse the disease progress. Extensive SAR studies of a beta-amino acid lead led to the discovery of the current development compound MK-0431, which is a potent, orally active DP-IV inhibitor (IC_{50} = 18 nM) with excellent pharmacokinetic properties in mice, rats, dogs, and monkeys. The design, SAR and biological properties of these novel DP-IV inhibitors, leading to current development compound MK-0431 and its analogs, will be discussed in this presentation.

209.

COMPARING THE CONFORMATIONAL BEHAVIOR OF A SERIES OF HIV-1 PROTEASE INHIBITOR DRUGS USING THE LOW MODE: MONTE CARLO CONFORMATIONAL SEARCH METHOD. *Hilda Castillo, Department of Chemistry, Hobart & William Smith Colleges, Box 4178, Geneva, NY 14456, Fax: 315-781-3860, castillo@hws.edu, and Carol Parish, Department of Chemistry, Hobart and William Smith Colleges*

Molecular modeling was used to understand the conformational behavior of nine potent HIV protease inhibitors: Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir and TMC-126. In an effort to understand the role of molecular flexibility in drug preorganization and protease binding we utilized conformational searching to locate all low energy structures of each system. The conformational searches were performed using the combined 50:50 Low Mode: Monte Carlo method and using the GB/SA continuum solvent model to simulate an aqueous environment and either the AMBER* or the OPLSAA force field. The resulting structures were then grouped into families based on structural similarities using the Xcluster program. Conclusions were drawn about the conformational flexibility of the inhibitor drugs and similarities and differences in conformational behavior were examined.

210.

RATIONALLY DESIGNED ORTHOGONAL LIGAND-RECEPTOR PAIR: IMPLICATED AS A PROBE TO UNDERSTAND THYROID HORMONE SIGNALING PATHWAYS AND ASSOCIATED DISEASES. *A. Quamrul Hassan and John T. Koh, Department of Chemistry, University of Delaware, Academy street, Newark, DE 19711*

Thyroid hormone (T3) regulates gene expression through multiple pathways including the nuclear receptors TR α and TR β , as well as membrane-initiated actions mediated by GPCRs. The interplay between these multiple pathways plays a critical role in a number of thyroid associated diseases including RTH (resistance to thyroid hormone), as well as certain forms of thyroid and pituitary cancer. To better understand the roles of these different T3-activated pathways, we have developed a highly selective (functionally orthogonal) thyroid hormone

analog that exclusively activates the mutant TR(H435A). Unlike many examples of reengineered ligand-receptor pairs which exploit the steric complement of functional groups (i.e. "bump and hole" engineered interfaces) in which the modified receptor typically retain activity with the endogenous ligand or substrate, our design strategy selectively targets residues involved in the ligand-dependent conformational switching mechanism needed for transactivation function. This reengineered ligand receptor pair represents one of the most selective systems yet reported.

211.

COMFA AND COMSIA ANALYSES OF PNEUMOCYSTIS CARINII, TOXOPLASMA GONDII AND RAT LIVER DIHYDROFOLATE REDUCASE (DHFR) INHIBITORS.

Aleem Gangjee and **Xin Lin**, Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburg, PA 15282, hiteshjain_1978@yahoo.com, hiteshjain_1978@yahoo.com

DHFR inhibitors form the basis of treatment for immunodeficient patients with opportunistic infections caused by *Pneumocystis carinii*(pc) and *Toxoplasma gondii* (tg). The existing treatments suffer from high costs, low selectivity and severe side effects. It would be desirable to develop new drugs which not only display high potency but are also selective towards DHFR from *P. carinii* and/or *T. gondii* over mammalian DHFR, such as rat liver (rl) DHFR. This effort can be expedited using molecular models of pcDHFR, tgDHFR and rIDHFR that can accurately predict biologically active compounds and provide pharmacophores as a guide for rational drug design. Thus, a dataset of 179 structurally diverse DHFR inhibitors reported from our laboratory was used to develop 3D QSAR models that correlate chemical structure and inhibitory potency for pcDHFR, tgDHFR and rIDHFR using CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Similarity Indices Analysis). The details of these models and their predictive power will be reported.

212.

COMPARING THE CONFORMATIONAL BEHAVIOR OF A SERIES OF ENEDIYNE NATURAL PRODUCT ANTICANCER AGENTS USING THE LOW MODE: MONTE CARLO CONFORMATIONAL SEARCH METHOD.

Rebecca Splain and **Carol Parish**, Department of Chemistry, Hobart and William Smith Colleges, Lansing Hall 206, Geneva, NY 14456, Fax: 315-781-3860, splain@hws.edu

Naturally occurring anticancer agents, such as calicheamicin, esperamicin, dynemicin A, and neocarzinostatin chromophore, are structurally diverse yet each contains a reactive, electron-rich enediyne moiety. Under certain conditions, the enediyne group undergoes a Bergman cyclization resulting in a *p*-benzyne diradical. This highly reactive diradical can abstract hydrogen atoms from cancer cell DNA resulting in cell death. In an effort to understand the role of molecular flexibility in drug preorganization and DNA binding we have performed an exhaustive search of the AMBER*/GBSA(water) and/or OPLSAA/GBSA(water) surfaces using the LM:MC 50:50 conformational searching method. An ensemble of low energy structures was generated for each system and this yielded information about comparable flexibility and conformationally accessible structures. These results will be presented and compared with recent experimental data.

213.

COMPUTATIONAL STUDY OF PHENAZINE ANTIBIOTICS.

Timothy Su, Chemistry and Biochemistry, University of Massachusetts Dartmouth, 285 Old Westport Road, North Dartmouth, MA 02747-2300, Fax: 508-999-9167, **Dragic Vukomanovic**, Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, and **John A. Stone**, Chemistry Department, Queen's University

Pyocyanin (Pyo, 5-methyl-phenazinoe) produced by a Gram negative bacterium *Pseudomonas aeruginosa* is known to play an important role as an electron transfer agent and catalyst in a variety of pharmacological effects. It is also a natural antibiotics. 1-hydroxyphenazine (1-HP), which is believed to be a metabolite of Pyo, is a more potent antibiotic. Studying the reduction/protonation of Pyo and 1-HP is crucial in understanding their bioactivities.

A computational study at the B#LYP/6-31G* level suggests that 1-HP could be generated via reduction/protonation-initiated demethylation of Pyo. Full reduction of Pyo converts the planar structure, with sp² hybrid at the ring nitrogen, to a non-planar sp³ hybrid with an angle of 156°. 1-HP, however, remains planar upon full reduction. This might be one of the reasons why 1-HP

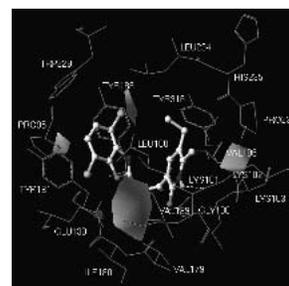
is a more potent antibiotic than Pyo since a non-planar structure is thought to have difficulty intercalating with DNA or producing toxic-oxy radicals.

214.

DOCKING, COMFA AND COMSIA STUDIES OF HIV-1 REVERSE TRANSCRIPTASE INHIBITORS OF THE PYRIDINONE DERIVATIVE TYPE.

José Luis Medina-Franco, **Sergio Rodríguez-Morales**, **Alicia Hernandez**, **Cecilia Juárez-Gordiano**, and **Rafael Castillo**, Department of Pharmacy, Universidad Nacional Autónoma de México, Avenida Universidad 3000, Mexico City 04510, Mexico, Fax: +52-5622-5329, medinajl@correo.unam.mx

Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) were performed on a set of pyridinone derivatives. A molecular alignment obtained by docking of compounds into the non-nucleoside reverse transcriptase inhibitor binding site of HIV-1 was used. Robust and predictive 3D-QSAR models were obtained with q₂ values of 0.706 and 0.723 for CoMFA and CoMSIA, respectively. These models were validated by an external test set. The 3D-QSAR and docking results help to understand the type of interactions that occur between pyridinone derivatives with the non-nucleoside reverse transcriptase inhibitor binding pocket, and explain the viral resistance to pyridinone derivatives upon mutation of amino acids Tyr181 and Tyr188. The results obtained provide information for a better understanding of the drug resistant mechanisms of HIV-1 reverse transcriptase.



215.

MOLECULAR MECHANISMS OF ADEFOVIR RESISTANCE IN RTN236T HBV POLYMERASE MUTANT AND ITS SENSITIVITY IN 3TC RESISTANT HBV POLYMERASE MUTANTS: A MOLECULAR DYNAMICS STUDY.

Vikas Yadav and **C. K. Chu**, College of Pharmacy, University of Georgia, Athens, GA 30602, Fax: 706-542-5381, yadavv@rx.uga.edu

Hepatitis B Virus (HBV) infection is a major problem worldwide and is an important cause of chronic liver disease and cirrhosis. Adefovir dipivoxil is the recent addition to available treatment options for chronic HBV patients. However, after 96 weeks of therapy with adefovir dipivoxil, a novel mutation from asparagine to threonine at residue rt236 in domain D of the HBV polymerase has been reported. This prompted us to study the molecular basis of resistance conferred by this novel mutation on the efficacy of adefovir diphosphate (ADV-DP). Molecular dynamic simulations of ADV-DP with the wild type and various mutant HBV-polymerase-DNA complexes have demonstrated that this mutation doesn't affect the binding affinity of natural substrate (dATP) significantly, but it decreases the binding affinity of ADV-DP towards rtN236T HBV polymerase drastically. Lamivudine resistant mutations (rtMet204Val, rtMet204Ile, and rtLeu180Met) results in increased van der Waals contacts between ADV-DP and mutated residues, which accounts for the better binding affinity of ADV-DP towards these mutants. The work presented here demonstrates the molecular basis of enhanced activity of ADV-DP against lamivudine-resistant mutants and its decrease in susceptibility for rtN236T HBV polymerase mutant. (Supported by NIH AI32351 & AI25899)

216.

HIGHLY SELECTIVE P38-ALPHA INHIBITORS FOR TREATMENT OF INFLAMMATORY DISEASES: RAPID IDENTIFICATION AND PROGRESSION TOWARDS DRUG LEADS.

Ioana Popa-Burke, **John Dickson**, **Jose Mendoza**, **Jennifer Clark**, **Robert P. Mohnney**, **Jacqueline L. Norris**, **Paul Bernasconi**, **Scott Galasinski**, **Kevin Williams**, **William P. Janzen**, and **C. Nicholas Hodge**, Amphora Discovery Corp, 800 Capitola Drive, Durham, NC 27713, Fax: 919-806-3477, Ioana.Popa-Burke@amphoracorp.com

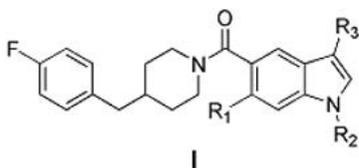
The p38 MAP kinases are a family of serine/threonine protein kinases that play an important role in cellular responses to extracellular stress signals. Several

dual inhibitors of p38-alpha/beta have shown efficacy in arthritic and inflammatory diseases in clinical trials. We have developed and implemented a method for identifying potent and selective compounds for optimization into drug candidates. A diverse library of druggable, purified and quantitated molecules was assembled. Standardized enzymatic assays provided very accurate inhibition data, which allows for observation of SAR directly from the primary HTS. All compounds were screened against a collection of more than 45 enzymes, allowing for removal of promiscuous and non-selective inhibitors very early in the discovery process. Follow-up enzymology studies included measurement of concentration of compound in buffer, yielding accurate determination of Ki and IC50 values, as well as MOA. This approach led to the rapid identification of multiple series of drug leads for p38-alpha, which are highly selective against all other enzymes tested, including the three other p38 isoforms. We will present our results around one such series of p38-alpha inhibitors, including identification, SAR, synthesis, selectivity profiles, enzymatic and cellular data in their progression towards drug candidates.

217.

DISCOVERY AND BIOLOGICAL EVALUATION OF P38 α MAP KINASE INHIBITOR SX-011. *Qing Lu¹, Babu Mavunkel¹, Sarvajit Chakravarty¹, John Perumattam¹, Greg Luedtke¹, Zheng Chen¹, Yong jing Xu¹, Sundeep Dugar¹, Andrew Protter¹, George Schreiner¹, Ramona Almiraz², Brian Scott¹, Maureen Laney¹, Margaret Henson¹, John Lewicki², Adrian Moore³, Sarah Lee⁴, Earnest Brahn⁴, and David Liu⁵.* (1) Scios, Inc, 6500 Paseo Padre Parkway, Fremont, CA 94555, lu@sciosinc.com, (2) Osel, Inc, (3) William Harvey Research Institute, (4) UCLA School of Medicine, (5) Fibrogen Inc

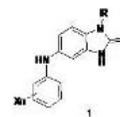
p38 α MAP kinase is an intracellular soluble serine threonine kinase which is activated in response to stress, growth factors and cytokines, such as IL-1 β and TNF- α . Its activation has been shown to further activate proteins and transcription factors that lead to the production of several key pro-inflammatory and inflammatory cytokines. p38 α MAP kinase has an important patho-physiological role in diseases, such as rheumatoid arthritis, where chronic inflammation is said to play a causal role. In recent years there have been several reports of efforts to find small molecule inhibitors of this enzyme as potential therapy in several disease areas. This presentation describes the SAR, in-vitro and in-vivo characterization of a representative (SX-011) from a class of highly specific, indole based piperidine amide inhibitors of p38 α of the general structure I.



218.

DISCOVERY AND DESIGN OF NOVEL BENZIMIDAZOLONE AS INHIBITORS OF P38 MAP KINASE. *Abdelhakim Hammach, Mark Ralph, Faith Corbo, Antonio Barbosa, Pinrong Liu, Fariba Soleymanzadeh, Daniel Goldberg, Christopher Sarko, Brian Mckibben, Neil Moss, Ming Hong Hao, Andre White, Kevin Qian, Chris Pargellis, Rachel Kroe, Jessi Wildeson, Richard Nelson, Tazmeen Fadra, Alison Capolino, Mohammed Kashem, Lori Patnaude, Jeff Madwed, Carol Torcellini, Paul Kaplita, Tom Farrel, Hanbo Hu, Mehran Yazdania, and Kelli Kavanaugh,* Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Rd, PO box368, Ridgefield, CT 06877, hhammach@rdg.boehringer-ingelheim.com

P38 Mitogen activated protein (MAP) kinase, a member of a group of serine-threonine kinases, has been shown to regulate the production of the pro-inflammatory cytokines TNF-alpha and IL-1. Inhibition of p38 is anticipated to have important therapeutic potential in inflammatory diseases such as rheumatoid arthritis, Crohn's disease and psoriasis. We utilized crystallographic information, molecular modeling and rational drug design to convert a hit obtained from high throughput screening to molecules of general structure 1. This presentation will focus on the design process for achieving key interactions with the protein, key SAR observations as well as the synthetic strategy towards these p38 inhibitors.



219.

NOVEL INHIBITORS OF P38 MAP KINASE. *Rupa Shetty¹, Kristofer K. Moffett¹, Dan Nguyen¹, Martha J. Kelly¹, Enrique L. Michelotti¹, Bruce D. Dorsey¹, Eric Springman², Marina Bukhtiyarova², Katrina Northrop², Xiaomei Chai², Michael S. Saporito³, Alexander R. Ochman³, and Michael Karpusas².* (1) Chemistry, Locust Pharmaceuticals, Inc, 512 Townshipline Rd, Four Valley Square, blue bell, PA 19422, Fax: 215-358-2030, rshetty@locuspharma.com, (2) Biochemist, Locust Pharmaceuticals, Inc, (3) Biology, Locust Pharmaceuticals, Inc

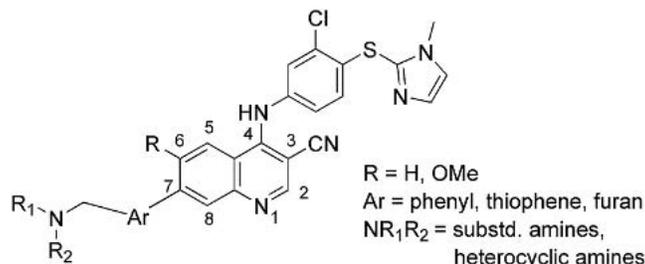
P38 MAPK kinase is a serine/threonine kinase that is activated in response to cellular stresses, growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis alpha (TNF-a). The central role of p38 activation in conducting and amplifying pro-inflammatory signals has led to substantial efforts to find inhibitors of this enzyme. Novel arthritis therapy that can be taken orally, exhibits a reduced side-effect profile and effectively combats the destructive effects of inflammation on joint tissue will impact on this unmet medical need.

In this presentation, we will describe the application of the Locust Core Technology to the identification of novel binding sites and the de novo design of low molecular weight inhibitors of p38 kinase. These inhibitors have been targeted to the ATP active site and the synthesis, biochemical and biological activities, and co-crystal structures of selected inhibitors will be presented.

220.

7-ARYL SUBSTITUTED-4-ANILINOQUINOLINE-3-CARBONITRILES AS POTENT MEK-1 KINASE INHIBITORS. *Dan M. Berger¹, Derek Cole¹, Minu Dutia¹, Erick Honores¹, Dennis W. Powell¹, Larry Feldberg², Donald Wojciechowicz², and Robert Mallon².* (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, bergerd@wyeth.com, (2) Discovery Oncology, Wyeth Research

The Ras-MAPK signaling pathway mediates the transmission of signals from growth factors and hormones to the nucleus, thereby regulating cellular growth, proliferation and survival. Aberrant signaling of this pathway is associated with the formation of certain human tumors, making the kinase components of the Ras-MAPK attractive targets for pharmaceutical intervention. Previously, we have described 4-anilino-6,7-dialkoxy substituted 3-quinolinecarbonitriles as potent MEK-1 inhibitors with exceptional activity against selected human tumor cell lines. In this poster, we present the synthesis and biological activity of a series of 7-aryl substituted quinoline-3-carbonitriles possessing the optimal [3-chloro-4-(1-methylimidazol-2-ylsulfanyl)]anilino group at the C-4 position.



221.

EFFECT OF LINKER GROUP AND HETEROATOM MODIFICATION ON A SERIES OF QUINOLINE 3-CARBONITRILE MEK-1 INHIBITORS: AN SAR STUDY. *Leila Abrous¹, Minu Dutia¹, Dennis W. Powell¹, Dan M. Berger¹, Karen Collins², Donald Wojciechowicz², and Robert Mallon².* (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, abrousl@wyeth.com, (2) Discovery Oncology, Wyeth Research

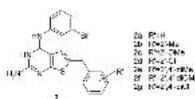
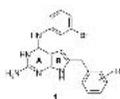
The Ras/Raf/MEK/MAPK signaling cascade plays a central role in cellular growth, proliferation and survival. Stimuli from hormones and growth factor receptors at the cell surface activate this pathway resulting in the transmission of signals to various transcription factors within the nucleus that mediate these processes. Abnormal signaling within this pathway has been associated with the formation of human tumors, making the kinase components of the Ras/Raf/MEK/MAPK signaling cascade attractive targets for pharmaceutical intervention.

It was previously reported that our 6,7-dialkoxy cyanoquinolines are good inhibitors of MEK-1 kinase in our enzyme and cell assays. Herein we highlight compounds designed to explore the effect of heteroatom and linker modification of this series on the biological activity in both enzyme and cells.



222. DESIGN AND SYNTHESIS OF 2-AMINO-4-(3-BROMOANILINO)-6-SUBSTITUTED BENZYLTHIENO[2,3-D]PYRIMIDINES AS INHIBITORS OF RECEPTOR TYROSINE KINASES. Aleem Gangjee¹, Yibin Qiu¹, and Michael A. Ihnat Jr.². (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, Fax: 412-396-5593, (2) Department of Cell Biology, The University of Oklahoma Health Science Center

Several different classes of growth factor receptors containing tyrosine kinases (RTK) are directly or indirectly involved in angiogenesis. Gangjee *et al.* designed, synthesized and evaluated novel 2-amino-4-(3'-bromoanilino)-6-substituted benzylpyrrolo[2,3-d]pyrimidines of general structure **1** as the first in a series of RTK inhibitors and antiangiogenic agents. Some of these compounds were dual inhibitors of RTKs and exhibited potent antiangiogenic activity (CAM assay). We replaced the NH in the B ring of **1** with a sulfur to determine the biological effect of a thiophene rather than a pyrrole. Thus, 2-amino-4-(3'-bromoanilino)-6-substituted benzylthieno[2,3-d]pyrimidines of general structure **2** were designed and synthesized. The synthesis and inhibitory activities against a variety of RTKs of analogs **2a-g** will be reported.



223. DEVELOPMENT OF 2,4,5 SUBSTITUTED PYRIDINES AS INHIBITORS OF AKT KINASE. John C. Hartnett¹, Zhicai Wu², Mark T. Bilodeau¹, George D. Hartman³, Stanley F. Barnett⁴, Deborah Defeo-Jones⁴, Ronald G. Robinson⁴, Astrid M. Kral⁴, Raymond E. Jones⁴, and Hans E. Huber⁴. (1) Department of Medicinal Chemistry, Merck Research Laboratories, P. O. Box 4, WP 14-2, West Point, PA 19486, John_Hartnett@merck.com, (2) Medicinal Chemistry, Merck & Co., Inc, (3) Department of Medicinal Chemistry, Merck and Co., Inc, (4) Department of Cancer Research, Merck Research Laboratories

Akt, also known as protein kinase B, is a serine/threonine kinase belonging to the AGC superfamily of kinases. There are three isoforms of the enzyme with >80% homology to one another. Akt is a critical downstream effector in the PI3K signal transduction pathway and is frequently activated in tumors by growth factor overexpression and mutation in tumor suppressor PTEN. Activation of Akt can lead to cell growth, survival, and tumor progression. This poster will show the design of SAR around the pyridine nucleus to optimize intrinsic and cellular potency. We have developed 2,4,5 substituted pyridines that have led to potent Akt1 and Akt2 inhibitors in both enzyme and cell based assays. We will also highlight the pharmacokinetics of an optimized inhibitor that has shown low clearance and long half-life in dogs.

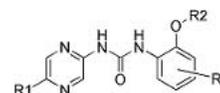
224. DEVELOPMENT OF DIARYL-NAPHTHYRIDINE INHIBITORS OF AKT KINASE. Adrienne E. Balitza¹, Stanley F. Barnett², Mark T. Bilodeau¹, Deborah Defeo-Jones², George D. Hartman¹, Jacob M. Hoffman¹, Hans E. Huber², Raymond E. Jones², Astrid M. Kral², Peter J. Manley¹, Ronald G. Robinson², and Anthony M. Smith¹. (1) Department of Medicinal Chemistry, Merck Research Laboratories, P. O. Box 4, WP 14-2, West Point, PA 19486, adrienne_balitza@merck.com, (2) Department of Cancer Research, Merck Research Laboratories

Akt, a serine/threonine kinase belonging to the AGC superfamily of protein kinases, has been identified as a central signaling mediator which promotes cellular proliferation, growth and survival. Overexpression and activation of Akt, also known as protein kinase B (PKB), has been detected in many types of human cancers including breast, prostate, ovarian and pancreatic. We have designed and synthesized a series of diaryl-naphthyridines, a new class of potent Akt kinase inhibitors developed for the treatment of cancer. Compounds from this series have been found to inhibit both Akt1 and Akt2 in enzyme and cellular based assays. Optimization of structure-activity relationships and synthetic details will be presented.

225. DISCOVERY OF PYRAZINYL UREAS AS INHIBITORS OF THE CELL-CYCLE CHECKPOINT KINASE CHK1. Edward A. Kesicki¹, John J. Gaudino², Adam W. Cook², Laurence E. Burgess², Robert J. Kaufman³, Barbara J. Brandhuber², Guy P. A. Vigers², Monique L. Howard¹, Margaret F. Weidner¹, Edna Dickinson¹, and Kathleen S. Keegan¹. (1) ICOS Corporation, 22021 20th Avenue SE, Bothell, WA 98021, Fax: 425-489-9257, ekesicki@icos.com, (2) Array BioPharma, (3) Gateway Chemical Technology, St. Louis, MO 63146

Chk1 is a serine-threonine protein kinase that plays a key role in cell cycle arrest following DNA damage, especially through control of the S and G2 checkpoints. Our hypothesis is that in the presence of DNA-damaging agents, tumor cells that already lack other key cell cycle checkpoints will be particularly sensitive to Chk1 inhibitors.

