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**J. R. McCarthy, Program Chair**

SUNDAY MORNING

**Graduate Predoctoral Fellow Symposium**
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**General Oral Session**
J. R. McCarthy, Organizer Papers 9-19

SUNDAY AFTERNOON

**Allosteric Kinase Inhibitors**
M. E. Fraley, Organizer Papers 20-24

**New Frontiers in Drug Delivery**
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SUNDAY EVENING

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**Robertson and Scarborough Awards Symposium**
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**Molecular Imaging in Drug Development and Chemistry**
G. Chiosis, Organizer Papers 212-216

MONDAY AFTERNOON

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**Molecular Imaging in Drug Development and Chemistry**
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THURSDAY AFTERNOON

**General Oral Session**
J. R. McCarthy, Organizer Papers 470-479

**MEDI 1**

## Targeting T- and B-cell lymphomas: Heterocyclic antagonists for alpha4-beta1 integrin

***Richard D. Carpenter**, rcarpenter@ucdavis.edu, Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, Kit S. Lam, kit.lam@ucdmc.ucdavis.edu, Division of Hematology & Oncology, Department of Internal Medicine, UC Davis Cancer Center, University of California, Davis, UC Davis Cancer Center, Sacramento, CA 95817, and Mark J. Kurth, mjkurth@ucdavis.edu, Department of Chemistry, University of California Davis, Davis, CA 95616*

Integrins are cell surface receptors that respond to and modulate a broad array of extracellular matrix proteins. Specifically, á4â1 integrin regulates lymphocyte trafficking and homing in normal adult cells, however activated á4â1 regulates tumor growth, metastasis, angiogenesis, promoting the dissemination of tumor cells to distal organs as well as facilitating tumor cell extravasation. The urea peptidomimetic ligand LLP2A was found to selectively bind activated á4â1 integrin of lymphoid malignancies (IC50 = 2 pM with Jurkat cells, = 47 pM with Molt-4 cells). The ligand-radio conjugate LLP2A-DOTA-111In has shown been shown to target both T- and B-lymphoma with high specificity in the xenograft model. Radio-uptake to the normal organs, except the kidneys, was minimal. To overcome the kidney uptake problem, we have focused on preparing comparably potent benzimidazole, benzoxazole, and benzothiazole KLCA analogs. At the physiological pH of the kidney, these KLCA analogs would be dianions (2-bisarylamino N-H + carboxylic acid) thereby making them less likely to be absorbed and subsequently more likely to be cleared from the kidney. Computational, synthetic, and in vitro and in vivo biological assay data will be presented that highlight the design of comparably potent ligands that offer improved renal clearance and a functionally-simplified molecule. Radiotherapeutic and radioimaging studies will also be presented to treat and diagnose T- and B-cell lymphomas.

**MEDI 2**

## Synthesis, characterization and derivatization of the arylomycin family of natural products

***Tucker C. Roberts**[1], troberts@scripps.edu, Peter A. Smith[1], Ryan T. Cirz[2], and Floyd E. Romesberg[1]. (1) Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Rd mc-262R, La Jolla, CA 92037, Fax: 858-784-7472, (2) Achaogen Inc, South San Francisco, CA 94080*

The increasing number of untreatable bacterial infections has created an urgent need to identify new antibiotics, especially those acting by novel mechanisms. Drugs based on the inhibition of pathogen proteases have been successful however this strategy has been limited by promiscuous inhibition of off-target human enzymes. Type I bacterial signal peptidase (Spase) is an essential protease conserved in all bacteria but its inhibitors are unlikely to encounter this problem due to its unique catalytic mechanism. We have recently completed the first total synthesis of a member of the arylomycin/lipoglycopeptide family of natural product Spase inhibitors, arylomycin A2. Structural and biological studies of the molecule indicate that both N-methylation and lipidation contribute to activity against Gram-negative and Gram-positive pathogens. These studies should help identify the determinants of the biological activity of arylomycin A2 and aid in the design of analogs to further explore and develop this novel class of antibiotic.

**MEDI 3**

**Small molecule probes for the investigation of biological processes**

***Douglas D. Young*** *and Alexander Deiters, Department of Chemistry, North Carolina State University, 2620 Yarbrough Drive, Box 8204, Raleigh, NC 27695*

Obtaining a greater understanding of complex biological processes is integral to the treatment of various diseases and disorders. The presented research describes the development of new tools to investigate gene expression and afford insights into biological systems. Specifically, new methodologies towards [2+2+2] cyclotrimerization reactions have been discovered leading to the synthesis of small arrays of compounds for biological screens. Additionally, photolabile protecting groups have been installed on biologically relevant molecules to control cellular events via light irradiation.

**MEDI 4**

**Rational design of T-shaped potassium channel blockers**

***Erica M. Wilson Lauterwasser***[1]*, ewilson@berkeley.edu, Leila H. Shirazi*[1]*, ewilson@berkeley.edu, Sarah Bell*[2]*, ewilson@berkeley.edu, Ehud Y. Isacoff*[2]*, ewilson@berkeley.edu, and Dirk Trauner*[1]*, trauner@berkeley.edu. (1) Department of Chemistry, University of California, Berkeley, 628 Latimer Hall, Berkeley, CA 94720, (2) Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720*

We have designed and synthesized a series of T-shaped reversible potassium channel pore blockers. These small molecules are proposed to occlude the potassium channel pore by the insertion of an ammonium terminated ligand. This mechanism of action is well precedented in the potassium channel blocking mechanism of the natural toxin peptides isolated from snakes, spiders, and scorpions. Further evidence of the binding hypothesis will be discussed.

**MEDI 5**

**Perturbing gene transcription with small molecule isoxazolidines**

***Sara J. Buhrlage****, Brian B. Brennan, Steven P. Rowe, Ryan J. Casey, and Anna K. Mapp, Department of Chemistry, University of Michigan, 930 N. University, Ann Arbor, MI 48109*

Misregulated transcription is associated with many diseases as either a cause or an effect. Thus, molecules that can restore normal gene expression levels to aberrantly expressed genes are highly desirable tools for studying disease and for use as therapeutics. With the goal of developing small molecules that can perturb transcription of target genes, isoxazolidines and short isoxazolidine oligomers that interact with transcriptional co-activator proteins have been designed, synthesized, and evaluated. Transcriptional co-activator proteins play an integral role in transcription serving as a bridge between DNA-bound transcription factors and components of the RNA polymerase holoenzyme and thus are promising targets for both activating and inhibiting target genes. We have shown that our small molecules designed to incorporate the key features of endogenous ligands for

transcriptional co-activator proteins do interact with several co-activators and function to alter gene expression levels in a cellular system.

**MEDI 6**

**Forces that stabilize the collagen triple helix**

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Collagen is the most abundant protein in animals. The canonical repeat of amino acids in collagen is Xaa-Yaa-Gly, where Xaa is often (2S)-proline and Yaa is often (2S,4R)-4-hydroxyproline. Despite the importance of collagen, a consensus on the molecular factors controlling collagen triple-helix structure and stability remains elusive. The important role of preorganization in defining triple-helical structure and maintaining its stability will be discussed. Specifically, our findings have shown that hyperstable collagen triple helices are accessible via preorganization of backbone dihedrals and proline rings in individual peptide strands for collagen triple-helix formation. Our developing understanding of the factors that control triple-helix structure and stability is enabling advances in a variety of collagen-based biomaterials applications.

**MEDI 7**

**Design, synthesis, and evaluation of ligands for the Grb2 SH2 domain: Exploring molecular preorganization**

*Stephen F. Martin[1],* ***Johnathan E. DeLorbe****[1], jdtex66@mail.utexas.edu, Martin G. Teresk[1], and Aaron P. Benfield[2]. (1) Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station, A5300, Austin, TX 78712, (2) Department of Carcinogenesis, University of Texas M.D. Anderson Cancer Center, Smithville, TX*

Preorganization of flexible ligands into their biologically active conformations is generally believed to have a favorable effect upon binding entropy and thus be advantageous for binding, yet there is a lack of scientific evidence supporting this generalization. The Martin group has reported that for the Grb2 SH2 domain, certain preorganized ligands do in fact bind with higher affinities than their flexible counterparts. However, in an unprecedented finding, we observed that the entropies of binding for these preorganized ligands, while still favorable, were disfavored relative to their less potent flexible controls. Studies directed towards elucidating the underlying energetic and structural effects arising from the introduction of conformational constraints into flexible ligand molecules are ongoing. Ultimately, this research could lead to the development of new strategies for designing high affinity ligands possessing constraints while also helping to understand the principles associated with protein-ligand interactions.

**MEDI 8**

**Application of a cycloisomerization strategy to the synthesis of icetexane and cortistatin natural products and structural analogs**

***Eric M. Simmons**, Alison R. Hardin, Xuelei Guo, Jennifer R. Yen, and Richmond Sarpong, Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720*

The icetexane and cortistatin natural products are seven-membered ring containing compounds that possess diverse biological activity. The icetexane diterpenoid komaroviquinone displays nanomolar activity against T. cruzi, the parasite that causes Chagas' disease. It also acts as an antagonist toward the CCR5 receptor and may prove to be an effective anti-HIV agent. Cortistatin A is the most potent member of a family of steroidal alkaloids that display nanomolar anti-angiogenic actvitiy, making it an attractive lead for the development of anticancer compounds. Our efforts toward both families utilize a key alkynyl indene cycloisomerization reaction to generate a benzocycloheptadiene that contains the complete natural product core. The diene provides a versatile synthetic handle which can be used to elaborate the core framework. Utilizing this strategy, a number of natural products have been synthesized, and a series of analogs designed to probe the structural elements required for biological activity have been prepared and assayed.

**MEDI 9**

**Thiadiazolopiperazinyl ureas as inhibitors of fatty acid amide hydrolase**

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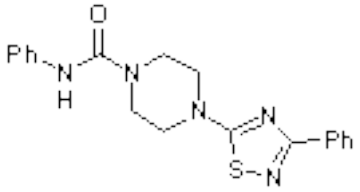
A series of thiadiazolopiperazinyl aryl urea fatty acid amide hydrolase (FAAH) inhibitors is described. The molecules were found to inhibit the enzyme by acting as slowly turned over substrates, likely forming a transient covalent bond with Ser241. SAR and PK properties are presented.



**MEDI 10**

## Discovery of di-aryl triazolopyridazine cannabinoid receptor (CB1) antagonists

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A series of novel bicyclic triazolopyridazine cannabinoid receptor-1 (CB1) antagonists is described. We previously reported a series of di-aryl pyrazine carboxamide CB1 antagonists, and the progression of this series to include fused bicyclic triazolopyridazine CB1 antagonists is reported herein. The bicyclic series leads to compounds with greater in vitro potency and selectivity (CB1/CB2) as compared to the monocyclic series. In vitro and in vivo profiling of the triazolopyridazine CB1 antagonists is described.

**MEDI 11**

## New core for cPLA$_2$α inhibitors: Beyond indoles

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Cytosolic phospholipase A$_2$α (cPLA$_2$α) selectively cleaves the *sn-2* position of arachidonyl glycerophospholipids to generate arachidonic acid. Arachidonic acid is converted by downstream enzymes to a variety of inflammatory mediators, including leukotrienes, prostaglandins, and thromboxanes. The lysophospholipid remaining after arachidonic acid cleavage can be acetylated to form yet another inflammatory mediator, platelet activating factor (PAF). Selective inhibition of cPLA$_2$α could provide a novel therapeutic with applications in many disease states including rheumatoid arthritis, osteoarthritis, asthma, multiple sclerosis, and atherothrombosis. We have previously disclosed indole inhibitors of cPLA$_2$α; here we present our work on a new core. In this presentation,

we will present the various synthetic routes employed to prepare these new cPLA2α inhibitors and data from isolated enzyme and whole blood assays, pharmacokinetic studies, and animal models.

**MEDI 12**

**Discovery of PSI-421, a P-Selectin inhibitor with improved pharmacokinetic properties and oral efficacy in models of vascular injury**

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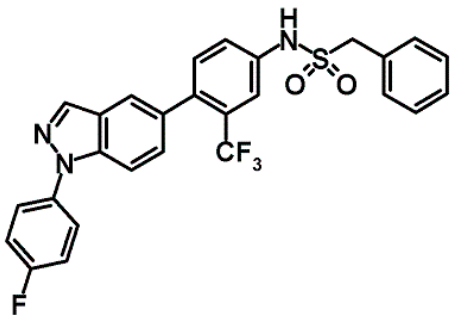
The adhesion molecule P-Selectin is expressed on activated platelets and endothelial cells, and its ligand PSGL-1 is constitutively expressed on leukocytes. Disruption of the P-selectin/PSGL-1 interaction may have significant therapeutic potential in vascular inflammation and thrombosis. Consequently, inhibition of this interaction by means of a small molecule P-selectin antagonist is an attractive strategy for the treatment of diseases like atherosclerosis and DVT. High-throughput screening and subsequent optimization of the hits had led to the identification of PSI-697, which is currently in the clinic. We will present the continuation of this work and the discovery of a second-generation series, the cyclopropyl quinoline salicylic acids. These compounds have improved aqueous solubility and pharmacokinetic properties, and have shown oral efficacy in animal models of both arterial and venous injury. The lead PSI-421, is currently in predevelopment.

**MEDI 13**

**Design of indazole based, nonsteroidal glucocorticoid receptor agonists**

***Christopher M. Yates****, Molecular Discovery Research, GlaxoSmithKline, 5 Moore Drive, Durham, NC 27709*

Glucocorticoid receptor (GR) agonists have been shown to have potent anti-inflammatory activity. We describe the design and synthesis of three arrays based on computation docking methods and the optimization of one chemotype to several potent non-steroidal agonists. A lead compound was chosen based on its potency and desirable pharmacokinetics for further profiling in gene expression experiments and *in vivo*. We were able to demonstrate that this compound is identical to traditional steroidal agonists in profile and potency, but due to high plasma protein binding *in vivo* efficacy was diminished.

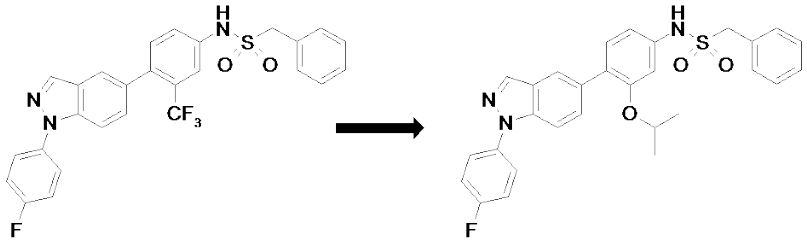


**MEDI 14**

**Modulation of the glucocorticoid receptor through displacement of the AF2 helix**

***Ryan P. Trump**, Discovery Medicinal Chemistry, GlaxoSmithKline, 5 Moore Dr, Research Triangle Park, NC 27709, Fax: 919-483-6053*

Modulation of the glucocorticoid receptor (GR) has the potential to treat inflammation, diabetes, and depression with an improved safety profile over conventional GR agonists and antagonists. We describe the modification of a GR non-steroidal agonist to progressively displace the AF2 helix resulting in the reduction of the intrinsic efficacy of the compounds. We profile these compounds extensively using co-factor recruitment, gene expression, and phenotypic assays to evaluate the potential of these compounds to be safer GR drugs. The data indicate that reducing the efficacy of GR agonist should result in an improved therapeutic index for the drug.



**MEDI 15**

**Science and serendipity: Discovery of novel, orally bioavailable adenosine $A_{2A}$ antagonists for the treatment of Parkinson's disease**

***Allan M. Jordan**, Medicinal Chemistry, Vernalis (R+D) Ltd, Granta Park, Great Abington, Cambridge CB21 6GB, United Kingdom, Fax: +44 (0)1223 895556*

The human adenosine receptor is a G-protein coupled receptor which is delineated into four distinct sub-types, designated $A_1$, $A_{2A}$, $A_{2B}$ and $A_3$. The adenosine $A_{2A}$ receptor plays an important role in regulating smooth and well-coordinated movement, in part by modulating the activity of dopamine sensitive neurons in the striatum. There is strong, mounting evidence that adenosine $A_{2A}$ receptor antagonists may provide a novel point of therapeutic intervention for Parkinson's disease with a lower incidence of side effects commonly associated with other treatments. However, though the xanthine-based agent KW-6002 has now completed clinical trials for this debilitating condition, the discovery and development of selective, potent and metabolically stable compounds with good oral bio-availability remains a challenging proposition.

As part of our ongoing efforts to discover new treatments for this condition, we discovered that the (-)-diastereoisomer of the antimalarial drug mefloquine is a reasonably potent and moderately selective adenosine $A_{2A}$ receptor antagonist (61 nM, 4-fold selective against the human $A_1$ receptor). Using this compound as a startpoint, a series of iterations led to the identification of several novel series of $A_{2A}$ antagonists and these investigations ultimately lead us to the discovery of V2006, which is now undergoing Phase II clinical trials.

This presentation will reveal a novel, small-molecule class of adenosine $A_{2A}$ receptor antagonists which display a high degree of potency and selectivity against the other adenosine receptor sub-

types. Detailed examination of the series indicated high solubility and oral bioavailability, excellent brain penetration and rapid onset of action. Moreover, a number of these compounds displayed strong activity in *in vivo* models predictive of clinical efficacy.

**MEDI 16**

**Discovery of clinic candidate pf-4217903-a highly potent and exquisitely selective c-met inhibitor**

***J. Jean Cui**, Mitchell Nambu, Michelle Tran-Dube, Hong Shen, Mason Pairish, Lei Jia, Hengmiao Cheng, Jacqui Hoffman, Phuong Le, Catherine Johnson, Robert Kania, Michele McTigue, Neil Grodsky, Kevin Ryan, Max Parker, Shinji Yamazaki, Helen Zou, and James G. Christensen, PGRD La Jolla Laboratories, Pfizer, Inc, 10770 Science Center Dr, San Diego, CA 92121*

c-Met receptor tyrosine kinase is an attractive oncology target due to its critical role in human oncogenesis and tumor progression. An oxindole hydrazide lead was identified during a HTS against c-Met target and subsequently demonstrated an unusual degree of selectivity against a broad array of other kinases. The co-crystal structure of oxindole hydrazide c-Met inhibitor with c-Met kinase domain revealed a very unique binding mode associated with the exquisite selectivity. Structure-based drug design and medicinal chemistry lead optimization produced PF-4217903, a highly potent and exquisitely selective c-Met inhibitor. PF-4217903 had low nM potency against c-Met in both in vitro cell assays and in vivo target modulation studies, demonstrated effective tumor growth inhibition in c-Met dependent tumor models, and exhibited good oral PK properties. PF-4217903 demonstrated over 1000-fold selectivity against a diverse array of >150 different tyrosine and serine-threonine kinases. PF-4217903 is currently in Phase I clinical studies for oncology applications.

**MEDI 17**

**Small molecule disruptors of the Rb-Raf-1 protein-protein interaction: Tumor growth inhibitors**

***Nicholas J. Lawrence**, Daniele Pernazza, Piyali Dasgupta, Rebecca L. Kinkade, Adam A. Carie, Xin Wu, Roberta Pireddu, Said M Sebti, and Srikumar P. Chellappan, Drug Discovery Program, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612*

The retinoblastoma tumor suppressor protein, Rb, is a fundamental regulator of the mammalian cell cycle, and most human tumor cells present inactivation or interference of the Rb-regulatory pathway. By specifically binding and phosphorylating Rb, the serine-threonine kinase Raf-1 initiates a cascade of events that eventually leads to its and inactivation, which in turn leads to cell growth. Our search for small molecule inhibitors of Rb-Raf-1 binding has identified two benzylisothiouronium salts from a screen of a 2000 compound library. Various analogues of the hits were synthesized and evaluated for their ability to disrupt Rb-Raf-1 binding. We have identified a series of benzylisothiouronium derivatives as potent disruptors of the Rb-Raf-1 binding with $IC_{50}$ values ranging from 80 to 500 nM. One of these 2,4-dichlorobenzylisothiourea suppresses human tumor growth in nude mice. The benzylisothioureas and analogues are the basis for a new strategy for anticancer drug development, and provide proof of principle that small molecules can be used to halt tumor growth by disrupting the Rb-Raf-1 interaction.

**MEDI 18**

## Radical induced redox chemistry of platinum-containing anticancer drugs

***Katy L. Swancutt***[1]*, k_swancutt@yahoo.com, Stephen P. Mezyk*[1]*, smezyk@csulb.edu, and James J. Kiddle*[2]*, james.kiddle@wmich.edu. (1) Department of Chemistry and Biochemistry, California State University at Long Beach, 1250 Bellflower Blvd, Long Beach, CA 90840, (2) Department of Chemistry, Western Michigan University, Kalamazoo, MI 49008*

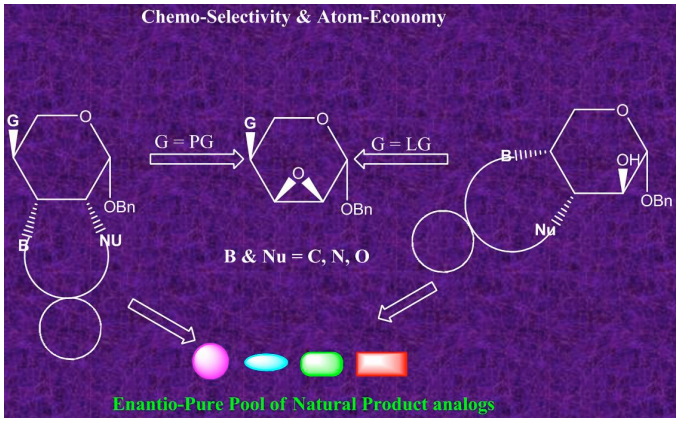
Cisplatin (cis-Diamminedichloroplatinum(II)) , has been used as a versatile and highly effective treatment for various cancers. Unfortunately, the amounts that can be prescribed are limited by its nephrotoxicity. Of the multiple cisplatin analogues that have been synthesized and tested, Carboplatin (cis-diammine[1,1-cyclobutane-dicarboxylato]platinum(II)), has become a common, successful, alternative that exhibits reduced toxicity while retaining significant anti-cancer properties. In addition, many Pt(IV) and mixed Pt(II)/Pt(IV) multi-nuclear Pt containing drugs have been synthesized and tested for anti-cancer properties over the past 40 years. We have recently begun investigating the source of these drugs' toxicity, notably their role in the formation of the superoxide radical anion under physiological conditions. We report here the absolute kinetics and reaction mechanisms of the free radical induced hydroxyl radical and hydrated electron oxidation and reduction reactions with several different Pt(II) and Pt(IV)-containing drugs and model compounds, and how these species are involved in superoxide formation.