High-throughput screening against Chk1 yielded several ATP-competitive diaryl ureas with the general structure shown below. Initial SAR in this series will be presented establishing two major points: 1. A clear preference for pyrazine as one of the aryl groups; 2. Simple substitutions that provide increased potency and solubility.



226. IDENTIFICATION OF A NEW CLASS OF SRC KINASE INHIBITORS. Diane H. Boschelli¹, Biqi Wu¹, Ana C. Barrios Sosa¹, Haris Durutlic¹, Fei Ye¹, Yuri Raifeld¹, Jennifer M. Golas², and Frank Boschelli². (1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, (2) Discovery Oncology, Wyeth Research

Various 4-anilino-3-quinolinecarbonitriles have been reported to inhibit the activity of Src, a non-receptor tyrosine kinase that plays a key role in many cell signaling pathways. In a search for new templates for Src inhibitors, the 3-quinolinecarbonitrile core was replaced by other heterocyclic systems. One of these new templates provided increased Src inhibitory activity over that of an isomeric system. The synthesis and SAR of these analogs will be presented.

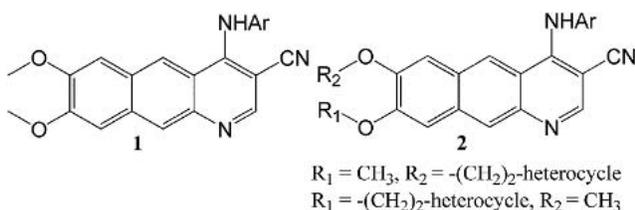
227. OPTIMIZATION OF A NEW CLASS OF SRC KINASE INHIBITORS. Ana C. Barrios Sosa¹, Diane H. Boschelli¹, Biqi Wu¹, Haris Durutlic¹, Jennifer M. Golas², and Frank Boschelli². (1) Chemical and Screening Sciences, Wyeth Research, 401 N Middletown Rd., Pearl River, NY 10965, (2) Discovery Oncology, Wyeth Research

We recently reported the identification of a new template for Src kinase inhibitors. These compounds have a different core than the known 3-quinolinecarbonitriles but retain the anilino group of the earlier series. The preferred anilino groups are 2,4-dichloro-5-methoxyanilino and 3,4,5-trimethoxyanilino, which were the preferred anilino groups in the 3-quinolinecarbonitrile series. In addition, various water solubilizing groups were added to this new core

structure in the hope of increasing the cellular activity. The synthesis and SAR of these analogs will be presented.

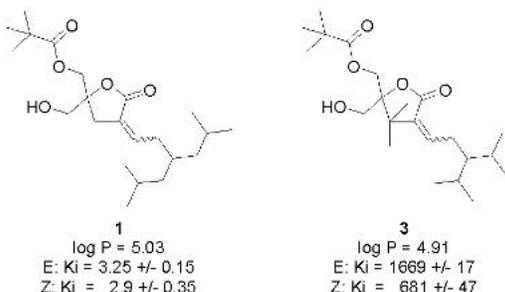
228. SYNTHESIS AND SAR OF 7,8-DIALKOXY-4-ANILINO BENZO[G]QUINOLINE-3-CARBONITRILES AS POTENT SRC KINASE INHIBITORS. *Minu Dutia¹, Garry H. Birnberg¹, Yanong D. Wang¹, Frenel DeMorin², Diane H. Boschelli¹, Dennis W. Powell¹, Jennifer M. Golas³, and Frank Boschelli³.* (1) *Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, dutiam@wyeth.com,* (2) *Currently at Amgen Corporation,* (3) *Discovery Oncology, Wyeth Research*

The tyrosine kinase (TK) Src plays a key role in the regulation of certain cellular pathways and it has been implicated in several disease states, including cancer, stroke and osteoporosis. Thus, a small molecule Src kinase inhibitor may prove useful for the treatment of cancer as well as other proliferative diseases. It was previously disclosed that 4-anilino-7,8-dialkoxybenzo[g]quinoline carbonitriles (1) were potent Src kinase inhibitors. Heterocyclic amine water-solubilizing groups were added at the C-7 or C-8 position in an effort to enhance aqueous solubility and cellular activity. In this presentation, the synthesis and SAR of analogs (2) will be described.



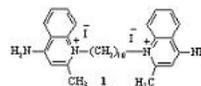
229. HYDROPHOBIC LIGAND-PROTEIN INTERACTIONS VS. LIGAND-LIPID INTERACTIONS OF DAG-LACTONES WITH PROTEIN KINASE C (PK-C). *Dina M. Sigano¹, Hirokazu Tamamura¹, Nancy E. Lewin², Megan L. Peach¹, Marc C Nicklaus¹, Peter M. Blumberg², and Victor E. Marquez¹.* (1) *Laboratory of Medicinal Chemistry, National Institutes of Health, National Cancer Institute, 376 Boyles Street, P.O. Box B, Frederick, MD 21702, Fax: 301-846-6033, dsigano@nih.gov,* (2) *Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Institutes of Health*

Over the past few years, we have attempted to bridge the substantial gap in PK-C binding affinity that exists between the phorbol esters and DAG by constraining the glycerol backbone into DAG-lactones; and by incorporating highly branched alkyl chains which are not only capable of making important hydrophobic contacts with the protein (specific interactions), but also provide adequate lipophilicity to facilitate partitioning into the lipid-rich membrane environment (non-specific interactions). With the idea of minimizing the non-specific interactions without reducing lipophilicity, we explored a strategy of transferring this lipophilicity from the side chain (1) to the lactone "core" (3). Surprisingly, both E-3 and Z-3 showed a significant decrease in binding affinity. From this and other results, we conclude that the binding pocket of the C1 domain of PK-C is sterically restricted; and that the C-3 position of the DAG-lactones must remain intact without substitution.



230. SYNTHESIS OF DEQUALINIUM ANALOGUES AND THEIR INHIBITORY POTENCIES WITH PROTEIN KINASE C. *Chandima Abeywickrama, Arthur D Baker, and Susan A. Rotenberg, Department of Chemistry and Biochemistry, Queens College of the City University of New York and CUNY Graduate School and University Center, 65-30, Kissena Boulevard, Flushing, NY 11367, Fax: 718-997-5531, cabeywickrama@hotmail.com*

Dequalinium diiodide 1, is an important antitumor and antimetastatic agent that prior to its discovery as a PKC inhibitor was originally used as an antimicrobial agent, that included its role as the active ingredient in mouthwash. Structure-activity analysis shows that certain structural attributes of this compound are critical for inhibition of PKC activity. We will describe the preparation and activity of various new compounds.



231. SELECTIVE ITK INHIBITORS.3. OPTIMIZATION OF THE 2-AMINO-5-(THIOARYL)THIAZOLES. *Jagabandhu Das¹, John Wityak¹, Chunjian Liu², Robert V. Moquin¹, Joseph A. Furch¹, James Lin¹, Steven H. Spergel¹, Arthur M. Doweiko³, Amrita Kamath⁴, Hongjian Zhang⁵, Kathleen D. O'Day⁶, Becky Penhallow⁶, Chen Yi Hung⁶, Steven Kanner⁶, Tai An Lin⁶, John H. Dodd¹, and Joel C Barrish¹.* (1) *Lawrenceville Discovery Chemistry, Bristol-Myers Squibb PRI, Provinceline Rd and Route 206, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6804, jagabandhu.das@bms.com,* (2) *Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute,* (3) *Pharmaceutical Research Institute, Bristol-Myers Squibb,* (4) *Metabolism and Pharmacokinetics, Bristol-Myers Squibb Company,* (5) *PCO, Bristol-Myers Squibb PRI,* (6) *Lawrenceville Discovery Biology, Bristol-Myers Squibb PRI*

Itk(Emt, Tsk) is a member of the Tec family of non-receptor tyrosine kinases expressed mainly on CD4+ T-cells. Mice deficient in Itk exhibit defects in T-cell signaling and development leading to reduced IL-2 production. Selective Itk inhibitors may therefore have utilities as immunosuppressive agents in the treatment of rheumatoid arthritis, graft rejection, and other T-cell mediated immunological disorders. Synthesis and SAR optimization in the 2-amino-5-(thioaryl)thiazoles leading to the identification of a selective and potent Itk inhibitor will be presented.

232. SUBSTITUTED AMINOBENZIMIDAZOLE PYRIMIDINES AS CYCLIN-DEPENDENT KINASE INHIBITORS. *Sharad K Verma¹, Sanjeeva Reddy², Dhanalpalan Nagarathnam¹, Jianxing Shao¹, Lei Zhang¹, Jin Zhao¹, Yamin Wang¹, Tindy Li¹, Eric Mull¹, Chunguang Wang¹, Qingming Zhu¹, Martha Altieri², Thu Thi Anh Dang², and Jerold Jordan².* (1) *Department of Chemistry, Bayer Pharmaceuticals, 400 Morgan Lane, West Haven, CT 06516, Fax: 203-812-3655, sharad.verma.b@bayer.com,* (2) *Department of Cancer Research, Bayer Pharmaceuticals*

The cyclin-dependent kinases (CDKs) play a critical role in tumor growth and progression. In an effort to identify potent inhibitors of CDK1, a series of pyrimidines were synthesized and tested. This led to the identification of 1, a bis-aminobenzimidazole-substituted pyrimidine, as a potent inhibitor of CDK1. Further modifications of 1 led to analogs with improved potency. The synthesis and structure-activity relationships of this series of compounds will be discussed.



233.

SYNTHESIS AND DISCOVERY OF PYRAZINE-PYRIDINE BIHETEROARYL AS A NOVEL SERIES OF POTENT VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2) INHIBITORS. *Gee Hong Kuo, Aihua Wang, Stuart Emanuel, Alan DeAngelis, Rui Zhang, Peter J. Connolly, William V. Murray, Robert H. Gruninger, Jan Sechler, Angel Fuentes-Pesquera, Dana Johnson, Steven A Middleton, Linda Jolliffe, and Xin Chen, Drug Discovery Division, Johnson and Johnson Pharmaceutical Research, 1000 Route 202, P.O. Box 300, Raritan, NJ 08869, Fax: 908-526-6469, gkuo@prius.jnj.com*

Pathological angiogenesis is associated with disease states such as cancer, diabetic retinopathy, rheumatoid arthritis, endometriosis and psoriasis. There is much evidence that direct inhibition of the kinase activity of VEGFR-2 will result in the reduction of angiogenesis and the suppression of tumor growth. Attempts to optimize a CDK1 inhibitor by using palladium-catalyzed C-C bond, C-N bond formation reactions to assemble diverse biheteroaryl molecules led to the unexpected discovery of a pyrazine-pyridine biheteroaryl as a novel series of potent VEGFR-2 inhibitor. Compound **15** which had $IC_{50} = 0.084 \mu M$ at VEGFR-2, showed very modest selectivities against FGFR-2 ($IC_{50} = 0.21 \mu M$), PDGFR ($IC_{50} = 0.36 \mu M$) and GSK-3 ($IC_{50} = 0.478 \mu M$) while it exhibited more than 10-fold selectivities against EGFR ($IC_{50} = 1.36 \mu M$) and Insulin-R kinase ($IC_{50} = 1.69 \mu M$). On the other hand, compound **15** exhibited more than 100-fold selectivities against calmodulin kinase 2, casein kinase-1 or -2, CDK1, CDK4, mitogen-activated protein kinase (MAPK), protein kinase A (PKA), PKC β 2 and PKC γ ($IC_{50} > 10 \mu M$). Compound **15** also displayed high inhibitory potency at VEGF-stimulated HUVEC ($IC_{50} = 0.005 \mu M$) and good selectivity against cell lines such as HUVEC, HASMC and MRC5.

234.

4(3H)-QUINAZOLINONE LIBRARY SYNTHESIS FROM VIRTUAL TO REALITY: A KINASE INITIATIVE PROJECT LIBRARY. *Tracy L. Deegan¹, Richard A. Wildonger¹, John W. Lee¹, Robert J. Murphy¹, Dingwei Yu², Mark J. Duffield³, Kevin Daniels³, and Lisa Schaffter⁴.* (1) Enhanced Synthesis Group, Cancer Chemistry, AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451, Fax: 781-839-4650, tracy.deegan@astrazeneca.com, (2) Cancer Chemistry, AstraZeneca R&D Boston, (3) EST Lead Informatics, AstraZeneca R&D Boston, (4) CIRA Core Analytical Chemistry, AstraZeneca R&D Boston

A virtual library of 4(3H)-quinazolinones was developed for the Kinase Initiative Project (KIP) using several stand-alone software packages integrated with other web-based applications developed in-house. A subset of the virtual library was synthesized using solid-phase multiple parallel synthesis. 4(3H)-quinazolinones are known biologically relevant compounds and are viewed as attractive potential kinase inhibitors.

235.

STRUCTURE-ACTIVITY RELATIONSHIPS OF RATIONALLY DESIGNED HSP90 INHIBITORS. *Randell C. Clewenger, Brian S. J. Blagg, and Gang Shen, Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Malott 4070, Lawrence, KS 66045-7562, Fax: 785-864-5326*

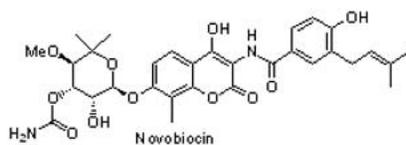
Based on the co-crystal structures of geldanamycin and radicicol bound to the N-terminal ATP binding site of Hsp90, a series of rationally designed molecules has been prepared and assayed for Hsp90 ATPase inhibition. These analogs help to understand the role of various functionalities in the above-mentioned compounds. The design, synthesis, and inhibition of ATPase activity of these compounds will be presented.

236.

THE DESIGN AND SYNTHESIS OF NOVOBIOCIN ANALOGUES AS HSP90 C-TERMINAL INHIBITORS. *Xiao Ming Yu and Brian S. J. Blagg, Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Malott 4070, Lawrence, KS 66045-7562, Fax: 785-864-5326*

Recently, novobiocin was shown to bind to the C-terminal nucleotide-binding site on Hsp90 competitively vs. ATP. Binding to this motif results in the inhibition of Hsp90's protein folding machinery. In an effort to elucidate the C-terminal ATP binding site and determine structure-activity relationships, new novobiocin derivatives have been prepared. These analogues contain both

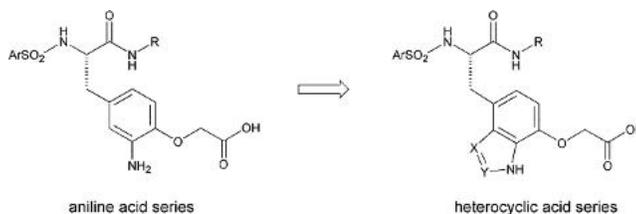
modified sugar and coumarin moieties. The synthesis and results of these studies will be discussed.



237.

DESIGN AND EVALUATION OF MONO-CHARGED INHIBITORS OF PTP1B. *David A. Mareska¹, Robert D. Groneberg², Xicheng Sun², Eli Wallace¹, Mareli Rodriguez¹, Andras Toro¹, David Clarke¹, Hideo Suzuki¹, Kevin Ash³, Jeff Yingling³, Jim Rizzi⁴, Guy Vigers³, Barb Brandhuber³, Laurence E. Burgess¹, Kevin Koch¹, Mark Norman⁵, Rick Lindberg⁵, John McCarter⁵, and Mike Kelly⁵.* (1) Department of Lead Optimization, Array BioPharma Inc, 3200 Walnut Street, Boulder, CO 80301, Fax: 303-449-5376, david.mareska@arraybiopharma.com, (2) Department of Lead Optimization, Array Biopharma, (3) Department of Biology, Array BioPharma Inc, (4) Department of Computational Technology, Array BioPharma Inc, (5) Amgen Inc

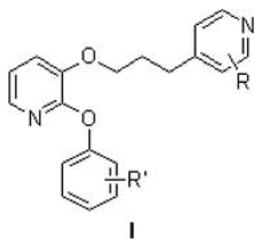
Protein Tyrosine Phosphatase 1B (PTP1B) has been demonstrated to negatively regulate insulin receptor activity and has thus been identified as a therapeutic target for treatment of type 2 diabetes. The identification of cell-permeable PTP1B inhibitors has been challenging, as active site inhibitors must mimic a dianionic phosphotyrosine. We have developed monocharged, small molecule inhibitors to address the issue of permeability while maintaining potency against PTP1B. After identifying an aniline acid series of inhibitors, a more drug-like series of heterocyclic acids was designed and prepared. The design, synthesis, and in vitro activities of these monocharged inhibitors will be presented.



238.

2,3-DISUBSTITUTED PYRIDINE DERIVATIVES AS NON-EMETIC PHOSPHODIESTERASE TYPE 4 INHIBITORS. *Tomohiro Nigo¹, Shunya Nakamura², Satoki Yoshioka², Yasuhiro Teranishi³, Mari N. Itoh², and Motoji Kawasaki¹.* (1) Discovery Chemistry I group, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita, Osaka 564-0053, Japan, Fax: +81-6-6338-7656, tomohiro-nigo@dainippon-pharm.co.jp, (2) Discovery Pharmacology I group, Dainippon Pharmaceutical Co., Ltd, (3) Advanced Pharmacology Research group, Dainippon Pharmaceutical Co., Ltd

Selective phosphodiesterase type 4 (PDE4) inhibitors have attracted increased interest for treatment of asthma and COPD. However, the early generations caused dose-limiting side effects of nausea and emesis that had hampered their clinical development. And the new generation of PDE4 inhibitors with reduced these side effects are now under developments. In our investigation for anti-asthmatic agents, we found that a new series of 2,3-disubstituted pyridine derivatives (I) demonstrated in vitro PDE4 inhibiting activities ($IC_{50} \sim 10 \text{ nM}$). And these compounds effectively suppressed the antigen-induced bronchoconstriction in guinea pigs (1-30 mg/kg, p.o.), while they caused emesis in ferrets at the effective doses. But further modification of the substituents at pyridine ring finally led to the large reduction of emetic side effects. Thus, typical compounds showed good effectiveness in the models of bronchoconstriction and inflammation (3-30 mg/kg, p.o.), while they did not induce emesis in ferrets (~300 mg/kg, p.o.). The synthesis and structure-activity relationship of these compounds will be presented.



239.

ANTI-ASTHMATIC ACTIVITY OF OS-0217, A NOVEL, ORALLY ACTIVE PHOSPHODIESTERASE 4 INHIBITOR IN THE GUINEA PIGS, MICE AND HUMAN EOSINOPHILS. *Shunya Nakamura*¹, *Satoki Yoshioka*¹, *Yasuhiro Teranishi*², *Tomohiro Nigo*³, *Motoji Kawasaki*³, and *Mari N. Itoh*¹. (1) *Discovery Pharmacology I group, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita, Osaka 564-0053, Japan, Fax: +81-6-6337-5109, shunya-nakamura@dainippon-pharm.co.jp*, (2) *Advanced Pharmacology Research group, Dainippon Pharmaceutical Co., Ltd*, (3) *Discovery Chemistry I group, Dainippon Pharmaceutical Co., Ltd*

Phosphodiesterase type4 (PDE4) is localized in airway smooth muscle and inflammatory cells, which are involved in pathogenesis of chronic respiratory inflammatory disorders such as asthma. Inhibition of PDE4 leads to an increase of cAMP levels resulting in airway smooth muscle relaxation and suppression of activation of inflammatory cells. However, inhibition of the PDE4 in the brain causes nausea and vomiting as side effects, which become a limiting factor on clinical development of the PDE4 inhibitors. We developed a novel, orally active PDE4 inhibitor, OS-0217. OS-0217 relaxed guinea pig isolated trachea precontracted with histamine and inhibited antigen-induced contraction of guinea pig isolated trachea and inhibited OVA-induced bronchospasm in anesthetized guinea pigs. In conscious guinea pigs, OS-0217 prevented immediate- and late-asthmatic responses and subsequent inflammatory cells infiltration into BALF. In mice, OS-0217 also ameliorated inflammatory cells infiltration into BALF. Otherwise, OS-0217 did not elicit emesis even at a dose of 300mg/kg in ferrets. These results suggest that OS-0217 will be a useful and safe therapeutic drug for the treatment of asthma. Details of the results will be discussed.

240.

SYNTHESIS OF DEUTERIUM LABELED SILDENAFIL, TADALAFIL AND VARDENAFIL. *Heiko Junga* and *Naidong Weng*, *Bioanalytical Chemistry, Covance Laboratories Inc, 3301 Kinsman Blvd., Madison, WI 53704, Fax: 608-242-2735, heiko.junga@covance.com*

Sildenafil-d8 and its main metabolite (Desmethyl sildenafil-d8) were synthesized in two steps. The deuterium label was introduced via synthesis with 1-methylpiperazine-d8 or piperazine-d10 for the metabolite. Tadalafil-d3 was synthesized in three steps. Methyl-d3-amine was used to introduce the label. Vardenafil-d5 was synthesized in six steps. The deuterium label was introduced via synthesis with bromoethane-d5. These internal standards allowed the development of simple and rugged LC-MS/MS methods.

241.

IDENTIFICATION AND SAR OF POTENT INHIBITORS OF PHOSPHODIESTERASE 7 (PDE7). *Junqing Guo*¹, *Marianne Carlsen*¹, *Joseph Barbosa*¹, *James Kempson*¹, *Claude A. Quesnelle*¹, *Marco Dodier*¹, *Andrew Watson*², *Karen Donaldson*², *Deborah Lee*², *Gary Starling*², *William J. Pitts*¹, *John H. Dodd*¹, *Peter Kiener*², *Murray McKinnon*², and *Joel Barrish*¹. (1) *Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, Fax: 609-252-6804, junqing.guo@bms.com*, (2) *Immunology, Inflammation, and Pulmonary Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute*

Phosphodiesterases (PDEs) hydrolyze the second messenger molecules cAMP and cGMP to affect cellular signaling. PDE's are involved in a myriad of important physiological functions and as such continue to be a major target for pharmacological intervention on the part of the pharmaceutical industry. A recent publication demonstrated that suppression of PDE7 up-regulation by anti-sense oligonucleotides inhibited both T cell proliferation and IL-2 production in CD3xCD28 stimulated T cells. This expression profile suggests inhibitors of PDE7A would have broad application as an immunosuppressant. The synthesis

of potent inhibitors of PDE 7 and the structure-activity relationships (SAR) derived from in vitro studies are presented.

242.

DESIGN AND SYNTHESIS BIOTINYLATED LIGANDS EXHIBITING HIGH GRB2 SH2 DOMAIN-BINDING AFFINITY. *Zhen Dan Shi*¹, *Hongpeng Liu*², *Manchao Zhang*², *Lindsey R. Roberts*³, *Robert J Fisher*³, *Dajun Yang*², *Donald Bottaro*⁴, *Marston Linehan*⁴, and *Terrence R. Burke Jr.*¹. (1) *Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, Fax: 301-846-6033, shiz@ncifcrf.gov*, (2) *Department of Hematology/Oncology, University of Michigan Medical School*, (3) *Protein Chemistry Laboratory, SAIC-Frederick*, (4) *Urology Oncology Branch, CCR, NCI, NIH*

The growth factor receptor-bound protein 2 (Grb2) provides critical connectivity between growth factor receptor protein-tyrosine kinases and Ras signaling involved in the etiology of several cancers. Predicated on the binding of pTyr-containing peptides to Grb2 SH2 domains in beta-bend conformations, we prepared a number of high affinity ligands that contain both phosphonate and carboxy-based phosphoryl replacements. In order to identify potential physiological targets of these agents in whole cell systems, we recently synthesized a biotinylated macrocyclic tetrapeptide mimetic. Although biotin is normally introduced at the N-terminus of peptides, this was deemed to be inadvisable in the present context due to potential interference in interactions with binding to the critical Grb2 SH2 domain alpha-A2 Arg residue. Accordingly, biotinylation was C-terminally located. Of note, the resulting biotin-containing analogue maintained high (single digit nanomolar) binding affinity. As an extension of this research, C-terminal biotinylation has been achieved in an open chain non-phosphorus-containing tetrapeptide mimetic. The design, synthesis and preliminary utilization of these analogues will be presented.