**MEDI 19**

## Diversity-oriented synthesis: Enantioselective synthesis of a pool of small molecules as drug candidates

***Taleb H. Al-Tel***[1]*, altelth@duke.edu, Salim S. Sabri*[1]*, Jalal Zahra*[2]*, and Mazen Qato*[1]*. (1) College of Pharmacy, University of Sharjah, University Street, Sharjah 27272, United Arab Emirates, (2) Chemistry, University of Jordan, Amman, Jordan*

Diversity oriented synthesis, which aims to produce a wealth of structural complexity, may prove to be an effective tools of exploring effective routes toward the link between chemistry and medicine.The key synthesis objective is to generate a collection of structurally complex and diverse compounds capable of modulating any biological pathway or process of interest.¬1 In this lecture we will present our efforts in the discovery of Neuraminidase inhibitors, a possible drug candidates for Flu pandemics. Furthermore, the enantioselective synthesis of skeletally diverse compounds inspired by natural analogues and related biologically active compounds for many purposes will be presented.



**MEDI 20**

**Discovery and characterization of allosteric inhibitors of Bcr-Abl kinase**

***Nathanael S. Gray**, Dana Farber Cancer Institute, Harvard Medical School, Seeley G. Mudd building, 628A, 250 Longwood Ave., Boston, MA 02115*

Protein kinases have rapidly become one of the most pursued protein families in the quest for new drugs. The vast majority of inhibitors target various conformations of the ATP-binding site which often results in the compounds exhibiting multiple kinase targets. For example, inhibition of Bcr-Abl kinase activity by the ATP-competitive inhibitor imatinib for the treatment of Chronic Myeloid Leukemia (CML) currently serves as the paradigm for targeting dominant oncogenes with small molecules. We recently reported the discovery of GNF-2, a “mono” selective non-ATP competitive inhibitor of cellular Bcr-Abl kinase activity. We will demonstrate using a combination of biochemical, cellular and biophysical approaches that GNF-2 binds to the Abl- myristate binding site and allosterically inhibits kinase activity. GNF-5, an analog of GNF-2 with improved pharmacokinetic properties, displays efficacy in a Bcr-Abl dependent animal model. Combined treatment of GNF-5 with the ATP-competitive inhibitor nilotinib suppressed the emergence of resistance mutations *in vitro* and displayed *in vivo* efficacy against the recalcitrant T315I Bcr-Abl mutant in a murine bone-marrow transplantation model. These results demonstrate that a therapeutically relevant inhibition of Bcr-Abl activity can be achieved using inhibitors that bind to the myristate binding site and that combined treatment of allosteric and ATP-competitive inhibitors can address mutations that induce resistance to either agent alone.

**MEDI 21**

**Development of inhibitors of Protein Kinase B (AKT) using fragment based lead discovery**

***Steven J. Woodhead**, Department of Medicinal Chemistry, Astex Therapeutics, 436 Cambridge Science Park, Cambridge CB4 0QA, United Kingdom*

The AKT pathway is an important mediator of tumor cell growth and survival and activation of this pathway is associated with several resistant forms of cancer. Using fragment based screening techniques, novel, low molecular weight inhibitors of AKT were identified and then elaborated using a fragment growing approach. Iterative structure-based design, supported by protein-ligand structure determination, permitted the rapid optimisation of a series of potent and highly ligand efficient lead compounds. Through rational design, these lead compounds were then further optimised and developed in to high affinity, allosteric inhibitors of AKT.

**MEDI 22**

**Allosteric Akt kinase inhibitors**

***Philip E Sanderson**, Department of Medicinal Chemistry, Merck and Company, Merck Research Laboratories, WP 14-3, West Point, PA 19486*

Serine/threonine kinase Akt (PKB) is a key component of the PI3K/Akt signaling pathway. This pathway mediates cell survival, proliferation and growth and it is activated in the majority of solid tumors. Moreover, pathway activation correlates with tumor progression and enhanced Akt activity is associated with resistance to traditional and targeted therapies. Consequently Akt is an attractive target for the development of targeted cancer therapy. Akt can be inhibited by molecules which bind at an allosteric, pleckstrin homology (PH) domain dependent site. This has enabled the development of a class of compounds which are highly selective for Akt over other kinases and which have a spectrum of selectivity between the three Akt isozymes. Potent and efficacious Akt1/2 selective compounds from this class will be described.

**MEDI 23**

**Development of thioquinazolinones, allosteric Chk1 kinase inhibitors**

***Antonella Converso**, Department of Medicinal Chemistry, Merck & Co, WP14-2, 770 Sumneytown Pike, P.O. Box 4, West Point, PA 19486, Fax: 215-652-7310*

Following DNA damage, normal cells arrest and attempt repair via tumor suppressor protein p53 and via checkpoint kinase Chk1. Between 50 and 70% of all cancers, however, present defects in their p53 DNA damage response pathway and must rely solely on Chk1 to induce arrest for repair. Chk1 inhibition in these cancers would deprive them of the only cell-repair mechanism available, causing abrogation of DNA-damage-induced arrest and premature progression into mitosis. Inhibition of Chk1 should therefore sensitize p53-deficient cancer cells to DNA damaging agents without enhancing toxicity toward non-malignant cells, thereby widening the therapeutic window for clinically-utilized DNA damaging agents.

An HTS campaign was designed to identify allosteric inhibitors of Chk1. Activity was observed at Km for ATP and at sub-physiological concentrations of ATP, leading to the discovery of a non-ATP competitive thiaquinazolinone series. An X-ray crystal structure for the complex of our best inhibitor bound to Chk1 was solved, indicating that it binds to an allosteric site ~13 Å from the ATP binding site.

**MEDI 24**

**Discovery of allosteric MEK inhibitors**

***Eli M. Wallace**, Department of Lead Optimization, Array BioPharma Inc, 3200 Walnut Street, Boulder, CO 80301*

The extra-cellular regulated kinase (ERK) pathway is involved in growth, proliferation, and survival, all of which are dysregulated in oncogenesis. This pathway is constitutively activated in several human tumor types, including those from skin, colon, pancreas, kidney, ovary, thyroid and lung. Activation of the pathway has been shown to arise by multiple mechanisms such as over-expression of growth factor receptor tyrosine kinases or mutations in upstream regulators such as Ras and Raf. The final step in the activation of ERK is its phosphorylation by mitogen-activated protein kinase kinase (MEK). The MEK-ERK signaling module is highly specific as the only known substrate for MEK phosphorylation is ERK and the only known activator of ERK is MEK. As such, inhibition of MEK is an attractive target for anti-cancer therapy. In this presentation, the design, preparation and biological

characterization of several classes of potent, selective, orally bioavailable allosteric MEK inhibitors will be described.

**MEDI 25**

**Injectables for prevention of pain and peritoneal adhesions**

***Daniel S Kohane**, Anesthesiology/Critical Care Medicine, Children's Hospital Boston, Harvard Medical School, Bader 628, 300 Longwood Ave., Boston, MA 02466, Fax: 617-730-0453*

Biomaterials and delivery technologies have come to play major roles in the delivery of drugs to a variety of anatomical locations. Here we will address issues in delivery to peripheral nerve and the peritoneum. Due to the broad extent of the research in these topics, we will be restricted to covering themes that are broadly applicable with emphasis on design criteria, major challenges, what has been done, and lessons learned, rather than a detailed review of the field.

**MEDI 26**

**Drug eluting stent technology**

***Josiah N. Wilcox**, Dept. Science & Technology, Medtronic CardioVascular, 3576 Unocal Place, Santa Rosa, CA 95403*

Drug eluting stents (DES) are widely used in an effort to reduce the incidence of restenosis and target lesion revascularization after coronary artery stenting. There are four components of a DES including the stent, the balloon catheter delivery system, the drug and a polymer that binds the drug to the stent and/or controls its release in a timed fashion. The most important considerations relative to successful development of a DES are the choice of drug, the kinetics of drug release and the polymeric coating. This presentation will discuss the relative advantages of slow and fast release DES drug formulations as well as the importance of polymer biocompatibility on long term safety and efficacy of DES.

**MEDI 27**

**Systemic delivery of RNA interference for metabolic and oncology targets**

***Muthiah Manoharan**, Department of Drug Discovery, Alnylam Pharmaceuticals Inc, 300 Third Street, Cambridge, MA 02142*

RNA interference (RNAi) is a powerful biological process for specific silencing of mRNAs in diversified eukaryotic cells. By introducing chemical modifications into synthetic siRNA (small interfering RNAs) building blocks, desirable "drug-like" properties can be imparted to the siRNAs. siRNAs containing chemical modifications show enhanced resistance towards nuclease degradation, suppression of immune stimulation as well as reduced "off-target" effects. To achieve in vivo delivery, certain chemical conjugates and novel formulations are being investigated. Alnylam is developing a pre-clinical and clinical pipeline of RNAi-based therapeutics to treat numerous diseases. Using the systemic treatment paradigm, we have demonstrated the ability to silence several liver gene targets,

including PCSK9, that are important for treating metabolic diseases. PCSK9 has been genetically and experimentally implicated in LDLc regulation. We have shown in several animal models that silencing of PCSK9 in the liver by systemically delivered siRNA lowers both circulating PCSK9 protein levels in blood and plasma cholesterol levels. In the oncology area, we are developing an RNAi therapeutic for liver malignancies comprising liposomally formulated siRNAs targeting VEGF and the mitotic kinesin, KSP (Eg5, Kif11). For each target, potent and specific siRNA duplexes have been identified following extensive screening in cell culture. As expected, silencing of KSP in vitro leads to cell death in multiple tumor cell lines, while silencing of VEGF leads to inhibition of VEGF secretion into cell culture medium. To achieve hepatic delivery, liposomal formulations have been evaluated and shown to achieve silencing of hepatic gene expression with multiple siRNAs directed against distinct targets, including VEGF and KSP. To evaluate the therapeutic potential of this approach, pre-clinical safety and efficacy studies are being conducted.

**MEDI 28**

**Topical adenosine A2A receptor agonists for the treatment of poorly healing wounds**

***Bruce N. Cronstein*** *and Paul R. Esserman, Department of Medicine, Division of Clinical Pharmacology, NYU School of Medicine, 550 First Ave, New York, NY 10016, Fax: 212-263-1048*

Adenosine and its receptors play important roles in a number of physiologic and pharmacologic processes. Recent studies indicate that adenosine A2A receptors play central roles in promoting granulation tissue, new blood vessels and matrix, formation in dermal wounds. Making use of this understanding of the role of adenosine A2A receptors new agents have been designed to stimulate wound healing in poorly healing wounds, such as those suffered by patients with Diabetes Mellitus. Topical application of adenosine A2A receptor agonists stimulates new blood vessel formation and new collagen production by multiple mechanisms. These mechanisms will be discussed. In addition, clinical development of topical adenosine A2A receptor agonists for the treatment of diabetic foot ulcers is progressing and these results will be discussed.

**MEDI 29**

**Ocular drug delivery: Challenges and opportunities**

***Ashim K. Mitra****, Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri Curator's Professor of Pharmacy and Chairman, 5005 Rockhill Road, Room 108C, Kansas City, MO 64110-2499, Fax: 816-235-5190*

Ocular drug delivery has long been a challenging task to pharmaceutical scientists seeking to treat various ocular diseases affecting the anterior and posterior segments. In order to deliver therapeutic agents to target tissues, the unique anatomical barriers of the eye must be circumvented effectively, without causing any patient discomfort or alteration in protective physiological mechanisms. Topical mode of administration is the most preferred and convenient route to deliver drugs to the anterior segment. But the ocular bioavailability is extremely limited due to a highly selective corneal epithelium and various pre-corneal physiological processes resulting in the loss of drug. Drug delivery to the posterior segment is equally difficult due to the presence of blood aqueous barrier (BAB) and blood retinal barrier (BRB). The BRB is mainly comprised of retinal pigment epithelium (RPE) which regulates the diffusion of substances from the blood into the vitreous and retina. Hence the current challenge lies in not simply developing new therapeutic targets, but also finding more effective drug

delivery technologies which do not cause alterations in the protective ocular mechanisms. These challenges have been successfully met in our laboratory by novel drug delivery strategies targeting the diseases affecting the anterior and posterior segment of the eye. Examples highlighting one novel delivery mechanism/system developed for anterior and posterior segment will be discussed.

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**MEDI 30**

**Community-based collaborative drug discovery for neglected infectious diseases and cancer**

***Barry A. Bunin**, Collaborative Drug Discovery, Inc, 1818 Gilbreth Road, Suite 220, Burlingame, CA 94403, Fax: 650-522-9498*

Case studies from scientists working in secure collaborative groups to rapidly develop drug candidates for commercial and humanitarian markets will be presented. The first case study involves overcoming drug resistance which is the major problem for malaria. New approaches that allow scientists working together to develop new drugs faster are desperately needed. The discovery of alternatives to Verapamil, a known chemosensitizer to overcome both tumor and malaria resistance, will be presented using novel collaborative drug discovery technologies to help specialists work together in a global network. A detailed example showing how chemosensitizers addressing chloroquine resistance can be identified combining results from the University of Cape Town (South Africa) with structurally related compounds from the University of California at San Francisco (USA) and similar FDA/Orphan (courtesy Dr. Lipinski) approved drug compounds will be presented. This new collaborative technology allows researchers to build up networks of technical experts around therapeutic or target areas thus facilitating discovery of new drug candidates. Other case studies will presented including: a Malaria Computational and Experimental around large set of historical small molecule animal SAR data case study (UNC, St. Jude), a Malaria UGI-4CC Open Collaboration case study (Drexel-Indiana-UCSF), a Tuberculosis Public Private Partnership case study (TAACF, Lilly, Cornell), and a GPCR gene-family wide Ki community Database (PDSP, UNC). The community-based platform is currently being used *openly* to help develop new treatments for neglected infectious diseases such as malaria, Chagas Disease, and African Sleeping Sickness and *securely* against commercial cancer targets.

**MEDI 31**

**Imaging probe development center: A new synthetic chemistry facility producing imaging probes at the NIH**

***H. Wu**, C. Wilson, G. Kaur, H. Li, N. Neale, Z. Shi, A. Sulima, B. Teng, O. Vasalatiy, B. Xu, S. Cofiell, E. Frohardt, B. Ruddy, and G. L. Griffiths, Imaging Probe Development Center, National Heart, Lung, and Blood Institute, National Institutes of Health, 9800MCD, Rockville, MD 20850*

The Imaging Probe Development Center (IPDC), part of the Molecular Libraries and Imaging Program of the NIH Roadmap for Medical Research Initiative (http://nihroadmap.nih.gov/), recently became fully operational in Rockville, MD. It is dedicated to the production of known and novel molecular imaging probes for the NIH intramural community, and it is intended that the wider scientific community will benefit from its resources in the future. The Center has been set up with the belief that molecular imaging, and the probe chemistry underpinning it, will constitute key technologies going

forward. IPDC is staffed by a team of chemists representing a variety of scientific expertise centered on synthetic and imaging chemistries and the probes produced include optical, radionuclide and magnetic resonance agents. IPDC is expected to play a key part in interdisciplinary collaborative imaging projects throughout the 27 NIH Institutes and Centers and to support translational R&D from basic research through clinical development. Some examples of probes already prepared or under preparation, along with a brief outline of the diverse applications involved, will be provided to illustrate the breadth of the program, which can also be viewed at:
http://nihroadmap.nih.gov/molecularlibraries/ipdc/

**MEDI 32**

**Optimization of the pyridopyrazinone scaffold as novel inhibitors of PDE5**

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Efforts to identify long-acting PDE5 inhibitors led to the discovery of the pyridopyrazinones as a novel class of selective inhibitors. This poster describes efforts around optimization of this class of compounds focusing primarily on improving physical/chemical propteties while maintaining excellent potency and selectivity. Compounds suitable for once-a-day dosing are described.

**MEDI 33**

**Peptides inhibitors of F11R/JAM-A adhesion molecules**

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F11-R receptor was characterized as an adhesion protein, called also aka JAM-A (or JAM-1), which under normal physiological conditions is expressed constitutively on the surface of the platelets and localized within tight junctions of endothelial cells (EC). The utilization of specific F11R/JAM-A peptide antagonists and recombinant proteins supported the role of F11R/JAM-A in the process of platelets adhesion to inflamed endothelial cells and identified plaque formation leading to inflammatory thrombosis and atherosclerosis where the platelets have a critical influence in the progression and development of the cardiovascular disease. Thus, the development of new drugs antagonizing the F11R/JAM-A function could evolve as an effective strategy for the treatment of atherosclerosis, heart

attacks and stroke. We present one of the first trials toward development of peptide-based inhibitors of F11R/JAM-A function. Among many trials, the peptide D-Lys-Ser-Val-Ser-D-Arg-Glu-Asp-Thr-Gly-Thr-Tyr-Thr-Cys-CONH2 proved to be a potent inhibitor of human platelets aggregation in vitro. Further molecular docking experiments showed that this peptide makes favorable hydrophobic and electrostatic interactions within the proposed binding site of JAM-1 (X-Ray structure 1nbq.pdb was used as template).

**MEDI 34**

**Development of a dual-modality optical and magnetic resonance imaging probes targeted to integrins**

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Imaging methods such as MRI and optical that could noninvasively and repeatedely measure integrin expression would be useful in characterizing tumors and in monitoring responses to therapeutic agents. The coregistration of different molecular imaging modalities provides complementary information. Thus development of multifunctional probes for concurrent imaging applications has become an attractive area of investigation. Molecular interactions between RGD peptides and integrins are known to mediate many biological and pathological processes, this has led to an increased interest in the development of RGD-based peptidomimetic or non-peptidic compounds with high-affinity and improved selectivity for integrin receptors. In this study, we synthesized and characterized multimeric nonpeptidic compounds constructed on a rigid adamantane scaffold-containing near-infrared (NIR) fluorescent dye and (MRI) specific metal Gd-DOTA probe for tumor-targeting of αvβ6 integrin, a fibronectin/tenascin receptor, αvβ3 a promiscuous receptor for vitronectin, fibronectin, fibrinogen, and αvβ5 a vitronectin receptor. Further study is in progress.

**MEDI 35**

**Differential recognition of Gram-positive and -negative synthetic peptidoglycan fragments by Toll Like receptor 2**

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The innate immune system constitutes the first line of defense against invading pathogens that rapidly respond by initiating an acute inflammatory responses. Over-activation of this inflammatory response can however, lead to the clinical symptoms of septic inflammatory response (SIR) syndrome and includes life –threatening symptoms such as viscular fluid leakage, tissue damage, hypotension and organ failure. The molecular basis for innate immune detection of peptidoglycan (PGN), a primary component of bacterial cell wall, by Toll-like receptor 2 (TLR2) is poorly understood. PGN are large polymers composed of alternating beta-(1-4)-linked N-acetylglucosamine (GluNAc)

and N-acetylmuramic acid (MurNAc) residues, which are cross linked by short peptide bridges. The carboxylic acid of N-acetylmuramic acid is linked to stem peptide bridges of four or five alternating L- and D-amino acids. We synthesized a wide range of well-defined synthetic PGN fragments derived from Gram-positive and –negative bacteria and employed surface plasmon resonance binding studies, using a wide range of well defined synthetic PGN fragments both Gram-positive and –negative bacteria to demonastrate that TLR2 can recognize peptidoglycan. The established structure-activity relationship demonstrates that host as well as pathogen can exploit structural modification between PGN of different bacterial strains to modulate or evade immune detection. Cellular activation studies employing highly purified and chemically modified PGN support the structure binding studies. The data presented indicates a detailed knowledge of the interaction of PGN with TLR2 at the molecular level may provide an opportunity for the development of new therapeutic strategies for the treatment of SIR.

**MEDI 36**

**Discovery of tear gases and their analogs as extremely potent activators of the human TRPA1 receptor**

***Harrie JM. Gijsen****, Didier Berthelot, Bert Brône, and Marc Mercken, Johnson and Johnson Pharmaceutical Research and Development, Turnhoutseweg 30, B-2340 Beerse, Belgium*

The TRPA1 channel is activated by a number of pungent chemicals, such as allylisothiocyanate present in mustard oil, and thiosulfinates present in garlic, via a reversible covalent bond formation with cysteine residues present in the ion-channel. In a high throughput screen aimed at the identification of TRPA1 ligands, a series of 6,11-dihydro-5H-dibenz[b,e]azepines or 5,6-dihydromorphantridines was discovered to behave as moderate to potent agonists of the TRPA1 receptor. Careful analysis of these hits revealed that these compounds had been partly oxidized to the corresponding morphanthridines which were proven to be responsible for the observed activity. The structural similarity to the known tear gas dibenz[b,f][1,4]-oxazepine (CR) has led to the discovery that most of the known tear gasses are potent TRPA1 activators. This presentation will show the process of this discovery, as well as the initial SAR around the morphanthridine and dibenz[b,f][1,4]-oxazepine class of TRPA1 agonists. With EC50's ranging from 1 microM-0.1 nM, we will demonstrate that their activity is not just determined by the lipophilic and electrophilic nature common to most TRPA1 agonists. Compared to the micromolar potency of agonists such as allylisothiocyanate, the 1000 fold increase in potency of some of the current agonists has made them useful tools in the discovery of TRPA1 antagonists. The identification of the molecular target for tear gasses may open up possibilities to alleviate the effects of tear gasses via treatment with TRPA1 antagonists. In addition these results may contribute to the basic knowledge of the TRPA1 channel that is gaining importance as a pharmacological target.

**MEDI 37**

**Investigations into the thermodynamic basis of fragment-based drug design**

***Erin M Wilfong****, Yu Du, Allison Schmitt, and Eric J. Toone, Department of Chemistry, Duke University, Box 90317, Durham, NC 27708*

While the number of known protein structures is expanding exponentially, a corresponding increase in the number of rationally designed drugs has not occurred. The paucity of rationally designed drugs is

a consequence of our minimalistic understanding of the forces that drive molecular association and ligand binding. Without an understanding of why a ligand binds its receptor, it is virtually impossible to predict a priori which ligands will bind a specific drug target.

Recently, fragment based drug design (FBDD) has emerged as a popular structure based approach to lead discovery. Despite the success of FBDD for myriad proteins, the thermodynamic basis for its success remains elusive. Using stromelysin-1 (MMP-3) as a model system and two previously described ligands, we have characterized extensively the thermodynamic principles of additivity and cooperativity in the context of FBDD. The results of these studies and their implications for drug discovery will be discussed.

**MEDI 38**

**New linker technologies for antibody drug conjugates of auristatins**

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The clinical activities of antibody-drug conjugates (ADCs) for cancer therapy have prompted a great deal of research towards understanding the factors that affect efficacy and tolerability. ADCs offer a potential improvement over conventional chemotherapies by preferentially targeting tumor cells, while sparing normal cells from chemotherapeutic damage. Successful therapy with ADCs requires several parameters to be addressed. The monoclonal antibody should be highly specific and in some cases internalize upon binding to the tumor cell antigen. The drug component should have high potency and be inactivated when conjugated to the antibody. In addition, the drug must be stable for extended periods, yet still be able to inflict cell death once released in the vicinity or within tumor cells. Efforts have been focused on creating linkers that are stable in circulation while promoting facile cleavage in tumor cells. Presented here are the results from recent modifications made at the maleimide position where the linker is attached to the reactive thiols of the reduced antibody. Thioether-*N*-arylsuccinimides, derived from *N*-arylmaleimides, are unique in that they readily undergo hydrolysis at physiological pH. Factors that affect this rate of hydrolysis include pH, temperature, and functional groups present on the aryl ring. One such ADC, 1F6-M-Bz-vcMMAE, contains a hydrolyzed para-succinimidobenzoyl function and was found to be highly stable when incubated in rat plasma, with less than 10% of the drug lost from the ADC after 7 days. The synthesis, stability studies, in vitro, and in vivo data will be presented for some of the molecules from this series.

**MEDI 39**

**New RNA selective ligands**

***Webster Santos****, Department of Chemistry, Virginia Tech, Blacksburg, VA 24061*

We report the discovery and development of a new class of ligands with RNA-binding properties: branched peptides. Several branched peptide combinatorial libraries have been synthesized on photocleavable TentaGel resins using split and pool synthesis, and tested for RNA binding using a high throughput “on-bead” screening strategy. These compounds have been assayed for binding to

fluorescently labeled TAR RNA, a short, stem-loop structure important for HIV replication. The results of our binding studies as well as their biophysical and biochemical characterizations will be presented.

**MEDI 40**

**Searching for a needle in a haystack of needles: Investigating the bioactive conformation of dictyostatin**

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Flexible bioactive organic molecules exist as ensembles of multiple low-energy conformations in solution, one of which may represent the bioactive conformation. The challenge of determining these conformations cannot be solved by NMR spectroscopy alone as conformational averaging in NMR gives rise to single, averaged, virtual structures. To address this problem, we have applied NAMFIS (NMR Analysis of Molecular Flexibility In Solution) to the highly flexible tubulin-binding agent dictyostatin, a potential anticancer lead. By using a combination of geometry-derived constraints from NMR (three-bond coupling constants (3JHH) and NOESY-derived intramolecular proton-proton distances) and extensive conformational sampling using multiple force fields, we have deduced a dozen or so conformations that represent the dominant conformer ensemble for dictyostatin in solution; conformers that differ from previously proposed single conformations for the molecule. Utilizing the NAMFIS conformers, we explored the binding pose and conformation of dictyostatin in β-tubulin consistent with some of the emerging SAR of synthetic analogs.

**MEDI 41**

**Synthesis and activity of 1-(3-amino-2-hydroxy-1-phenylpropyl)indolin-2-ones: Discovery of selective norepinephrine reuptake inhibitor WAY-315193 (NRI-193)**

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Norepinephrine (NE) is a major neurotransmitter in both the central and peripheral nervous system involved in regulating a wide variety of body functions. Extracellular levels of NE can be increased by

blocking NE reuptake at the NE transporter (NET). Drugs that inhibit NE reuptake either selectively or in combination with serotonin or dopamine have demonstrated efficacy in the clinic for a variety of indications such as attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), pain disorders (e.g. fibromyalgia), and vasomotor symptoms (VMS). Through the search for new compounds with improvements in both potency and selectivity, we identified a novel class 1-(3-amino-2-hydroxy-1-phenylpropyl)indolin-2-ones. These compounds, in both binding and cellular functional assays, showed NE reuptake inhibition while maintaining selectivity (>100) against the human serotonin and dopamine transporters. The properties of this series will be reported, focusing on the development of WAY-315193 for the treatment of disorders associated with NE deficiency.

**MEDI 42**

**Synthesis and affinity of bisphosphonate prodrugs to target the intestinal bile acid transporter**

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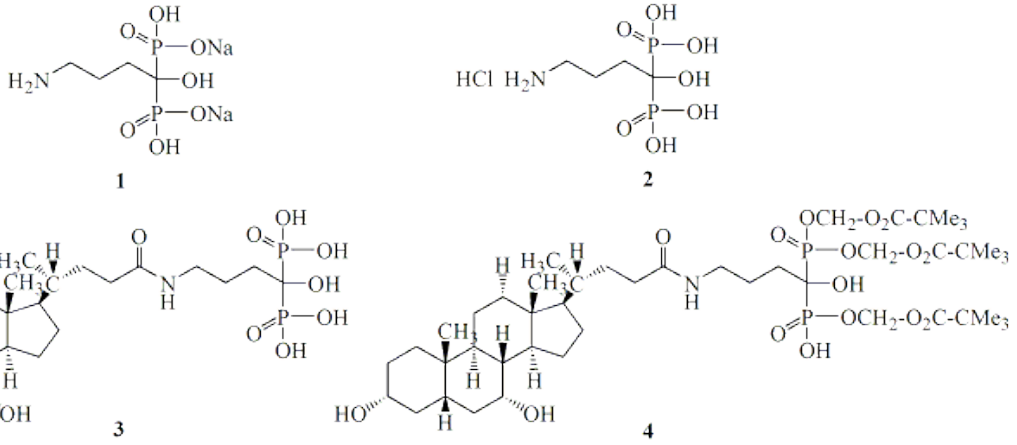
hASBT is a potential candidate for prodrug targeting to increase oral drug bioavailability because of its high capacity and efficiency for bile acid recovery. Alendronate 1, a bisphosphonate used for the treatment of osteoporosis, has oral bioavailability less than 1%. Its oral absorption could be enhanced by conjugation with naturally occurring bile acid such as chenodeoxycholic acid (CDCA) which is hASBT substrate. Synthesis of HCl salt 4 of alendronic acid was begun with one pot reaction between the acid chloride of phthaloyl-protected GABA and tris(trimethylsilyl)phosphate. Phthaloyl group was removed by hydrolysis with 6M HCl. Tris-pivalolyloxy group was introduced via esterification of CBZ-protected alendronic acid with chloromethyl pivalate. CBZ group was removed by catalytic hydrogenation. Compound 2 and its tris-pivalolyloxy were coupled to CDCA to give alendronate-CDCA conjugates 3 and 4, respectively. These conjugates were evaluated for binding to hASBT via inhibition of taurocholate uptake into hASBT-MDCK monolayers. Compound 4 inhibited hASBT-mediated taurocholate uptake in a concentration-dependent manner. Inhibition Ki of compound 4 of taurocholate was 1.20 +/- 0.27 micromolar, which is in the same range of native bile acids. Compound 3 was not soluble in inhibition study buffer, such that Ki was not measurable. Compound 4 represents a potential prodrug of alendronate, which is designed to target hASBT to increase oral alendronate bioavailability. Compound 4 exhibited high binding affinity to hASBT. Uptake studies of compound 4 will be performed.

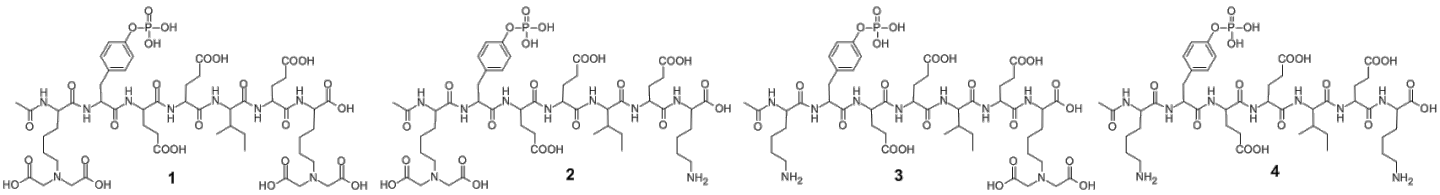


**MEDI 43**

## Synthesis and evaluation of peptides containing iminodiacetate groups as binding ligands of the Src SH2 domain

***Guofeng Ye***[1]*, guofengye@mail.uri.edu, Aaron D. Schuler*[2]*, aschuler@syntrixbio.com, Yousef Ahmadibeni*[1]*, yahmadibeni@mail.uri.edu, Joel R. Morgan*[2]*, jmorgan@syntrixbio.com, Absar Faruqui*[2]*, afaruqui@syntrixbio.com, John Zebala*[2]*, jzebala@syntrixbio.com, and Keykavous Parang*[1]*, kparang@uri.edu. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881, Fax: 401-874-5787, (2) Syntrix Biosystems, Inc, Auburn, WA 98001*

Phosphopeptide pTyr-Glu-Glu-Ile has been introduced as the optimal Src SH2 domain ligand. Peptides Ac-K(IDA)pYEEIEK(IDA) (**1**), Ac-K(IDA)pYEEIEK (**2**), Ac-KpYEEIEK(IDA) (**3**), Ac-KpYEEIEK (**4**) containing 0-2 iminodiacetate (IDA) groups in N- and C-terminal lysine residues were synthesized. UV titration studies showed that **1** can interact with $Ni^{2+}$ (1:1; $K_d$ = 234.7 nM). Fluorescence Polarization assay showed that peptide **1** had a higher binding affinity ($K_d$ = 0.6 μM) to the SH2 domain when compared with Ac-pYEEI ($K_d$ = 1.7 μM) and control peptides (**2-4**, $K_d$ = 2.9-52.7 μM). The binding affinity of **1** was reduced by more than 2 fold ($K_d$ = 1.6 μM) upon addition of $Ni^{2+}$ (300 μM) but restored in the presence of EDTA (300 μM) ($K_d$ = 0.8 μM), possibly due to the metal chelating properties of IDA groups and/or cyclization of the peptide in the presence of the metal. This study shows that the peptides containing IDA groups can be valuable tools for the protein-substrate interaction studies (Supported by NIH Grant # R44CA099126).




**MEDI 44**

## Synthesis and immunological properties of oligosaccharide fragment derived from the cell wall of Bacillus anthracis: A diagnostic tool for anthrax

***Mahalakshmi Vasan***[1]*, mvasan@chem.uga.edu, Jana Rauvolfova*[1]*, Margreet Wolfert*[1]*, Christine Leoff*[1]*, Elmar Kannenberg*[1]*, Conrad P. Quinn*[2]*, caq7@cdc.gov, Russell Carlson*[1]*, rcarlson@ccrc.uga.edu, and Geert-Jan Boons*[1]*, gjboons@ccrc.uga.edu. (1) University of Georgia, Complex Carbohydrate Research Center, 315 Riverbend Road, Athens, GA 30602, (2) Microbial Pathogenesis and Immune Response Laboratory, CDC/NCID, Atlanta, GA 30333*

B. anthracis is a Gram-positive, spore-forming bacterium that causes anthrax in humans and other mammals. The difficulty associated with the early recognition of inhalation anthrax has led to a renewed interest in anthrax vaccines and early disease diagnostics. The secondary cell wall of Bacillus anthracis contains an unusual polysaccharide (PS), which may represent an important target for vaccine and diagnostics development. The inherent microheterogenity of this PS makes it difficult to determine the immunodominant epitope responsible for the immune responses. Therefore various oligosaccharides fragments of this PS have been synthesized in a convergent manner and we have found through a detailed structure activity relationship studies that a live- and irradiated spore vaccine

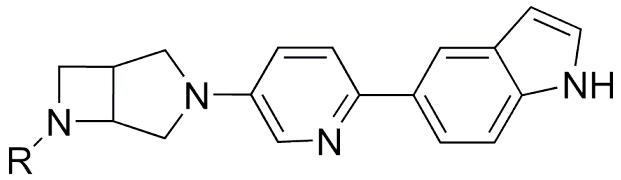
and polysaccharide linked to the carrier protein KLH can elicit IgG antibodies that recognize isolated polysaccharide and the relatively small synthetic saccharides. A surprising and important finding was that irradiated spores elicit anti-polysaccharide antibodies, and thus it appears that not only vegetative cells but also B. anthracis spores express the polysaccharide. The implication of this finding is that a polysaccharide-based vaccine may provide immunity towards vegetative cells as well as spores. Finally, we have located important antigenic components of the various antisera using synthetic saccharides. The data provide an important proof-of-concept step in the development of vegetative and spore-specific reagents for detection and targeting of non-protein structures in B. anthracis. These structures may in turn provide a platform for directing immune responses to spore structures during the early stages of the B. anthracis infection process.

**MEDI 45**

**Synthesis and structure activity relationship (SAR) studies of {[3,6-diazabicyclo[3.2.0]-heptan-3-yl]pyridin-2-yl}-indoles as novel and potent α7 neuronal nicotinic receptors (NNRs) agonists with cognition-enhancing properties**

***Jianguo Ji**, William H. Bunnelle, Robert S. Bitner, and Murali Gopalakrishnan, Neuroscience Research, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, Fax: 847-937-9195*

The cognitive deficits associated with central nervous system (CNS) diseases, including Alzheimer's disease (AD) and schizophrenia, are significant unmet medical needs. The convergence of clinical and preclinical evidence suggests that α7 neuronal nicotinic receptors (NNRs) play an important role in cognitive processes. Selective α7 NNR agonists hold considerable promise for treating cognitive deficits in neurodegenerative and psychiatric disorders. As part of the ongoing NNR program at Abbott, our team recently discovered a series of {[3,6-diazabicyclo[3.2.0]-heptan-3-yl]pyridin-2-yl}-indoles as potent selective α7 agonists. The synthesis, structure-activity relationship, pharmacological profiles and in vivo activity studies of these novel a7 NNR agents will be presented.




**MEDI 46**

**Design and synthesis of piperazinyl-piperidinyl quinolines as 5-HT$_{1A}$ antagonists**

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Alzheimer's disease (AD) is the most common cause of dementia. It is estimated that 5 million Americans are afflicted with AD and healthcare costs in the US associated with AD approach $100B

per year. AD is usually diagnosed by short-term memory loss and progresses with increasing impairment until death occurs. Current available therapies for AD include noncompetitive NMDA antagonists and cholinesterase inhibitors. These agents provide symptomatic relief, but suffer from a moderate patient response and a short duration of efficacy. It has been postulated that 5-$HT_{1A}$ antagonism could modulate the cholinergic and glutamic neurotransmitter systems to provide for more effective cognitive enhancement. In our efforts to identify 5-$HT_{1A}$ antagonists, we discovered a series of piperazinyl-piperidinyl quinolines. The identification, synthesis and SAR of this novel class of compounds will be described.

**MEDI 47**

**Dual acting norepinephrine reuptake inhibitors and 5-$HT_{2A}$ receptor antagonists I: Synthesis and activity of novel 3-(phenylsulfonyl)-1*H*-indoles**

***Gavin D. Heffernan***[1]*, hefferg@wyeth.com, Richard D. Coghlan*[1]*, Eric S. Manas*[1]*, Robert E. McDevitt*[1]*, mcdevib@wyeth.com, Yanfang Li*[1]*, Paige E. Mahaney*[1]*, mahanep@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Albert J. Robichaud*[1]*, Peter Alfinito*[2]*, Jenifer A. Bray*[2]*, Scott Cosmi*[2]*, Grace H. Johnston*[2]*, Thomas Kenney*[2]*, Elizabeth Koury*[2]*, and Darlene C. Deecher*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 732-274-4505, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Norepinephrine (NE) is a major neurotransmitter in both the central and peripheral nervous system regulating a variety of body functions. Drugs that inhibit NE reuptake either selectively, or in combination with serotonin (5-HT), have shown clinical efficacy in a variety of indications such as mood disorder, attention-deficit hyperactivity-disorder, pain, and vasomotor symptoms. Additionally, 5-$HT_{2A}$ receptor antagonism has been reported to play a role in depression and in temperature dysregulation. Thus, a dual acting norepinephrine reuptake inhibitor (NRI)/5-$HT_{2A}$ antagonist could be beneficial in treating a number of disorders. A structural analysis of 5-$HT_{2A}$ antagonists indicated a subset shared a common pharmacophore with NRIs. A pharmacophore model was derived for dual NRI/5-$HT_{2A}$ antagonists and was used to virtually screen compound libraries. The discovery, synthesis and properties of a novel class of 3-(phenylsulfonyl)-1*H*-indoles that have nanomolar affinity for both the norepinephrine transporter and 5-$HT_{2A}$ receptor will be described.

**MEDI 48**

**Dual acting norepinephrine reuptake inhibitors and 5-$HT_{2A}$ receptor antagonists II: Synthesis and activity of novel spiro[cyclohexane-1,3'-[3*H*]indol]-2'(1'*H*)-ones**

***Gavin D. Heffernan***[1]*, hefferg@wyeth.com, Fei Ye*[1]*, yef@wyeth.com, Casey C. McComas*[1]*, mccomac@wyeth.com, Michael Marella*[1]*, marellm@wyeth.com, Joseph P. Sabatucci*[1]*, sabatuj@wyeth.com, Callain Y. Kim*[1]*, kimcy@wyeth.com, An T. Vu*[1]*, VuA@wyeth.com, Paige E. Mahaney*[1]*, mahanep@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Peter Alfinito*[2]*, Jenifer A. Bray*[2]*, Scott Cosmi*[2]*, Grace H. Johnston*[2]*, Thomas Kenney*[2]*, Elizabeth Koury*[2]*, and Darlene C. Deecher*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 732-274-4505, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Norepinephrine (NE) and serotonin (5-HT) are key neurotransmitters involved with the pathophysiology of depression. Norepinephrine reuptake inhibitors (NRIs) increase extracellular

concentrations of NE by blocking its reuptake by the norepinephrine transporter (NET). Drugs that inhibit NE reuptake either selectively, or in combination with serotonin (5-HT), have shown clinical efficacy in a variety of indications such as mood disorder, attention-deficit hyperactivity-disorder, pain, and vasomotor symptoms.

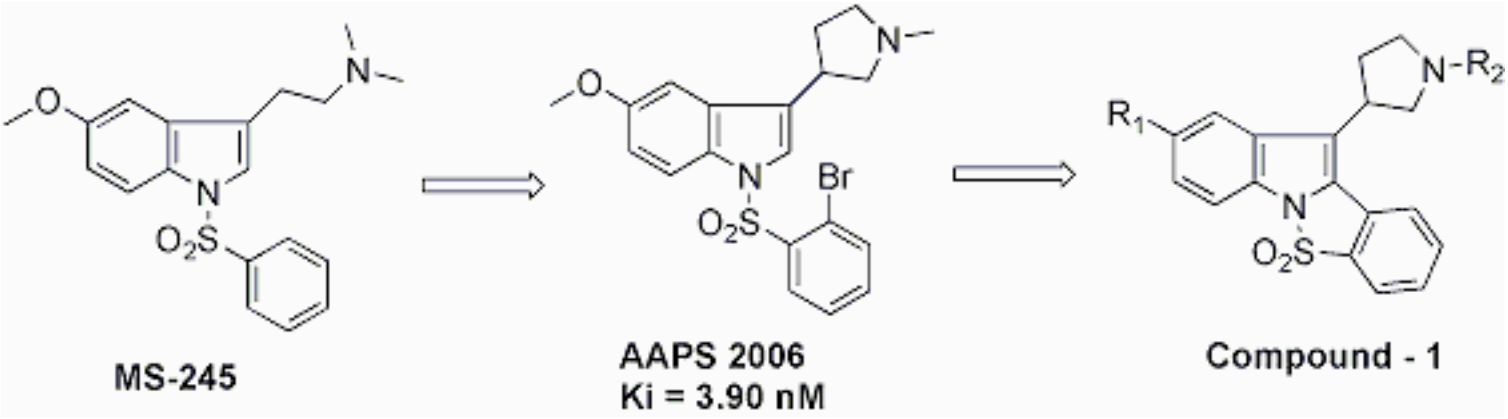
The role of 5-$HT_{2A}$ receptor modulators in depression has also been examined. Patients exhibiting resistance to standard antidepressant drug therapies benefit from adjunctive treatment with atypical antipsychotics, which act through 5-$HT_{2A}$ receptor antagonism. As part of a program to identify novel, dual acting NRI/5-$HT_{2A}$ antagonists, we evaluated the 1-(3-amino-1-phenylpropyl)indolin-2-one series of NRIs for 5-$HT_{2A}$ antagonist activity. The discovery, synthesis and properties of a novel class of spiro[cyclohexane-1,3'-[3*H*]indol]-2'(1'*H*)-ones that have nanomolar affinity for both the NET and 5-$HT_{2A}$ receptor will be described.

**MEDI 49**

## Novel tetracyclic tryptamine derivatives with rigidized side chain, as potential 5-HT6 receptor ligands

***Rama Sastry Kambhampati****, Adireddy Dwarampudi, Venugopalarao Bhatta, Laxman Kota, Anil K. Shinde, and Ramakrishna V. S. Nirogi, Discovery Research - Medicinal Chemistry, Suven Life Sciences Ltd, Serene Chambers, Road No. 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India*

5-HT6R, belonging to the serotonin receptor family and expressed exclusively in the brain, is a promising and novel target for CNS disorders such as schizophrenia, anxiety, impairment of learning, memory and obesity. MS-245 was one of the first examples of 5-HT6R antagonists. Earlier we have disclosed the results of our studies pertaining to effects of rigidization of the side chain of the tryptamines, which gave highly potent and selective ligands (AAPS 2006, San Antonio). In continuation of these studies we have synthesized tetracyclic compounds 1 through rigidization of aryl sulfonyl with C2 of indole. Most of these compounds are highly potent 5-HT6R ligands, with good activity in animal models of cognition like NORT and water maze. Synthesis, physicochemical properties, in-vitro binding data, SAR and pharmacology will be described in this poster.



**MEDI 50**

## Synthesis and SAR of a novel series of dual SSRI / 5-$HT_{1A}$ receptor antagonists: Incorporation of benzothiophene moieties in the SSRI pharmacophore

*Deborah A. Evrard[1], evrardd@wyeth.com, **Yanfang Li**[1], liy1@wyeth.com, Gary Stack[1], Soo Yi[1], Megan Tran[1], Boyd Harrison[1], Geoffrey Hornby[2], Deborah L. Smith[2], Kelly M. Sullivan[2], Jeannette Golembieski[2], Lee E. Schechter[2], and Terrance H. Andree[2]. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543*

Selective serotonin reuptake inhibitors (SSRIs) are antidepressants generally characterized by fewer side effects than traditional tricyclic antidepressants (TCAs). However, there is a lag time of 2-8 weeks before full efficacy of an SSRI is observed, which is believed to be due to stimulation of the serotonin (5-HT) 5-$HT_{1A}$ autoreceptor by the SSRI-induced elevation of 5-HT levels in the vicinity of the serotonergic neuron cell body. Thus the combination of an SSRI and a 5-$HT_{1A}$ receptor antagonist might be expected to result in a faster-acting antidepressant. Here we present research aimed at the development of a dual acting molecular entity that is a 5-$HT_{1A}$ receptor antagonist and a 5-HT transporter (5-HTT) inhibitor. The synthesis and SAR of a series of novel compounds containing benzothiophenes in the putative 5-HTT binding domain are described.