243.

POTENT AND HIGHLY SELECTIVE CYCLOOXYGENASE-2 (COX-2) INHIBITOR FROM A NOVEL, PYRIDYL METHARYL SERIES. *Subhash P. Khanapure*, *Michael E. Augustyniak*, *Richard A. Earl*, *David S. Garvey*, *L. Gordon Letts*, *Allison M. Martino*, *Madhavi G. Murty*, *David S. Schwab*, *Matthew J. Shumway*, *Andrzej M. Trocha*, *Delano V. Young*, *Irina S. Zemtseva*, and *David R. Janero*, *NitroMed, Inc, 12 Oak Park Drive, Bedford, MA 01730, Fax: 781-275-1127, skhanapure@nitromed.com*

We have recently reported a novel series of metharyl derivatives that are potent and highly selective COX-2 inhibitors. In this presentation, we report the synthesis and structure-activity relationship (SAR) studies of a series of pyridine metharyl benzene(4-methylsulfone) derivatives as selective COX-2 inhibitors. Aryl substituents linked to the central pyridyl ring by a carbonyl spacer resulted in potent, highly selective COX-2 inhibitors. The spacer group was critical for optimizing COX-2 inhibition in human whole blood (HWB). A benzene(4-methylsulfonyl) substitution at the 3-position of the central pyridyl ring was essential for COX-2 selectivity and potency (e. g., COX-2 IC50 for compound (A) = 0.25 microM and COX-1 IC50 for compound (A) = 14 microM in HWB assay). By contrast, a benzene(4-methylsulfone) substitution at the 2-position of the central pyridyl ring abrogated the COX-2 inhibition. Our data support identification of a potent and highly selective COX-2 inhibitor.

244.

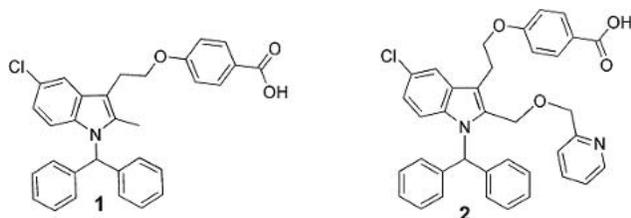
SYNTHESIS OF [11C]-TMI: A POTENTIAL PET TRACER FOR IMAGING COX-2 EXPRESSION. *J. S. Dileep Kumar*¹, *Mark D. Underwood*¹, *Jaya Prabhakaran*¹, *Ramin V. Parsey*¹, *Victoria Arango*¹, *Vattoly J Majo*¹, *Norman R. Simpson*², *Anna R Cooper*¹, *Julie Arcement*¹, *Ronald L. Van Heertum*², and *J. John Mann*³. (1) *Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, Fax: 212-543-6017, dk2038@columbia.edu*, (2) *Department of Radiology, Columbia University*, (3) *Department of Psychiatry, Radiology & Division of Neuroscience, Columbia University & New York State Psychiatric Institute*

COX-2 selective inhibitors are potent non steroidal anti-inflammatory drugs (NSAIDs) with fewer side effects and have been routinely used in arthritis, headaches and other inflammatory processes, and tested in the treatment of cancer, stroke and Alzheimer's disease. Thus positron labeling of COX-2 selective inhibitors may permit in vivo imaging of COX-2 localization and activity in these diseases to monitor the inflammatory process and to relate NSAIDs

blockade of COX-2 to therapeutic effect. In this connection, synthesis of [11C]-3-(4-methanesulfonylphenyl)-4-phenyl-5-trifluoromethylisoxazole ([11C]TMI), a highly selective COX-2 selective inhibitor has been investigated. Thiobutyric acid S-[4-(4-phenyl-5-trifluoromethyl-isoxazol-3-yl)phenyl] ester, the precursor molecule for the radiolabeling was synthesized from 4-methylsulfonyl benzaldehyde in five steps with 23% overall yield. Using [11C]methyl iodide followed by oxidation with oxone resulted in the formation of [11C]TMI in 40% yield (decay corrected). The specific activity of [11C]TMI was >2000 Ci/ mmol with a chemical and radiochemical purity of >99%. The details of the synthesis and in vivo validations of [11C]TMI will be presented.

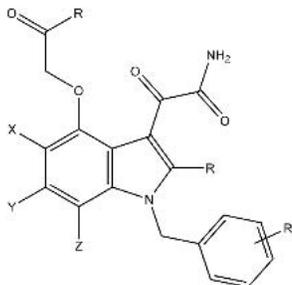
245. NOVEL BENZIMIDAZOLE, CARBOLINE, AND INDOLE DERIVATIVES AS CPLA2 INHIBITORS. *Baihua Hu¹, Alex Oliphant¹, John Ellingboe¹, John C McKew², Steve Tam², Frank E. Lovering², Mark Behnke², Jennifer Thomason², Marina Shen³, Wen Zhang³, and James D. Clark³.* (1) Chemical and Screening Science, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, hub@wyeth.com, (2) Department of Chemical and Screening Sciences, Wyeth Research, (3) Department of Inflammation, Wyeth Research

Cytosolic phospholipase A2 (cPLA2) is the enzyme selectively cleaves the sn-2 position of arachidonic acid-containing glycerophospholipids. This enzyme is considered responsible for the release of arachidonic acid which is later converted into a variety of inflammatory mediators (such as leukotrienes, thromboxanes and prostaglandins) (refs: 1. J.D. Clark, et al, J. Lipid Mediators and Cell Signalling 1995, 12, 83; 2. N. Uozumi, et al, Nature, 1997, 390(6660), 618). The ability to stop this whole downstream process of inflammatory mediators by the inhibition of a single enzyme, cPLA2, makes this a very attractive target for inflammatory diseases, such as rheumatoid arthritis, asthma, and osteoarthritis. The initial lead 1 was generated from our earlier study. It is a modestly potent cPLA2 inhibitor with IC50 of 2.7 mM. After independent modification of site N1 and C3 of compound 1 a new potential lead (2) was developed which will be presented in this poster.



246. SYNTHESIS AND EVALUATION OF CARBOCYCLIC-FUSED INHIBITORS OF HUMAN NONPANCREATIC SECRETORY PHOSPHOLIPASE A2. *Douglas W. Beight, Donald G. Carlson, Larry W. Hartley, J. Scott Sawyer, and Edward C. R. Smith, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-276-1417, beight@lilly.com*

A recent effort at Lilly showed 5-, 6-, and 7-substituted indoles (1) to be potent and selective inhibitors of human nonpancreatic secretory phospholipase A2 (sPLA2). To further explore this SAR, we designed a series of 5,6- and 6,7-carbocyclic-fused indoles and found them to be potent inhibitors of sPLA2. Synthetic strategies will be discussed and data will be presented for these compounds.



247. THE SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF A SERIES OF N-SUBSTITUTED GLYCOLAMIDES OF NAPROXEN: NITRIC OXIDE DONOR CONTAINING NAPROXEN PRODRUGS. *Ramani R. Ranatunge, Michael E. Augustyniak, Vijay Dhawan, James L. Ellis, David S. Garvey, David R. Janero, L. Gordon Letts, Stewart K. Richardson, Matthew J. Shumway, A. Mark Trocha, Delano V. Young, and Irina S. Zemtseva, NitroMed Inc, 12 Oak Park Drive, Bedford, MA 01730, Fax: 781-275-1127, rbandarage@nitromed.com*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. Naproxen is one of the most popular NSAIDs for the treatment of arthritic pain, but associated with its use are adverse gastrointestinal (GI) complications ranging from stomach irritation to life threatening GI ulceration and bleeding. Recently, selective inhibitors of the cyclooxygenase (COX) enzyme isoform, COX-2 have been shown to possess the beneficial anti-inflammatory and analgesic properties of NSAIDs with enhanced GI tolerance. However, some evidence suggests that adverse reactions such as GI irritation, ulceration as well as renal and cardiovascular liabilities are associated with prolonged use of COX-2 selective inhibitors. Thus, there is still a need for cyclooxygenase inhibiting non-steroidal anti-inflammatory drugs with improved safety profiles. As an alternative to COX-2 selective inhibitors, we and others have developed GI-sparing NSAIDs involving the chemical coupling of a nitric oxide (NO) donor moiety to NSAIDs. Here, we report the synthesis and anti-inflammatory activity of a series of glycolamide prodrugs of naproxen, containing a nitrate group as the NO-donor.

248. DESIGN AND SYNTHESIS OF INHIBITORS OF HUMAN GOLGI α -MANNOSIDASE II BASED ON THE AZASUGAR SWAINSONINE. *S. Anand¹, Udayan Das², Douglas A. Kuntz³, David R Rose³, John M. Rimoldi¹, and Aloysius Siriwardena².* (1) Department of Medicinal Chemistry, University of Mississippi, Laboratory for Applied Drug Design and Synthesis, University, MS 38677, Fax: 662-915-5638, sanand@olemiss.edu, (2) Department of Chemistry and Biochemistry, University of Mississippi, (3) Department of Medical Biophysics, University of Toronto

Several azasugars, like swainsonine, are powerful inhibitors of human golgi α -mannosidase II (HGM II). The promise they hold in cancer treatment has amplified interest in their study. However, swainsonines inhibition of human lysosomal α -mannosidase (HLM) causes a serious side effect known as swainsonine-induced mannosidosis. We have recently reported a number of heterocycles related to swainsonine that show marked selectivity for HGM II over HLM. These hydroxylated pyrrolopyrimidine lactams have been obtained via an efficient cascade reaction and have the potential to be structurally modified with the goal of mimicking the aglycon portion of the natural substrate. In order to accentuate the inherent selectivity for HGM II observed for these leads, we have used computer modeling and docking analysis to aid in the creation of new lead inhibitors for HGM II. The solid-phase protocol for library construction of the hydroxylated pyrrolopyrimidine lactams will also be presented.

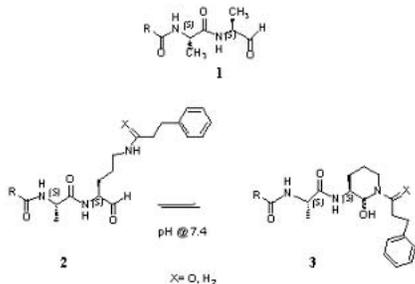
249. DESIGN AND SYNTHESIS OF POTENT SMALL MOLECULE INHIBITORS OF α -AMYLASE. *Xinhua Li, Amarjit Nijjar, Abinash Mishra, Mark Staveski, Gary Asmussen, Michael Booker, Robert Burrier, Alla Kloss, Randy Holmes-Farley, Harry Mandeville, and Pradeep Dhal, Drug Discovery and Development, Genzyme Corporation, 153 Second Avenue, Waltham, MA 02451, Fax: 781-672-5823, xinhua.li@genzyme.com*

α -Amylase catalyzes the hydrolysis of α D-(1,4)-glucan linkages in starch, producing oligosaccharide fragments. Inhibition of pancreatic α amylase and α glucosidase has proven useful in controlling postprandial blood glucose levels by slowing the digestion of starch and oligosaccharides. Tendamistat is a potent proteinous inhibitor of α -amylase with a Ki value of 0.2 nM. Structural analyses of tendamistat bound to amylase have shown that tripeptide sequence Trp-Arg-Tyr binds to the active site of the enzyme. Small molecule amylase inhibitors are desired as potential treatment for type II diabetes. We have synthesized a series of small molecules based on the structure of the tripeptide sequence of tendamistat. Compounds with inhibitory activity (1 – 10 μ M) have been obtained. The most active compound has IC50 of 0.9 μ M. In this poster, the design and synthesis of these compounds as well as preliminary SAR will be discussed.

250. DESIGN AND SYNTHESIS OF PEPTIDE HEMIAMINALS AS PROTEASE INHIBITORS.

Tina M. Ross, Department of Chemistry, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., P.O. Box 776, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-4985, tross@prdu.s.jnj.com, and William P. Malachowski, Department of Chemistry, Bryn Mawr College

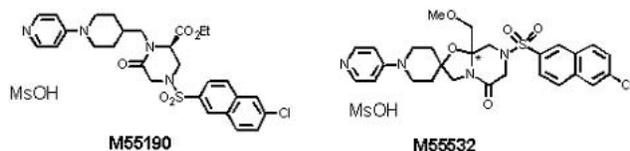
Peptide aldehydes (1) have been well recognized as effective inhibitors of proteases. Hemiaminals (3), which have the same oxidation state as aldehydes, might also serve as protease inhibitors, while allowing extended-binding interactions in the enzyme active site. In this poster presentation, we document the synthesis of hemiaminals (3) and enzyme inhibition results. The synthetic strategies to make 3 and the current progress on the synthesis will be discussed.



251. DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW POTENT FACTOR Xa INHIBITOR.

Hidemitsu Nishida, Takafumi Mukaihira, Fumihiko Saitoh, Yoshitaka Hosaka, Tomokazu Matsusue, Ikuya Shiromizu, Masatsugu Kamiya, Hiroyasu Naba, Shuhei Ohnishi, Hidenori Mochizuki, and Kazutoshi Yanagibashi, Mochida Pharmaceutical Co., Ltd, Research Center, 722, Jimba-Aza-Uenohara, Gotemba 412-8524, Japan, Fax: +81-550-89-0945, hnishida@mochida.co.jp

Factor Xa is a key enzyme in the coagulation cascade responsible for generation of thrombin by limited proteolysis of its zymogen, prothrombin. Previous reports from our labs have detailed the development of a 1-(4-pyridyl)-piperidine group without guanidino- and/or amidino groups, exemplified by M55190. In our efforts to develop structurally novel Factor Xa inhibitors, spiro[5H-oxazolo[3,2-a]pyrazine-2(3H),4'-piperidine]-5-one skeleton was designed, based on M55190, and developed through SAR studies. From among these compounds, M55532 was selected as a candidate for further development, as it inhibited human factor Xa with a K_i value of about 2 nM.

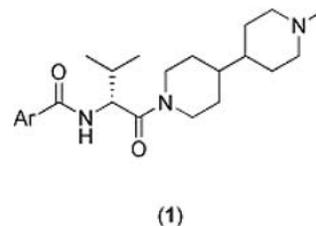


252. NON-AROMATIC D-AMINO ACID-DERIVED INHIBITORS OF HUMAN FXA.

Michael R. Wiley¹, Sarah M. Smith¹, Jolie A. Bastian¹, Nickolay Y. Chirgadze¹, Trelia J. Craft¹, Ronald S. Foster¹, Jeffrey B. Franciskovich¹, Larry L. Froelich¹, Peter R. Guzzo², Janelle Haynes¹, Ming Min Hsia², Valentine J. Klimkowski¹, Jeffery K. Kyle¹, Michael J. Mayer², Donetta Gifford-Moore¹, Christopher W. Murray³, John W. Liebeschuetz³, Jothirajah Marimuthu¹, John J. Masters¹, John E. Reilly², Daniel J. Sall¹, Scott M. Sheehan¹, Jeffrey K. Smallwood¹, Gerald F. Smith¹, Richard D. Towner¹, Brian M. Watson¹, Stephen C. Young³, and Eugene F. Fogut¹. (1) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, (2) Albany Molecular Research Inc, (3) Tularik Ltd

Recently, we have described several studies on the SAR of D-phenylglycine derived inhibitors of fXa, which derive considerable binding energy from the interaction of the aryl amino acid side-chain with the disulfide binding site, adjacent to the S1 pocket of the fXa. As part of these investigations, we have explored the use of non-aryl glycine amides such as (1), that are not as susceptible to racemization in the amide coupling step. This presentation will

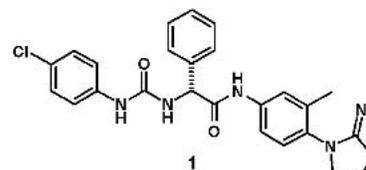
disclose SAR trends for a variety of amino acid derivatives from the series along with X-ray structures of selected analogs to further illustrate the nature of the interaction of the amino acid side-chain with the disulfide pocket. Representative anticoagulant profiles for selected compounds will also be presented.



253. NOVEL SOLUBILIZING S4-RESIDUES FOR FACTOR Xa INHIBITORS: SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 1-ARYL-2-IMINO-PYRROLIDINE AND -PIPERIDINE DERIVATIVES.

Bertram Cezanne, Dieter Dorsch, Werner W. K. R. Mederski, Christos Tsaklakidis, Johannes Gleitz, and Soheila Anzali, Preclinical Research & Development, Merck KGaA, Frankfurter Strasse 250, 64271 Darmstadt, Germany, bertram.cezanne@merck.de, dieter.dorsch@merck.de

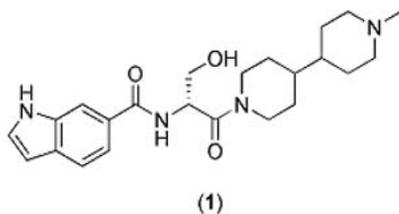
Factor Xa is a serine proteinase, which cleaves prothrombin to thrombin, leading to clot formation. It is widely recognized as a very attractive target for the development of new antithrombotic agents. Factor Xa possesses two distinct binding pockets, P1, which has been found to bind hydrophobic chlorophenyl residues well, and P4, which has a more extended shape and binds two-ring S4-residues like biphenyl or heterocyclyl-phenyl. In our search for potent and soluble factor Xa inhibitors, we found that compounds with S4-residues bearing a basic cyclic amidine moiety such as 1-aryl-2-imino-pyrrolidine or -piperidine showed both high potency and good aqueous solubility. The binding mode of these compounds was studied by X-ray structure analysis of a complex of compound 1 with factor Xa. We will report on the syntheses and biological properties (in vitro and in vivo) of several factor Xa inhibitors with S4-residues having a cyclic amidine moiety.



254. SAR INVESTIGATION OF HETEROATOM CONTAINING NON-ARYLGLYCINE INHIBITORS OF HUMAN FXA.

Michael R. Wiley¹, Jolie A. Bastian¹, Daniel J. Sall¹, Sarah M. Smith¹, Nickolay Y. Chirgadze¹, Christopher L. Cioffi², Y. Y. Cheung², Trelia J. Craft¹, Ronald S. Foster¹, Larry L. Froelich¹, Peter R. Guzzo², Ming M. Hsia², John W. Liebeschuetz³, Valentine J. Klimkowski¹, Jeffrey A. Kyle¹, Michael J. Mayer², Donetta S. Gifford-Moore¹, Christopher W. Murray³, Jinhong Pan², John E. Reilly², Jeffrey K. Smallwood¹, Gerald F. Smith¹, Richard D. Towner¹, and Stephen C. Young³. (1) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, (2) Albany Molecular Research Inc, (3) Tularik Ltd

As part of our overall effort to investigate the non-aryl glycine series of fXa inhibitors, we have explored the incorporation of heteroatoms into the side chain of the amino acid, as exemplified by (1). Typically the amino acid side chain binds in the lipophilic disulfide pocket of fXa, thus the addition of polar functional groups can have a detrimental effect on enzyme affinity. However, this decrease in binding affinity can be compensated by reduced non-specific interactions with plasma constituents, ultimately resulting in increased anticoagulant potency. In this presentation, we will disclose the synthesis and binding affinity SAR of this class of fXa inhibitors, as well as the anticoagulant profiles of selected compounds.



255.

SBDD OF NOVEL FXA INHIBITORS: USING THE CRYSTAL STRUCTURES OF HUMAN FXA COMPLEXED WITH OUR NOVEL INHIBITORS AND NEW PHARMACOPHORE. Tomokazu Matsue, Ikuya Shiromizu, Hidemitsu Nishida, Takafumi Mukaihira, Fumihiko Saitoh, Yoshitaka Hosaka, Hideaki Morishita, Hidenori Mochizuki, and Shuhei Ohnishi, Research Center, Mochida Pharmaceutical Co., Ltd, 722, Jimba-Aza-Uenohara, Gotemba 412-8524, Japan, Fax: +81-550-89-0945, matsusue@mochida.co.jp

The crystal structures of M55532 and 10 derivatives that are prototype FXa inhibitors in a complex with human FXa were determined by us and registered with PDB in Mar-2001. In this conference, we are to discuss the binding mode and method of SBDD in more detail. Also, we will refer to a new pharmacophore, derived from co-crystal structures of our compounds, capable of providing information useful in identifying or designing the orally bioavailable FXa inhibitor. In our analysis, as M55532 has a rigid conformation (N,O-spiro acetal scaffold) and is so suitable for this pharmacophore to have the potent FXa inhibitory activity.

256.

SWITCHING THE CONFIGURATION FROM L TO D OF P1' SUBSTITUENTS IS INCREASING INHIBITORY ACTIVITY FOR THROMBIN OF DPHE-PRO-DARG-P1'-CONH2 PEPTIDES. Cristina C. Clement and Manfred Philipp, Chemistry Department, Lehman College, City University of New York, 250 Bedford Park Blvd West, Bronx, New York City, NY 10468, cclement_us@yahoo.com

A structure-activity relationship (SAR) for reversible inhibitory activity toward thrombin of tetrapeptides from series DPhe-Pro-DArg-P1'-CONH2 is reported. The P1' position was varied with D and L amino acids. The significant differences between the Kis of tetrapeptides from the series DPhe-Pro-DArg-P1'-CONH2 (varying from 2 to 50 fold) suggest that the interaction between the amino acid at P1' position and the S1' pocket in thrombin is very specific and requires small and polar amino-acids in P1'. There is a significant change in the affinity for interaction with thrombin as the configuration for the same amino-acid in P1' position is changing from L to D. Specifically, a switch from L-Thr into D-Thr in P1' was correlated with a 13 fold increase in the inhibitory activity. Similarly, a switch from L-Ala to D-Ala in P1' was increasing the affinity 8 fold. These differences in the binding affinities upon switching from L into D for amino-acids in P1' were confirmed both kinetically and through isothermal titration calorimetry (ITC) data (e.g. the heat released upon binding to thrombin for peptides with L-Ala in P1' is lower (1.2 kcal/mole of injectant) than the heat released during the titration of the same peptide into thrombin but with D-Ala in P1' (6.5 kcal/mole of injectant). The structural basis for this favorable switch in the affinity is further investigated through molecular modeling experiments

257.

DEVELOPMENT OF POTENT INHIBITORS OF THROMBIN DERIVED BY LINKING OF FRAGMENTS DETECTED BY SCREENING USING X-RAY CRYSTALLOGRAPHY. Miles S. Congreve¹, Gianni Chessari¹, Deborah J. Davis¹, Steven Howard¹, Rob L. M. Van Montfort¹, Christopher W. Murray¹, Nigel Howard², and Chris Abell². (1) Astex Technology, 436 Cambridge Science Park, Milton Road, Cambridge CB4 0QA, United Kingdom, Fax: +44-1223-226201, m.congreve@astex-technology.com, (2) The University Chemical Laboratory

A set of fragments (100-300MWt), selected by virtual screening, were soaked into crystals of thrombin and analyzed by x-ray crystallography. A number of hits were identified by interpretation of ligand electron density in the active site region. The majority of these hits bound in the S1 specificity pocket and representative structures and binding modes are presented. In addition, hits were also identified that bound outside of the S1 pocket in an unprecedented way for small molecules binding to thrombin. Structure-based design ap-

proaches are described that enabled such fragments to be modified to increase potency and then to be linked with one of the S1 binding fragments. This led to identification of a potent and novel series of non-amidine inhibitors with potential value as anti-thrombotic agents.