**MEDI 51**

## Ab initio quantum mechanical calculations on aryl guanidine ligands for the 5HT3 ion channel receptor

***Sheryl D Baldwin***[1], *sdbaldwi@vcu.edu, Kiran Boggavarapu[2], kiran@mcneese.edu, Malgorzata Dukat[3], mdukat@vcu.edu, RA. Glennon[3], glennon@vcu.edu, and P. Jena[4], jena@vcu.edu. (1) Center for Study of Biological Complexity, Virginia Commonwealth University, 1000 West cary Street, Suite 220, PO Box 842030, Richmond, VA 23284-2030, (2) Department of Chemistry, McNeese State University, Lake Charles, LA 70609, (3) Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298-0540, (4) Physics Department, Virginia Commonwealth University, Richmond, VA 23284*

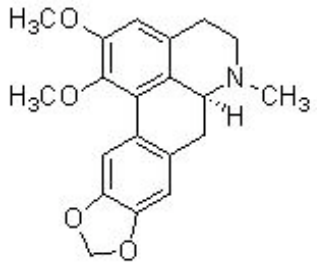
Arylguanidines are thought to bind to 5-HT3 receptors in a manner similar to serotonin. 5-HT3 receptors are the only ion channel receptors among the serotonin family of receptors. QSAR studies indicated that affinity is dependent upon the electron withdrawing nature of the substituents at specific positions. In general, it was also shown to depend upon the molecular polarizability. However, a fundamental understanding of the science behind ligand-receptor interaction was desired, so ab initio self-consistent field molecular orbital calculations were performed on these substituted arylguanidine compounds. Local reactivity descriptors, dipole moments, polarizabilities, electron affinity, and other electronic properties have been investigated to determine the effects of the electronic structure. A description of the dependence of binding of these compounds with the 5-HT3 receptors will be presented, with an explanation derived from fundamental quantum mechanical properties. Impact of local reactivity factors in binding will be discussed.

**MEDI 52**

**Development of 5HT2A antagonists based on the aporphine alkaloid nantenine**

***Stevan Pecic**, **Sandeep Chaudhary**, Wayne W Harding, and Onica Le Gendre, Department of Chemistry, Hunter College, 695 Park Avenue, New York City, NY 10065*

MDMA (3,4-methylenedioxy-N-methylamphetamine) is a semi-synthethic derivate of the phenethylamine family, whose primary effect is stimulation of secretion as well as inhibition of re-uptake of large amounts of serotonin as well as dopamine and nor-epinephrine in the brain. MDMA also acts directly on a number of receptors, including á1-adrenergic and 5-HT2A receptors. “Ecstasy” use is accompanied by several adverse physiological effects including the development of hyperthermia, organ failure and death in extreme cases. No selective antagonists for the physiological and behavioral effects of MDMA have yet been identified. The recently discovered, structurally-similar, plant alkaloid (+)-nantenine (9,10-methylenedioxy-1,2 dimethoxy-aporphine) may represent such a compound. Nantenine (1) is an aporphine alkaloid isolated from the Japanese fruit of Nandina domestica. Nantenine shares structural similarities to MDMA and is an antagonist at serotonin 5-HT2A and adrenergic á1 receptors. Up to the present time, very little SAR studies have been performed on nantenine in relation to its antagonist activity at these receptors. A study of the SAR of nantenine at these receptors is a critical prerequisite for the design of molecules with potent in vitro antagonist activity and which will have some therapeutic benefit. It is the goal of this project to synthesize analogs of nantenine and to explore the functional group and spatial characteristics of the molecule which are required for antagonist activity at 5HT2a receptors. The analogs will also be evaluated for their ability to block the discriminative stimulus (a model of behavioral reinforcement) effects of MDMA in mice. These combined efforts will allow for the development of potent 5HT2a antagonists based on the nantenine core structure through iterative synthesis and in vitro screening and will also identify molecules with potent in vivo MDMA antagonist activity.




**1**

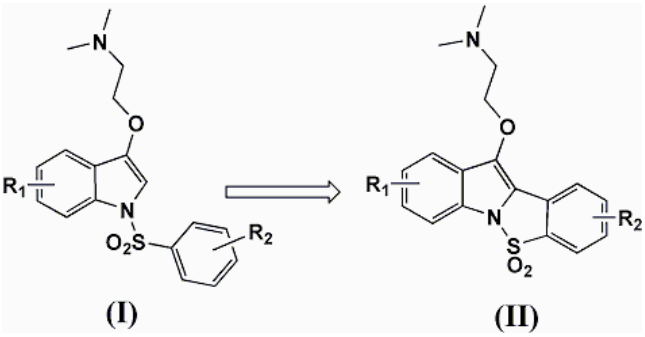
**MEDI 53**

**Novel conformationally restricted 3-aminoalkoxy indole derivatives as 5-HT6 receptor ligands**

***Anand V. Daulatabad**, Ramakrishna V. S. Nirogi, Anil K Shinde, and Rama Sastry Kambhampati, Discovery Research - Medicinal Chemistry, Suven Life Sciences Ltd, Serene Chambers, Road No. 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India*

Identification and usefulness of 5-HT6 receptor ligands for CNS disorders such as schizophrenia, depression and impairment of learning and memory has been the focus of several reports in the last decade. Earlier we have disclosed 3-aminoalkoxy-N-arylsulfonyl indoles (I) as highly potent and

selective (more than 100 folds over related GPCRs) 5-HT6R antagonists for cognitive impairment and obesity. Effect of chronic treatment with lead compound from this series (I) at 30 and 60 mg/kg showed significant reduction in body weight, serum triglyceride and leptin levels. In continuation of these efforts, we have designed a novel series of rigidized 3-aminoalkoxy indoles (II). The preliminary molecular modeling studies indicated that the proposed compounds retain the pharmacophoric arrangements required for the binding at the receptor. Many of the synthesized compounds are potent and selective 5-HT6R antagonists. The details of chemistry, SAR, pharmacokinetic and pharmacology data will be discussed in the poster.




**MEDI 54**

**Design, synthesis, and biological evaluation of novel pyridoazepine derivatives as potent and selective serotonin 5-HT2C receptor agonist**

***Nhut Diep**, Gian-Luca Araldi, and Alexander Bischoff, Medicinal Chemistry and Process Development, Forest laboratories institute, 45 Adams Ave, Hauppauge, NY 11788*

The azepine ring system represents an important template that has attracted considerable interest in the search for novel pharmaceutical agent. As part of our program on the synthesis of pyridoazepine systems to study their structure-activity relationship for serotonin 5-HT2C, a new series of azepine-pyridine has been synthesized. This poster will illustrate the extensive exploration of the pyridine region of the molecule and a variety of synthetic strategies that were developed, including the installation of halides through the pyridodiazonium ion species and various functional groups. Also, a ring expansion reaction of the 4-piperidone as a versatile route to regiospecific syntheses of various functionalities for pyridoazepine analogs will be described.

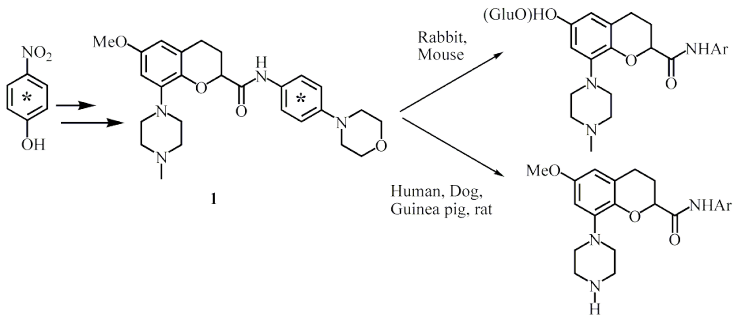
**MEDI 55**

**Synthesis and metabolism of a potent 5HT1B antagonist**

***Charles S. Elmore**, Chad.elmore@astrazeneca.com, Department of CNS Chemistry, AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850-5437, Fax: 302-886-5382, Dandan Wang, dandan.wang@astrazeneca.com, Department of Development DMPK and Bioanalysis, AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850, and Minli Zhang, minli.zhang@astrazeneca.com, Department of Discovery DMPK, AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850*

Depression is a major target of drug research since it is the leading cause of disability in the US and the currently marketed treatments have considerable deficiencies. It has been hypothesized that

antagonism of the $5HT_{1B}$ receptor which controls release of serotonin into the synaptic cleft would serve as a effective depression treatment while avoiding the latency period that is often encountered with SSRIs. Compound **1** is a high affinity ligand for the $5HT_{1B}$ receptor and was required in C-14 labeled form for detailed Adsorption, Distribution, Metabolism and Excretion (ADME) studies. The synthesis of the tracer in four steps from [*u*-$^{14}$C]p-nitrophenol and a summary of the metabolism results in human, rat, dog, guinea pig and rabbit hepatocytes will be presented. There was a shift in the major metabolic pathway based on species; in human, rat, dog and guinea pig the *N*-desmethyl metabolite was formed as the major metabolite while in mouse and rabbit, the *O*-desmethyl metabolite and its corresponding glucuronide were the major metabolites.

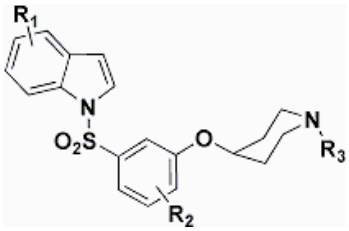



**MEDI 56**

**Piperidinyloxy aryl sulfonamides: New chemical class of selective 5-HT6 receptor antagonists as potential anti-obesity agents**

***Anil K Shinde**, Adireddy Dwarampudi, Veena Reballi, Venugopalarao Bhatta, Laxman Kota, Rama Sastry Kambhampati, and Ramakrishna V. S. Nirogi, Discovery Research - Medicinal Chemistry, Suven Life Sciences Ltd, Serene Chambers, Road No 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India*

5-HT6R antagonists work through reducing the food intake by activation of satiety center and also possibly through induction of catabolism. 5-HT6R antagonists from Biovitrum, Epix and Dr. Esteve's lab have entered into clinical trials for obesity. As a part of our efforts toward the development of diverse ligands for 5-HT6R, we have identified a novel series of piperidinyloxy aryl sulfonamides as potential ligands for obesity. The effective lead generation and optimization methods have resulted in a series of potent 5-HT6R ligands with Ki in the range of 1 - 5 nM. Lead compound from the series was tested in male Wistar rats for its effect on food intake (day and night time) and body weight. At 30 mg/Kg p. o. dose it exhibited significant reduction in food intake and body weight gain as compared to the control group. Few compounds showed activity in cognition model NORT and water maze as well. The synthesis, in-vitro binding data along with SAR and in-vivo efficacy data of the lead molecule will be presented.

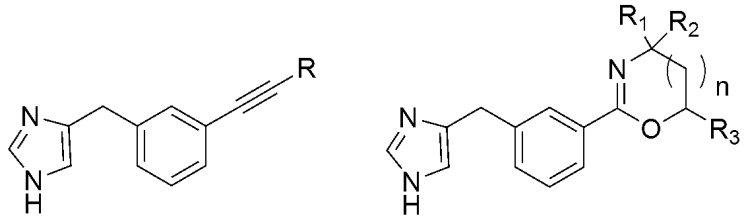



**MEDI 57**

**4-Benzyl-1H-imidazoles with oxazoline- and alkyne-termini as histamine H-3 receptor agonists**

***Maikel Wijtmans***[1]*, wijtmans@few.vu.nl, Sylvain Celanire*[2]*, Erwin Snip*[1]*, Edith Gelens*[1]*, Remko Bakker*[1]*, Henk van der Goot*[1]*, Saskia Hulscher*[1]*, Bas-Jan Venhuis*[1]*, Michel Gillard*[2]*, Philippe Collart*[2]*, Bernard Christophe*[2]*, Benedicte Lallemand*[2]*, Florence Lebon*[2]*, Henk Timmerman*[1]*, Rob Leurs*[1]*, Patrice Talaga*[2]*, and Iwan J. P. de Esch*[1]*. (1) Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, Netherlands, Fax: 31-020-5987610, (2) UCB Pharma, R&D, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*

Therapeutic research on the histamine H3 receptor ($H_3R$) has focused mostly on antagonists/inverse agonists and to a lesser extent on agonists. However, $H_3R$ agonists may be useful in treating ischemic arrhythmias, migraine, asthma, obesity, diabetes mellitus and liver cholestasis. Not only has the lower availability of $H_3R$ agonists hampered full exploration of their therapeutic potential, it has also prevented an unequivocal understanding of the structural requirements for receptor activation. We present our findings in the development of rigid $H_3R$ agonists based on the 4-benzyl-1H-imidazole template. Starting from a high throughput screening hit, the benzyl sidechain was altered with lipophilic groups. Alkyne- or oxazolino-substituents gave excellent affinities and activities up to the single digit nM range. Our findings further substantiate the growing notion that basic ligand sidechains are not necessary for receptor activation and reveal the oxazolino group as a hitherto unexplored functional group in $H_3R$ research.




**MEDI 58**

**Novel 2-(piperazin-1-yl)quinoline analogs as combined selective serotonin reuptake inhibitors and 5-HT1A receptor antagonists**

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Selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants with fewer side effects than the older tricyclics. However, SSRIs require weeks of treatment before efficacy is observed. This delay in efficacy is believed to be due to stimulation of inhibitory 5-HT1A autoreceptors; the onset of antidepressant activity is consistent with a time-dependent desensitization of 5-HT1A autoreceptors. Combining SSRI and 5-HT1A receptor antagonism within one molecule should maximize serotonergic function and result in an immediate increase in synaptic levels of 5-HT in forebrain

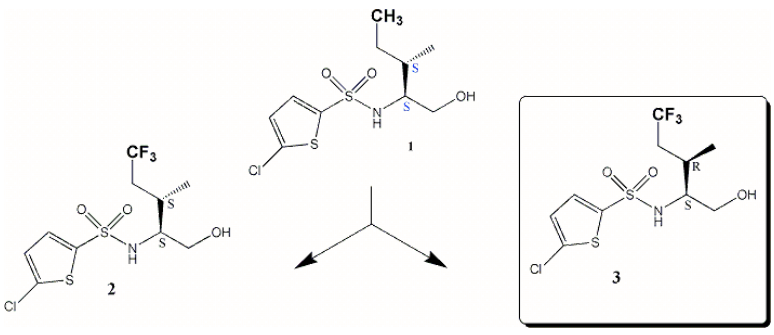
regions. Both preclinical and clinical data have positioned SSRI/5-HT1A antagonism as one of the key targets for developing novel antidepressant therapeutics. In this poster, we will report the synthesis and biological evaluation of a series of novel 2-(piperazin-1-yl)quinoline analogs. A representative compound from this series was thoroughly profiled in vitro selectivity and in vivo pharmacokinetic assays. In addition, this compound was demonstrated to produce an immediate and dose-dependent increase in cortical extracellular levels of 5-HT following oral administration as measured by in vivo microdialysis experiments.

**MEDI 59**

**Enantioselective synthesis of 5-chloro-N-[(1S,2R)-4,4,4-trifluoro-1-(hydroxymethyl)-2-methylbutyl]thiophene-2- sulfonamide (3) via the Evans chiral auxiliary: An orally active gamma-secretase inhibitor**

***George Diamantidis***[1]*, diamang@wyeth.com, Anthony Kreft*[1]*, krefta@wyeth.com, Madelene M. Antane*[1]*, antanem@war.wyeth.com, Suzan Aschmies*[2]*, Kevin Atchison*[2]*, Derek C. Cole*[3]*, Thomas Comery*[2]*, Comeryt@wyeth.com, William G. Gallaway*[1]*, Gallaww@wyeth.com, Boyd L. Harrison*[1]*, Yun Hu*[2]*, Udaykumar Jain*[1]*, jainu@wyeth.com, Mei Jin*[2]*, Robert Martone*[2]*, Aram Oganesian*[4]*, June Sonnenberg-Reines*[2]*, Lynn Resnick*[1]*, Roy Sun*[2]*, Joseph R. Stock*[3]*, Zheng Wang*[1]*, wangzwyeth.com, Zheng Hu*[2]*, Hua Zhou*[2]*, and J. Steven Jacobsen*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, CN 8000, Princeton, NJ 10965, (2) Discovery Neuroscience, Wyeth Research, Princeton, NJ, Princeton, NJ 08543, (3) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (4) Drug Safety & Metabolism, Wyeth Research, Collegeville, PA, Collegeville, PA 19426*

Amyloid beta-peptide (beta-amyloid, Ab) plaques found in the brains of Alzheimer's disease (AD) patients are formed by aggregation of Ab peptide, produced by sequential cleavage of amyloid precursor protein (APP), by two aspartic proteases. Initial cleavage by beta-secretase (BACE-1) generates the membrane bound beta-C-terminal fragment (beta-CTF or C99). Subsequent cleavage within the transmembrane region by gamma-secretase, a complex of proteins including, presenilin-1 (PS1), nicastrin, anterior parynx defective-1 (Aph-1), and presenilin enhancer-2 (Pen-2), results in formation of Ab fragments, predominantly Ab40 and the more aggregatory Ab42. Methods of lowering Ab levels in brain are currently sought as novel disease modifying therapies for treatment of AD. The key discovery in the continued evolution of 5-chlorothiophen-2-sulfonyl-isoleucinol (1) analogs was the observation that the trifluoromethyl analog 3 [IC50(Ab42) = 48 nM, IC50(Ab40) = 21 nM] possessed high inhibitory potency for gamma-secretase inhibition, showed reduced levels of oxidative metabolism and had promising oral bioavailability. These properties enhanced the potential utility of this series for treating Alzheimer's disease (AD). The single enantiomer 3 was initially made via an achiral Strecker amino acid synthesis and 3 was isolated from the racemic mixture after extensive chiral HPLC purification. An improved asymmetric synthesis of 3 using Evans' chiral alkylation technology will be the focus of this poster presentation.



**MEDI 60**

**Rapid P1 SAR of brain penetrant tertiary carbinamine derived BACE inhibitors**

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Alzheimer's disease (AD) is now the most common neurodegenerative condition, causing much financial and emotional burden in terms of caring for affected patients. The deposition of amyloid ≤]-peptide(A≤]) in the brain is one of the characteristics of AD pathogenesis. A≤] is formed by sequential processing of the amyloid precursor protein(APP) by two aspartyl proteases, ≤]-secretase followed by ≤^-secretase. BACE-1 (≤]-site APP Cleaving Enzyme) knockout mice show a complete absence of A≤] production but are otherwise similar to wild type animals. BACE-1 is thus an attractive therapeutic target for the treatment of AD. The one pot synthesis of 2 via Schiff base 1 alkylation provided analogs of a brain penetrant BACE-1 inhibitor discovered in our laboratories. This methodology provided a convenient and rapid means to explore the P1 region of these types of inhibitors and avoided the multi-step synthesis of ƒÑ-substituted alanines that were intermediates in earlier approaches to these targets. SAR of these potent small molecule inhibitors of BACE-1 will be presented.

**MEDI 61**

**Design, synthesis and testing of benzimidazle based inhibitors of CDK5**

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In Alzheimer's disease two proteins form characteristic proteinaceous deposits: aβ aggregates to generate β amyloid plaques while hyperphosphorylated tau generates neurofibrillary tangles (NFTs). We designed, synthesized, and tested a novel series of substituted benzimidazoles as CDK5/p25 inhibitors with the goal of developing selective CDK5 inhibitors. Such inhibitors should assist in elucidating the role of CDK5/p25 in tau hyperphosphorylation and possibly NFT formation. Design, synthesis, computer modeling and in vitro testing will be presented.

**MEDI 62**

**The design and synthesis of benzofuran analogs as beta-amyloid aggregation inhibitors.**

***Jeewoo Lee***[1]*, jeewoo@snu.ac.kr, Dong-Wook Kang*[1]*, Mi-Hyun Kim*[1]*, Jin-Mi Kang*[1]*, Hyuk-Min Kim*[1]*, Hee Kim*[2]*, Hee Jin Ha*[2]*, Eun Joo Nam*[2]*, Hye Min Ju*[2]*, and Young Ho Kim*[2]*,*

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by dementia, cognitive impairment, and memory loss. AD is characterized by the accumulation of senile amyloid plaques composed of A-beta peptide and numerous neurofibrillary tangles formed from filaments of highly phosphorylated tau proteins in the brain. The insoluble amyloid plaques is formed by a process called amyloidosis whereby A-beta peptide aggregates into toxic and insoluble fibres. Thus, an attractive therapeutic strategy in principle is to inhibit and preferably reverse A-beta peptide aggregation itself, because this appears to be the first step in the pathogenic process of amyloidosis that is not associated with some natural biological function. Recently, we discovered that a series of benzofuran inhibited the A-beta peptide aggregation in vitro and displayed promising activities in in vivo models. The syntheses, in vitro and in vivo activities, PK and toxicities of benzofuran analogues will be presented.

**MEDI 63**

**Identification of a novel iodo-compound as an amyloid imaging agent for Alzheimer's disease**

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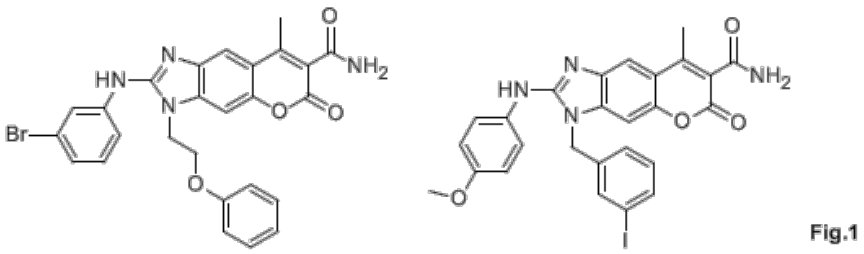
Alzheimer's disease (AD) is a leading cause of dementia in the elderly and is characterized by cerebral A-beta-amyloid deposition. A definite clinical diagnosis of AD is currently impossible. Using combinatorial chemistry and high throughput screening methods, we have identified a novel lead compound named LRL22 (Fig. 1) that binds to A-beta aggregates and protects neurons from A-beta-induced toxicity with an EC50 of 187 nM. A series of LRL-compounds have been designed, synthesized and biologically evaluated. LRL50 (Fig. 1), an iodo analog of LRL22 with higher potency, passes the blood-brain barrier, and labels amyloid plaques fluorescently in vivo in transgenic PS-APP AD mice as well as ex vivo in human AD brain tissue. LRL50 can be easily labeled with I-124 for PET/CT scan and I-123 for SPECT/CT scan. Such imaging agents can be used for AD diagnosis, progression tracking, and monitoring treatment responses.




LRL 22 LRL50

Fig.1

**MEDI 64**

**Synthesis of iodine-123 labeled curcumin as a potential amyloid imaging agent**

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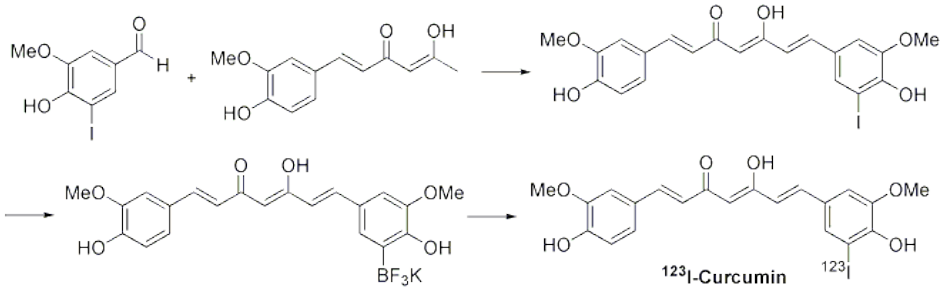
Studies suggest that curcumin's anti-fibrillogenic activity involves fibril binding and destabilization as well as direct inhibition of amyloid fibril growth. Iodine-123 labeled curcumin was synthesized and evaluated in a preliminary biodistribution study in mice.




**MEDI 65**

**Synthesis and SAR of acyl guanidines as BACE-1 inhibitors**

***Yunhui Zhang**, Yong-Jin Wu, Huan He, Lorin Thompson, Joe Shi, Shirong Zhu, Samuel Gerritz, Andrew Good, Jodi Muckelbauer, Catherine R. Burton, Jeremy H. Toyn, Charlie F. Albright, Andy Tebben, and John Macor, Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492*

A series of acyl guanidines has been synthesized as BACE-1 inhibitors. The impact of various substituents has been investigated, and these efforts have culminated in the identification of several acyl quanidines with potent BACE-1 inhibitory activity. The synthesis and SAR of these compounds will be presented.

**MEDI 66**

**Kinetics and analysis of the selective inhibition of cyclooxygenase-2 by an indomethacin-5-ROX conjugate**

***Anna L. Blobaum**, MD. Jashim Uddin, Brenda C. Crews, and Lawrence J. Marnett, Department of Biochemistry, Vanderbilt University, 854 Robinson Research Building, 23rd Avenue South @ Pierce, Nashville, TN 37232, Fax: 615-343-7534*

Indomethacin (INDO) is a potent and non-selective inhibitor of both cyclooxygenase isoforms (COX-1 and COX-2) that exhibits slow, tight-binding and functionally irreversible inhibition/binding kinetics.

The fluorescent moiety 5-ROX was successfully tethered through a 4 carbon di-amide linker to an indomethacin scaffold to create a COX-2 selective inhibitor (LM-4777) capable of targeting COX-2 up-regulated in cells and nude mouse xenografts. Kinetically, LM-4777 associates with COX-2 slower than indomethacin and has a very slow, almost immeasurable off-rate for inhibition, confirming previous in vivo imaging and metabolism data. Mutagenesis studies showed that the indomethacin component of LM-4777 was binding similarly to INDO in the active site of COX-2, utilizing the methyl-binding pocket and avoiding major interactions with Val-523 in the COX-2 side pocket. Differences between LM-4777 and indomethacin binding were observed at the constriction site and in the lobby region, suggesting that the linker and fluorophore components of LM-4777 were making novel interactions in these regions compared to INDO.

**MEDI 67**

**Structure-activity relationships of 2,7-diamino-thiazolo[5,4-d]pyrimidines as TRPV1 antagonists**

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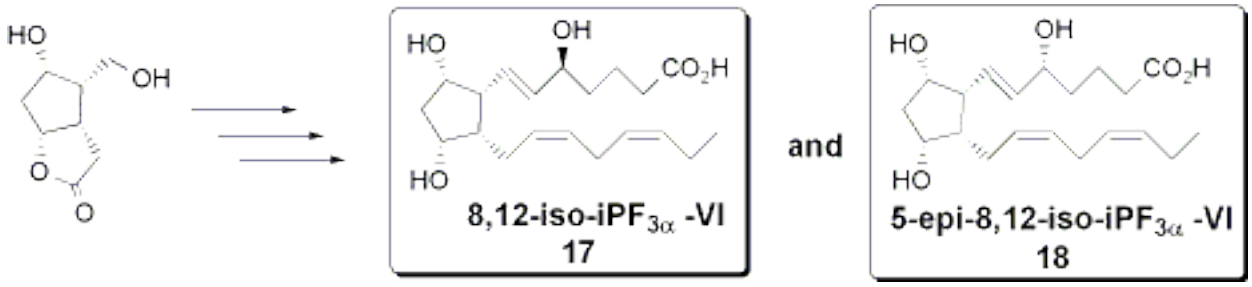
The transient receptor potential vanilloid 1 (TRPV1 or VR1) receptor is a ligand-gated, non-selective cation channel that is primarily expressed in nocieptive fibers. TRPV1 is activated by wide range of stimuli including heat (>43 °C), low pH, and vanilloid ligands such as capsaicin and resinferatoxin (RTX) to name a few. TRPV1 knockout mice have demonstrated an impaired ability to develop inflammatory thermal hyperalgesia suggesting that TRPV1 has an important role in the development of inflammatory pain. In our work toward the discovery of novel TRPV1 antagonists, we recently reported 2,7-diamino-thiazolo[5,4-d]pyrimidines as potent TRPV1 antagonists. This poster will describe the synthesis and structure-activity relationships of 2,7-diamino-thiazolo[5,4-d]pyrimidines.

**MEDI 68**

**Eicosapentaenoic acid derived isoprostanes: Synthesis and discovery of two major isoprostanes**

***Chih-Tsung Chang***[1]*, cchang@fit.edu, Pranav Patel*[1]*, Namin Kang*[1]*, John A Lawson*[2]*, Wen-Liang Song*[2]*, Garret A FitzGerald*[2]*, and Joshua Rokach*[1]*. (1) Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology, 150 W University Blvd, Melbourne, FL 32901, Fax: 321-674-7743, (2) Institute for Translational Medicine and Therapeutics and Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104*

Isoprostanes (IPs) are products of free radical induced peroxidation of polyunsaturated fatty acids and are used as markers of oxidative stress in inflammatory diseases such as Atherosclerosis and Alzheimer's. We are reporting the total synthesis of two major all-syn EPA derived IPs, 8,12-iso-iPF$_{3\alpha}$ **18** and 5-epi-8,12-iso-iPF$_{3\alpha}$ **17**. These two synthetic probes will be used to discover and identify their presence in human urine.

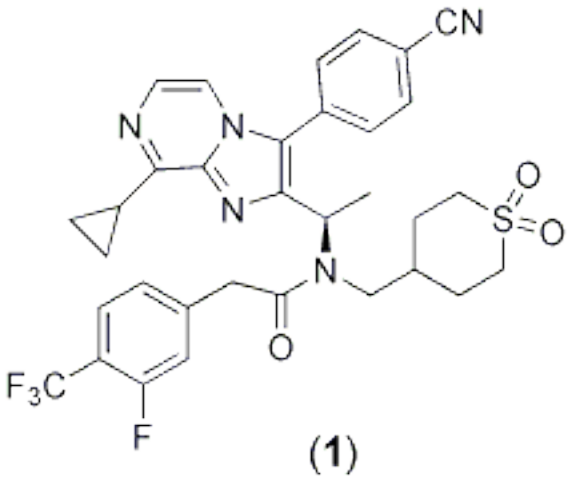



**MEDI 69**

**Pyrazine-imidazole derivatives as potent CXCR3 antagonists**

***Xiaohui Du**, Xiaoqi Chen, Karen Ebsworth, Kirk Henne, Bryan Lemon, Ji Ma, Shichang Miao, Timothy J. Sullivan, George Tonn, Tassie L. Collins, and Julio C. Medina, Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080*

CXCR3 is a G-protein-coupled receptor expressed predominantly on CD4+ and CD8+ T cells with the Th1 phenotype and plays a role in their migration into sites of inflammation. CXCR3 and its ligands, MIG (CXCL9), IP-10 (CXCL10) and ITAC (CXCL11) have been implicated in a variety of inflammatory and autoimmune diseases such as transplant rejection, psoriasis, rheumatoid arthritis and multiple sclerosis. Thus, it has been postulated that blocking CXCR3 may prevent the recruitment of inflammatory cells and alleviating these diseases. As a continuation of our efforts in this area, we will describe in this poster the discovery of a new series of potent CXCR3 antagonists featuring a pyrazine-imidazole core structure. Optimization of this series for potency and improved pharmacokinetic properties led to the discovery of several compounds, typified by (1), suitable as tool compounds for in vivo study. We will discuss the potency of these inhibitors using an ITAC mediated in vitro cell migration assay as well as a whole blood receptor occupancy assay. In addition, the efficacy of compound (1) in a bleomycin-induced lung inflammation model will be discussed.




**(1)**

**MEDI 70**

**Discovery and SAR studies of carboline- and pyrazinoindolone-based MK2 inhibitors**

***Donghong Amy Gao**, Medicinal Chemistry Department, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, Ridgefield, CT 06877, Fax: 203-791-6072*

MAPKAP-K2 (MK-2), a direct substrate of p38 MAPKs, has been shown to play an important role in the production of pro-inflammatory cytokines, such as tumor necrosis factor-á (TNF-á), interleukin-1â (IL-1â) and IL-6. Thus inhibition of MK-2 kinase activity may potentially be useful for treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Two classes of MK-2 inhibitors based on carboline or pyrazinoindolone templates are highlighted. Extensive SAR efforts lead to compounds with single-digit nanomolar molecular potency. Further optimization of pyrazinoindolone-based inhibitors provides compounds with the sub-micromolar cellular potency.

**MEDI 71**

**Pyrimidinopyridones: Design and synthesis of a novel class of FMS inhibitors as potential anti-inflammatory agents**

***Hui Huang**, Daniel A. Hutta, Huaping Hu, James Rinker, William H. Parsons, Renee L. DesJarlais, Carsten Schubert, Ioanna P. Petrounia, Margery A. Chaikin, Robert Donatelli, Carl L. Manthey, and Mark R. Player, Medicinal Chemistry, Johnson & Johnson PRD, 8 Clarke Drive, Cranbury, NJ 08512, Fax: 609-655-6930*

Over-expression of macrophage has been associated with chronic inflammation and tumor progress. The proliferation and survival of macrophages, monocyte, and their progenitors are driven by macrophage colony stimulating factor (M-CSF or CSF-1). FMS, a type III receptor tyrosine kinase, is the exclusive receptor of CSF-1. Inhibition of FMS provides a novel approach for the treatment of inflammatory diseases. A series of pyrimidinopyridones has been designed, synthesized and shown to be potent and selective inhibitors of FMS. The change of an ester to an amide substitution at the pyridone core gave enhanced potency. A further change of the amide to the hydroximate significantly improved the PK profiles of the series. Selected FMS inhibitors also showed efficacy on blocking CSF-1 signaling in vivo in a mouse pharmacodynamic model.

**MEDI 72**

**Design, synthesis and structure-activity relationship of novel CCR2 antagonists**

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Monocyte Chemotactic Protein-1 (MCP-1) is a member of the chemokine family of pro-inflammatory proteins that are involved in recruitment, chemo-trafficking and activation of leucocytes (monocytes, lymphocytes, esinophils, basophiles, NK cells) by the activation of CCR2 receptors. MCP-1 is expressed not only from monocytes but also in host of other cells that includes T-cell and macrophages. There is a strong body of evidence to suggest that MCP-1 have been associated with chronic auto-inflammatory diseases such as rheumatoid arthritis and atherosclerosis. Thus a therapeutic intervention that involves blocking CCR2 receptors may offer remedial measures for these chronic conditions. The disclosure herein reports our initial efforts towards the identification of cyclopentamino analogs of 1 as a potent CCR2 receptor antagonist that display high affinity and functional potency for the human CCR2 receptors. Our focus will be the syntheses, establishment of SAR and biological assays for the analogs of 1. Lastly, the cross species pharmacokinetic profile for the best analog in this novel lead class will be also briefly presented.

**MEDI 73**

**Synthesis and study of new anti-inflammatory lipid mediators**

*Nicos A. Petasis[1], petasis@usc.edu, **Jeremy Winkler**[1], jeremywi@usc.edu, Jasim Uddin[1], muddin@usc.edu, Kalyan C. Nagulapalli[1], nagulapa@usc.edu, Min Zhu[1], minzhu@usc.edu, and Charles N. Serhan[2]. (1) Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90089-1661, (2) Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115*

A new paradigm for the treatment of a variety of inflammatory disorders has evolved with the discovery of novel lipid mediators that behave as endogenous anti-inflammatory and pro-resolution agents. We have recently been investigating a number of such lipid mediators derived from arachidonic acid and polyunsaturated ω-3 fatty acids, as well as their biostable analogs that serve as their agonists, including members of the lipoxin, resolvin and protectin families. Herein, we will report our recent work in this area, including the synthesis and study of a number of new molecules of this type.

**MEDI 74**

**Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides and sulfonylureas as novel antagonists of the CXCR2 receptor**

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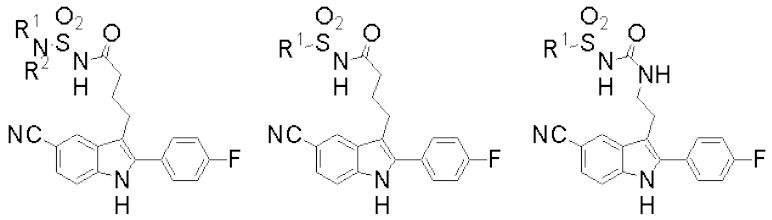
Recruitment of neutrophils and monocytes is a normal physiological response to infection and tissue damage. However, excessive numbers of these cells can produce additional tissue damage by releasing proteases, oxygen radicals and other mediators. Proteases in particular can stimulate mucus secretion and other airway events associated with COPD and various airway diseases. It is postulated that the CXCR2 chemokine receptor, when activated by a chemokine such as IL-8, mediates neutrophil migration. Blocking this activation with a CXCR2 antagonist should impact neutrophil migration and have an effect on airway disease. Series of novel acylsulfamide 1, acylsulfonamide 2 and sulfonylurea 3 bioisosteres of indole-substituted carboxylic acids were prepared as CXCR2 antagonists. The chemistry to synthesize these novel inhibitors and their structure-activity relationships will be discussed. One potent orally bioavailable inhibitor had excellent PK properties and was active in a lung injury model in hyperoxia-exposed newborn rats.



**1** **2** **3**

**MEDI 75**

## Design and synthesis of 3-phenylsulfonylmethyl cyclohexylaminobenzamide-derived inhibitors of CC chemokine receptor 2 (CCR2)

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We report the synthesis of 3-phenylsulfonylmethyl cyclohexylaminobenzamides (**2**) as CCR2 inhibitors for the potential treatment of inflammatory diseases. The *in vitro* structure-activity relationships of **2** are described. Several of the urea-derived compounds display low-nanomolar binding affinity for CCR2.


racemic-(1,2,4)-*cis*-**1**

CCR2 (R = *i*-Pr:
Binding $IC_{50}$ = 5.2 nM)

racemic-(1,3,4)-*cis*-**2**

**MEDI 76**

**Discovery and optimization of novel cyclohexylaniline-based GPR4 antagonists**

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GPR4 was found as an orphan GPCR highly expressed in the lung tissues, and recently reported to be activated by acidification. The activation of GPR4 is thought to lead some inflammatory events such as the production of chemokines and the neutrophils migration to inflammation sites, suggested from our experiments. Using luciferase-reporter assay system detecting constitutive activity of GPR4, we discovered the first small-molecule GPR4 antagonist **K-285**, which inhibited the neutrophilic chemokine production and subsequent neutrophils migration in mouse lung injury model. However, **K-285** is metabolically unstable in human liver microsomes and induces QT prolongation, presumably due to high lipophilicity of its core structure: dibenzo[*b*,*f*]azepine. In this study, we have explored core-hopping to solve these issues and found a series of cyclohexylaniline-based novel GPR4 antagonists. Herein we will discuss the synthesis and SAR of these derivatives, leading to **K-924** and **K-992** with improved pharmacokinetics and promising pharmacological properties.

**MEDI 77**

**Bioassay-guided isolation of African ethnobotanical anthelmintics**

***Carrie Waterman**, Department of Chemistry, University of the Sciences in Philadelphia, 4653 Locust St., Philadelphia, PA 19139*

Currently one third of the World's population is infected with parasitic worms. The burdens of these diseases include retarded physical growth and mental incapacity. Since intestinal worms are endemic to Africa, new anthelmintic compounds should be found in the plants used by traditional healers for treating worm infections. The use of C. elegans as a model organism in our bioassay- guided fractionation successfully demonstrates which plant extracts, subsequent fractions, and isolated compounds have significant nematocidal activity. Our newly developed anthelmintic bio-assay utilizes tetrazolium salts (MTT) to determine worm mortality, a method superior to assays based on worm movement observations. LCMS and NMR are currently being used to isolate and characterize the active constituents from one plant, which is suspected to be an ellagic acid derivative. Characterization of isolates can be used to improve the efficacy of traditional treatments and allow for the development of novel anthelmintic drugs.

**MEDI 78**

**Measurement of equilibrium solubility under kinetic timeframe: Results from the evaluation of BD solubility scanner for aggregation and solubilization.**

***Yun W. Alelyunas*** *and Cindy Shen, Department of Chemistry, AstraZeneca, 1800 Concord Pike, CRDL 123, Wilmington, DE 19803*

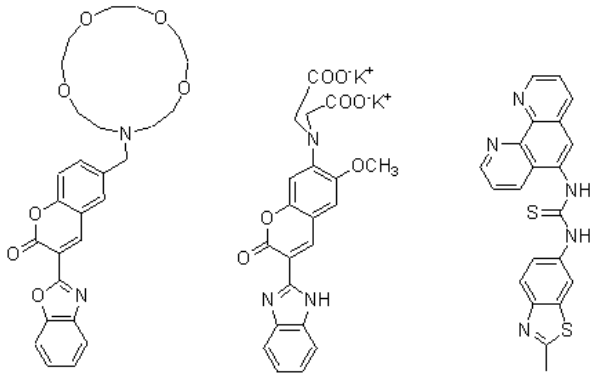
Purpose: To evaluate BD Bioscience Flow Cytometry Solubility Scanner for aggregate detection and solubility measurement. Methods: The evaluation was carried out using 129 diverse test compounds with solubility ranging from sub uM to >100 uM. A 10 mM DMSO stock solution of test compound was serially diluted with DMSO to produce a concentration gradient from 100 uM to 0.8 uM. Aqueous buffer (pH 7.4 100 mM with or without BSA presence) was added to the final solution where the DMSO concentration was 1%. A first measurement was made immediately after mixing for particle detection. A second measurement was carried out after the solution was stored at room temperature for 3 hours for differentiation of aggregation versus precipitation. Results: The BD solubility scanner was able to determine particle formation at the uM range. Addition of BSA in buffer resulted in shifting of precipitation to aggregation, and aggregation to complete solubilization. Comparison of flow cytometry data with that of HPLC thermodynamic solubility indicated good correlation of flow cytometry precipitation with equilibrium solubility where solubility is < 10 uM. Conclusions: The BD solubility scanner holds promise in aggregation and solubility assessment of drug candidates. It is the first instrument that we know of that can detect poorly soluble compound under kinetic timeframe that correlates with equilibrium solubility.

**MEDI 79**

**Synthesis and ion selectivity studies of potential fluorescent ion indicators**

***Haralambos E. Katerinopoulos****, Emmanuel Roussakis, George K. Tsikalas, and Styliani Voutsadaki, Department of Chemistry, University of Crete, Voutes Campus, Heraklion, Crete 71003, Greece, Fax: 30-2810-545-001*

A series of compounds, aimed to be used as fluorescent probes for biological ions, have been synthesized and the fluorescent properties of their free and ion-bound forms were studied. The fluorescent properties of these probes are due to the extended conjugation of chromophores such as substituted coumarins and benzothiazols, whereas their ion chelating properties are due to the presence of ionophores such as [1,10]phenanthrolin-5-amine, N,N-bis(2-pyridinylmethyl)amine, mono- and polyaza macrocyclics, and polycarboxylate moieties. Based on their structural features and their spectral profile, these probes are classified as Photoinduced Electron Transfer (PET) or Photoinduced Charge Transfer (PCT) indicators. Their ion selectivity is discussed in terms of the ionophore structure and the extent of conjugation in their framework.




Representative structures of fluorescent ion indicators

**MEDI 80**

**Iodine oxidation of cysteine-rich peptides in solid and solution phase.**

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Disulfide bridges play a fundamental role in maintaining biologically active conformations of several natural and synthetic peptides. There are several methods by which intramolecular multiple disulfide bonds are formed in synthetic peptides and proteins. The disulfide bond formation is accomplished using either an oxidizing agent or mild basic conditions. All methods have several limitations, including side reactions of oxidation sensitive residues, use of hazardous oxidants and difficulties in their post oxidation removal.

Based on the different chemical activities of 4-methoxyltrityl (Mmt), trityl (Trt) and acetamidomethyl (Acm)-protecting groups we developed two straightforward and easy methods for multiple disulfide bond formation of cysteine-rich peptides using iodine oxidation in solution and solid phase that improve purity of the desired compounds. These methods are applicable to different peptides, such as polyphemusin, endothelin-3, orexin-A and other cysteine-rich peptides.

**MEDI 81**

**Radiolabeling and efficacy evaluation of lumbrokinase from earthworm Lumbricus rubellus in Sprague-Dawley rats**

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Lumbrokinase, a fibrinolytic enzyme isolated from the earthworm, Lumbricus rubellus is currently being investigated for its role in removing blood clots in conditions like thrombosis. The present investigation details a method for the synthesis of [$^{99m}$Tc]lumbrokinase and its distribution in a biological system. Radiolabelling of lumbrokinase with [$^{99m}$Tc] was accomplished by using tetraborohydrate exchange resin (BER) which afforded [$^{99m}$Tc]lumbrokinase with a radiochemical purity of > 90% as determined by radio-TLC and HPLC. Biodistribution studies in the blood, liver, heart, spleen, kidney and lung of Sprague-Dawley rats revealed that the maximum percentage of the injected dose (% ID) and the percentage of the injected dose per gram organ weight (% ID/g) of [$^{99m}$Tc]lumbrokinase were found in the blood when compared to the other organs at time periods of 0.5, 1, 2, 4, 8, 12 and 24 h after administration of a single dose of the radiotracer (3.7 MBq/0.1 mL). Results suggest that lumbrokinase is mainly concentrated in the target organ, namely the blood and hence can be effectively used in treating blood clotting diseases like thrombosis.