258.

DISCOVERY AND OPTIMIZATION OF 4-BIPHENYL SULFONYL THIOPHENE AMIDINES AS A NOVEL CLASS OF POTENT AND SELECTIVE COMPLEMENT C1S INHIBITORS. Ehab M. Khalil¹, Nalin Subasinghe¹, Jeremy M. Travins¹, Farah Ali¹, Heather Rae Hufnagel¹, Shelley K. Ballentine¹, Micheal D. Gaul¹, Richard M. Soll¹, Maxwell D. Cummings², Renee L. DesJarlais², Carl Crysler³, and Roger Bone³. (1) Medicinal Chemistry, 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Dr, Suite 104, Exton, PA 19341, ekhalil@prdus.jnj.com, (2) Computational Chemistry, 3-Dimensional Pharmaceuticals, Inc, (3) Discovery Biology, 3-Dimensional Pharmaceuticals, Inc

Complement fixation is a critical and highly regulated component of innate immunity, providing the host with an initial line of defense against infection. Aberrant activation of complement, however, is implicated in a number of disorders including ischemia-reperfusion injury, hereditary angioedema, and hyperacute rejection in organ transplantation. The serine protease C1s is one of the first enzymes in the classical complement pathway and consequently it has been recognized as a novel target for small-molecule pharmacological intervention in a number of complement-mediated disease areas. Starting from an early thiophene amidine lead, we have developed the 4-biphenyl sulfonyl thiophene amidines as a highly potent and selective class of C1s inhibitors. The synthesis, SAR, and selectivity of this class of C1s inhibitors will be described.

259.

SYNTHESIS AND SAR OF SOME ARYL- AND HETEROARYLSULFONYL THIOPHENEAMIDINES AS INHIBITORS OF THE COMPLEMENT SERINE PROTEASE C1S. Jeremy M. Travins¹, Nalin L. Subasinghe¹, Ehab M. Khalil¹, Farah Ali¹, Joan Gushue¹, Heather Rae Hufnagel¹, Shelley K. Ballentine¹, Hui Huang¹, Michael D. Gaul¹, Roger Bone², Richard M. Soll¹, Carl Crysler², Renee L. DesJarlais³, and Maxwell D. Cummings³. (1) Medicinal Chemistry, 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Drive, Exton, PA 19341, jtravins@prdus.jnj.com, (2) Discovery Biology, 3-Dimensional Pharmaceuticals, Inc, (3) Computational Chemistry, 3-Dimensional Pharmaceuticals, Inc

The complement cascade is a major component of the innate immune system and is involved in the destruction of invading microorganisms and the clearance of immune complexes. Overactivation of the classical pathway of complement has been implicated in humorally-mediated graft rejection, hereditary angioedema, vascular leak syndrome, and ischemia reperfusion injury. We have targeted the serine protease C1s, an enzyme specific to the classical pathway of complement, for small-molecule pharmacological intervention. Based on a simple phenylsulfonylthiopheneamidine lead, we have synthesized several novel thiopheneamidines to explore the SAR and improve the physicochemical properties of this class of C1s inhibitors. The synthesis and SAR of such compounds will be described.

260.

DESIGN, SYNTHESIS AND SAR OF SUBSTITUTED PYRANOINDOLES AS INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) USEFUL IN THE TREATMENT OF ATHEROTHROMBOSIS AND FIBRINOLYTIC DISORDERS. David Z. Li¹, Hassan Elokda¹, Geraldine McFarlane¹, and David L. Crandall². (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, LIZ2@wyeth.com, (2) Cardiovascular and Metabolic Diseases Research, Wyeth Research

High levels of plasminogen activator inhibitor-1 (PAI-1) have been associated with impaired fibrinolysis. PAI-1 has been implicated in a variety of chronic and acute diseases originating from fibrinolytic impairment such as deep vein thrombosis, coronary heart disease, pulmonary embolism, polycystic ovary syndrome, etc. Accordingly, agents that inhibit PAI-1 would be of utility in treating these disorders. We have developed a series of substituted indole carboxylic acid derivatives as PAI-1 inhibitors. The lead compound in the series, PAI-039 (1) is efficacious in the rat thrombosis model when given orally at 1 mpk. Current work is focused on expanding the SAR of the indole series. Our goal is to discover potent and selective novel PAI-1 inhibitors. A series of pyranoindoles was explored. Compound (2) inhibited PAI-1 with an IC50 of 2.28

μM and was shown to have *in vivo* efficacy in the thrombosis model. Design, synthesis and SAR of this class of compounds as well as *in vivo* efficacy of the lead compound (2) will be presented.



261.

DESIGN, SYNTHESIS AND SAR ANALYSIS OF ANTHRAX LETHAL FACTOR PROTEASE INHIBITORS. *Cho Tang¹, Ondrej Simo¹, Melissa Nagata¹, Guan sheng Jiao¹, Sean O'Malley¹, Mark Goldman², Lynne Cregar², Dominique Nguyen², and Thomas Hemscheidt³.* (1) Department of Chemistry, Hawaii Biotech, Inc, 99-193 Aiea Heights Drive, #200, Aiea, HI 96701, Fax: 808-792-1348, ctang@hibiotech.com, osimo@hibiotech.com, (2) Department of Drug Discovery, Hawaii Biotech, Inc, (3) Department of Chemistry, University of Hawaii at Manoa

Cationic compound HB-165485 was discovered at Hawaii Biotech as potent inhibitor of anthrax lethal factor protease. Pre-exposure of mice to HB-165485 significantly delayed time-to-death following lethal toxin administration. The design and synthesis of a series of HB-165485 related analogs will be presented. The SAR analysis of these compounds will also be discussed.

262.

DEVELOPMENT OF A NOVEL INHIBITOR OF DPP-IV USING A BYPRODUCT AS THE LEAD COMPOUND. *Kazunobu Kira¹, Richard.S.J. Clark¹, Hironori Ikuta¹, Seiji Yoshikawa², Nobuyuki Yasuda¹, Kazuto Yamazaki¹, Tadashi Nagakura¹, Osamu Takenaka³, and Taisuke Uehara⁴.* (1) Frontier Research Laboratory, Eisai Co.Ltd, Tokodai 5-1-3, Tsukuba 300-2635, Japan, Fax: 298-47-8489, k-kira@hhc.eisai.co.jp, (2) Process Chemistry Laboratories: Section 2, Eisai Co.Ltd, (3) Department of Drug Metabolism and Pharmacokinetics, Eisai Co.Ltd, (4) Structural Analysis. Analytical Research Laboratories, Eisai Co. Ltd

GLP-1 is an incretin released from L cells in the gut in response to the oral ingestion of nutrients. It has multiple actions contributing to normalization of elevated blood glucose levels, but is rapidly processed by dipeptidyl peptidase IV (DPP-IV), leading to an extremely short active half-life. Inhibition of DPP-IV is therefore expected to be beneficial in the treatment of diabetes. As part of an effort to develop novel inhibitors of DPP-IV, a systematic study using a byproduct (produced during the large scale synthesis of ER-260891) as a lead compound has been performed and resulted in some promising compounds. It should be noted that a byproduct (only 0.34 % yield) changed into a powerful lead compound.

263.

DIPEPTIDYL PEPTIDASE IV INHIBITORS DERIVED FROM β-AMINOACYLPYPERIDINES BEARING A FUSED THIAZOLE, OXAZOLE, ISOXAZOLE, OR PYRAZOLE. *Wallace T. Ashton¹, Rosemary M. Sisco¹, Hong Dong¹, Kathryn A. Lyons¹, Huaibing He¹, George A. Doss², Barbara Leiting³, Reshma A. Patel³, Joseph K. Wu³, Frank Marsilio³, Nancy A. Thornberry³, and Ann E. Weber¹.* (1) Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-5350, wally_ashton@merck.com, (2) Department of Preclinical Drug Metabolism, Merck Research Laboratories, (3) Department of Metabolic Disorders, Merck Research Laboratories

One of the most attractive current targets for the treatment of type 2 diabetes is glucagon-like peptide 1 (GLP-1), an incretin hormone that stimulates glucose-dependent insulin biosynthesis and secretion. However, GLP-1 itself lacks oral activity and is rapidly degraded by dipeptidyl peptidase IV (DP-IV). Inhibition of DP-IV could promote sustained elevation of endogenous GLP-1 levels, thereby improving glucose tolerance with minimal risk of hypoglycemia. Previous work from these laboratories has described novel β-aminoacyl derivatives of triazolol- or imidazolol-fused piperazines as potent, selective, orally bioavailable inhibitors of DP-IV. We now report the synthesis and biological evaluation of analogous β-aminoacylpiperidines bearing fused five-membered rings (thiazoles, oxazoles, isoxazoles, and pyrazoles). The effects of regioisomerism and substitution were

investigated, resulting in the identification of some potent and relatively selective DP-IV inhibitors. In particular, one analog (DP-IV IC₅₀ = 26 nM) exhibited good oral bioavailability (F = 55%) and acceptable half-life (t_{1/2} = 3.3 h) in the rat.

264.

FUSED TRICYCLIC PIPERAZINE AMIDES DERIVATIVES AS NOVEL DIPEPTIDYL PEPTIDASE-IV INHIBITORS. *Anthony Mastracchio¹, Scott D. Edmondson¹, Emma R. Parmee¹, Huaibing He², Barbara Leiting³, Kathryn A. Lyons², Frank Marsilio³, Reshma A. Patel³, Joseph K. Wu³, Matthew J. Wyvratt⁴, Michael H. Fisher⁴, Nancy A. Thornberry³, and Ann E. Weber⁵.* (1) Department of Basic Chemistry, Merck & Co, P.O. Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-5350, anthony_mastracchio@merck.com, (2) Department of Medicinal Chemistry, Merck & Co. Inc, (3) Department of Metabolic Disorders, Merck & Co., Inc, (4) Department of Medicinal Chemistry, Merck and Company, (5) Department of Medicinal Chemistry, Merck & Co., Inc

Dipeptidyl peptidase-IV (DP-IV) is responsible for the rapid processing of incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which plays a role in the biosynthesis and secretion of insulin. Inhibition of DP-IV increases circulating levels of GLP-1 and GIP leading to higher blood insulin levels and DP-IV inhibitors have been shown to lower fasting and post-prandial blood glucose levels in humans. Consequently, inhibition of DP-IV is emerging as a new approach for the treatment of type-II diabetes and also offers a number of potential advantages over existing diabetes therapies including a lowered risk of hypoglycemia and the potential for weight loss. Previous research from Merck laboratories led to the discovery of substituted homophenylalanine piperazine amides as potent DP-IV inhibitors. In an effort to improve the *in vitro* and pharmacokinetic profile of this series, derivatives with fused tricyclic piperazines were synthesized. This presentation will describe the synthesis and biological properties of these novel DP-IV inhibitors.

265.

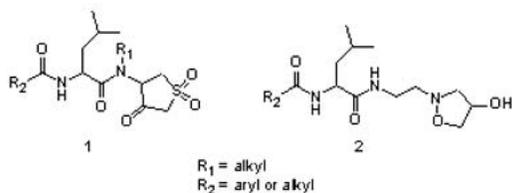
NOVEL PIPERAZINE-SUBSTITUTED, HETEROCYCLIC COMPOUNDS AS SELECTIVE, COMPETITIVE DPP-IV INHIBITORS. *Richard.S.J. Clark¹, Fumiyoshi Matsuura¹, Kazunobu Kira¹, Seiji Yoshikawa², Hironori Ikuta¹, Nobuyuki Yasuda¹, Tadashi Nagakura¹, Kazuto Yamazaki¹, and Osamu Takenaka³.* (1) Frontier Research Laboratory, Eisai Co.Ltd, Tokodai 5-1-3, Tsukuba 300-2635, Japan, Fax: 298-47-8489, r-clark@hhc.eisai.co.jp, (2) Process Chemistry Laboratories: Section 2, Eisai Co.Ltd, (3) Department of Drug Metabolism and Pharmacokinetics, Eisai Co.Ltd

GLP-1 is an incretin released from L cells in the gut in response to the oral ingestion of nutrients. It has multiple actions contributing to normalization of elevated blood glucose levels, but is rapidly processed by dipeptidyl peptidase IV (DPP-IV), leading to an extremely short active half-life. Inhibition of DPP-IV is therefore expected to be beneficial in the treatment of diabetes. A compound identified from HTS of an in-house library was developed into several series of potent and selective DPP-IV competitive inhibitors, leading to the identification of several promising candidates for clinical introduction. This poster will describe the SARs for these compounds, and also outline their biological properties.

266.

PREPARATION AND SAR OF NOVEL SELECTIVE CATHEPSIN S INHIBITORS. *Mark A. Ashwell, Yanbin Liu, Belew Mekonnen, Pierre Roboissen, and Mark Cronin, Medicinal Chemistry, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, yliu@arqule.com*

Proteases are an attractive target for the development of potent, selective and bioavailable small molecule inhibitors. We set out to develop a parallel chemistry strategy to furnish a biased set of protease inhibitors. The cysteine protease family was selected as the target since it is emerging as an important class of proteases with important functions in a variety of human diseases. Amides derived from 4-keto-3-aminosulfolane and 2-(isoxazolidin-2-yl)ethanamine provided templates for a library expansion project which led to the establishment of *in vitro* SAR (1 and 2) and the identification of potent and selective cathepsin S inhibitors.



267.

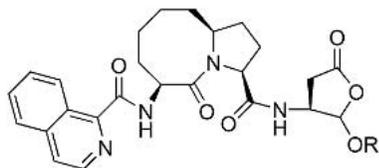
DISCOVERY OF A NOVEL CASPASE INHIBITOR AND PROTECTION OF LIVER DAMAGE IN MOUSE MODELS. *Hye Kyung Chang*¹, *Mijeong Park*², *Junggyu Park*², *Sungsub Kim*¹, and *Yeongsoo Oh*². (1) Drug Discovery, LG Life Science, 104-1 Munji-dong, Yusung-gu, Daejeon, 305-380, South Korea, Fax: 82-42-866-5754, hkjang@lgs.co.kr, (2) Development, LG Life Science

Apoptosis and cell proliferation are well-balanced processes in normal physiological conditions. Excessive apoptosis by the activation of caspase family has been implicated in a number of acute and chronic liver diseases. In this investigation, the efficacy and pharmacological property of a small, irreversible caspase inhibitor LB84318 will be discussed in the mouse liver injury model. In the LPS/GIaN model, LB84318 dramatically reduced or completely blocked elevation of serum ALT level via oral and iv administration. The protective effect of LB84318 was well maintained at least 10-12 hrs. Furthermore, in survival studies, LB84318 treated animals (0.3 mg/kg, single, oral) were all survived, but all control animals died in 8-24 hr. LB84318 was also highly effective in the Fas-model. LB84318 was very safe in preliminary toxicology studies (MTD > 600mg/kg/day). These results indicate that LB84318 is an excellent and safe clinical candidate for the treatment of apoptotic liver diseases.

268.

SYNTHESIS AND DISCOVERY OF PGE-527667, AN ORALLY BIOAVAILABLE CASPASE-1 INHIBITOR. *David L. Soper*, *Steven V. O'Neil*, *Yili Wang*, *Kofi A. Oppong*, *Christopher D. Ellis*, *Michael C. Laufersweiler*, *Thomas P. Demuth Jr.*, *Amy N. Fancher*, *Wei Lu*, *Richard L. Wang*, *William P. Schwecke*, *Charles A. Cruze*, *Maria Buchalova*, *Marina Belkin*, and *John A. Vos*, Procter and Gamble Pharmaceuticals, 8700 Mason-Montgomery Road, Mason, OH 45040, Fax: 513-622-2675, soper.dl@pg.com

Interleukin-1 β converting enzyme (Caspase-1, ICE) is involved in the processing of Pro-IL-1 β to the active cytokine IL-1 β , which has been implicated in a variety of disease states within the inflammation cascade. Inhibition of ICE may have therapeutic value in the treatment of inflammation and degenerative diseases (e.g. osteoarthritis). We report the synthesis and evaluation of a pyrrolo[1,2-a]jzocine 8,5 bicyclic scaffold as a template for reversible ICE inhibitors. The synthesis proceeded through ring closing metathesis to form the 8-membered ring in high yield. The structure activity relationship showed a preference for meta-substituted phenyl or bicyclic aryls. Compounds obtained by the reduction of the olefin formed in the metathesis increased potency. The active form, **PGE-3935199**, gave excellent potency in the enzyme inhibition and THP-1 whole cell assays, IC₅₀ of 0.6 and 54 nM respectively. The PK studies on the prodrug **PGE-527667** showed 30% oral bioavailability with a 1.1 hour half-life.



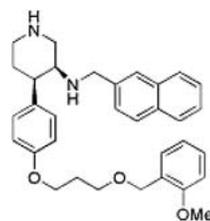
R = H **PGE-3935199**
Et **PGE-527667**

269.

DEVELOPMENT OF NOVEL AMINO-ARYL-PIPERIDINE-BASED RENIN INHIBITORS. *Wayne L. Cody*, *Daniel D. Holsworth*, *Noel A. Powell*, *Mehran Jalaie*, *Erlu Zhang*, *Wei Wang*, *Brian Samas*, *John Bryant*, *Robert Ostroski*, *Michael Ryan*, and *Jeremy J Edmunds*, Michigan Laboratories, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Wayne.Cody@pfizer.com

Recently, non-peptides were identified as potent active site inhibitors of renin. These amino-aryl-piperidines have two stereocenters that exist in a relative trans orientation. Herein, we report the development of a novel series of inhibitors of renin, typified by Compound 1, which has 61 nM affinity for renin and is

characterized by a cis orientation of the two stereocenters and the incorporation of an exocyclic secondary amine. The relative stereochemistry was proven 1H-NMR and X-ray crystallographic studies. We will present the synthetic strategy for Compound 1, the developing SAR and in vivo activity in the double transgenic mouse.

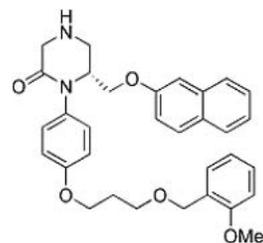


Compound 1
Renin IC₅₀ = 61 nM

270.

DEVELOPMENT OF NOVEL NON-PEPTIDIC KETOPIPERAZINE-BASED RENIN ENZYME ANTAGONISTS. *Daniel D. Holsworth*¹, *Noel A. Powell*¹, *Wayne L. Cody*¹, *Cuiman Cai*¹, *Dennis Downing*¹, *Emma Clay*¹, *Mehran Jalaie*², *Michael Ryan*¹, *John Bryant*¹, *Robert Ostroski*¹, and *Jeremy J Edmunds*¹. (1) Michigan Laboratories, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax: 734-622-3909, daniel.holsworth@pfizer.com, (2) Discovery Technologies, Pfizer Global Research & Development

Recently, we have developed a new class of potent non-peptidic renin enzyme antagonists for the treatment of hypertension. The rationale, synthetic strategy, molecular modeling data and in vivo activity of Compound 1 in the double transgenic mouse model will be presented.

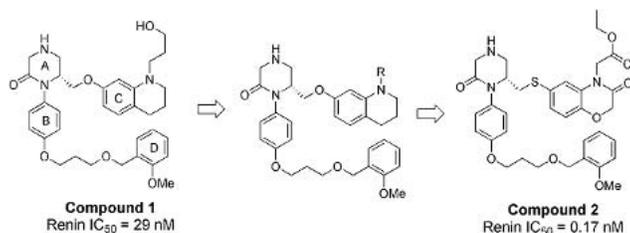


Compound 1
Renin IC₅₀ = 54 nM

271.

KETOPIPERAZINE-BASED RENIN INHIBITORS 2. OPTIMIZATION OF THE "C" RING. *Noel A. Powell*¹, *Daniel D. Holsworth*¹, *Wayne L. Cody*¹, *Xue Min Cheng*¹, *Chitase Lee*¹, *Noe Erasga*¹, *Dennis M. Downing*¹, *Cuiman Cai*¹, *Emma Clay*¹, *Mehran Jalaie*¹, *Erlu Zhang*¹, *John Bryant*¹, *Michael Ryan*¹, *Jeremy J Edmunds*¹, *Tingsheng Li*², *Aparna Kasani*², *Eric Hall*², *Rajandra Subedi*², *Mohammad Rahim*², and *Samarendra Maiti*². (1) Michigan Laboratories, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Wayne.Cody@pfizer.com, (2) Naeja Pharmaceuticals

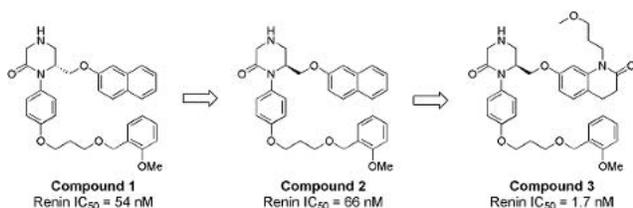
Compound 1 is a potent inhibitor of renin in vivo and in vitro. Herein, we will report a structure-based design approach utilizing X-ray crystallography that has enhanced the potency more than 100-fold resulting in non-peptidic subnanomolar (IC₅₀ = 0.170 nM) inhibitors as exemplified by Compound 2. The developing SAR in this series will be described. We will discuss our current efforts to improve the ADME properties, including solubility, cLogP, half-life in human liver microsomes, and the inhibition of cytochrome P450 isoenzymes.



272.

KETOPIPERAZINE-BASED RENIN INHIBITORS. 3. THE S-ENANTIOMER IS ALSO ACTIVE. *Noel A. Powell¹, Emma Clay¹, Fred L. Ciske¹, Daniel D. Holsworth¹, Chitase Lee¹, Mehran Jalaie², John Bryant¹, Michael Ryan¹, and Jeremy J Edmunds¹.* (1) Michigan Laboratories, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax: 734-622-3909, noel.powell@pfizer.com, (2) Discovery Technologies, Pfizer Global Research & Development

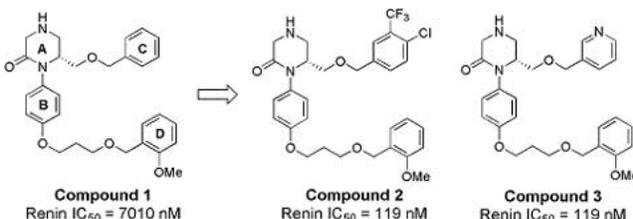
We have recently reported the discovery of a series of ketopiperazine-based inhibitors of renin. These reversible inhibitors have been shown bind in the active site of renin, and may be useful for the treatment of hypertension. This series is typified by Compound **1** which possesses an aryl-ketopiperazine template with a single stereocenter of *R*-configuration, and exhibits a renin IC₅₀ of 54 nM. Herein, we will report our discovery that the enantiomeric ketopiperazine of *S*-configuration, Compound **2**, exhibits equivalent potency. We will describe the binding modes of the enantiomers **1** and **2** as revealed by X-ray crystallography, as well as the SAR surrounding the optimization of potency that led to the discovery of Compound **3**, a potent renin inhibitor.



273.

KETOPIPERAZINE-BASED RENIN INHIBITORS. 4. SAR OF C RING BENZYL ETHERS. *Noel A. Powell¹, Emma Clay¹, Daniel D. Holsworth¹, Mehran Jalaie², John Bryant¹, Michael Ryan¹, Tingsheng Li³, Arparna Karsana³, Samarendra Maiti³, and Jeremy J Edmunds¹.* (1) Michigan Laboratories, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax: 734-622-3909, noel.powell@pfizer.com, (2) Discovery Technologies, Pfizer Global Research & Development, (3) Naaja Pharmaceuticals

We have recently reported the discovery of a series of ketopiperazine-based inhibitors of renin. These reversible inhibitors have been shown to bind in the active site of renin, and may be useful for the treatment of hypertension. Herein, we wish to disclose our SAR efforts surrounding the use of benzyl ethers as "C" ring motifs, e.g. Compound **1**, which was a weak inhibitor of renin with a renin IC₅₀ of 7010 nM. We will describe the optimization of the "C" ring benzyl ether to Compound **2**, which incorporates a 3-trifluoromethyl-3-chlorobenzyl ether and exhibits 59-fold greater renin potency. We will also describe the surprising discovery that introduction of a 3-pyridyl ether resulted in Compound **3**, which also exhibited a renin IC₅₀ = 119 nM. Further SAR around Compound **3**, as well as X-ray crystallographic data, will also be described.