**MEDI 82**

## Design and synthesis of selective PC-PLC and PLA2: Sensitive self quenching near-infrared fluorescing probes

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We have designed, synthesized and tested in vitro and in vivo a number of phosphatidylethanolamine (PtdEtn) and phosphatidylcholine (PtdCho) derivates. All such derivatives bear a near-infrared fluorescing dye Pyropheophorbide a (Pyro) attached at the sn2-position of the glycerol backbone without or with a C6 and C12 spacer. The quencher can be another Pyro molecule at the sn1-position or a Black Hole Quencher-3 (BHQ) molecule linked to the nitrogen atom of PtdEtn. The probes revealed a very high activity and specificity to appropriate phospholipases. Pyro-PtdEtn-BHQ is highly sensitive only to phosphatidylcholine-specific phospholipase C (PC-PLC). Another probe Pyro-C12-PtdEtn-BHQ is more responsive to phospholipase A2 (PLA2). These probes will be useful for detection and photodynamic therapy of tumors which over express PC-PLC (for example ovarian cancer) and PLA2 (for example prostate cancer).

**MEDI 83**

## Somatostatin receptor (sst1-5) activation in human retinal pigment epithelium cell cultures leads to cytostatic and apoptotic events

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This study investigated the differential effects of somatostatin and its receptors (sst1-5 receptors) on cell proliferation of human retinal pigment epithelium (RPE) cells. Human RPE cells (D407) were employed and MTT, APOpercentage and tryptan blue assays were performed to study the cytostatic, apoptotic and necrotic effects of somatostatin (10-10-10-4M) and somatostatin receptor (sst1-5) selective ligands (10-12-10-4M). Somatostatin and selective ligands for all five somatostatin receptor subtypes (sst1-5) decreased cell proliferation in a concentration-dependent manner. The observed decrease in cell number was due to cytostatic signaling via sst2, sst3, and sst4 receptors, apoptosis via sst1, and sst5 and cytotoxic effects at the highest concentration of ligands used (10-4M), mainly via sst1 and sst5 activation. This study provides novel information regarding the cytostatic, apoptotic and / or cytotoxic effects of somatostatin in hRPE cells. These distinct signalling mechanisms are due to the differential activation of its receptors.

**MEDI 84**

**Novel cell binding assay to screen for small peptides that modulate paracellular permeability**

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Zonula occludens toxin (ZOT) and ΔG, a 12 kDa ZOT fragment, are paracellular permeability enhancers and promising drug delivery candidates. Previously, AT-1002, the N-terminal 6 amino acids of ΔG was identified as the minimal sequence required for permeability enhancement of a differentiated Caco2 cell monolayer. The goal of this study was to establish a Caco2 cell binding assay for AT-1002. We found that low concentrations of [I]125Tyr-1 and FITC-C6 modified AT-1002 did not bind efficiently to cells. Interestingly, co-incubation of labeled AT-1002 with excess unlabeled AT-1002 substantially increased labeled AT-1002 binding. However, excess of AT-1002 analogs that were inactive in permeability induction assays did not increase labeled AT-1002 binding. Importantly, an inhibitor of AT-1002 mediated permeability also blocked increased labeled AT-1002 binding. Thus, we have established a cell binding assay that correlates with Caco2 permeability modulation which is useful for discovering new permeability modulators and for mechanism of action studies.

**MEDI 85**

**Scavenging for reactive compounds from high throughput screening**

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*Abstract text not available.*

**MEDI 86**

**New analogs of nonyl acridine orange with improved FRET to Pc 4 for study of the role of cardiolipin in photodynamic therapy**

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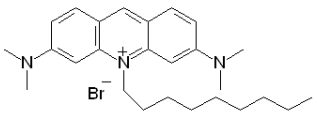
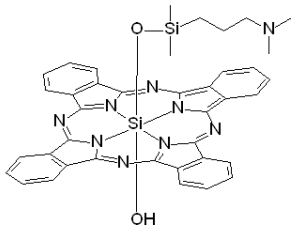
Photodynamic therapy (PDT) using the silicon phthalocyanine $SiPc(OSi(CH_3)_2(CH_2)_3N(CH_3)_2)(OH)$ (Pc 4) is now in clinical trials at University Hospitals of Cleveland. It shows promise for the treatment of cancer and other disorders. Pc 4 localizes mainly in mitochondria and the endoplasmic reticulum.

Mitochondria are considered the most sensitive target for PDT for directly triggering PDT-induced apoptosis. Because of the very short lifetime of $^1O_2$, the main toxic species in PDT, $^1O_2$ reacts within very short distance (<10nm) of its site of formation (which is the site of binding of Pc 4). Previous fluorescence resonance energy transfer (FRET) studies between 10-N-nonyl acridine orange (NAO), a specific molecular probe for cardiolipin (CL), and Pc 4 provided evidence that Pc 4 is localized near CL, a position where an initial event leading to cell death occurs under PDT. CL, an unsaturated phospholipid, is easily attacked by $^1O_2$ and is found uniquely in inner membrane of mitochondria and at the contact sites. CL with its propensity for oxidation is a potentially important target for PDT and other oxidative therapies, because it is associated with essential mitochondrial proteins, including cytochrome c and the Bcl-2 family proteins. Unfortunately, the NAO-Pc 4 FRET efficiency is poor because the peak overlap between NAO and Pc 4 is not good. Accordingly new NAO analogues with improved spectral properties for the quantification of the changes in CL using FRET were synthesized and their FRET to Pc 4 in MCF7-c3 cells was evaluated. Among these, the 9-cyano substituted NAO analogues with hexyl and nonyl groups at 10-N position were found to have good incorporation into cellular mitochondria, and showed stronger FRET with Pc 4 than the NAO-Pc 4 couple did. This makes them possible alternatives to NAO for future photodynamic therapy (PDT) studies.




NAO




Pc 4

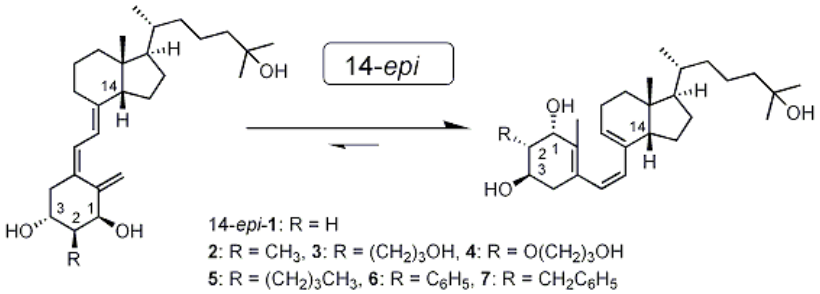
**MEDI 87**

## Synthesis and biological evaluation of novel 2-substituted 14-*epi*-previtamin $D_3$ analogs

*Daisuke Sawada[1], **Yuya Tsukuda**[1], ytsukuda@pharm.teikyo-u.ac.jp, Nozomi Saito[1], Tomoyuki Katayama[1], Hiroshi Saito[2], Ken-ichiro Takagi[2], Kazuya Takenouchi[2], Seiichi Ishizuka[2], Midori Takimoto-Kamimura[2], Masashi Takano[1], mtakano@pharm.teikyo-u.ac.jp, and Atsushi Kittaka[1], akittaka@pharm.teikyo-u.ac.jp. (1) Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Sagamihara, Kanagawa 229-0195, Japan, Fax: +81-42-685-3714, (2) Teijin Institute for Bio-Medical Research, Tokyo 191-8512, Japan*

1alpha,25-Dihydroxyvitamin $D_3$ (**1**) is the active metabolite of vitamin $D_3$ and plays an important role in calcium and phosphorus homeostasis as well as cellular proliferation and differentiation. It is well established that the vitamin $D_3$ triene structure exists in the thermal "previtamin D/vitamin D" equilibrium through [1,7]-sigmatropic rearrangement in a ratio of 6/94 at 37 $^oC$. In 1994, Okamura and co-workers reported synthesis and characteristic properties of 14-*epi*-**1**, whose equilibrium of the

triene chromophore was found to be displaced to the previtamin D form in a ratio of 95/5, after heating at 80 $^{o}$C. While the previtamin form of **1** is a poor activator in the genomic action process, the previtamin $D_3$ is thought to be a potent activator of the non-genomic action through putative membrane vitamin D receptor. We synthesized new 2alpha-substituted 14-*epi*-previtamin $D_3$ analogs (**2**-**7**) to evaluate their biological activities, for example, binding affinity for the chick intestinal VDR and osteocalcin transcriptional activity on HOS cells. We found that 1alpha,25-dihydroxy-2alpha-methyl-14-*epi*-previtamin $D_3$ (**2**) showed 8.4% VDR binding affinity of that of **1**, which was the strongest one among **2**-**7**, while the mother compound 14-*epi*-**1** exhibited only 0.5%. Compound **2** showed moderate osteocalcin transcriptional activity on HOS cells. Novel 2beta-substituted 14-*epi*-previtamin $D_3$ analogs will be also discussed.




**MEDI 88**

**Substituted diarylsulfones as modulators of secreted frizzled related protein-1 (SFRP-1), an antagonist of the Wnt signaling pathway.**

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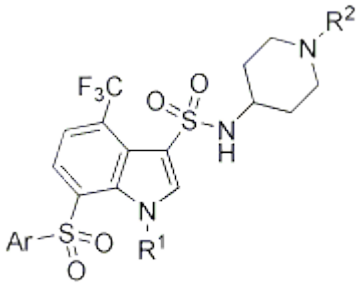
Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1, expressed by cells and secreted into the local environment, is a Wnt antagonist. In osteoblast cells antagonism of Wnt may lead to a decrease in bone formation. Consequently, the goal of the program was to develop small molecule inhibitors of SFRP-1, which may be useful for the treatment of bone disorders such as osteoporosis. Through modifications of a diarylsulfone sulfonamide scaffold the trifluoromethyl sulfonamide (I) was identified as being optimal. This scaffold proved useful in producing a variety of sulfonamides with excellent binding to SFRP-1; however, in general this series has suffered from the metabolic fate of N-dealkylation. Replacement of the sulfonamide to address the issue of N-dealkylation, along with the synthesis of selected targets and the SAR of the compounds prepared, will be presented.

**MEDI 89**

## Design and synthesis of indole sulfonamides as inhibitors of secreted frizzled related protein-1 (SFRP-1)

***Gregory S. Welmaker***[1]*, welmakg@wyeth.com, Matthew A. Wilson*[1]*, wilsonm8@wyeth.com, William J. Moore*[1]*, moorew2@wyeth.com, Jeffrey C. Kern*[1]*, KernJ@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Ronald L. Magolda*[1]*, magoldr@wyeth.com, Keith Pitts*[2]*, Girija Krishnamurthy*[2]*, Krishng@wyeth.com, Barbara Stauffer*[3]*, StauffB@wyeth.com, Ramesh Bhat*[3]*, and Peter V. N. Bodine*[3]*, BodineP@wyeth.com. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Studies have shown that certain Wnt proteins interact with a family of proteins named “frizzled” that can function as either direct receptors for Wnt proteins or as a component of a Wnt receptor complex. Secreted frizzled related protein-1 (SFRP-1) is expressed in osteoblasts and osteocytes and has been identified as a Wnt antagonist. SFRP-1 knockout mice demonstrate increased bone formation, possibly due to the observed decrease in osteoblast/osteocyte apoptosis. In an effort to identify modulators of SFRP-1, a series of indole sulfonamides A was designed based upon a hit identified by HTS. The syntheses and biological activity of these compounds will be described.




A

**MEDI 90**

## Design, synthesis, and biological evaluation of a novel indole series of secreted frizzled related protein-1 (SFRP-1) inhibitors

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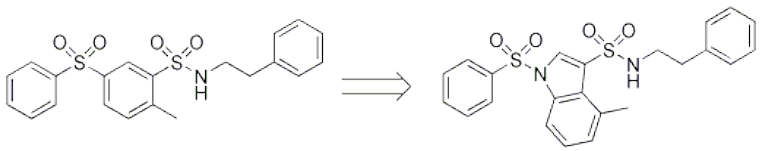
Secreted Frizzled-Related Protein-1 (SFRP-1) is a novel anabolic target for osteoporosis. Deletion of the SFRP-1 gene in mice leads to decreased osteoblast apoptosis and increased trabecular bone formation. An SFRP-1 inhibitor should be able to reverse osteoporotic bone loss by increasing osteoblast life and also allowing these cells to produce more bone. Compound 1 was identified

through high-throughput screening as a SFRP-1 inhibitor. Modeling around compound 1 led to exploring chemistry that replaces the central phenyl ring with an indole (compound 2). The chemistry and biological data will be presented.



Compound 1 Compound 2

**MEDI 91**

## Secreted frizzled-related protein-1 (SFRP-1) antagonists: Synthesis and SAR of a series 6-membered ring constrained analogs

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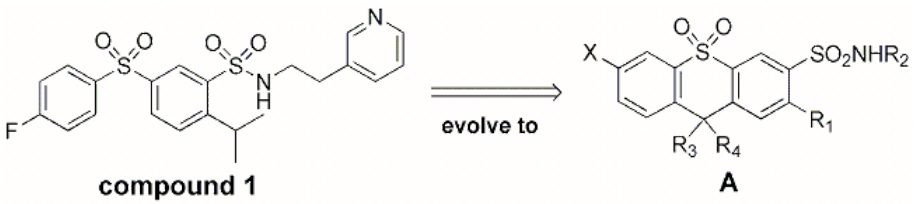
Secreted Frizzled related protein-1 (SFRP-1), expressed by cells and secreted into the local environment, is a Wnt antagonist. Antagonism of Wnt leads to a decrease in beta-cat, which consequently suppresses gene expression. In the case of osteoblast cells, important in the bone remolding process, this decrease in gene expression may lead to a decrease in bone formation. Recent studies in mice have shown that deletion of SFRP-1 leads to decreased osteoblast apoptosis and increased bone formation. The goal of the program was to identify orally available small molecule inhibitors of SFRP-1. Such a drug may be useful for the treatment of bone disorders, including bone resorption disorders such as osteoporosis, and for regulation of bone in humans. Based on an original lead compound in the program (compound 1), a strategy involving the preparation of the corresponding conformationally constrained 6-membered ring analogs (generic structure A) was pursued. It was found that most of the constrained analogs maintained similar activity when compared with the non-constrained analogs; however, some of the constrained analogs offered advantages in activity, solubility and stability.




compound 1 A

**MEDI 92**

## Linked piperazine-dione derivatives as helical mimetics for the disruption of bcl-2-family proteins

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Disregulation of the apoptotic processes is one of the major causes of diseases, such as cancer, inflammatory, autoimmunity, and neurodegenerative disorders. Within the B-cell lymphoma-2 (Bcl-2) family, the balanced interactions between anti and pro-apoptotic proteins play a major role in regulating apoptosis. Several studies have indicated that overexpression of anti-apoptotic Bcl-2 and Bcl-xL proteins is associated with tumor progression and drug resistance. Previously reported compounds that inhibit the interaction between pro-apoptotic BH3 domains and Bcl-2 family proteins contain hydrophobic scaffolds that can diminish their use as potential drug leads. Herein we present the design and synthesis of hydrophilic alpha-helix mimics based on hydrazine linked piperazine-dione repeat units for the disruption of Bcl-2 proteins. Several of these compounds have been synthesized in our lab, and the most promising lead has a biological activity of 4.7 μM in fluorescence polarization assays.

**MEDI 93**

## XIAP selective imidazopyridine-containing SMAC mimetics

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The inhibitor of apoptosis (IAP) proteins are a group of proteins that are involved in the regulation of cell death. In the course of our work on small molecule IAP antagonists, small alterations in the basic peptide scaffold were discovered to impart binding selectivity for one or another of the IAPs. Specifically, using an imidazopyridine to link the peptidic portion of our molecules to the aromatic ring buried in a hydrophobic pocket resulted in selectivity for binding to the BIR3 domain of XIAP over the corresponding domains in cIAP1, cIAP2 and ML-IAP. In an effort to understand the origins of this selectivity, three small molecule antagonists were soaked into ML-IAP crystals and their structure determined.

**MEDI 94**

## Development of diverse AFC analogs to probe the binding pocket of Icmt

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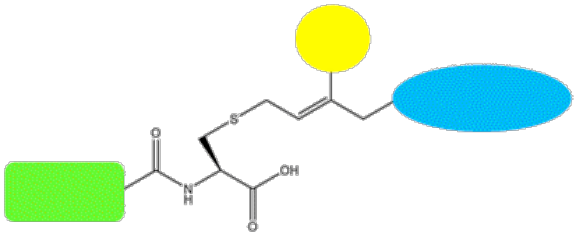
Protein post-translational modifications are essential transformations for proper cellular signaling. The membrane-bound enzyme isoprenylcysteine carboxyl methyltransferase (Icmt) is responsible for the methylation of the oncogenic Ras protein, and inhibition of Icmt thus has potential for cancer therapy. We have begun SAR investigations of N-Acetyl-S-Farnesyl-L-Cysteine (AFC), the minimal substrate of Icmt, to develop substrate-based Icmt inhibitors. Initial work has focused on the amide linkage of AFC and has led to low micromolar inhibitors (BMCL 2006, 4420). The prenyl moiety can be functionalized to further understand the scope of substrates and inhibitors for Icmt. Isoprene-mimetics containing functionalities capable of undergoing Pd-catalyzed transformations have been incorporated into AFC. This flexible synthetic strategy will allow for the preparation of diverse AFC analogs to further understand the unknown binding pocket of Icmt and develop more potent inhibitors of this potential anti-cancer target.

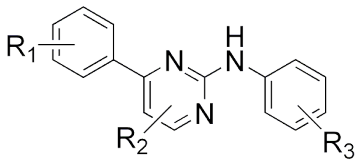



**MEDI 95**

***N*,4-Diphenylpyrimidin-2-amines as inhibitors of Janus kinases**

***David G Bourke**, James Palmer, Andrew Donohue, John Feutrill, Laura Andrau, Marcel Kling, Thao Nguyen, Michelle McNally, Xian Bu, Chris Burns, Harrison Sikakanyika, Emmanuelle Fantino, Margarita Kurek, Max Joffe, Soo San Wan, Naomi Court, and Patricia Bukczynska, Cytopia, 576 Swan Street, Richmond Victoria 3121, Australia*

Imbalances in the JAK-STAT pathway have been implicated in autoimmune disorders, inflammatory disease, myeloproliferative disorders (MPDs) and various cancers. The discovery that a constitutively active mutation in JAK2 (V617F) is central to the pathogenesis of MPDs including Polycythaemia Vera has accelerated the search for selective JAK2 kinase inhibitors. *N*,4-diphenylpyrimidin-2-amines have been identified to be inhibitors of JAK and other kinases. Several synthetic approaches to a series of *N*,4-diphenylpyrimidin-2-amines will be shown. In addition enzymatic and cellular activities along with effects on downstream signaling events will be discussed.




$R_1$=Alkyl and hetroaryl

**MEDI 96**

**The design, preparation and profiling of potent and selective chk2 activators**

***Chris Brassard**, Jeff Link, Robb Nicewonger, and Mark A. Ashwell, Arqule, 19 Presidential Way, Woburn, MA 01801*

Herein we describe the application of in silico predictive methods and parallel chemistry to advance structure activity relationships (SAR) for series of molecules identified as inducers of the

phosphorylation of Chk-2. A Hit Generation (HG) campaign employing an in-house developed, quantitative, cell-based assay system utilizing a high-content analysis (HCA) platform identified from within ArQule chemistry space promising hits. These molecules were shown to increase levels of p-Chk2 in HeLa cells and were further analyzed for Chk-2 dependent cytotoxicity in a high-content cell death assay in combination with siRNA silencing of Chk2 expression.

Chk2 kinase, a tumor suppressor and key transducer of DNA damage checkpoints, plays a key role in blocking the cell cycle at various stages of mitosis, as well as inducing DNA repair and these molecules offer an attractive approach to the discovery of new targeted anti-cancer therapeutics. Select in vitro data will be presented to highlight the structure-activity relationships.

**MEDI 97**

**Synthesis of acyclic imido-substituted chloro-1,4-naphthoquinone derivatives in anticancer studies**

***Yakini Brandy*** *and Oladapo Bakare, Department of Chemistry, Howard University, 525 College Street, Washington, DC 20059*

The kinases in the Ras-Mapk signaling pathway are attractive targets for the development of novel therapeutic intervention in human carcinomas. We have previously reported 2-chloro-3-(N-succinimidyl)-1,4-naphthoquinone as a selective MEK1 inhibitor. An open chain analog, 2-chloro-3-dibutyrylamino-1,4-naphthoquinone, was found to possess multi-kinase inhibitory activities and exhibited selective cytotoxicity against a panel of renal and prostate cancer cell lines. In continuation of our studies to develop more potent and selective compounds in our prostate cancer program, we have designed the synthesis of several acyclic imido-substituted chloro-1,4-naphthoquinone analogs. The reaction of 2-amino-3-chloro-1,4-naphthoquinone with sodium hydride followed by nucleophilic acyl substitution reaction of the resulting nucleophile on appropriate acid chloride furnished a mixture of the amido- and imido-substituted derivatives. The target imido-substituted analogs were isolated by column chromatography on silica gel and/or by recrystallization from appropriate solvents. These compounds were characterized by infrared (IR) spectroscopy, nuclear magnetic resonance spectroscopy (1H & 13C-NMR) and electrospray-ionization mass spectrometry.

**MEDI 98**

**Design, synthesis and SAR discussion of 6-amine substituted triazolopyrazine derivatives as highly selective, potent and soluble c-Met/HGFR Inhibitor**

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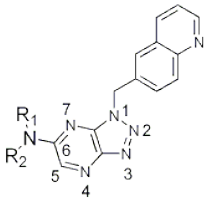
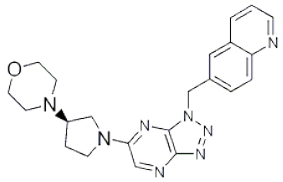
The c Met receptor tyrosine kinase is one of the RTKs most frequently mutated or abnormally activated in late stage human cancers, and plays a critical role in regulation of tumor progression, invasive growth, and tumor angiogenesis. The triazolopyrazine core was discovered to yield potent

and highly selective c-Met inhibitors.1 In order to rapidly investigate the SAR off the 6 position of the triazolopyrazine core, and to address the poor solubility associated with neutral compounds, based on crystal structure analysis of c-Met with inhibitors from triazolopyrazine series, pyrrolidine and pyrazines with moderate basic amines were introduced at the 6 position. For example, compound 1 demonstrated very good biochemical activity, cellular activity and aqueous solubility. This poster will discuss the design, synthesis of this series of compounds. The SAR including biochemical activity, cellular activity, binding analysis by crystal structure determination with compound 1, in vitro and in vivo metabolic stability will also be discussed.