274.

DISCOVERY OF NOVEL HYDANTOINS AS SELECTIVE NON-HYDROXAMATE INHIBITORS OF TNF-ALPHA CONVERTING ENZYME (TACE). *James E. Shepeck II, John L. Gilmore, Anle Yang, Chu Biao Xue, Xiaohua He, Daniel Chen, Maryanne B. Covington, Richard R. Liu, John Giannaras, and James J W. Duan,* Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Route 206 and Provinceline Road, Princeton, NJ 08543, Fax: 619-252-3993, jim.shepeck@bms.com

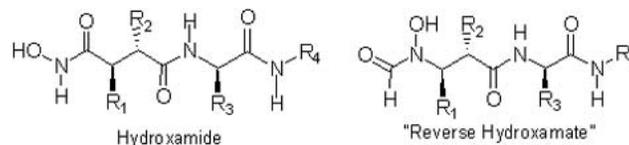
Tumor Necrosis Factor-alpha (TNF-alpha) is a well-established pro-inflammatory cytokine that is involved in numerous autoimmune disorders, notably rheumatoid arthritis, psoriasis, and inflammatory bowel disease. An attractive method of reducing TNF-alpha is by using small molecule inhibitors of the metalloprotease

(TACE) that is responsible for proteolytically cleaving membrane-bound pro-TNF-alpha (26 kDa) to soluble TNF-alpha (17 kDa). The vast majority of TACE (and MMP) inhibitors incorporate a hydroxamic acid that confers potent Ki's by acting as an active site Zn ligand. We report the discovery of a series of inhibitors which have replaced the ubiquitous hydroxamate with a hydantoin and exhibit high potency and selectivity for TACE.

275.

REVERSE HYDROXAMATE DERIVATIVES AS TNF-α CONVERTASE INHIBITORS. *Robert W. Wieth¹, Marc W. Andersen², Robert C. Andrews², J. David Becherer³, Dulce G. Bubacz², D. Mark Bickett³, Joseph H. Chan², James G. Conway³, David J. Cowan², Micheal D. Gaul⁴, Millard H. Lambert², M. Anthony Leesnitzer³, Darryl L. McDougald², Justin L. Mitchell³, Marcia L. Moss³, David L. Musso², Michael H Rabinowitz⁵, Michele C. Rizzolio³, Timothy K. Tippin³, Janet R. Warner³, and L. Graham Whitesell³.* (1) High Throughput Chemistry, GlaxoSmithKline, P O Box 13398, 5 Moore Drive, Research Triangle Park, NC 27709-3398, Fax: 919-315-0430, Robert.W.Wieth@gsk.com, (2) Department of Medicinal Chemistry, GlaxoSmithKline, (3) Department of Molecular Biochemistry, GlaxoSmithKline, (4) 3-Dimensional Pharmaceuticals Inc, (5) Department of Medicinal Chemistry, R.W. Johnson Pharmaceutical Research Institute

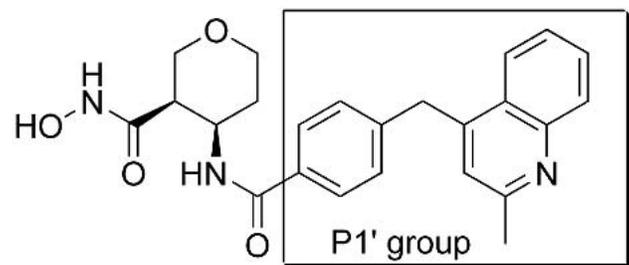
Hydroxamides such as Marimastat have been investigated as TNFα convertase enzyme (TACE) inhibitors for the last decade for use in arthritis and cancer treatment. We wished to examine the *N*-formyl-*N*-hydroxyl amides (reverse hydroxamates) as alternatives to the standard hydroxamides and see what differences they might have in enzyme inhibition as well as pharmacodynamics and metabolism. A series of reverse hydroxamates was synthesized, with the best examples showing both potent enzyme inhibition, as well as good selectivity to other metalloprotease enzymes. The *in vivo* activity varied widely, mostly based on R1 and R2 substitution pattern, with some compounds quite active in cellular assays, but most of the compounds still had liabilities in their oral bioavailability and half-life.



276.

TACE INHIBITORS: DISCOVERY OF 4-(2-METHYLQUINOLIN-4-YLMETHYL)PHENYL AS AN EFFECTIVE P1' GROUP. *Xiao Tao Chen, Ronald L. Corbett, Bahman Ghavimi, Chu Biao Xue, Zeld R. Wasserman, Rui Qin Liu, Maryanne B. Covington, Mingxin Qian, Krishna G. Vaddi, David D. Christ, Karl D. Hardman, Maria D. Ribadeneira, James M. Trzaskos, Robert C. Newton, James J. W. Duan, and Carl P. Decicco,* Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O.Box 4000, Princeton, NJ 08543-4000, xiao-tao.chen@bms.com

This presentation will describe our continuing efforts in search for potent and selective inhibitors of tumor necrosis factor-alpha converting enzyme (TACE). Modification on the P1' group in the beta-amino hydroxamic acid series led to discovery of 4-(2-methylquinolin-4-ylmethyl)phenyl as another effective P1' group. The synthesis and the structure-activity relationship of this series will be presented.



277.

REVERSE HYDROXAMATE-BASED SELECTIVE TACE INHIBITORS. *Masanao Shimano*¹, *Noriyuki Kamei*¹, *Tomohiro Tanaka*¹, *Kentaro Kawai*¹, *Kyosei Miyawaki*¹, *Akihiko Okuyama*¹, *Yoshiko Murakami*², *Yoshio Arakawa*², *Makoto Haino*², and *Tatsuhiko Harada*². (1) Department of Chemistry, Kaken Pharmaceutical Co., Ltd, 14, Shinomiya, Minamikawara-cho, Yamashina-ku, Kyoto 607-8042, Japan, Fax: 81-75-594-0790, shimano_masanao@kaken.co.jp, (2) Department of Drug Discovery Research, Kaken Pharmaceutical Co., Ltd

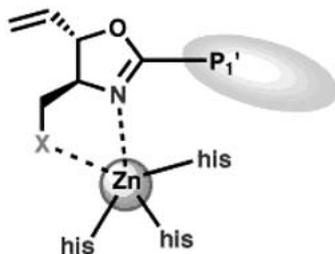
TNF- α converting enzyme (TACE) is essential to process TNF- α from the membrane-bound form into the soluble form. Therefore TACE inhibitors may be one of the attractive targets in the anti-TNF- α therapy. TACE is structurally categorized into the ADAM (a disintegrin and a metalloprotease) family, but its catalytic site is quite similar to that of matrix metalloproteinases (MMPs). MMPs are involved in the degradation and remodeling of connective tissues, and about 20 MMPs have been uncovered so far. Since the complete clarification of each MMP's functions leaves tremendous efforts still to be done and some broad-spectrum and partially selective MMP inhibitors have been reported to cause musculoskeletal side effects in clinical trials, we have tried to seek selective TACE inhibitors over MMPs to preclude any unexpected side effects caused by the inhibition of the MMPs. We will present the design, syntheses and structure-activity relationships of reverse hydroxamate-based selective TACE inhibitors.

278.

SYNTHESIS AND EVALUATION OF NOVEL HETEROCYCLIC MMP INHIBITORS.

Gregory R. Cook, *Wei Xu*, and *E. Manivannan*, Center for Protease Research, Department of Chemistry, North Dakota State University, Ladd Hall, Fargo, ND 58105, Fax: 701-231-8831, gregory.cook@ndsu.nodak.edu, wei.xu@ndsu.nodak.edu

The matrix metalloproteinases (MMPs) are a class of proteolytic enzymes responsible for the remodelling of extracellular tissues. There are over 25 distinct MMPs which have been identified and they are ubiquitous in biological systems. Because of their activity of degrading tissues, the MMPs are highly regulated under normal conditions. Unusual levels of various MMPs have been observed in a number of disease states including alzheimers, arthritis, multiple sclerosis, cancer growth and metastasis, damage cascades following stroke, among others. Thus, the ability to regulate MMPs may have a significant impact as therapeutic treatments for many ailments. We have obtained significant preliminary results on the efficacy of oxazoline-based compounds for the inhibition of the class of MMPs known as the gelatinases, which are one of the main targets for cancer chemotherapy.



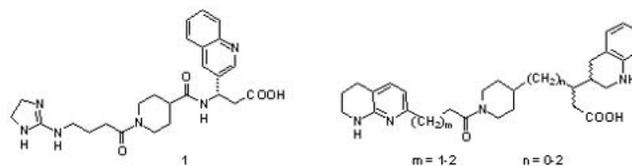
279.

1,2,3,4-TETRAHYDROQUINOLINES: POTENT, ORALLY BIOAVAILABLE

$\alpha_V\beta_3/\alpha_V\beta_5$ INTEGRIN ANTAGONISTS. *Shyamali Ghosh*¹, *William A. Kinney*¹, *Bart De Corte*¹, *Li Liu*¹, *Jef C. Proost*¹, *Andrew S. Thompson*², *Ian Chen*², *Reiko Kawahama*², *Rosemary Santulli*¹, *Robert Tuman*¹, *Robert A. Gallema*¹, *Dana L. Johnson*¹, *Bruce P. Damiano*¹, and *Bruce E. Maryanoff*¹. (1) Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, P.O. Box 0776, Spring House, PA 19477, Fax: 215-628-4985, sghosh1@prdu.jnj.com, (2) J-Star Research, Inc

In exploring for vitronectin receptor ($\alpha_V\beta_3/\alpha_V\beta_5$) antagonists as potential treatments for cancer, arthritis, osteoporosis, and diabetic retinopathy, we identified a new tetrahydroquinoline (THQ) series. This THQ series has good potency and improved oral bioavailability as compared to the corresponding quinoline compounds. Lead compound 1 was modified to increase its lipophilic character and decrease its basicity. The amide bond was exchanged with a carbon-carbon bond and the aminoimidazoline group was replaced with a tetrahydronaphthridine. Throughout these changes, although potency was

maintained, no improvement in oral bioavailability was observed. However, when the quinoline was selectively reduced to the 1,2,3,4-THQ we obtained a combination of good potency and good oral bioavailability. Synthetic chemistry, the optimization of biological activity, and the separation of 1,2,3,4-THQ isomers will be discussed.



280.

IN VITRO AND IN VIVO EVALUATION OF A KETONE-CONTAINING $\alpha_V\beta_3$

INTEGRIN ANTAGONIST FOR THE TREATMENT FOR OSTEOPOROSIS. *Robert*

Meissner, *James J. Perkins*, *Amy E. Zartman*, *Le T. Duong*, *John E. Fisher*, *Carmen Fernandez-Metzler*, *Michael A. Gentile*, *Yuan Meng*, *George D. Hartman*, *Donald B. Kimmel*, *Chih Tai Leu*, *Kara Merkle*, *Rose M. Nagy*, *Brenda L. Pennypacker*, *Thomayant Prueksaritanont*, *Gregg A. Wesolowski*, *Gideon A. Rodan*, *Sevgi B. Rodan*, and *Mark E. Duggan*, Departments of Medicinal Chemistry, Bone Biology and Endocrinology, Drug Metabolism, and Pharmacology, Merck Research Laboratories, West Point, PA 19486, Fax: 215-652-7310, robert_meissner@merck.com

The vitronectin receptor $\alpha_V\beta_3$ is a member of the integrin family and is highly expressed in osteoclasts, cells that are responsible for the resorption of bone. Antibodies to $\alpha_V\beta_3$ and the peptide echistatin have been shown to inhibit bone resorption *in vitro* and *in vivo*. More recently, small-molecule mimetics of the RGD amino acid triad have been identified with similar activities.

The design, synthesis, and biological evaluation of a novel class of ketone-containing $\alpha_V\beta_3$ antagonists will be described. The evolution of this class from amide precursors will be examined, as will the effect of chain substitution on potency, physical properties and pharmacokinetic profile. An antagonist from this series will be described that is a candidate for clinical evaluation as a treatment for osteoporosis.

281.

NON-PEPTIDIC $\alpha_V\beta_3$ ANTAGONIST CONTAINING INDOL-1-YL PROPIONIC

ACIDS. *Joan Gushue*¹, *Kristi Leonard*¹, *Wenxi Pan*¹, *Beth Anaclerio*¹, *Zihong*

*Guo*¹, *Renee L. DesJarlais*², *Jennifer Lattanze*³, *Crystler Carl*³, *Juan Jose Marugan*¹, *Carl Manthey*¹, *Bruce Tomczuk*¹, *Tianbao Lu*¹, *Tom Markotan*¹, *Marge Chaikin*³, *Robert Donatelli*³, *Norman Hubert*⁴, *Stephen Eisennagel*⁴, *Malini Desgupta*⁴, and *Harvey Fries*⁴. (1) Medicinal Chemistry, 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Drive, Suite 104, Exton, PA 19341, (2) Computational Chemistry, 3-Dimensional Pharmaceuticals, (3) Discovery Biology, 3-Dimensional Pharmaceuticals, (4) Analytical Chemistry and Pharmacokinetics, 3-Dimensional Pharmaceuticals

We describe the synthesis and structure/activity relationship of RGD mimetics that are potent inhibitors of the integrin $\alpha_V\beta_3$. Indol-1-yl propionic acids containing a variety of basic moieties at the 5-position, as well as substitutions alpha and beta to the carboxy terminus were synthesized and evaluated.

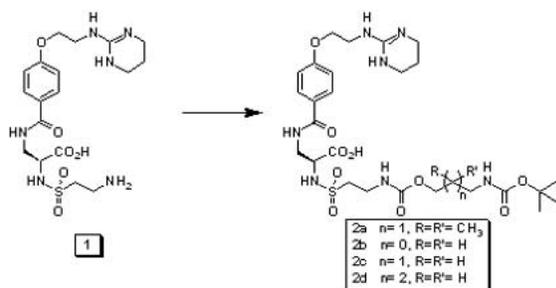
282.

SECOND GENERATION $\alpha_V\beta_3$ INTEGRIN ANTAGONISTS. *Narasimhan Danthi*¹,

*Christopher A. Burnett*¹, *Jianwu Xie*¹, *Zhimin Shen*², and *King C. P. Li*¹. (1) Molecular Imaging Laboratory, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, ndanthi@cc.nih.gov, (2) Vaccine Research Center, National Institute of Allergy and Infectious Diseases

Integrin $\alpha_V\beta_3$ is a heterodimeric membrane-spanning cellular receptor protein that has been implicated in the formation of new blood vessels (angiogenesis) and tissue remodeling in major diseases such as osteoporosis, rheumatoid arthritis, macular degeneration, and cancer. The $\alpha_V\beta_3$ integrin is a widely-recognized target for the development of imaging and therapeutic agents of these diseases. Here, we report the synthesis and *in vitro* binding affinity of a series of aliphatic carbamate derivatives prepared from our first generation $\alpha_V\beta_3$ -selective integrin antagonist 1. All four second generation compounds (2a-d) reported here have increased binding affinity to $\alpha_V\beta_3$ when compared to our first generation compound in the cell adhesion assays. The presence of

latent synthetic handles renders **2a-d** with enhanced potential for angiogenic targeting systems which can be used both for *in vivo* imaging and therapy of many diseases, particularly cancer.

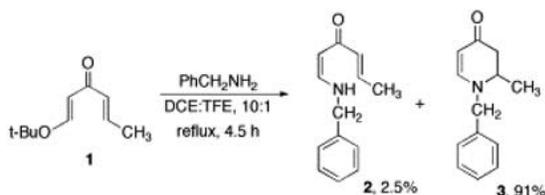


283. NOVEL MICROWAVE ASSISTED SYNTHESIS OF N-HYDROXY, AND N-METHOXY IMIDES AS POTENTIAL ANTICANCER AND ANTIDEPRESSANT AGENTS. *Yousef M. Hijji and Ellis Benjamin, Department of Chemistry, Morgan State University, 1700 E. Cold Spring Lane, Baltimore, MD 21251, Fax: 443-885-8286, yhiiji@morgan.edu, ellis@chemist.com*

A common functionality found in many antidepressants, anticonvulsants, and HIV pharmaceuticals is the imide moiety. Several rapid high-yield microwave techniques for the synthesis of unsubstituted, N-hydroxy, and N-methoxy imides are presented here. Two novel microwave techniques for the synthesis of unsubstituted cyclic imides was established using cyclic anhydrides, ammonium chloride, with DMAP (catalytic) (69 – 90 %) yield, and cyclic anhydrides with ammonium acetate (59 – 100 %) yield. A second synthetic technique using cyclic anhydrides with methoxylamine hydrochloride and hydroxylamine hydrochloride provided the imides in 61 – 99 percent yield. A direct synthesis of thalidomide accomplished in a two-step one-pot synthesis using DMAP, NH₄Cl, Phthalic Anhydride, and Glutamic Acid in a conventional microwave for 6 minutes 30 seconds (52 %).

284. SYNTHESIS OF DIHYDROPYRIDONES. *Michael Harmata and Dong Reyoul Lee, Department of Chemistry, University of Missouri-Columbia, 601 S. College Avenue, Columbia, MO 65211, Fax: 573-882-2754, harmatam@missouri.edu, drlee55@hotmail.com*

The reaction of primary amines with dienones such as **1** results in the formation of dihydropyridones in high yields. Various aspects of this reaction will be presented, including the synthesis of dienones using the retro-Nazarov reaction.



285. AUTOMATING TLC TO FLASH PURIFICATION GRADIENT METHODS CONTAINING POLAR SOLVENTS. *Jack Liu, Sjaan K. Armentrout, and Peter Rahn, Biotage, Inc, 1725 Discovery Drive, Charlottesville, VA 22911, Jliu@biotage.com*

In the microwave assisted reductive amination synthesis with silica-cyanoborohydride, the reaction mixture was monitored via TLC using dichloromethane and methanol solvent system. Purification of the products using Flash chromatography with the same solvent mixture was less than ideal. This work demonstrates the solution to non-reproducible separations using a new algorithm utilized to generate the gradient separation conditions for Flash chromatography by entering the TLC retention and solvent composition data even when polar solvents are required. The new Flash system's algorithm quickly and conveniently produces a suitable gradient program that separates the synthesis products based on the original TLC retention data. This poster illustrates how the Flash system utilizes this TLC data to automatically separate the products using an appropriate gradient method. In particular, successful purifications of

the reductive amination compounds with methanol/dichloromethane gradients based on original TLC data will be shown. Several other examples of this new technology are demonstrated covering a broad range of differences in retention factors and solvent systems.

286. INCREASING PURIFICATION THROUGHPUT USING A NEW AUTOMATED FLASH CHROMATOGRAPHIC SYSTEM. *Jack Liu and Peter Rahn, Discovery Chemistry Group US, Biotage, P.O. Box 8006, Charlottesville, VA 22906, Fax: 434-979-4743, Jliu@biotage.com*

Purification throughput is limited when using traditional flash chromatographic systems. An array of substituted ureas is synthesized, and purification optimization and high sample throughput are emphasized in this study. Enhancement of purification throughput is addressed in this paper by utilizing a new automated flash chromatographic system. Results of this study show that the purification parameters and sample multiplicity are optimized at system level. The purification of the small library containing various ureas demonstrates that an optimized purification method can be automatically achieved with this new purification system solely based on the retention factors from thin-layer chromatography (TLC). Using the new flash purification system, sample throughput is significantly improved when compared to a single-column system since each sample required less than fifteen minutes to purify using the automated, optimized elution method. No user intervention was required when switching between various solvents and samples. In addition, the system significantly simplifies the scale-up process as shown when purifying ureas in the mg to gram range.

287. MINIMIZING SOLVENT IMPACT ON PURIFICATION OF NITROGEN-CONTAINING COMPOUNDS. *Jack Liu and Peter Rahn, Discovery Chemistry Group US, Biotage, P.O. Box 8006, Charlottesville, VA 22906, Fax: 434-979-4743, Jliu@biotage.com*

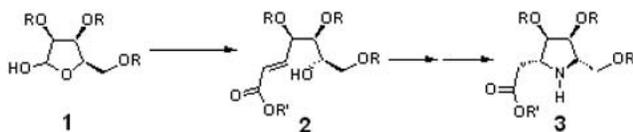
This paper evaluates the impact incompatible solvents have upon normal-phase chromatography purification. Incompatible solvents encountered in this study are typically hard to remove prior to purification by evaporation including very polar solvents such as DMF and DMSO having high boiling-points, or low-boiling-point alcohols that cause the compounds not to retain on the normal phase column. Various compounds including amides, amines and carbamates are synthesized using microwave and traditional synthesis techniques. The sample's solvent volume effect on the purification is also evaluated. Sample pre-treatment and loading techniques are investigated to minimize the solvent's impact on the purification process. Higher resolution is achieved when the sample is 'dry' loaded. To maximize performance and resolution of the flash column the sample mass and volume overloading effects are also discussed. Methods developed in this study illustrate techniques that simplify post-reaction workup procedures for chemists.

288. WITHDRAWN.

289. THE INTRAMOLECULAR MICHAEL ADDITION AS A ROUTE TO FIVE-MEMBERED IMINOCYCLITOLS. *Robert M. Moriarty, Department of Chemistry, University of Illinois, 845 W Taylor St, Fax: 312-996-0431, and Harpreet Kaur, Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor St., Room # 4500, Fax: 312-996-0431, harpreet@uic.edu*

Iminocyclitols are the compounds of keen interest in the area of cancer, viral diseases such as HIV and Hepatitis, etc. Because of their role as glycosidase inhibitors, they have important applications in a variety of diseases involving

carbohydrate processing. As a consequence of these medicinal chemical applications, a number of synthetic routes have been published. Because of our need for high substituted compounds in this series, we now report a novel and versatile synthesis for which the key step is an intramolecular Michael addition. The stereochemistry and mechanistic pathway for the formation of 3 will be presented.



290. SOLUBILITY STUDIES OF AMINE SALTS: DMSO VS. PH 7 BUFFER AS STOCK SOLUTIONS. Paige E. Mahaney¹, Larry M. Mallis², Scott Brecker², Chris Petucci², Gary Stack³, G. E. Morris Husbands³, and Eugene J. Trybulski¹. (1) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, mahanep@wyeth.com, (2) Discovery Analytical Chemistry - Chemical Technologies, Chemical and Screening Sciences, Wyeth Research, Collegeville, (3) Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, Princeton

DMSO is the preferred stock solvent for drug discovery due to its ability to dissolve a wide variety of organic molecules at high concentration, its low volatility, and its convenience for long-term storage. Studies were carried out to evaluate the use of DMSO as a stock solvent for amine salts. A set of compounds from a CNS program was selected based on diversity and number of counter-ions (n = 1, 2) and functional group representation. Compound solubility at 10 mM in DMSO was compared to compound solubility at 10 mM in pH 7 buffer solution. Additionally, to assess whether solubility and stability of the compounds could be maintained in buffer after freeze/thaw conditions, the plates were frozen for 2 weeks at -5 °C, thawed and retested for solubility as well as for compound stability. All solubility measurements were conducted via UV methods with the PSR4s Solubility Analyzer from plon® relative to external standards, and all stability determinations were conducted using LC/UV/MS methods.

The results indicate that 37% (133/360) of the amine salts tested and 72% (75/104) of the piperazine salts tested exhibited low apparent aqueous solubility when DMSO was used as the stock solvent. In contrast, when pH 7 buffer was used as the stock solvent, 68% of the compounds showed improved solubility, 25% showed equivalent solubility, and 7% had decreased solubility when compared to DMSO. After one freeze/thaw cycle, 95% (41/43) of the compounds tested exhibited equivalent or improved solubility when compared to the freshly prepared samples, and 98% (42/43) maintained integrity after freeze/thaw.

The results of this study suggest that amine salts, especially salts of dibasic amine compounds, require careful selection of stock solvents for biological assays.

291. PREDICTION OF INTESTINAL AND BLOOD BRAIN BARRIER PERMEABILITY UTILIZING IMMOBILIZED ARTIFICIAL MEMBRANE CHROMATOGRAPHY. Adeboye Adejare and Ahmed El-Gendy, Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104-4495, Fax: 215-895-1161, a.adejar@usip.edu, a.elgend@usip.edu

Feasibility of using immobilized artificial membrane (IAM) columns for screening permeability of drugs through biological membranes such as intestinal membrane and the blood brain barrier (BBB) was examined. A set of 21 structurally diverse and functionally unrelated compounds was studied by high performance liquid chromatography using IAM column. The aqueous capacity factors (log K_{IAMW}) of the compounds were correlated with their logarithms of octanol/water partition coefficient (log P) and the blood/brain partition coefficient (log BB). Log P and log BB are known as molecular descriptors for intestinal and BBB permeabilities, respectively. Good correlation was obtained between log K_{IAMW} and log P of the compounds (r = 0.956). Log K_{IAMW} values of the compounds also showed an acceptable correlation with log BB (r = 0.767). Inclusion of molecular weight with the log P or log K_{IAMW} data had a negative effect on correlation when the data was re-analyzed vs. log BB values. For a subset of 8

compounds, log K_{IAMW} showed a slightly better correlation with log % of human absorption than did log P. The data indicate that IAM partitioning chromatography is a promising tool for quick and reproducible prediction of membrane permeability of compounds.

292. AEI: NOVEL FURANOCOUMARIN INHIBITORS OF CYP3A4. Cheng Jen¹, Charles J. Kelley², David J. Greenblatt³, Lisa L. von Moltke³, James L. Weemhoff³, Su Xiang Duan³, and Barbara W. LeDuc¹. (1) Division of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, 179 Longwood Avenue, Boston, MA 02115, cheng.jen@students.mcp.edu, (2) School of Arts and Sciences, Massachusetts College of Pharmacy and Health Sciences, (3) Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine

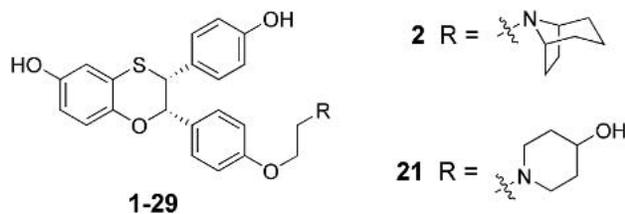
Ingestion of grapefruit juice (GFJ) by patients may increase bioavailability of some CYP3A substrate drugs. Several inhibitory components found in GFJ are furanocoumarins, e.g. 6'-7'-dihydroxybergamottin (DHB). We investigated whether synthetic furanocoumarins would inhibit CYP3A4. Midazolam (50 µM)/triazolam (250 µM) α -/4-hydroxylase activity, and testosterone (250 µM) 6 α -hydroxylase activity were used to illustrate inhibition of CYP3A in human (HLM) or rat (RLM) liver microsomes \pm preincubation with furanocoumarins. HLM midazolam α -hydroxylation was inhibited by (\pm)-DHB (IC₅₀ of 4.7 µM) and bergamottin (IC₅₀ of 10.3 µM). At 2 µM, GF-I-1-7 and GF-I-5 inhibited formation of rat 6 α -hydroxytestosterone 80% and 73%; DHB 2 µM inhibited 18%. In HLM, the IC₅₀ values for inhibition of triazolam α - and 4-hydroxylation by GF-I-1-7 were 0.83 and 1.35 µM, respectively. After preincubation, the IC₅₀ values for inhibition of triazolam α -hydroxylation by GF-I-1-1, GF-I-1-2, and GF-I-1-7 were 0.50, 0.49 and 0.47 µM, respectively. GF-I-1-7 was the most potent inhibitor of human/rat CYP3A.

293. STABILITY LIMITATION ON THE USE OF PHOSPHATE PROMOIETIES WITH RESONANCE-STABILIZED STRUCTURES IN PRODRUG DESIGN. Hanna Remes¹, Jarkko Rautio¹, Antti Mäntylä¹, Tomi Järvinen¹, and Jouko Vepsäläinen². (1) Department of Pharmaceutical Chemistry, University of Kuopio, P.O.Box 1627, Kuopio FI-70211, Finland, Fax: 35817162456, Hanna.Remes@uku.fi, (2) Department of Chemistry, University of Kuopio

Phosphate prodrugs are widely used to enhance the water-solubility of poorly water-soluble drug molecules. The phosphate promoiety can be attached to the functional group of a drug molecule, e.g. hydroxyl or amine group, either directly or via a spacer group. A promising approach to enhance the aqueous solubility of a drug molecule containing ketone functionality is to attach the phosphate promoiety to a parent drug via an oxime structure. Oximes are known to be hydrolyzed to the corresponding ketones by microsomal oxidative enzymes. We have synthesized directly to the drug molecule attached phosphate oxime prodrugs of two different kinds of ketone drugs, ketoprofen and nabumetone. However, the prodrug of ketoprofen, in which the phosphate oxime promoiety is conjugated to the resonance-stabilized system of two aromatic rings, was found to be chemically extremely labile. In this paper, the most probable reason for the instability of resonance-stabilized phosphate prodrugs is discussed.

294. SIDE CHAIN SAR OF DIHYDROBENZOXATHIIN SERAMS: BICYCLIC AND HETEROATOM-SUBSTITUTED AMINE SIDE CHAINS. Timothy A. Blizzard¹, Frank DiNinno², Jerry D. Morgan II², Helen Y. Chen², Jane Y. Wu², Candido Gude², Seongkon Kim², Wanda Chan², Elizabeth T. Birzin², Yi Tien Yang², Lee Yuh Pai², Zhoupeng Zhang², Edward C. Hayes², Carolyn DaSilva², Wei Tang², Susan P. Rohrer², James M. Schaeffer², and Milton L. Hammond². (1) Merck Research Laboratories, RY800-B116 P.O. Box 2000, Rahway, NJ 07065, tim_bizzard@merck.com, (2) Merck Research Laboratories, Rahway, NJ 07065

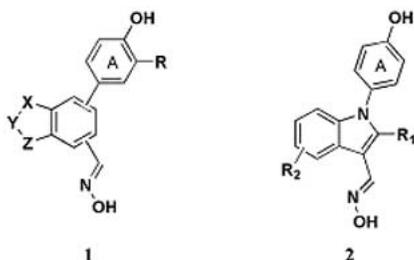
A series of benzoxathiin SERAMs (Selective Estrogen Receptor Alpha Modulators) (1-29) incorporating bicyclic (e.g., 2) or heteroatom-substituted (e.g., 21) side chains was prepared. In some cases, relatively minor modifications in the side chain resulted in significant effects on biological activity, especially in uterine tissue.



295.

4-HYDROXY-PHENYL ARYLOXIMES AS ESTROGEN RECEPTOR-BETA (ER β) SELECTIVE LIGANDS. Stephen Cohn¹, Heather Harris², Eric Manas¹, and Richard E. Mewshaw¹. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, CohnS@wyeth.com, (2) Women's Health Research Institute, Wyeth-Ayerst Research

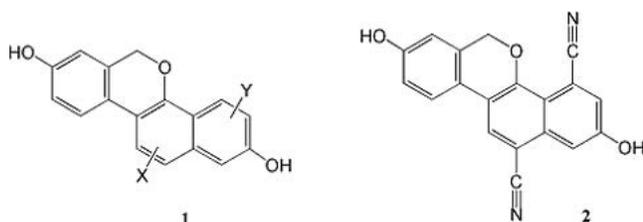
The development of potent and selective estrogen receptor beta (ER β) ligands is essential in identifying therapeutic possibilities for the ER β receptor. Recently, we discovered that oxime moieties could mimic the 17 β -OH group of estradiol. Herein, we will discuss the identification and development of 4-hydroxy-phenyl aryloximes as a novel class of selective, non-steroidal ER β ligands that exploit the oxime bioisosteres. Several substituted 4-OH-phenyl aryloximes exhibit significant affinity and selectivity for β receptor. The design, synthesis and SAR of the substituted 4-OH-biphenyl oxime template **1** and the indole oxime template **2** will be described.



296.

ESTROGEN RECEPTOR β SELECTIVE LIGANDS: EXPLOITING DIFFERENT BINDING MODES WITHIN THE 6-H-CHROMENE[C,H] DIOL TEMPLATE. Richard J. Edsall Jr.¹, Richard E. Mewshaw¹, Cuijian Yang¹, Eric S. Manas¹, Heather A. Harris², James C. Keith Jr.³, Yelena Leathurby³, and Leo M. Albert³. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, edsallr@wyeth.com, (2) Women's Health Research Institute, Wyeth Research, (3) Department of Cardiovascular and Metabolic Diseases, Wyeth Research

Recently our laboratories have been committed toward identifying novel Estrogen Receptor selective ligands using genistein as a starting point. Our efforts have resulted in the discovery of several new classes of molecules based on mimicking the crucial molecular features of genistein within a variety of scaffolds (i.e. biphenyls, phenyl-naphthalenes, quinolines). We will report the structure-activity relationships of a novel series of ligands based on the 6-H-chromene[c,h] diol template (**1**). We also discuss our design strategy that focused on attempts to exploit different binding modes to achieve enhanced ER β selectivity. A number of potent and selective ligands were found in this series, including compound **2** which has an IC₅₀ value of 2.1 nM, and is 131 fold selective for ER β . In addition, one member of the series was observed to have a dramatic beneficial effect in both the HLA-B27 transgenic rat model of inflammatory bowel disease and the Lewis rat adjuvant-induced arthritis model.



297.

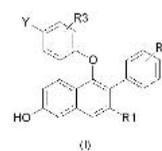
STRUCTURE-BASED APPROACH TOWARDS POTENT AND SELECTIVE ERR γ (ESTROGEN-RELATED RECEPTOR γ) CHEMICAL TOOLS. Esther Y. Chao, Jon L. Collins, Aaron B. Miller, Lisa A. Orband-Miller, Robert T. Nolte, Liping Wang, and William Zuercher, Discovery Research Highthroughput Chemistry, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709-3398, Fax: 919-315-0430

Estrogen-related receptor- γ (ERR γ) is a constitutively active orphan nuclear receptor. Despite a high degree of structural similarity between ERR γ and the estrogen receptors- α and β , ERR γ is not regulated by the natural ligand of the ERs, estradiol. However, previous reports have disclosed the ER modulator 4-hydroxytamoxifen (4-OHT) as a potent but non-selective inverse agonist of ERR γ . In order to elucidate ERR γ function and to assess the receptor's utility as a pharmacological target, we initiated efforts to develop a potent and selective ERR γ ligand based on the 4-OHT scaffold. Our program was guided by crystal structures of 4-OHT bound to ERR γ and ER α . Details of our efforts towards the development of a potent and selective ERR γ chemical tool will be presented.

298.

SYNTHESIS AND ESTROGEN BINDING ACTIVITY OF SUBSTITUTED NAPHTHALENES: POTENTIAL SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS). Adwoa Akwabi-Ameyaw¹, Jing Fang¹, Dennis Heyer¹, Subba R. Katamreddy¹, Aaron B. Miller¹, Jennifer P. Peckham¹, Frank Navas III¹, Lisa A. Orband-Miller², David Gray³, and Jean Shearin². (1) Department of Medicinal Chemistry, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709-3398, adwoa.a.akwabi-ameyaw@gsk.com, (2) Department of Biology, GlaxoSmithKline, (3) Department of Biology, GlaxoSmithKline R & D

Estrogen receptors (ERs) are ligand-modulated nuclear receptors (NR) that have important physiological effects in many tissues including breast, uterus, bone, liver, the cardiovascular system, and the central nervous system. Selective estrogen receptor modulators (SERMS) act on the estrogen receptor in a tissue-selective manner and may therefore exhibit fewer side effects than hormone replacement therapy (HRT) in the treatment of osteoporosis and hot flush. A series of substituted naphthalenes (**1**) have been reported to bind to the estrogen receptor and are potential SERMS. Herein, we describe the synthesis and ER-binding activity of a series of naphthalenes in which analogues containing various R₂, R₃, and Y groups were readily prepared from a common late-stage intermediate.



299.

INDENONES: SELECTIVE ER/NF- κ B INHIBITORS. William R. Solvibile¹, Mark A. Ashwell², Doug Harnish³, Christopher Chadwick⁴, Susan Chippari³, Thomas Kenney³, and Lucinda Shaw⁵. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, solvibw@wyeth.com, (2) Medicinal Chemistry, ArQule Inc, (3) Cardiovascular/Metabolic Diseases, Wyeth Research, (4) Life Diagnostics Inc, (5) Sirna Therapeutics

Inflammation is now recognized as a key component in a number of diseases such as atherosclerosis, rheumatoid arthritis and inflammatory bowel disease (IBD). The transcription factor nuclear factor- κ B (NF- κ B) has been shown to be involved in both the early and late stages of the inflammatory-proliferative process. We have identified non-steroidal estrogen receptor (ER) ligands that selectively inhibit NF- κ B transcriptional activity but are devoid of conventional estrogenic activity. These pathway selective ligands do not promote the classic actions of estrogens such as stimulation of uterine proliferation or ER mediated gene expression but are potent anti-inflammatory agents. Herein we describe the

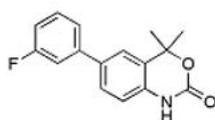
preparation and structure activity relationships (SARs) of a novel series of small molecules derived from 2-phenyl-3-phenylamino-inden-1-one.

300.

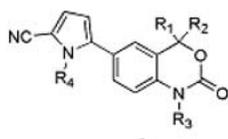
1,4-DIHYDRO-BENZO[D][1,3]OXAZIN-2-ONES CONTAINING A 6-(5'-CYANOPYRROL-2-YL) GROUP AS PROGESTERONE RECEPTOR MODULATORS.

Puwen Zhang¹, Eugene A. Terefenko¹, Jeff Kern¹, Andrew Fensome¹, Mark A. Collins¹, Valerie Hudak¹, Jay Wrobel¹, Yun Zhu², Jeffrey Cohen², Richard Winneker², and Zhiming Zhang². (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, zhangp@wyeth.com, (2) Women's Health Research Institute, Wyeth Research

We have recently reported that 6-aryl benzoxazinones such as 1 are progesterone receptor (PR) antagonists (Zhang, et al. J. Med. Chem., 2002, 45(20), 4379). Substitution of 6-phenyl moiety with a 6-(5'-cyanopyrrol-2-yl) group on the benzoxazinone scaffold caused the functional activity of this series to switch from PR antagonist to PR agonist in the alkaline phosphatase assay (alk. phos.) using the human T47D breast carcinoma cell line (e.g. 2a, Wrobel, et al. 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003, MEDI-230; Collins, et al., Bioorg. Med. Chem. Lett., in press). To further examine the structure and activity relationship of the benzoxazinone core, a series of benzoxazinones 2 were prepared that were substituted with a 5'-cyanopyrrol-2-yl moiety at the 6-position. A number of analogs showed an improvement for PR agonist potency compared to 2a. Interestingly, numerous 6-(5'-cyanopyrrol-2-yl)-benzoxazinones exhibited PR antagonist activity when a lower alkyl group was substituted in the 1-position. In this presentation, the synthesis and in vitro SAR of novel 6-aryl benzoxazinones will be discussed.



1, PR alk. phos. IC₅₀ = 8.2 nM



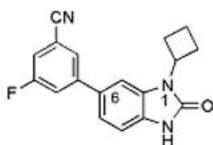
2
(2a, R₁, R₂, R₄ = Me, R₃ = H
PR alk. phos. EC₅₀ = 1.1 nM)

301.

SYNTHESIS AND SAR STUDIES OF 6-ARYL-1,3-DIHYDRO-BENZOIMIDAZOL-2-ONES AS PROGESTERONE RECEPTOR ANTAGONISTS.

Eugene A. Terefenko¹, Jeff Kern¹, Andrew Fensome¹, Jay Wrobel¹, Zhiming Zhang², Yuan Zhu², Jeffrey Cohen², Richard Winneker², and Puwen Zhang¹. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Colegeville, PA 19426, terefee@wyeth.com, zhangp@wyeth.com, (2) Women's Health Research Institute, Wyeth Research

We have previously reported that 6-aryl benzimidazolones are progesterone receptor (PR) antagonists (Zhang, et al. Bioorg. Med. Chem. Lett. 2001, 11, 2747) and the nature of the group at the 1-position and the 6-aryl moiety played a critical role in PR antagonist potency. These findings prompted us to examine a broad array of 1-position substituents and different 6-aryl moieties. These subsequent novel benzimidazolones were evaluated for PR antagonist activity in the T47D alkaline phosphatase assay with about 10-fold increase in PR antagonist potency as compared to ones reported earlier in the same series. In this presentation, the synthesis and in vitro SAR of the expanded series of novel 6-aryl benzimidazolones will be discussed.



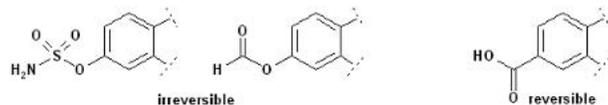
1, PR alk. phos. IC₅₀ = 3.3 nM

302.

HUMAN STEROID SULFATASE, A POTENTIAL DRUG TARGET FOR ANTIANDROGEN/ANTIESTROGEN THERAPY: FROM SUBSTRATE DERIVED

INACTIVATORS TO POTENT REVERSIBLE INHIBITORS. **Erwin P. Schreiner**, Peter Nussbaumer, Philipp Lehr, Amarylla Horvath, Barbara Wolff, Anthony P. Winiski, and Andreas Billich, Novartis Institute for Biomedical Research, Brunner Strasse 59, A-1235 Vienna, Austria, Fax: +43-1-86634-354, erwin.schreiner@pharma.novartis.com

Steroid sulfatase (E.C. 3.1.6.2., STS) catalyzes the hydrolysis of steroid-3-O-sulfates to yield the corresponding steroids. The enzyme has emerged as an attractive drug target, because it is crucial for the local production of active estrogens and androgens from their systemically circulating sulfated precursors, such as estrone sulfate and dehydroepiandrosterone sulfate (DHEAS) in diseased tissues. Potential indications comprise estrogen-driven breast cancer and androgen-dependent skin diseases, such as androgenetic alopecia and acne, which is our current focus. Starting from the irreversible enzyme blocker estrone sulfamate (EMATE) we identified a series of potent nonestrogenic irreversible inhibitors of STS by replacing the steroidal part by predominantly bicyclic phenols. Searching for a substitute of the sulfamate moiety resulted in discovery of aryl formates as a novel type of STS blockers. Finally, formal rearrangement of the ester group lead to aromatic acids, which due to their existence in the anion stage at physiological conditions represent substrate analogues, and, therefore, act as reversible inhibitors of STS. The most active inhibitors show K_i values of about 0.5 μM, similar to that reported for EMATE (0.47 μM). Data on inhibition of the isolated enzyme, in cell-based assays as well as skin are presented and discussed.



303.

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF SOME

NONSTEROIDAL SELECTIVE ANDROGEN RECEPTOR MODULATORS.

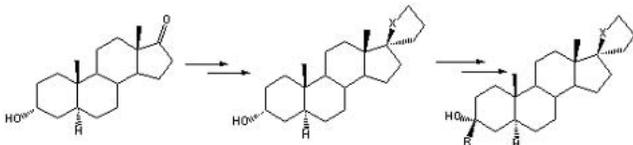
Vipin A. Nair¹, Suni M. Mustafa¹, Michael L. Mohler¹, Scott Fischer², James T. Dalton², and Duane D. Miller¹. (1) Department of Pharmaceutical Sciences, University of Tennessee, Health Science Center, 847 Monroe Avenue, RM 327, Memphis, TN 38163, Fax: 901-448-6828, vnair1@utmem.edu, (2) Division of Pharmaceutics and Pharmaceutical Chemistry, The Ohio State University

The androgen receptor is an important cellular regulatory protein that plays a critical role in numerous physiological processes, including the development and maintenance of male secondary sexual characteristics. Synthetic androgens and antiandrogens have therapeutic value in the treatment of various androgen dependent conditions ranging from regulation of male fertility to prostate cancer. Steroidal androgen receptor agonists and antagonists used clinically suffer from a number of undesirable side effects. The search for non-steroidal antiandrogens that will mimic the pharmacological effects of testosterone, led to the development of compounds like flutamide, nilutamide and bicalutamide which are widely used for the treatment of metastatic prostate cancer. The commonly accepted structure-activity relationship borne out of these ligands suggest the importance of an electron deficient aromatic ring, branched alkyl group at the amidic carbonyl, the need for a strong hydrogen bonding and a conformational preorganization which assigns a coplanarity for the amide linkage and hydroxyl group. Electron attracting substituents in the aromatic ring can enhance the proton donor capability of the hydroxyl group by increasing the acidity of the amide moiety. It may be noted that all of these non-steroidal compounds have a trifluoromethyl group at the 3-position in the aromatic ring. In this context it was quite interesting to generate an androgen receptor ligand replacing the trifluoromethyl group by an electron deficient atom which serves as a suitable bioisosteric moiety. The synthesis of these selective androgen receptor modulators and its structure activity relationships form the subject matter of this presentation.

304.

SYNTHETIC NEUROSTEROIDS: SYNTHESIS OF 3 β AND 17-SUBSTITUTED ANDROSTAN-3 α OLS. Rupa S Shetty¹, Leelakrishna Kondaveti¹, Lin Wang², and David Y.W. Lee¹. (1) Bioorganic and Natural Products/Dept of Psychiatry, McLean Hospital/Harvard Medical School, MRC-311, 115 Mill Street, Belmont, MA 02478, Fax: 617-855-2040, krishna_kondaveti@hms.harvard.edu, (2) NPI, Inc

Neurosteroids are a novel class of compounds, which are, synthesized de novo in the brain and influence the brain excitability by binding to a distinct modulatory site on GABA_A-receptor chloride ionophore complex. The most active Neurosteroids like 3 α , 5 α -THP, its 5 β -epimer 3 α , 5 β -THP and 3 α , 5 α -THDOC are endogenously occurring metabolites of steroid hormones Progesterone and Deoxycorticosterone. For SAR studies several 3 α -hydroxy, 3 β and 17-substituted compounds of androstane series were synthesized.



305.

DESIGN, SYNTHESIS AND IN VIVO EVALUATION OF GAMENDAZOLE[®], A NOVEL ORALLY ACTIVE MALE CONTRACEPTIVE AGENT. Ramappa Chakrasali¹, Sudhakar R. Jakkraj¹, Joseph S. Tash², Sheri A. Hild³, Barbara Attardi³, and Gunda I. Georg¹. (1) Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045, Fax: 785-864-5836, georg@ku.edu, (2) Department of Molecular and Integrative Physiology, University of Kansas Medical Center, (3) BIOQUAL, Inc

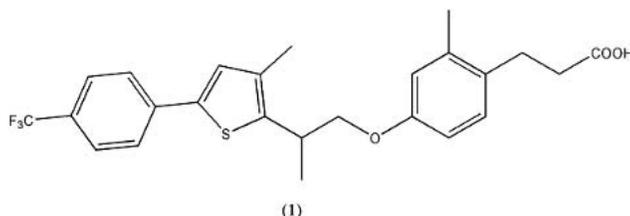
We have developed a new series of potent, orally active non-steroidal non-hormonal male contraceptives that inhibit spermatogenesis. From a series of more than 80 novel analogues, Gamendazole, an indazole-3-acrylic acid derivative was selected for preclinical development. Based on decline in testis weight 5 days after a single oral dose, Gamendazole showed an ED₅₀ of 0.8 mg/kg. Late stage spermatogenesis (spermatid head counts) was markedly reduced seven days after either a single oral or after seven consecutive daily doses of 6 mg/kg. Mating trials with normal cycling female rats showed complete suppression of fertility within four weeks of treatment which persisted for an additional two weeks. Recovery of fertility was gradual and by eighteen weeks about half of the treated animals had regained fertility. Normal numbers of normally developed conceptuses were observed in those animals that regained fertility.