**1** (HCl salt)

MW 416.21
c-Met Ki 0.0146 μM
c-Met A549 Cell
$IC_{50}$ 0.0148 μM
Aqueous sol: > 1 mg/ml

**MEDI 99**

**Inhibitors of Cdc48/p97 AAA ATPase as potential anticancer therapeutics**

***Tsui-Fen Chou***[1]*, tfchou@caltech.edu, Amanda C. Jones*[2]*, Brian M. Stoltz*[2]*, and Raymond J. Deshaies*[1]*. (1) Division of Biology, California Institute of Technology, 1200 E. California Blvd, MC 156-29, Pasadena, CA 91125, Fax: 626-395-5739, (2) Department of Chemistry, California Institute of Technology, Pasadena 91125*

Cdc48/p97 is an important AAA-ATPase that mediates turnover of proteins involved in tumorgenesis. Using p97 crystal structures as a guide, we derivatizated a PP1 like compound to incorporate electrophiles that are likely to react with a cysteine on the ATP-binding site of p97. One of the inhibitors (ACJI-99C) exhibited an IC50 ~0.6 uM for p97 and ~300 uM for yeast Cdc48 and ~100 uM for hNSF(hamster N-ethylmaleimide sensitive factor) in an in vitro ATPase assay. ACJI-99C-induced inactivation of p97 was protected by cysteine and DTT. Cys522 of p97 was shown to be critical for ACJI-99C inhibition by mass spectroscopy and mutagenesis. ACJI-99C exhibited anti-proliferation activity toward cancer cell lines with sub-micromolar GI50. After 1-hr incubation with ACJI-99C, poly-ubiquitinated proteins were accumulated in HeLa and RPMI-8226 cells, which recapitulated the effect of p97 depletion. We have identified a covalent inhibitor of p97 and demonstrated its potential to be an anti-cancer agent.

**MEDI 100**

**Structure based discovery of inhibitors of HPV E7 RB-binding core**

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The high-risk human papillomaviruses (HPV16, 18) are critical etiologic agents in human malignancy, most importantly in cervical cancer. While prophylactic vaccines are available commercially for the prevention of HPV infection and cervical cancer, theses vaccines do not prevent infection with several HPV types. The oncogenic HPVs encode the E6 and E7 proteins which are expressed in cervical cancers. E7 stimulates the cell cycle via its ability to bind and inactivate the cellular pRb protein. Furthermore, a core motif (L-X-C-X-E) of E7, which is conserved in almost all types of HPVs, is critical for its binding ability to pRb. Thus, small molecule inhibitors that bind to this core would alter the function of E7 protein and inhibit its ability to bind pRb. Through a new multi-step computer aided approach, we discovered several low micromolar lead compounds that altered the mobility of E7 protein in PAGE gel and subsequently inhibited human cervical cancer cell growth

**MEDI 101**

**Ligand based discovery of potent small molecules that up-regulate p75 neurotrophin receptor in vitro.**

***Sivanesan Dakshanamurthy***[1]*, sd233@georgetown.edu, Fatima S Khwaja*[2]*, khwajaf@georgetown.edu, Daniel Djakiew*[2]*, djakiewd@georgetown.edu, and Milton L. Brown*[3]*, mb544@georgetown.edu. (1) oncology, Lombardi Cancer Center, Georgetown University, reservoir road, W225/E401, NRB, washington, DC 20057, (2) Department of Biochemistry & Molecular Biology, Georgetown University, Washington, DC 20057, (3) Drug Discovery Program, Georgetown University Medical Center, Washington, DC 20057*

p75 is a central protein involved in axotomy-induced cell death of sensory and motor neurons, and its down-regulation has resulted in cancer proliferation. Previously, high dose aryl propionic acid analogs were shown to up-regulate the expression of P75NTR initiating tumor cell death through apoptosis. To further identify and optimize potent pharmacological molecules to up-regulate the P75NTR expression, we employed a new ligand based approach. In this approach, we developed several potential pharmacophore models by comparing the functional features of the experimentally active as well as inactive molecules. The most promising candidate compounds were selected from this group and screened against glioblastoma (U87) cell line for the P75NTR expression. Several of the compounds were at least eighteen times more effective at inducing the expression of P75NTR than the original lead.

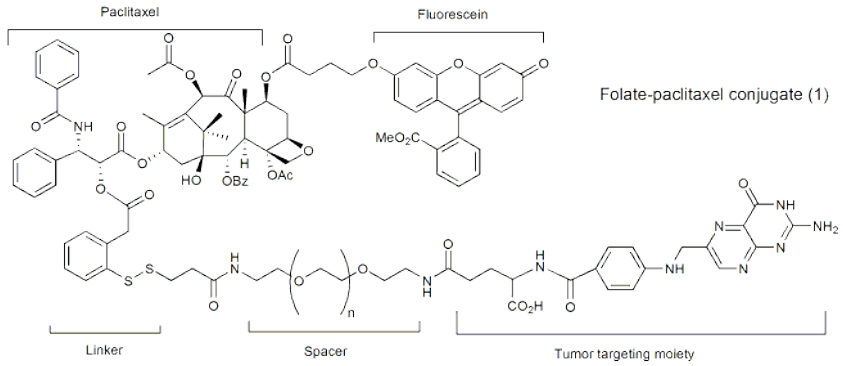
**MEDI 102**

**Synthesis and biological evaluation of novel tumor-targeting folate-taxane conjugates**

***Manisha Das****, mdas@ic.sunysb.edu, Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, and Iwao Ojima, iojima@notes.cc.sunysb.edu, Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

Numerous cancer cells overexpress folate receptors which make them an attractive target for tumor-targeting drug delivery. These receptors bind folic acid with a very high affinity and undergo efficient receptor-mediated endocytosis. Accordingly, we chose folic acid as the tumor-targeting molecule in our ongoing research program on tumor-specific chemotherapeutic agents. We have designed and

synthesized folate-taxane conjugates using a novel self-immolative disulfide linker and a PEG spacer. The internalization of a fluorescein-labeled folate-paclitaxel conjugate (**1**) into the tumor cell, the subsequent release of paclitaxel and its binding to the microtubules were successfully observed by means of CFM. Further biological evaluation of these drug-conjugates will also be presented.




**MEDI 103**

**Spliceosome inhibitors as anticancer agents**

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Recently two natural products, FR901464 and pladienolide, which were previously shown to possess selective and potent in vivo anticancer activity, have been found to act by the same novel mechanism of action, targeting the SF3b subunit of the spliceosome. A significant amount of work has led to several total syntheses of these fascinating natural products4 and also culminated in some remarkably active analogs, which possess nearly all of the structural features of the parent compounds. The presence of a clear therapeutic window for these compounds, especially pladienolide, stimulated our interest in the development of totally synthetic analogs as potential leads for human cancer therapy. Using a pharmacophore hypothesis based on common interaction elements present in both pladienolide and FR901464, we have designed new compounds related to FR901464 that have only 3 chiral centers (6 less than FR901464!). Using this design, we developed a highly practical enantioselective and diastereospecific synthesis of this new class of potent compounds that show activity similar to that of the natural products. This synthesis allows for the facile introduction of analogs and is suitable for the development of lead compounds for cancer therapy. This presentation will focus on the synthesis and the bioactivity of our new compounds.

**MEDI 104**

**Single to multiple targets: Design of multiple kinase inhibitors**

***S Vadivelan*** *and Jagarlapudi Sarma, Informatics, GVK Biosciences Private Limited, 37 Sterling Road, Nungambakkam, Chennai - 600 034, India, Fax: 91-44-66293199*

It is estimated that bringing a drug from idea to market takes approximately 12 years and costs US $802 millions. The main reasons for failure of drug are efficacy (30%), toxicity (20%) and pharmacokinetic issues (10%). Virtual screening approaches can use either the 3D structure of the target (target-based virtual screening or docking) or use active and inactive ligands (ligand based approaches) to determine and rank those structures most likely to bind. The success of a virtual screen is defined in terms of finding interesting new scaffolds rather than many hits. There is a growing recognition that molecules that modulate multiple targets simultaneously can be beneficial for treating a range of diseases. The screening of fragment libraries and further scaffold hoping might offer an attractive opportunity for discovering lead. There is 57% sequence similarity between the catalytic sites of CDK2 and GSK3â kinases and ~50% similarity between the binding sites. Hence it is assumed that common inhibitors can be designed against them. So we have designed multiple inhibitors against CDK2 and GSK3â enzymes.

**MEDI 105**

**Novel purine derivatives as potent dual Src/Abl tyrosine kinase inhibitors**

***Yihan Wang**, William C. Shakespeare, Wei-sheng Huang, Raji Sundaramoorthi, Scott Lentini, Sasmita Das, Shuangying Liu, Geeta Banda, David Wen, Xiaotian Zhu, Qihong Xu, Jeff Keats, Frank Wang, Scott Wardwell, Yaoyu Ning, Joseph T. Snodgrass, Mark I. Broudy, Karin Russian, John Iulucci, David Dalgarno, Tim Clackson, and Tomi K. Sawyer, ARIAD Pharmaceuticals, Inc, 26 Landsdowne Street, Cambridge, MA 02139, Fax: 617-494-8144*

Src is the prototypical member of a family of kinases (Src Family Kinases, SFKs) whose aberrant activity is associated with an invasive phenotype in both early and advanced solid tumors. Bcr-Abl, the constitutively activated fusion protein product of the Philadelphia chromosome (Ph), is the principal oncogene underlying the pathology of chronic myelogenous leukemia (CML). Src and Abl exhibit high sequence homology, thus many compounds targeting Src are also effective inhibitors of Abl. Previously at ARIAD, we identified a series of 9-hydroxyphenethylpurines as potent dual Src/Abl inhibitors. To further probe the purine core as a template for such compounds, alternative 2-atom linkers between the template and a pendant hydrophobic substituent were explored. Here we describe our use of a vinyl group linker, which led to a series of stable, synthetically accessible, purine-based dual Src/Abl inhibitors. Despite concerns about the potential metabolic instability of the vinyl linkage, the compounds posses good PK properties.

**MEDI 106**

**Asymmetric synthesis and evaluation of 2-(3-chloro-phenyl)-2-hydroxy-nonanoic acid amide**

***Gary C. Davis**[1], gcd2c@virginia.edu, Yali Kong[1], yk4n@virginia.edu, Mikell Paige[2], map65@georgetown.edu, Sivanesan Dakshanamurthy[3], sd233@georgetown.edu, Owen McManus[4], owen_mcmanus@merck.com, Maksymilian Chruszcz[5], mc3h@virginia.edu, Wladek Minor[5], and Milton L. Brown[2], mb544@georgetown.edu. (1) Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904, (2) Drug Discovery Program, Georgetown University Medical Center, Washington, DC 20057, (3) oncology, Lombardi Cancer Center, Georgetown University, washington, DC 20057, (4) Ion Channels, Merck Research labs, Rahway, NJ 07065, (5) Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA 22908*

Voltage-gated sodium channels are known to be expressed in neurons and other excitable cells. Recently, voltage-gated sodium channels have been found to be expressed in human cancer cells. Alpha-Hydroxy-alpha-phenyl amides are a new class of small molecules that are potent voltage-gated sodium channel inhibitors. The hydroxyamide motif was discovered to be an isotere of the hydantoin ring, which is currently used in the clinic in sodium channel blockers such as phenytoin. Cyclocondensation of (R)-3-chloromandelic acid with pivaldehyde furnished both the cis- and trans-2,5-disubsituted dioxolanones, also known as Seebach and Frater's chiral template. Using this chiral template, we synthesized both enantiomers of 2-(3-chloro-phenyl)-2-hydroxy-nonanoic acid amide, and evaluated their ability to functionally inhibit both $hNa_v1.5$ and $hNa_v1.7$. Finally, we evaluated these compounds against human prostate cancer cells that contain $hNa_v1.5$ and $hNa_v1.7$ for antiproliferative effects.

**MEDI 107**

**Discovery and synthesis of a novel fluorescent carbazole that up-regulates the tumor suppressor gene RASSF1A in human prostate cancer cells**

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The loss of Ras-association domain family 1A (RASSF1A) protein expression, which results from gene silencing by hypermethylation, disrupts cell cycle control and provides for apoptotic resistance in cancer cells. The reversal of this tumorigenic phenotype can be induced by ectopic expression of RASSF1A. Previously, the natural product mahanine was shown to reverse the epigenetic silencing and restore RASSF1A expression via inhibition of DNA methyltransferase. Restoration of RASSF1A expression resulted in the potent inhibition of human androgen independent prostate cancer cell proliferation. Recently, we discovered synthetic carbazole precursors of mahanine that up-regulate RASSF1A. In comparison to mahanine, our lead compound is more potent at inhibiting human prostate cancer cell proliferation without associated cytotoxicity. Moreover, the compound is fluorescent and its intracellular distribution was observed. In this study, we present our novel carbazole as a small molecule lead that restores RASSF1A expression and inhibits the growth of human prostate cancer cells.

**MEDI 108**

**Novel dimers of epi-podophyllotoxin**

***Norma Dunlap*** *and* ***Tracy L. J. Salyard****, Department of Chemistry, Middle Tennessee State University, Box X-074, Murfreesboro, TN 37132, Fax: 615-898-5182*

Numerous analogs of epi-podophyllotoxin, bearing amine and ether substituents at C4 have been reported. Several of these semi-synthetic drugs derived from podophyllotoxin, including etoposide and teniposide, are used clinically in cancer therapy.

The mechanism of these analogs involves an increase in topoisomerase II- mediated DNA breaks, and inhibition of topoisomerase II's ability to ligate the cleaved DNA. Activity depends on one

molecule of etoposide binding on each strand of DNA, requiring two drugs per event. Evidence suggests that the two drugs act independently of each other. One implication for drug design, is that linked dimers of epi-podophyllotoxin analogs may have increased activity over the monomers.

Although many C4 substituted epi-podophyllotoxins have been reported, there are few reports of dimers. The syntheses of several ether-linked dimers are reported here. These covalently linked analogs of epi-podophyllotoxin should provide further insight into the two-drug model and potentially provide novel antitumor agents.

**MEDI 109**

**2,3-Dimethoxy-8,9-methylenedioxybenzo[i]phenanthridines substituted at the 11- and 12-positions as novel topoisomerase I-targeting antitumor agents**

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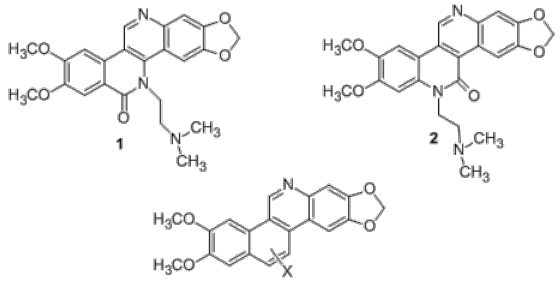
ARC-111 (1) is a potent non-camptothecin TOP1-targeting agent that has exhibited potent antitumor activity in athymic nude mice with human tumor xenografts. Its reversed lactam derivative (2) is a potent TOP1-targeting agent and is highly cytotoxic to several human tumor cell lines. Methods were developed for the synthesis of several structurally related 11- and 12-substituted benzo[i]phenanthridines. In addition to preparation of analogs with N,N-dimethylaminoalkyl substituents at the 11- and 12-position, several 11- and 12-carboxamides were synthesized. Comparative studies were performed to assess the relative TOP1-targeting activity and cytotoxicity of these benzo[i]phenanthridine derivatives.




**MEDI 110**

**Cationic compounds for chemotherapy of chagas disease: Guanylhydrazones and aminoguanyl amides**

***Jose Daniel Figueroa-Villar***[1]*, figueroa@ime.eb.br, Luzineide Wanderley Tinoco*[2]*, lwtinoco@nppn.ufrj.br, Jorge Cardoso Messeder*[1]*, and Marcia Narciso Borges*[3]*. (1) Department of Chemistry, Medicinal Chemistry Group, Military Institute of Engineering, Praça General Tiburcio 80, Rio de Janeiro 22290-270, Brazil, Fax: 5521-2546-7059, (2) Núcleo de Pesquisas de Produtos*

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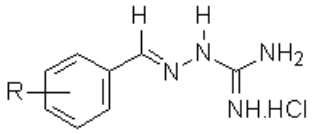
Chagas disease, which is a deadly disease caused by the protozoan Trypanosoma cruzi, affects about 15 million people in Latin America and has no cure. We have first discovered that a large family of mono-cationic aromatic guanylhydrazones (1) was effective in vitro against the trypomastigote forms of this parasite. Further NMR and molecular modeling studies indicated that this kind of compounds may act by interaction with the parasite membrane and DNA. This data was used to design and synthesize a second generation of this kind of compounds, which was shown to be orally effective on infected mice in a high dose (100 mg/kg), but with low toxicity. In order to decrease the toxicity there were prepared a series of easily hydrolyzed cationic compounds: Aminoguanyl amides (2), which showed to be as effective as the guanylhydrazones.

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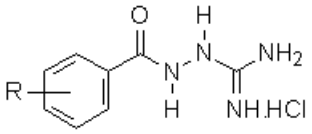


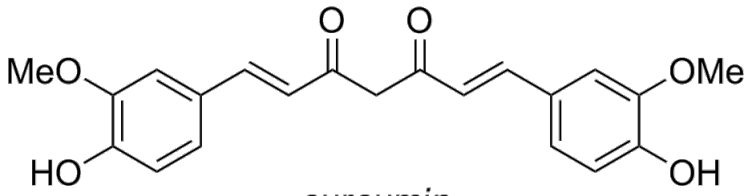

2

**MEDI 111**

**Synthesis and antiproliferative activity of curcumin analogs**

***James R. Fuchs***[1]*, fuchs.42@osu.edu, Jonathan P. Etter*[1]*, Pui-Kai Li*[1]*, li.27@osu.edu, Dalia Abdelhamid*[1]*, Nicholas Regan*[1]*, Deepak Bhasin*[1]*, Bulbul Pandit*[1]*, pandit.6@osu.edu, Chenglong Li*[1]*, li.728@osu.edu, Katryna Cisek*[1]*, Jiayuh Lin*[2]*, Ling Cen*[2]*, and Brian Hutzen*[2]*. (1) Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University, College of Pharmacy, Riffe Building, 496 W. 12th Ave., Columbus, OH 43210, Fax: 614-292-2435, (2) Center for Childhood Cancer, Columbus Children's Research Institute, The Ohio State University, Columbus, OH 43205*

Curcumin, a natural product isolated from the rhizome of Curcuma longa, has been shown to have useful antioxidant, anti-inflammatory, antiangiogenic, and antiproliferative properties due to its interaction with numerous biological targets. Although not as potent as many other cytotoxic agents, curcumin has been demonstrated to be safe in humans at relatively high doses (10 grams/day), making it an attractive target for chemotherapeutic drug discovery efforts. Unfortunately, however, it also suffers from poor bioavailability and stability issues. Therefore, the design and preparation of more potent, stable, and target-selective curcumin analogues is highly desirable. A thorough study of analogues designed to probe both steric and electronic requirements for anticancer activity in breast, colon, and prostate cancer cells is ongoing. Accordingly, our synthetic efforts to prepare these compounds and an investigation into their affected molecular targets will be reported.




*curcumin*

**MEDI 112**

## New anticancer agents based on noncoxib analogs of celecoxib

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Although celecoxib (Celebrex) was initially developed as an anti-inflammatory agent based on its ability to inhibit cyclooxygenase-2 (COX-2), it was subsequent found to exhibit novel anticancer properties that are not associated with COX-2 inhibition. We have recently been investigating the development of new anticancer agents based on structural analogs of celecoxib that do not inhibit COX-2 but do retain potent anticancer actions by inducing apoptosis and suppressing tumor growth. Herein we will report our recent work in this area, including the design, synthesis and investigation of a number of new analogs of this type.

**MEDI 113**

## Design, synthesis and SAR evaluation of substituted maleimides as GSK3 inhibitors

***Franck Gallier**[1], gallier@uic.edu, **Irina Gaysina**[1], igaysina@uic.edu, Denise Holzle[1], dholzl1@uic.edu, Aruna Mahesh[1], arumah@uic.edu, Ki Kim[1], pkhkim@gmail.com, Sylvie Y. Blond[1], Blond@uic.edu, and Alan Kozikowski[2], kozikowa@uic.edu. (1) Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The University of Illinois at Chicago, Chicago, IL 60612, (2) Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612*

Glycogen synthase kinase, GSK-3, is a serine/threonine protein kinase that regulates a diverse array of cell functions by phosphorylation of different proteins. There are two highly homologous forms of GSK-3 in mammals, GSK-3$\alpha$ and GSK-3$\beta$. GSK-3$\beta$ is one of the kinases involved in the hyperphosphorylation of tau leading to the formation of neurofibrillary tangles, whereas GSK-3$\alpha$ has recently been found to be associated with the production of $\alpha$-amyloid plaques - the two major hallmarks of Alzheimer's disease. GSK3 is thus a potential therapeutic target for the treatment of Alzheimer's disease and other taupathies. Recently, we have identified the 3-benzofuranyl-4-indolylmaleimides as potent and relatively selective GSK-3 inhibitors. To get better insights into the SAR of this family of molecules, a small library of substituted maleimides was generated based on molecular modeling predictions. The synthesis and biological evaluation of these new maleimides are presented.

**MEDI 114**

## Potent and selective thiazolyl- and triazolylphenyl-based HDAC inhibitors with anticancer and antimalarial activities

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Histone deacetylases (HDACs) are promising targets for cancer and malaria chemotherapy. In mammalian cells, the HDACs are divided into four classes that depend on their sequence/structural homology to yeast deacetylases, expression patterns, and catalytic mechanisms. The discovery of the rules governing the inhibition of the various HDAC isoforms is likely to be key to identifying improved therapeutics that act as epigenetic modulators of gene transcription. A library of thiazolyl- and triazolylphenyl-based HDAC inhibitors was created. It has been shown that modification of the CAP region of this set of compounds plays a role in selectivity for HDAC1 versus HDAC6. These new HDAC inhibitors were studied for both their anticancer and antimalarial activity, which served to validate the superior activity of this subclass of inhibitors in the inhibition of pancreatic cancer cell lines and malarial parasites.

**MEDI 115**

## Specific myosin light chain phosphatase inhibitors as potential therapeutic agents for human prostate cancer

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Myosin light chain phosphatase (MLCP) is an important protein in the regulation of cellular motility and division. We developed and synthesized a fluorescent small molecule (17e) that selectively inhibits MLCP. We found the growth of human prostate cancer cell lines with upregulated amounts of MLCP proves to be more sensitive when treated with our selective MLCP inhibitor. We used the fluorescent properties of 17e to image its entry and compartmentalization in human prostate cancer

cells. 17e causes an increase in the mitotic index of CA46 cells and FACS analysis demonstrated that this was due to 17e causing G2/M arrest. 17e treated prostate cancer cells showed both the microfilament and microtubule networks were disrupted. This disruption significantly reduced PC-3 cells ability to migrate towards a chemoattractant in a Boyden chamber experiment. Finally, our target validation studies with human prostate cancer tissue establishes a relationship between MLCP expression and Gleason's score.