306.

DESIGN AND SYNTHESIS OF 3-(2-METHYL-4-[2-[3-METHYL-5-(4-TRIFLUOROMETHYL-PHENYL)-THIOPHEN-2-YL]-PROPOXY]-PHENYL)-PROPIONIC ACID AS A POTENT SELECTIVE PPAR DELTA AGONIST. Xiaodong Wang, Guoxin Zhu, Robert Barr, Chahrzad Montrose-Rafizadeh, John J. Osborne, Nathan Yumibe, Donald R. Jett, Richard W Zink, and Nathan B Mantlo, Lilly Research Laboratories, Eli Lilly and Company, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46032, Fax: 317-277-2035, sheldon_wang@lilly.com

Pre-clinical studies in obese rhesus monkeys and ob/ob mouse indicated that a selective PPAR delta agonist changes the serum lipoprotein composition by increasing high density lipoprotein cholesterol (HDLc) while decreasing low density lipoprotein (LDLc) and fasting triglycerides by regulating the reverse cholesterol transporter ATP-binding cassette A1 (ABCA1) and cholesterol efflux from many tissues. These results suggested that a selective PPAR delta agonist could provide a new treatment for dyslipidemia and arteriosclerosis associated with metabolic syndrome X. In search of potent and selective PPAR delta agonists, a new class of compounds featuring 2,3,5-tri-substituted thiophenes

was designed and synthesized. This presentation discloses the chemistry and SAR study around 3-(2-methyl-4-[2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy]-phenyl)-propionic acid (1).



307.

NOVEL PPAR δ AGONISTS VIA THIOPHENE-ASSISTED STEREOSPECIFIC 1,2-METHYL MIGRATION. Christopher R. Schmid¹, Robert Barr², Timothy Braden¹, Chahrzad Montrose-Rafizadeh², John J. Osborne¹, and Richard W Zink³. (1) Chemical Process Research and Development, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285-4813, crs@lilly.com, braden_timothy@lilly.com, (2) Discovery Chemistry Research and Technology, Eli Lilly and Company, (3) Lilly Research Laboratories, Eli Lilly and Company

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308.

WITHDRAWN.

309.

SYNTHESIS AND NUCLEAR RECEPTOR ACTIVITIES FOR RING-EXPANDED AND -CONTRACTED HOMOLOGS OF (9Z)-UAB30, A CHEMOPREVENTIVE RXR-SELECTIVE RETINOID. Anil M. Deshpande, Kimberly K. Vines, Donald D. Muccio, and Wayne J Brouillette, Department of Chemistry, University of Alabama at Birmingham, 901 south 14th Street, Birmingham, AL 35294, Fax: 205-934-2543, anilmd@uab.edu

Retinoids that are selective ligands for retinoid X receptors (RXRs) offer promise as breast cancer chemopreventive agents. In an ongoing research effort to design and synthesize new retinoids that conformationally define the C6-C7 torsion angle, we recently reported (9Z)-UAB30, derived from α -tetralone, as a breast cancer chemopreventive RXR-selective retinoid. In order to explore the importance of the tetralone's cyclohexyl ring on the C6-C7 torsion angle and RXR activity, ring altered analogs of (9Z)-UAB30 were designed. Here we will present the synthesis of ring expanded (7-membered) and ring contracted (5-membered) homologs of (9Z)-UAB30 and the effects of these changes on RXR selectivity and potency.

310.

DISCOVERY OF NOVEL ORALLY EFFICACIOUS SMALL MOLECULE IL-12 PRODUCTION INHIBITORS. Elena Kostik, Shijie Zhang, Teresa Przewloka, Mitsunori Ono, Lijun Sun, Yumiko Wada, Dinesh Cimmanamada, Zachary Demko, Noriaki Tatsuta, Guiqing Liang, Qianfan Wang, Dan Zhou, Yaming Wu, and Keizo Koya, Synta Pharmaceuticals Corp, 45 Hartwell Avenue, Lexington, MA 02421, Fax: 781-274-8228, ekostik@syntapharma.com

It has been clearly demonstrated that Interleukin-12 (IL-12), a p35/p40 heterodimer, is integral to the pathogenesis of Th1-mediated autoimmune or immunological disorders. IL-12 plays a pivotal role in the immune response in rheumatoid arthritis, Crohn's disease (CD), and psoriasis. Thus, selective inhibition of IL-12 overproduction is a viable intervention to modulate these autoimmune disorders. Herein we describe the synthesis and SAR studies of a series of novel IL-12 production inhibitors. Optimized inhibitors demonstrated potent in vitro activity against IL-12 production in human PBMC with IC₅₀ less than 10 nM. In vivo adjuvant arthritis (AA) and inflammation bowel disease models, lead compounds exhibited significant oral efficacy at 20mg/kg.

311.

STRUCTURAL REQUIREMENT OF NEW CHALCONES FOR THE INHIBITORY ACTIVITY OF INTERLEUKIN-5. Sang Hun Jung¹, Cho Soo-Hyun¹, Jee Hyun Lee¹, Jung Hun Ju², Mi Kyung Kim³, Seung Ho Lee⁴, Jae Chun Ryu⁵, and Youngsoo Kim². (1) College of Pharmacy, Chungnam National University, Daejeon 305-764, South Korea, Fax: 82-42-823-6566, jungshh@cnu.ac.kr, (2) College of Pharmacy and Research Center for Bioresource and Health, Chungbuk National University, (3) College of Medicine, Chungbuk National University, (4) College of Pharmacy, Yeungnam University, (5) Toxicology Laboratory, Korea Institute of Science and Technology

Interleukin (IL)-5 appears to be one of the main proinflammatory mediators among a growing number of cytokines and chemokines that induce eosinophilic inflammation. Interfering with the action of IL-5 represents one of the new immunomodulatory therapeutic strategies in the treatment of allergic diseases including bronchial asthma. Compared to established immunosuppressive agents like corticosteroids, a major advantage of this strategy is the specificity of reducing eosinophilic inflammation, thus possibly acting nearly without side effects. However small organic compounds to inhibit IL-5 activity have been rarely found. Sophoricoside and its analogs (Figure 1) were isolated from *Sophora japonica*, a plant of Leguminosae family, as inhibitors of interleukin (IL)-5 bioactivity, and showed differential inhibition on IL-3 and GM-CSF bioactivities. During the study of these isoflavonone analogs, structurally related chalcone analogs have been found as novel inhibitors against IL-5. Accordingly, structure activity relationship of chalcones are investigated. Among them, 4-[3-(2-benzyl-6-hydroxyphenyl)-3-oxopropen]benzoic acid shows the compatible activity with that of sophoricoside.

312.

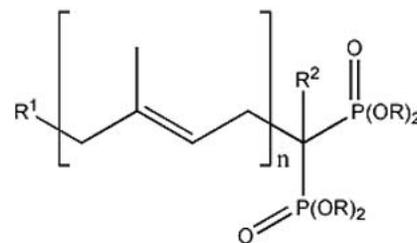
ANTIDIABETIC ACTIVITY OF GALLOTANNIN. Yulin Ren¹, Klaus Himmeldirk², Yunsheng Li¹, Jae Kyung Kim¹, and Xiaozhuo Chen¹. (1) Chemistry and Biochemistry and Biomedical Science, Chemistry and Biochemistry Department, and Department of Biomedical Science, Ohio University, Athens, Ohio State, Ohio 45701, Richland Avenue, Athens, Ohio State, Athens, OH Ohio 45701, Fax: 740-593-4795, reny@ohio.edu, (2) Department of Chemistry and Biochemistry, Department of Chemistry and Biochemistry, College of Art and Science, Ohio University, Athens, Ohio State, Ohio 45701

Diabetes, a new term coined to emphasize the close association of type 2 diabetes with obesity, has become an epidemic in the United States and the rest of the developed world. Recently, we have found that pentagalloylglucose (PGG), a naturally occurring gallotannin, exhibits anti-diabetic activities in fat cells. In order to identify its pharmacore, we synthesized a series of analogues and then screened them for their antidiabetic activity. On the basis of this research, we found that gallic acidic residues attached to some positions of glucose are important for the antidiabetic activity of PGG. On the other hand, the stereochemistry at the anomeric center of glucose is necessary as well. The α -isomers of anti-diabetic analogues of PGG often show much stronger activity than the β -isomers. We believe that our research results will improve the understanding of the mechanism of action of gallotannin, advance the knowledge of gallotannin chemistry, and potentially lead to the development of new anti-diabetic drugs.

313.

IMPACT OF TERPENOID BISPHOSPHONATES ON ISOPRENOID METABOLISM. Larry W. Shull¹, Andrew J. Wiemer², Raymond J. Hohli², and David F. Wiemer¹. (1) Department of Chemistry, University of Iowa, 537 CB, Iowa City, IA 52242-1294, Fax: 319-335-1270, larry-shull@uiowa.edu, (2) Department of Internal Medicine, University of Iowa

Methylene bisphosphonates are in widespread use for the treatment of osteoporosis. Studies of the molecular mechanisms that underlie this activity have suggested that this moiety may serve as a mimic of the pyrophosphate group, and support investigation of bisphosphonate analogues of other metabolic pyrophosphates. Synthesis of an array of terpenoid bisphosphonates has been accomplished by the use of copper-mediated Grignard displacements of allylic THP ethers. The preparation of these compounds, and the impact of branching and substitution on the activity of the resulting bisphosphonates, will be reported.



314.

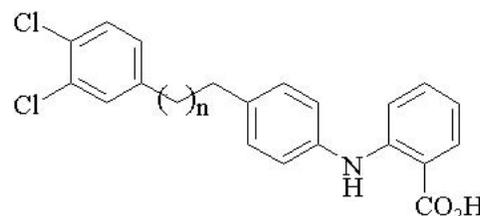
DESIGN AND SYNTHESIS OF BENZODIAZEPINE-DERIVED CYCLIC MALONAMIDES AND AMINOAMIDES AS POTENT APP INHIBITORS. Michael G. Yang¹, Jian Liang Shi¹, Dilip P. Modi¹, Jennifer Wells¹, Brian M. Cochran², Mark A. Wolf², Lorin A. Thompson¹, Mercy Ramanjulu¹, Cynthia M. Rominger¹, Arthur H. Roach¹, Robert Zaczek¹, Ruth R. Wexler¹, and Richard E. Olson¹. (1) Discovery Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492-7660, michael.yang@bms.com, (2) Albany Molecular Research, Inc

Abstract-Amyloid beta peptides have been the subject of intense interest due to their role in the pathology of Alzheimer disease. We have found that benzodiazepine-derived cyclic malonamides and aminoamides are potent inhibitors of gamma-secretase, as demonstrated by sub-nanomolar presenilin binding and inhibition of cellular amyloid beta production. The syntheses and SAR trends of benzodiazepine-derived cyclic malonamides and aminoamides will be presented.

315.

PD 0118057 AND PD 0202091: SMALL MOLECULE INHIBITORS OF BETA-AMYLOID PEPTIDE. Corinne E. Augelli-Szafran¹, Feng Bian², Michael J. Callahan², Rose Feng², Akihiko Iwai³, Yingjie Lai¹, Harry LeVine III², William Lipinski², Lary C. Walker², and Tomoyuki Yasunaga³. (1) Medicinal Chemistry, Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax: 734-622-5165, corinne.augelli-szafran@pfizer.com, (2) CNS Pharmacology, Pfizer Global Research and Development, (3) Tsukuba Research Center, Yamanouchi Pharmaceutical Co., Ltd

Genetic, pathological and biochemical evidence shows that the abnormal aggregation of A-Beta is central to the formation of senile plaques and the pathogenesis of Alzheimer's disease. Current therapies for Alzheimer's disease are palliative and only modestly effective. A disease-modifying drug would be a major therapeutic breakthrough towards the treatment of this disease. Two key compounds, PD 0118057 and PD 0202091, will be highlighted in this presentation. Various physical, chemical and biological properties of these amyloid aggregation inhibitors will be discussed.



PD 0118057, n = 1

PD 0202091, n = 2

316.

SMALL MOLECULE MODULATION OF READ-THROUGH: CYCLIC α -PHENOXY-N-ARYL AMIDES AS POTENTIAL AGENTS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY AND CYSTIC FIBROSIS. James J. Takasugi¹, Attiya R. Khan, Richard G. Wilde, Neil G. Almstead, Ellen M. Welch, Jin Zhuo, and Marla L. Weetall, Department Medicinal Chemistry, PTC Therapeutics Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, jtakasugi@ptcbio.com

Compounds that allow read-through of nonsense mutations and restore full-length protein have the potential to treat 5 to 15 % of any given genetic disorder. Continuing on previous work in our laboratories a series of cyclic α -phenoxy-N-aryl amides was prepared and evaluated in a cellular assay containing a luciferase reporter with a nonsense mutation. In this assay,

luciferase protein is produced in the presence of compounds that allow read through of the nonsense mutation. Such compounds are potential agents for the treatment of genetic diseases, such as Duchenne muscular dystrophy, cystic fibrosis or cancers with nonsense-mutated tumor suppressors.

317.

SMALL MOLECULE MODULATION OF READ-THROUGH: HYDANTOIN-SUBSTITUTED BENZOIC ACIDS AS POTENTIAL AGENTS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY AND CYSTIC FIBROSIS. *Hongyu Ren*¹, *Richard G. Wilde*¹, *Seongwoo Hwang*¹, *Attiya R. Khan*², *Ellen M. Welch*¹, *Jin Zhuo*¹, *Marla L. Weetall*¹, and *Neil G. Almstead*¹. (1) Chemistry Department, PTC Therapeutics Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, hren@ptcbio.com, (2) Department Medicinal Chemistry, PTC Therapeutics Inc

A series of hydantoin (imidazolidinedione) compounds with carboxyaryl substitution was prepared and evaluated for their effect on readthrough of premature stop codons. A cell culture assay containing a reporter mRNA harboring a nonsense mutation was used for these evaluations. Such compounds are potential agents for the treatment of certain genetic diseases, including Duchenne muscular dystrophy and cystic fibrosis. A representative compound from the series was evaluated in mouse pharmacokinetic and in vivo efficacy models, and these results will be presented.

Between 10-30% of all genetic disorders are caused by the presence of a nonsense mutation that results in premature translation termination and the production of a truncated protein. For example, both Duchenne muscular dystrophy, affecting about one of every 3000 young males, and cystic fibrosis, affecting about one of every 3000 people, can be caused by a nonsense mutation. A continuation of our efforts to search for small molecules that are effective in reading through premature stop codons led to the discovery of a series of N, N'-diaryl imidazolidinones. SAR optimization has successfully identified compounds possessing high potency and efficacy in a cell culture assay that uses a luciferase reporter containing a premature stop codon. Leading compounds have also shown promising pharmacokinetic parameters and in vivo efficacy in animal models, and are potential agents for the treatment of Duchenne muscular dystrophy and cystic fibrosis.

318.

SMALL MOLECULE MODULATION OF READ-THROUGH: N,N'-DIARYL IMIDAZOLIDINONES AS POTENTIAL AGENTS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY AND CYSTIC FIBROSIS. *Guang Ming Chen*¹, *Gary M. Karp*¹, *Anthony Turpoff*¹, *Richard G. Wilde*², *Stephen W. Jones*², *Neil G. Almstead*², *Ellen M. Welch*², *Jin Zhuo*², and *Marla L. Weetall*². (1) Department of Medicinal Chemistry, PTC Therapeutics, Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, gchen@ptcbio.com, (2) PTC Therapeutics Inc

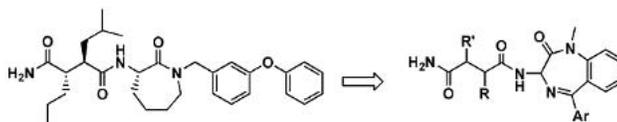
Alzheimer's disease (AD) is a neurodegenerative disease characterized by accumulation of extracellular beta amyloid plaques. Current treatment options for AD are symptomatic and do not address the etiology of the disease. Abnormal processing of amyloid precursor protein (APP) by secretases results in the formation of A β _{40,42}. These peptide fragments are the main constituents of amyloid plaques associated with AD. Recent efforts have focused on developing secretase inhibitors that decrease the production of A β _{40,42} in order to slow the accumulation of these plaques and possibly AD progression. The purpose of this study was to design and synthesize selective γ -secretase inhibitors with appropriate physicochemical properties, such as ability to cross blood-brain-barrier. Several adamantane and bicyclic sulfonamide compounds were designed and synthesized. Activities of compounds were determined using both cell culture and cell-free γ -secretase inhibition assays.

319.

SUCCINOYL BENZAZEPINONES AS γ -SECRETASE INHIBITORS. *Richard E. Olson*¹, *Nenghui Wang*¹, *William E. Frieze*¹, *William Buckner*¹, *Michael G. Yang*¹, *Jain Laing Shi*¹, *Brian M. Cochran*², *Kake Zhao*², *Timothy Forsythe*², *Leah Richardson*², *Mark Decaire*², *Mark A. Wolf*², *Arthur H. Roach*³, *Catherine R. Burton*³, *Jere M. Meredith Jr.*³, *Dietmar A. Seiffert*⁴, *Song Ren*⁵, *Pamela L. Golden*⁵, *Lauren Richards*⁵, *Scott A. Grossman*⁵, *Robert Zaczek*³, *David W. Robertson*¹, and *Ruth R. Wexler*¹. (1) Discovery Chemistry, Bristol-Myers Squibb Co, 5 Research Parkway, Wallingford, CT 06492-7660, Fax: 203-677-7884, richard.olson@bms.com, nenghui.wang@bms.com, (2) Medicinal Chemistry Department, Albany Molecular Research, Inc, (3) Neuroscience Biology Department, Bristol-Myers Squibb Co, (4) Chemical Enzymology Department, Bristol-Myers Squibb Co, (5) Metabolism and Pharmacokinetics Department, Bristol-Myers Squibb Co

The amyloid hypothesis suggests that the accumulation of the amyloidogenic A β peptide (A β) in brain underlies the pathology of Alzheimers Disease (AD). The inhibition of the secretases which process amyloid precursor protein (APP) to A β represents an attractive strategy for reducing A β levels. We have previously reported the discovery and optimization of a series of succinoyl caprolactams which demonstrate selective γ -secretase inhibition in cellular systems. Replacement of the caprolactam with various benzazepinones led to improvements in potency and in the pharmacokinetic profiles in dog. Identification and modifica-

tion of metabolic sites provided strategies for further enhancement of the in vivo profiles. The synthesis, SAR and pharmacokinetic properties of this series will be discussed.



320.

DESIGN AND SYNTHESIS OF NON-PEPTIDE γ -SECRETASE INHIBITORS.

Adeboye Adejare, Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104-4495, Fax: 215-895-1161, a.adejar@usip.edu, *Ryan M. Wells*, Department of Pharmaceutical Sciences, College of Pharmacy, Idaho State University, and *Todd E. Golde*, Mayo Clinic Jacksonville

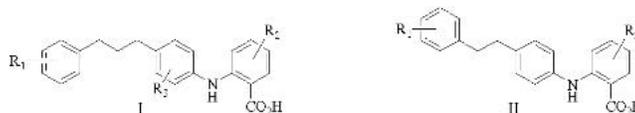
Alzheimer's disease (AD) is a neurodegenerative disease characterized by accumulation of extracellular beta amyloid plaques. Current treatment options for AD are symptomatic and do not address the etiology of the disease. Abnormal processing of amyloid precursor protein (APP) by secretases results in the formation of A β _{40,42}. These peptide fragments are the main constituents of amyloid plaques associated with AD. Recent efforts have focused on developing secretase inhibitors that decrease the production of A β _{40,42} in order to slow the accumulation of these plaques and possibly AD progression. The purpose of this study was to design and synthesize selective γ -secretase inhibitors with appropriate physicochemical properties, such as ability to cross blood-brain-barrier. Several adamantane and bicyclic sulfonamide compounds were designed and synthesized. Activities of compounds were determined using both cell culture and cell-free γ -secretase inhibition assays.

321.

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIP OF SUBSTITUTED N-PHENYL ANTHRANILIC ACID ANALOGS AS AMYLOID AGGREGATION INHIBITORS.

*Lloyd J. Simons*¹, *Corinne E. Augelli-Szafran*¹, *Bradley W. Caprathe*¹, *James M. Graham*¹, *Takenori Kimura*², *Yingjie Lai*¹, *Harry LeVine III*³, *Annette T. Sakkab*¹, *Yoshikazu Tasaki*², *Tomoyuki Yasunaga*², *Yuyang Ye*³, and *Nian Zhuang*¹. (1) Medicinal Chemistry, Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax: 734-622-5165, (2) Tsukuba Research Center, Yamanouchi Pharmaceutical Co., Ltd, (3) CNS Pharmacology, Pfizer Global Research and Development

It is believed that β -amyloid formation is a key event in the development of Alzheimer's disease. Amyloidosis is characterized by the accumulation of fibrillar proteins with a β -pleated sheet conformation in the tissues of a patient. Current therapies for the treatment of amyloidosis attempt to remove the source of precipitating β -amyloid with drugs that inhibit protein synthesis. In the course of recent studies to identify β -amyloid aggregation inhibitors, a series of N-phenyl anthranilic acid analogs (I and II) have been synthesized and studied for β -amyloid inhibition activity. The synthesis and structure-activity relationship of these analogs is discussed.



322.

BIODISTRIBUTION AND RADIATION DOSIMETRY OF [11C]-6-OH-BTA-1 IN BABOON. *Ramin V. Parsey*¹, *Levi O Sokol*¹, *Marie José Bélanger*¹, *J. S. Dileep Kumar*¹, *Norman R. Simpson*², *Theodore S. Wang*², *Ronald L. Van Heertum*², and *J. John Mann*³. (1) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, Fax: 212-543-6017, rparsey@neuron.cpmc.columbia.edu, dk2038@columbia.edu, (2) Department of Radiology, Columbia University, (3) Department of Psychiatry, Radiology & Division of Neuroscience, Columbia University & New York State Psychiatric Institute

Recent studies have demonstrated that one of the neutral analogues of the amyloid binding thioflavin-T, named [11C]-6-OH-BTA-1 (1), crosses the blood

brain barrier, and is a promising tracer for imaging plaques in vivo using positron emission tomography. We now report the biodistribution and dosimetry of [11C]-6-OH-BTA-1 in baboons. Three two-hour whole body studies were acquired in an ECAT ACCEL camera in a baboon after the bolus injection of [11C]-6-OH-BTA-1. Regions of interest (ROI) were drawn around the brain, liver, gallbladder, left and right kidneys, left and right lungs, and the urinary bladder. Since no fluid was removed from the animal, total body radioactivity was calculated using the injected dose calibrated to the ACCEL image units. Absorbed radiation doses were obtained for a standard adult male and adult female using the MIRDOSE3 program. The bladder wall received the highest estimated radiation dose (4.52×10^{-2} mGy/MBq) and is the critical organ. The bladder wall limits the single injection of [11C]-6-OH-BTA-1 to 1511 MBq in an adult male and 1107 MBq in an adult female in protocols conducted under the jurisdiction of a Radioactive Drug Research Committee in the US. This study demonstrates that biodistribution and dosimetry studies can be performed in baboons in a relatively simple and straightforward fashion and the data provide dosimetry estimates for human studies using this radiotracer. The details of radiation dose estimates and the methods employed will be presented.

323.

METABOLISM AND STRUCTURE ACTIVITY RELATIONSHIPS OF THE ANTI-EPILEPTIC DRUG FELBAMATE. *William F. McCalmont and Timothy L. Macdonald, Department of Chemistry, University of Virginia, McCormick Road P.O. Box 400319, Charlottesville, VA 22904-4319, Fax: 434-982-2302, wfm3s@virginia.edu*

Felbamate was approved by the FDA in July, 1993 for the treatment of several forms of epilepsy. From initial screening it exhibited an excellent therapeutic index and IC50 against several forms of epilepsy; however, after its widespread distribution it has been linked to significant toxicological side effects. This has led to a comprehensive study on the metabolism, and structure activity relationship of the parent compound. Here we discuss the metabolism of felbamate and a structural activity relationship profile used to assuage the side effects as well as optimize the potency of this useful antiepileptic drug.

324.

DESIGN, SYNTHESIS AND EVALUATION OF β -BENZAMIDO HYDROXAMIC ACID INHIBITORS OF TNF- α CONVERTING ENZYME (TACE). *Gregory R. Ott, Zhonghui Lu, Naoyuki Asakawa, Maryanne B. Covington, Mingxin Qian, Rui Qin Liu, Robert C. Newton, David D. Christ, Carl P. Decicco, and James J W. Duan, Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 302-695-7410, gregory.ott@bms.com*

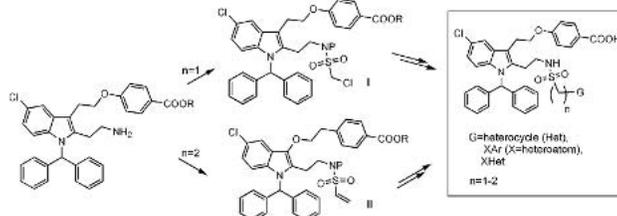
Tumor Necrosis Factor- α (TNF- α), a pro-inflammatory cytokine, has been the subject of intense interest for its role in numerous pathological diseases. Mediation of TNF- α production can be achieved by inhibiting the processing of the protein from the membrane-bound 26 kDa precursor to the 17 kDa soluble form by the metalloprotease TNF- α converting enzyme (TACE). Inhibitors of the enzyme TACE based on β -benzamido hydroxamic acid scaffolds have been extensively evaluated. Discovery of a β -benzamido hydroxamic acid which is potent in enzyme and cellular assays, selective against a wide panel of MMP and ADAM proteases, as well as orally bioavailable in multiple species will be presented.

325.

SULFONAMIDE ANALOGS OF INDOLE CPLA2 ALPHA INHIBITORS: ARE POTENT, WATER SOLUBLE INHIBITORS POSSIBLE? *Lihren Chen¹, Weiheng Wang¹, Katherine Lee¹, Marina Shen², Jing Lun Wu², Wen Zhang², Xin Xu³, Steve Tam¹, James D. Clark², and John C. McKew¹.* (1) Department of Chemical and Screening Sciences, Wyeth Research, 200 CambridgePark Drive, Cambridge, MA 02140, LChen@wyeth.com, (2) Department of Inflammation, Wyeth Research, (3) Department of Discovery Pharmacokinetics, Wyeth Research

Cytosolic Phospholipase A2alpha (cPLA2a) selectively cleaves sn-2 arachidonyl containing membrane phospholipids to yield precursors of pro-inflammatory molecules such as prostaglandins, leukotrienes and platelet-activating factor. cPLA2a inhibitors would be novel therapies for the treatment of arthritis, asthma or any other disease where these mediators play a role. Since cPLA2a works at the membrane cytosol interface and has a glycerol phospholipid as its natural

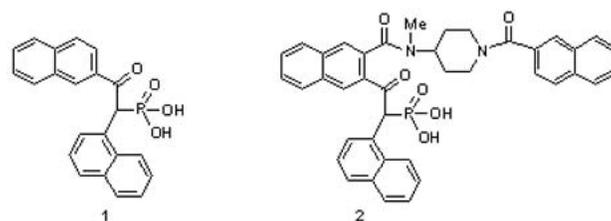
substrate, inhibitors are generally lipophilic with low bioavailability. Heteroatoms were introduced to the inhibitors to increase solubility. Chloromethylsulfonamide I and vinylsulfonamide II were reacted with a variety of heteroatom-containing nucleophiles. The use of intermediate II, surprisingly, was rarely used in the literature for the preparation of aromatic heterocycle-based sulfonamides. Potency, physicochemical properties, and PK of these inhibitors will be discussed.



326.

STRUCTURE-BASED DESIGN OF SERINE PROTEASE INHIBITORS: DISCOVERY OF CATHEPSIN G AND CHYMASE INHIBITORS CONTAINING A NOVEL β -KETOPHOSPHONIC ACID MOTIF. *Michael N. Greco¹, Michael J. Hawkins¹, Eugene T. Powell¹, Harold A. Almond¹, Thomas Corcoran¹, Lawrence de Garavilla¹, Jack A. Kauffman¹, Rosario Recacha², Debashish Chattopadhyay², Patricia Andrade-Gordon¹, Edward Giardino¹, and Bruce E. Maryanoff¹.* (1) Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477, Fax: 215-628-4985, mgreco@prdu.jnj.com, (2) Center for Biophysical Sciences and Engineering, University of Alabama at Birmingham

Cathepsin (Cat G), a chymotrypsin-like serine protease that is stored in the azurophilic granules of neutrophils and released on activation, has been implicated in various pathological conditions associated with inflammation, including chronic pulmonary diseases. We identified β -keto phosphonic acid **1** as a moderate inhibitor of Cat G (IC50 = 4.1 μ M) by high-throughput screening. We solved the X-ray crystal structure of **1**-Cat G and used the information in a structure-based optimization protocol, which led to **2** (IC50 = 38 nM). In further enzymatic profiling, **2** was found to be a potent inhibitor of chymase (IC50 = 2 nM), a chymotrypsin-like serine protease in mast cells that is released on activation and has also been implicated in inflammatory diseases. Studies with dual protease inhibitor **2** in animal models of inflammation have delivered positive findings, particularly with respect to airway inflammation and neutrophil influx. Details on the interactions of **2** within the active sites of Cat G and chymase will be discussed.

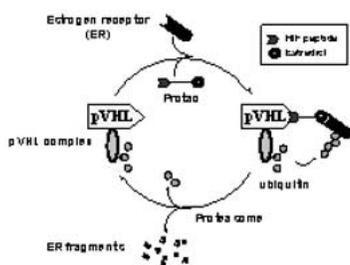


327.

TARGETED PROTEIN DEGRADATION INDUCED BY SMALL MOLECULES: A NOVEL STRATEGY IN CHEMICAL GENETICS. *Dong Zhang, Sun Hee Baek, and Kyung Bo Kim, College of Pharmacy, University of Kentucky, 907 Rose Street, Lexington, KY 40536, Fax: 859-257-7564, dzhan2@email.uky.edu*

The use of Protacs (Proteolysis Targeting Chimeric Molecules) has been characterized to be a novel generic strategy for targeting any protein for degradation by ubiquitin-dependent proteolysis in living cells. The design of Protacs includes a peptide derived from hypoxia-inducible factor-1a (HIF-1a) binding to von Hippel-Lindau tumor suppressor (pVHL), an E3 ubiquitin ligase, and a ligand of the target protein through a carbon linker. In the presence of an appropriate Protac, the target protein is selectively ubiquitinated and degraded taking advantage of the artificial modification of the E3 ligase: target protein interaction, such as MetAP-2 and estrogen receptor proteins in A549 and MCF7 cells. It has also been shown that upon treatment with Protac, breast cancer cell growth is significantly inhibited with a correlated decrease in ER and ER-regulated protein levels, indicating a potential alternative therapeutics for breast

cancer. This approach constitutes a “chemical knockout” of protein function in living cells.



328. NEW MELPHALAN PRODRUGS USEFUL IN ANTIBODY-DIRECTED ENZYME PRODRUG THERAPY (ADEPT). *Brian Toki, Charles Cerveny, Tim Bovee, and Peter Senter, Seattle Genetics, 21823 30th Dr. SE, Bothell, WA 98021, Fax: 425-527-4109, btoki@seagen.com*

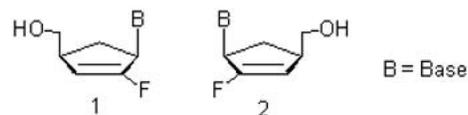
Antibody-Directed Enzyme Prodrug Therapy (ADEPT) is a two-stage form of cancer chemotherapy, which involves the administration of an antibody-enzyme conjugate followed by an anticancer prodrug that is activated by the targeted enzyme. We have previously described the properties of a cephalosporin-melphalan derivative, C-Mel, that leads to the generation of the clinically approved anticancer alkylating agent melphalan upon hydrolysis by targeted beta-lactamase. Upon release, melphalan is transported inside cells through low affinity interactions with amino acid transporters, and possibly by passive diffusion across cell membranes. With regard to melphalan there are reports in the literature that this is an inefficient process. Here, we report the syntheses of a panel of melphalan derivatives, consisting of ester, amide, and peptide adducts that are designed to promote facile intracellular drug access. Cephalosporin prodrugs of highly potent melphalan derivatives were synthesized and evaluated for activity with beta-lactamase, specific activation by antibody-enzyme conjugates, toxicity and in vivo therapeutic efficacy. The results demonstrate significant utility for highly potent derivatives of melphalan for targeted cancer therapy.

329. CAFFEYOYL-BASED AFFINITY ACETYLATORS OF HIV-1 INTEGRASE AS NOVEL PHARMACOLOGICAL TOOLS. *Sachindra S. Patil¹, Nick Shkriabai², Xuechun Zhang¹, Godwin C. G. Pais¹, Evguenia S. Svarovskaia³, Christophe Merchand⁴, Vinay K. Pathak³, Yves Pommier⁴, Stuart Le Grice⁵, Mamuka Kvaratskhelia², and Terrence R Burke Jr.¹. (1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, sachin@helix.nih.gov, (2) College of Pharmacy, Center for Retrovirus Research and Comprehensive Cancer Center, The Ohio State University, Health Science Center, (3) NCI-Frederick, NIH, (4) Laboratory of Molecular Pharmacology, National Cancer Institute, NIH, (5) HIV Drug Resistant Program, NIH*

HIV-1 integrase (IN) is an enzyme found in human immunodeficiency virus that while being required for the viral life cycle has no human homologue. For this reason IN has become an important target for the development of new AIDS therapeutics. Although efforts toward this end have spanned more than ten years, viable clinical candidates have been slow to emerge. One difficulty in developing IN inhibitors is the lack of X-ray crystal structures of enzyme/ligand complexes. Although substantial progress has been made in understanding the structure and function of IN and in the design of IN inhibitors, failure to clearly understand the locations and basis of enzyme-inhibitor interactions has limited structure-based design. The caffeoyl moiety has figured prominently in a variety of catechol-containing IN inhibitors. Caffeic acid phenylethyl ester (CAPE) is a prototypical member of this family. The caffeoyl group is also an important component of chicoric acid and related IN inhibitors. In order to define sites of interaction of IN with recently reported caffeoyl-containing variants of chicoric acid, we utilized these analogues as affinity covalent modifiers. Presented herein are aspects of this work. The concept of “affinity acetylation” is highly novel and it may be applicable to a wide range of biological systems.

330. D- & L-2'-FLUORO-2', 3'-UNSATURATED CARBOCYCLIC NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS. *C. K. Chu¹, Jianing Wang¹, Yunho Jin¹, and Raymond F. Schinazi². (1) Department of Pharmaceutical and Biomedical Sciences, The University of Georgia, College of Pharmacy, Athens, GA 30602, Fax: 706-542-5381, dchu@rx.uga.edu, wangj@rx.uga.edu, (2) Medical research 151H, Emory University/VA Medical center*

Carbocyclic nucleosides have received much attention due to their important biological activities, as well as their metabolic stabilities. Among nucleoside analogs, a fluorine substitution on the carbohydrate moiety has proved successful in producing effective antiviral agents. The 2', 3'-unsaturated analogs have also demonstrated promising bioactivities. By combining these two structural features, we synthesized 2'-fluoro-2', 3'-unsaturated carbocyclic nucleosides in both D- and L-series as potential antiviral agents. The target compounds **1** and **2** were stereospecifically synthesized starting from D-ribose. The key intermediates, D- & L-2-cyclopentenones, were prepared by the ring closing metathesis reaction, and were further converted to D- & L-2'-fluoro-2', 3'-unsaturated cyclopentenyl alcohols in 13 steps. The alcohols were condensed with protected purines and pyrimidines under the Mitsunobu conditions, followed by deprotection to afford the target nucleosides **1** & **2**. Antiviral evaluation against HIV and HBV of the synthesized nucleosides is in progress (Supported by NIH AI32351, AI25899 & VA).



331. DISCOVERY OF A POTENT LETHAL FACTOR INHIBITOR AS AN ADJUNCT THERAPY OF ANTHRAX INFECTION. *Yusheng Xiong¹, Wesley L. Shoop¹, Judyann Wiltsie¹, Andrea Woods¹, Jian Guo¹, James V. Pivnichny¹, Thomas Felcetto¹, Bruce F. Michael¹, Alka Bansal¹, Richard T. Cummings¹, Barry R. Cunningham¹, Arthur M. Friedlander², Cameron M. Douglas¹, Sangita B. Patel¹, Giovanna Scapin¹, Scott Salowe¹, Dennis M. Zaller¹, Kevin T. Chapman¹, Edward M. Scolnick¹, Dennis M. Schmatz¹, Kenneth Bartizal¹, Jeffrey D. Hermes¹, and Malcolm MacCoss¹. (1) Merck Research Laboratories, Rahway, NJ 07065, yusheng_xiong@merck.com, (2) US Army Medical Research Institute of Infectious Diseases*

Lethal Factor, a zinc-dependent metalloprotease, is a component of the primary toxin secreted by *Bacillus anthracis* in anthrax infection. We have identified potent small molecule inhibitors of LF that block the toxin action in cell culture. In the absence of antibiotics the LF inhibitors provide protection in a mouse intoxication model study, and are effective in lethal *B. anthracis* challenges in both mouse and rabbit infection models. Synthesis and SAR of the LF inhibitors will be discussed.

332. DISCOVERY OF CATIONIC INHIBITORS OF ANTHRAX LETHAL FACTOR PROTEASE. *Cho Tang¹, Ondrej Simo¹, Sean O'Malley¹, Melissa Nagata¹, Mark Goldman², Lynne Cregar², Dominique Nguyen², Petr Kuzmic³, Mahtab Moayeri⁴, Stephen Leppla⁴, Robert Liddington⁵, Thomas Hemscheidt⁶, and Guan sheng Jiao¹. (1) Department of Chemistry, Hawaii Biotech, Inc, 99-193 Aiea Heights Drive, #200, Aiea, HI 96701, Fax: 808-792-1348, ctang@hibiotech.com, (2) Department of Drug Discovery, Hawaii Biotech, Inc, (3) BioKin, Ltd, (4) National Institute of Allergy and Infectious Diseases, (5) The Burnham Institute, (6) Department of Chemistry, University of Hawaii at Manoa*

Anthrax is the human disease that results from infection by *Bacillus anthracis*. Until recently, this disease was generally associated with sporadic exposure of humans to *Bacillus* spores from wool or animal carcasses. Current vaccines are effective after multiple pretreatments and antibiotics/protein therapeutics are effective only if administered early in the infection cycle before the main anthrax toxin, lethal factor (LF) enters susceptible cells. Existing therapies do not target intracellular LF. In addition, new agents of terror have been envisioned that deliver LF via common human viral vectors directly into susceptible cells without the need for other *Bacillus*-mediated gene products. Studies were initiated to discover drugs that prevent the fatal toxicities resulting from anthrax LF-mediated proteolysis of intracellular MAP signaling pathway proteins. Using a

series of FRET-based screening assays to identify and characterize specific inhibitors of LF, we evaluated a small, focused library and identified several chemically-distinct classes of cationic LF inhibitors. A subset of these compounds was active in the presence of nucleic acids and, thus, was investigated as leads for optimization. Mechanistically, these compounds bind to two distinct sites on LF. Pre-exposure of mice to one of the early prototypic compounds, HB-165485, significantly delayed time-to-death following lethal toxin administration. SAR analysis of these compounds and related analogs will be discussed.

333.

INHIBITION OF THE MEASLES VIRUS CELL ENTRY: FUSION BLOCKADE.

Aiming Sun¹, Richard K. Plempner², Karl J. Erlandson², Ami Lakdawala¹, Andrew Prussia¹, Esin Akisener³, Ismail Yalcin³, Illkay Yildiz³, Ozlem Temiz-Arpaci³, Betul Tekiner³, Dennis C. Liotta¹, Richard W. Compans², and James P. Snyder¹. (1) Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, Fax: 404-712-8679, asun2@emory.edu, (2) Dept. of Microbiology & Immunology, School of Medicine, Emory University, (3) Dept. of Pharmaceutical Chemistry, Ankara University

Measles Virus (MV) constitutes a principal cause of worldwide mortality, accounting for approximately 1 million deaths annually. While a live-attenuated vaccine protects against MV infection, vaccination efficiency of young infants is low due to interference by maternal antibodies. Furthermore, in certain nations parental concerns about vaccination safety have contributed to recent MV outbreaks. Consequently, the development of novel inhibitors against MV and related viruses is highly desirable. Based on a homology model of the MV fusion-protein and a bowl-shaped pocket, we have identified a lead compound with low toxicity that specifically inhibits live MV and MV glycoprotein-induced membrane fusion with IC₅₀ = 20 microM. A second generation compound derived by structure-based design shows 200-fold increased antiviral activity, creating the basis for a series of novel MV therapeutics.

334.

CHEMICAL PROBES FOR γ -SECRETASE. **Michael S. Wolfe**, Center for Neurologic Diseases, Harvard Medical School and Brigham and Women's Hospital, 77 Avenue Louis Pasteur, H.I.M. 754, Boston, MA 02115

Production of the amyloid- β peptide (A β), the primary component of the characteristic cerebral plaques of Alzheimer's disease, requires intramembranous proteolysis of the A β precursor protein (APP) by γ -secretase. Transition-state analogue inhibitors were critical for characterizing and identifying this enzyme, a complex of multiple membrane proteins, with presenilin as the putative catalytic component of a novel aspartyl protease. The active site is thought to reside in the interior of the protease complex, sequestered away from the hydrophobic membrane lipids. The protease also apparently possesses an initial docking site for substrate on the outer surface of the complex that is distinct from the active site. Helical peptides based on the APP transmembrane domain can potently inhibit the enzyme, apparently through interaction with the initial substrate docking site. Conversion of the most potent helical peptides to affinity labeling reagents should allow identification of this docking site on the protease complex.

335.

GAMMA SECRETASE INHIBITORS AS POTENTIAL ALZHEIMER'S

THERAPEUTICS. **Ian Churcher**, Dept. of Medicinal Chemistry, Merck Sharp & Dohme, The Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR, United Kingdom

During the last decade, genetic and biochemical evidence has provided a rationale for a potential disease-modifying therapeutic approach to the treatment of Alzheimer's disease (AD). The hallmark lesions found in AD brains are extracellular proteinaceous deposits found either as amyloid plaques in the brain itself or as vascular amyloid surrounding the brain blood vessels. These deposits are composed primarily of a 40-42 amino acid peptide termed amyloid- β (A β) which is derived from amyloid precursor protein (β APP) by stepwise proteolytic cleavages. Soluble oligomers of A β have also been shown to be toxic. Gamma-secretase, the critical enzyme which releases the A β peptide from its membrane-bound precursor, has proven elusive although recent

advances have made its identity somewhat clearer. In addition it has been shown that γ -secretase mediates the processing of many substrates other than β APP. This talk will describe the identification of functional γ -secretase inhibitors and discuss potential issues associated with their development.

336.

INHIBITION OF γ -SECRETASE AS AN APPROACH TO DISEASE-MODIFYING

TREATMENT OF ALZHEIMER'S DISEASE. **Robert T. Jacobs**, Peter R. Bernstein, Cyrus J. Ohnmacht, James D. Rosamond, Ashok B. Shenvi, Thomas R. Simpson, Paul Ciaccio, Norman C. Ledonne, Frank Liu, Timothy M. Piser, Johanna Stahl, Gaochao Tian, and Barry D. Greenberg, CNS Discovery, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, robert.jacobs@astrazeneca.com

Accumulation of the amyloidogenic peptide A β as insoluble plaques in the brain is believed to be associated with initiation of a pathological cascade leading to neurodegeneration associated with Alzheimer's disease (AD). Strategies to reduce the level of brain A β are being aggressively pursued as an approach likely to benefit AD patients. A β is produced as the result of sequential proteolysis of a type I transmembrane protein, APP, by β - and γ -secretases. Whereas β -secretase is a well-characterized, soluble aspartyl protease, characterization of γ -secretase has been more elusive due to the fact that γ -secretase is a multimeric complex consisting of at least four transmembrane proteins-presenilin-1, nicastrin, aph-1 and pen-2. Despite this complexity, diverse small molecule inhibitors of γ -secretase activity have been reported. In this talk, our efforts to characterize the γ -secretase complex and to discover novel γ -secretase inhibitors will be described.

337.

ARYLSULFONAMIDES AS INHIBITORS OF A β PRODUCTION.

D. W. Smith¹, B. Munoz², J. Anderson², J. Arruda², D. Barten¹, P. Baskin², C. Bergstrom¹, J. Corsa¹, K. Felsenstein¹, V. Guss¹, G. Holtz², Y. Hu², M. Kounnas², W. Lau¹, A. Loo¹, J. Noonan¹, M. Parker¹, C. Polson¹, S. Roberts¹, J. Roope², C. Sloan¹, K. Srinivasan², R. Tomlinson², T. Tran², S. Wagner², O. Wallace¹, B. Wang², R. Wang¹, J. Wong¹, and F. Yang¹. (1) Discovery Chemistry, Bristol-Myers Squibb PRI, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7884, david.smith@bms.com, (2) Merck Research Laboratories SD

The accumulation of β -amyloid (A β) continues as a leading candidate in the etiology of Alzheimer's disease as described by the amyloid hypothesis. The production of A β results from the endoproteolytic cleavage of amyloid precursor protein (APP) by two enzymes, β -secretase (BACE) and γ -secretase. This presentation will describe the SAR of a series of benzenesulfonamide γ -secretase inhibitors as determined in a cell-based assay, as well as *in vivo* characterization of selected inhibitors. The initial lead in this series arose from an HTS campaign and ultimately gave rise to a compound selected for clinical evaluation. A detailed pharmacological characterization of the clinical candidate will be presented.

338.

DESIGN, SYNTHESIS, AND SAR OF NOVEL 1,5-BENZODIAZEPINE FUNCTIONAL

γ -SECRETASE INHIBITORS. **Warren J. Porter**¹, Jon K. Reel¹, James J. Droste¹, James E. Audia¹, Thomas C. Britton¹, Bruce Gitter¹, Steven S. Henry¹, Paul A. Hyslop¹, Sheila P. Little¹, Thomas E. Mabry¹, Patrick May¹, Stacey McDaniel¹, Jeffrey S. Nissen¹, Qing Shi¹, Lee H. Latimer², Jay S. Tung², Harry F. Dovey², Stephen B. Freedman², Dale B. Schenk², and Eugene D. Thorsett². (1) Lilly Corporate Center, Eli Lilly & Company, Indianapolis, IN 46285, wjp@lilly.com, (2) Elan Pharmaceuticals

Amyloid-beta peptide is the principle protein component of the cerebral plaques in Alzheimer's Disease and a significant body of evidence supports a pathogenic role for the peptide. The action of two proteases, β - and γ -secretase, generates the peptide from its precursor protein. We previously described the discovery of dipeptide functional γ -secretase inhibitors and some subsequent optimization. Herein, the design, synthesis, and structure-activity-relationship of a novel series of 1,5-benzodiazepine γ -secretase inhibitors will be presented. Additionally, *in vivo* amyloid-beta reduction in the brains of transgenic (PDAPP) mice will be presented for select inhibitors.