**MEDI 116**

**Discovery of selective SHP-2 phosphatase inhibitors via in silico screening and experimental assay**

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SHP-2 is a widely-expressed non-receptor protein tyrosine phosphatase that plays important roles in diverse processes such as development and hematopoiesis. Genetic mutations that cause hyperactivation of SHP-2 catalytic activity have been implicated to play a causal role in Noonan syndrome, various childhood leukemias, and sporadic solid tumors. In silico screening combined with validation by experimental assay was used to identify low-molecular weight compounds that inhibit SHP-2 phosphatase activity. So as to promote the discovery of selective inhibitors, a region of the protein thought to be important for substrate binding but different than the analogous pocket on the highly-homologous SHP-1 phosphatase was targeted. From a database of 1.3 million small molecules, 9 out of 165 computationally selected compounds were shown to inhibit SHP-2 activity. Among the four most active compounds, two have selectivity for SHP-2 over SHP-1.

**MEDI 117**

**Screening for small molecule inhibitors of the phosphatase SHP2**

***Jing He***[1]*, jing.he@moffitt.org, Divya Ramamoorthy*[1]*, ramamoorthy.divya@moffitt.org, Xin Wu*[1]*, Yunting Luo*[2]*, Harshani R. Lawrence*[1]*, Liwei Chen*[1]*, Shen-Shu Sung*[2]*, Jie Wu*[3]*, Said M. Sebti*[1]*, and Nicholas J. Lawrence*[2]*. (1) Drug Discovery, Moffitt Cancer Center, 12902 Magnolia Drive, MRC 4West, Tampa, FL 33612, (2) Drug Discovery Program, Moffitt Cancer Center, Tampa, FL 33612, (3) Molecular Oncology Program, Moffitt Cancer Center, Tampa, FL 33612*

Shp2 protein tyrosine phosphatase (PTP) mediates signal transduction of growth factor receptors and regulates cellular activities critical to tumor growth and metastasis. In the basal state, the interactions between the N-SH2 and PTP domains keep the phosphatase in an autoinhibited closed conformation. Upon growth factor or cytokine stimulation, the SH2 domains of Shp2 binds to tyrosine phosphorylated docking proteins such as Gab1 and Gab2, which activates Src, Ras, and the Erk1/2 (Erk) mitogen-activated protein (MAP) kinase pathway. Shp2 gain-of-function mutations are found in leukemias and solid tumors and are linked to Noonan syndrome. Although Shp2 is involved in pathogenesis of human cancers, it is not clear how Shp2 mediates tumorigenesis. No Shp2-selective

PTP inhibitor is currently available for chemical biology studies and experimental therapy. Shp2 is believed to be an important enzyme for targeted cancer therapy. We will report developments in our search for small organic molecules as potent and selective Shp2 inhibitors as chemical probes to further our understanding of the role and signaling mechanisms of Shp2 in human diseases and as potential drugs for cancer therapy. These have been discovered by high throughput screening, conducted both at the Moffitt Cancer Center and elsewhere. We will discuss the design and synthesis of focused libraries based on hits that have been prepared and assessed for Shp2 inhibitory activity.

**MEDI 118**

**Development of novel inhibitors of histone methyltransferase**

***Tomoya Hirano**, Kenta Hoshino, Naoko Iwanami, Yujiro Tanaka, and Hiroyuki Kagechika, School of Biomedical Science, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan, Fax: +81-3-5280-8127*

Histone modification by some enzymes, such as histone deacetylases (HDAC) and histone methyltransferases (HMT), plays an important role in regulating gene expression. To clarify physiological function of each HMT family enzyme, we developed novel inhibitors by using adenosylhomocysteiene (AdoHcy), that yields after methylating reaction by HMT and adenosylmethionine, as a lead compound. Several AdoHcy derivatives bearing an alkyl group at N6 position of adenine ring were designed based on the binding feature of AdoHcy and substrate peptide at each HMT active site. The HMT inhibitory activities of the synthesized compounds against SET7/9, an HMT that methylates not only lysine 4 of histone H3 (H3K4) but also tumor suppressor p53 or TAF10, were evaluated by ELISA using anti-methylated histone antibody. The results suggested that some derivatives with a bulky N-alkyl group have more potent inhibitory activity against SET7/9 than AdoHcy.

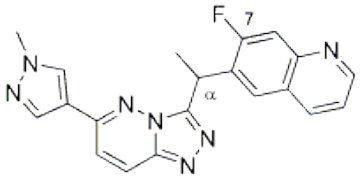
**MEDI 119**

**Design and synthesis of PF-04331956: An alpha-methyl/7-fluoro substituted triazolopyridazine derivative as a highly selective and potent c-Met/HGFR inhibitor**

***Jacqui Hoffman**[1], jacqui.e.hoffman@pfizer.com, Hengmiao Cheng[1], henry.cheng@pfizer.com, Phuong Le[1], J. Jean Cui[1], jean.cui@pfizer.com, Michelle Tran-Dube[1], Hong Shen[1], hong.shen@pfizer.com, Mitchell Nambu[1], Mason Pairish[1], Catherine Johnson[1], Robert Kania[1], Lei Jai[2], Michele McTigue[3], Neil Grodsky[1], Kevin Ryan[1], Max Parker[1], Shinji Yamazaki[1], Helen Zou[1], and James Christensen[4]. (1) PGRD La Jolla Laboratories, Pfizer, Inc, 10770 Science Center Dr, San Diego, CA 92121, (2) Oncology Chemistry, PGRD La Jolla Laboratories, Pfizer, Inc, San Diego, CA 92121, (3) 10770 Science Center Dr, San Diego 92121, (4) Cancer Biology, PGRD La Jolla Laboratories, Pfizer, Inc, San Diego, CA 92121*

The binding of hepatocyte growth factor (HGF) to the receptor tyrosine kinase (RTK) c-Met plays a key role in cellular physiology in a wide range of cellular targets including, epithelial and endothelial cells. These many actions are fundamentally important during development, homeostasis, and tissue regeneration. However, c Met is one of the RTKs most frequently mutated or abnormally activated in late stage human cancers and plays a critical role in the regulation of tumor progression, invasive growth, and tumor angiogenesis. The triazolopyrazine and triazolopyridazine cores were discovered to yield potent and highly selective c-Met inhibitors.1 Based on SBDD, incorporation of the alpha-

methyl/7-fluoro substitution in the triazolopyridazine series produced the picomolar potent analog PF-04331956. This poster will discuss the design and synthesis of PF-04331956. The biochemical and cellular activity, ADME and PK properties, will also be discussed. 1. See oral presentation by J. Jean Cui: “Discovery and Development of PF-4217903 as a Highly Potent and Exquisitely Selective c-Met/HGFR Inhibitor.”



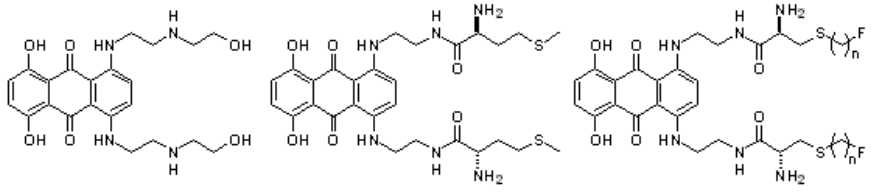
PF-04331956

**MEDI 120**

## Synthesis and biological activity of S-fluoroalkyl-substituted cysteine-anthraquinone conjugates as potential positron emission tomography imaging agents for multidrug resistance

***Ling-Wei Hsin*** *and Chi-Wei Wang, Institute of Pharmaceutical Sciences, National Taiwan University, No. 1, Jen-Ai Road, Section 1, Room 1336, Taipei 10018, Taiwan, Fax: 886-2-2351-2086*

Multidrug resistance (MDR) is among the most significant impediments to effective cancer chemotherapy. The ATP-binding cassette (ABC) transporters play important roles in MDR and therefore, determine the susceptibility of cancer patient to certain antitumor agents. An in vivo quantitative and sensitive method to measure the levels of ABC transporter expression and activity would be valuable for assessing the involvement of ABC transporters in MDR, predicting the outcome of cancer chemotherapy in individual patient, and the development of novel anti-cancer drugs and chemotherapeutic treatment strategies. WRC-213, a mitoxantrone (MX)-amino acid conjugate (MAC), was more potent than MX and subjected similar resistance against MX-resistant cancer cell line. Since MX is a well-known substrate for ABCB1 and ABCG2, the S-fluoroalkyl-substituted MACs may be useful for the development of 18F-labeled positron emission tomography tracers for molecular imaging of ABCB1 and ABCG2. Here, we report the synthesis and biological evaluation of S-fluoroalkyl-substituted cysteine-anthraquinone conjugates 1-4.



Mitoxantrone WRC-213 **1**: n = 1; **2**: n = 2; **3**: n = 3; **4**: n = 4.

**MEDI 121**

**Studies on the mechanism of inhibition of thymidine phosphorylase by 6-substituted-5-fluorouracil derivatives**

***Harsh V. Jain**, Roshni Rasheed, and Thomas I. Kalman, Department of Chemistry, University at Buffalo, The State University of New York, 359 Natural Sciences Complex, Buffalo, NY 14260, Fax: 716-645-6963*

Thymidine phosphorylase (TP), also known as platelet-derived endothelial growth factor, has been implicated in tumor angiogenesis, and is considered a promising target for anticancer drug development. A variety of 6-subsituted-5-fluorouracil derivatives were designed as transition state analogs and their inhibitory activities against *E. coli* and recombinant human TP were determined. 5-Fluoro-6-[(2-aminoimidazol-1-yl)methyl]uracil was found to be the most potent inhibitor with $K_i$-values of 11 nM (ecTP) and 17 nM (hTP), the fluorine contributing a 15-fold increase in activity, likely due to its lowering of the pKa of the corresponding zwitterion by 2 pH units. It was found that enzyme inhibition requires the presence of inorganic phosphate or arsenate. Kinetic studies established that the inhibitor must bind to the enzyme-phosphate or enzyme-arsenate binary complex, explaining the role of the basic side chain, which also contributes to the stabilization of the negatively charged pyrimidine ring resembling the transition state structure.

**MEDI 122**

**Toward the design of cell-permeable cap-dependent translation inhibitors**

***Yan Jia**, jiaxx011@umn.edu, Department of Chemistry, University of Minnesota, WDH 8-184, 308 Harvard st. SE, Minneapolis, MN 55455, and Carston R. Wagner, wagne003@umn.edu, Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455*

Eukaryotic initiation factor eIF4E, the rate limiting factor in cap-dependent translation, is considered to be an anti-cancer drug target. eIF4E binds directly to 7' methylated guanosine capped mRNA. Replacement of the 7-Me group of the monophosphate with different substituents has been shown to affect the binding affinity of the corresponding cap analogues to eIF4E. Among a variety of substitutions on N-7 position, 7N-benzyl guanosine monophosphate (7-Bn GMP) showed good binding affinity. A combinatorial docking of substituted benzyl bromide from Aldrich with GMP was carried out using CombiGlide from Schrodinger® to elucidate the effect of different functional groups on 7-benzyl GMP. A small library of 7N-substituted benzyl GMP analogues was synthesized and their dissociation constants were determined. To overcome cell membrane barrier, we designed cell permeable cargos coupled to 7-Bn GMP to deliver potential inhibitors of eIF4E. Effect of exogenous cap-free eIF4E on efficiency of cap-dependent translation was also studied.

**MEDI 123**

**Synthesis and evaluation of chalcones, privileged chemopreventive structures**

***Thomas E. Johnson**, Marie Hugger, and Chengguo Xing, Department of Medicinal Chemistry, University of Minnesota, 308 Harvard Street SE, 8-101 Weaver-Densford Hall, Minneapolis, MN 55455, Fax: 612-624-0139*

Chalcones are a class of organic compounds that possess varied biological properties – antitumor, antiinflammatory, and also chemopreventive properties. Recently, our laboratory has exhibited that the flavokawains, chalcone-based natural products derived from kava are chemopreventive against B[a]P and NNK induced lung tumorigenesis in the A/J mouse model. Additionally, chalcones have been reported to influence signal transduction pathways as well as enzymatic activities in a manner which may account for their chemopreventive activities. In light of these results, our laboratory has undertaken an effort to develop the chalcone scaffold into novel chemopreventive agents. To this end, our laboratory has synthesized a library of compounds with varying substituents at each position of the A and B ring of the chalcone structure. These compounds displayed varied effects regarding cytotoxicity and cell cycle arrest in a battery of human cancer cell lines. This presentation will discuss the biological evaluation of these compounds and their structure-activity relationships.

**MEDI 124**

**Flavokawains A and B: Chemopreventive constituents of kava against lung tumorigenesis**

***Thomas E. Johnson***[1]*, joh01871@umn.edu, Fekadu Kassie*[2]*, Pramod Upadhyaya*[2]*, upadh003@umn.edu, Stephen S. Hecht*[2]*, hecht002@umn.edu, and Chengguo Xing*[1]*, xingx009@umn.edu. (1) Department of Medicinal Chemistry, University of Minnesota, 308 Harvard Street SE, 8-101 Weaver-Densford Hall, Minneapolis, MN 55455, Fax: 612-624-0139, (2) University of Minnesota Cancer Center, Minneapolis, MN 55455*

Kava usage has been commonplace in the South Pacific Islands. A negative correlation between kava consumption and cancer incidence despite a high rate of smoking offers evidence that chemopreventive constituents are present in kava. The potential chemopreventive constituents of kava extract include the flavokawains - chalcone based natural products. Flavokawain A and B have also been shown to inhibit activation of NF-κB, a family of transcription factors innately linked to carcinogenesis. In light of the epidemiological and biological evidence, our laboratory investigated the effect of flavokawain A and B on inhibition of B[a]P and NNK induced lung tumorigenesis in the A/J mouse model. This presentation will discuss the results of flavokawain A and B administration on lung tumorigenesis inhibition in the A/J mouse model.

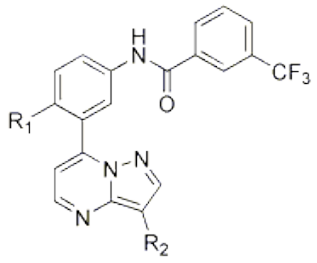
**MEDI 125**

**Synthesis and activity of pyrazolo[1,5-a]pyrimidines as B-Raf inhibitors**

***Kyung-Hee Kim***[1]*, kimk@wyeth.com, Jeremy I. Levin*[1]*, Minu Dutia*[1]*, George Diamantidis*[2]*, diamang@wyeth.com, Greg Ciszewski*[1]*, Ariamala Gopalsamy*[1]*, Yongbo Hu*[1]*, Larry Feldberg*[3]*, Eileen Frommer*[3]*, Steven Kim*[3]*, Karen Collins*[3]*, Donald Wojciechowicz*[3]*, and Robert Mallon*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (2) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ, Princeton, NJ 10965, (3) Oncology Research, Wyeth Research, Pearl River, NY 10965*

Small molecules that inhibit B-Raf offer a potential treatment for melanoma and other B-Raf dependent malignancies. We have discovered potent inhibitors of B-Raf, derived from an HTS hit, ethyl 7-(3-(3-(trifluoromethyl)benzamido)-phenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate ($R_1$ = H, $R_2$ = $CO_2Et$). This presentation will describe variations at $R_1$ and $R_2$ of **1**, guided by structure based design, in order to optimize activity. Some of these analogs, including several that have no

discernable hinge-region binders, showed excellent in vitro enzyme inhibition. The synthesis and activity of the analogs will be discussed.



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**MEDI 126**

**Synthesis and optimization of small molecule inhibitors of EWS-FLI1**

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Ewing's Sarcoma Family of Tumors (ESFT) is a rare malignancy. ESFT contains a reciprocal chromosomal translocation, t (11:22) that translates to EWS-FLI1. EWS-FLI1 protein has been identified as a critical target in Ewing's sarcoma family of tumors. We screened a small molecule library to identify a lead compound that inhibited EWS-FLI1 protein. Based on the structure of the lead compound, we optimized and synthesized a series of compounds targeting EWS-FLI1 protein. YK-4-279 was found to have significant cell proliferation inhibition (IC50 < 1 μM) on human Ewing's sarcoma TC32 cells. The effects of YK-4-279 resulted in cancer apoptosis as measured by a Caspase activity. We demonstrate that YK-4-279 is an effective inhibitor of EWS-FLI1 and may have potential use in the treatment of Ewing's sarcoma.

**MEDI 127**

**Neuroprotection studies of benzamide- and thioester/disulfide-based histone deacetylases inhibitors in oxidative stress-induced neuronal death**

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The histone deacetylases (HDACs) are able to regulate gene expression, and HDAC inhibitors (HDACIs) hold considerable promise in the treatment of cancer and a variety of neurodegenerative diseases. Modifications to the zinc binding group (ZBG) of the HDACIs can influence HDAC inhibitory potency, isoform selectivity, and neurotoxicity. We provide data that compare the ability of three

structurally different classes of HDACIs containing benzamide, hydroxamate, or thiol groups as the ZBG for their ability to protect cortical neurons in culture from oxidative stress-induced death. This study reveals that HDAC3 selective inhibition by certain benzamide-based ligands fails to block homocysteic acid induced oxidative stress in cortical neurons. Moreover, we show that prodrug-based sulphur-containing ligands, both thiolesters and disulfides, present protection profiles similar to those shown by the HDAC6 selective mercaptoacetamides, and thus further highlight the prospect of developing stable, low molecular weight HDACIs with BBB permeability for the treatment of neurodegenerative diseases.

**MEDI 128**

**Oxindole based inhibitors of the Shp2 protein tyrosine phosphatase**

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Shp2, encoded by the PTPN11 gene, is a protein tyrosine phosphatase (PTP) that mediates growth factor- and cytokine-stimulated cellular activities essential for oncogenesis. It is a positive regulator of Src family kinases (SFKs), Ras, and Erk MAP kinases. Shp2 mutations have been found in leukemias including juvenile myelomonocytic leukemia (JMML) and solid tumors including melanoma. In particular, PTPN11 is the most frequently mutated gene in JMML, accounting for 35-50% of cases. All Shp2 mutations found in human malignancies are gain-of-function mutations, resulting in constitutively active Shp2. Thus, Shp2 PTP is an important target for new cancer therapy. Screening of a small library has led to the identification of an inhibitor of Shp2. A focused library was designed incorporating the isatin scaffold and was screened for Shp2 and Shp1 activity. Several compounds were identified that selectively inhibit Shp2 phosphatase activity with low to sub-micromolar activity. A model for the selective binding of the active compounds will be presented.

**MEDI 129**

**Synthesis of pyrazole-type inhibitors of Hsp90 molecular chaperone**

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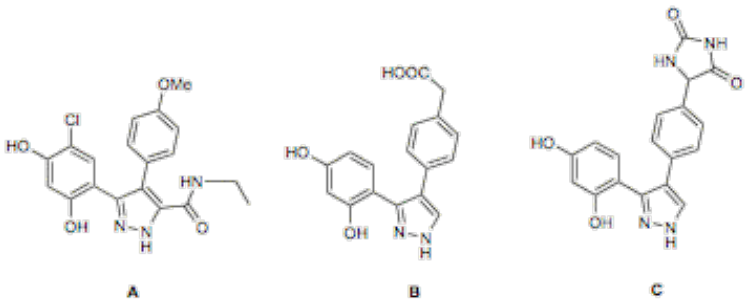
Molecular chaperones are proteins that have been said to play a role in the maintenance of conformation, stability, and function of the client protein within the cell. Heat-shock protein 90 (Hsp 90) is an ATP-dependent molecular chaperone that has several oncogenic client proteins involved in signal transduction, cell cycle regulation, and apoptosis, and has recently become a focus of interest as potential anticancer drug target.




A B C

A geldanamycin-derived inhibitor has entered phase II clinical trials and initial results are promising, providing proof of principle for Hsp90 inhibitors as cancer therapeutics. Pyrazole-type compounds such as **A** show some of the chemotypes recently identified as potent inhibitors of Hsp90. We now report the synthesis of two pyrazole-type compounds **B**, and **C** as potential inhibitors of Hsp90. The synthesis of compound **B** has been completed, and **C** is in progress.

**MEDI 130**

**Design, synthesis, and biological evaluation of 2,4-diamino-5-methyl-6-substituted-thieno[2,3-*d*]pyrimidine: A novel classical antifolate with dual thymidylate synthase and dihydrofolate reductase inhibitory acitivity as potential antitumor agent**

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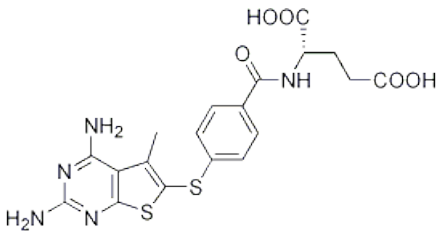
A novel classical antifolate *N*-{4-[(2,4-diamino-5-methylthieno[2,3-*d*]pyrimidin-6-yl)sulfanyl]-benzoyl}-L-glutamic acid **2** was designed, synthesized and evaluated as inhibitor of dihydrofolate reductase (DHFR), thymidylate synthase (TS) and as antitumor agent. 5-Methylthieno[2,3-*d*]pyrimidine-2,4-diamine **4** served as the key intermediate to which ethyl 4-mercaptobenzoate was appended at the 6-position via an oxidative addition reaction. The classical analogue **2** was synthesized by coupling the benzoic acid derivative **6** with diethyl L-glutamate hydrochloride followed by saponification. The classical compound **2** was an excellent inhibitor of human DHFR ($IC_{50}$ = 110 nM) as well as human TS ($IC_{50}$ = 360 nM). The classical analogue **2** is the first example, to our knowledge, of a 2,4-diamino thieo[2,3-*d*]pyrimidine classical antifolate that has inhibitory activity against both human DHFR and human TS. The design, synthesis and biological evaluation of compounds **2** will be presented and discussed.




**2**

**MEDI 131**

**Amiloride derivatives as uPA inhibitors**

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Urokinase-type plasminogen activator (uPA) is a trypsin-like serine protease that plays a crucial role in the regulation of plasminogen activation, tumor cell adhesion and migration. Hence, the inhibition of uPA holds much promise for development of new anti-cancer agents. As part of our ongoing research to discover small molecule inhibitors of uPA, we have developed 2-amidino and 2-amidoximo analogs of amiloride. Their synthesis and biological evaluation in uPA inhibition assays will be presented.

**MEDI 132**

**Synthesis of stilbenes and chalcone-based compounds for the treatment of colon cancer**

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In our earlier studies, two stilbene derivatives, (Z)-methyl-4-(3,5-dimethoxystyryl)benzoate and (Z)-1,3-dimethoxy-5-(4-methoxystyryl)benzene, were found to strongly inhibit the growth of HT-29 colon cancer cells in in-vitro assays ($IC_{50}$ = 0.27 and 0.028 μM, respectively). As a continuation of this study a series of compounds that include stilbene and chalcone derivatives was synthesized and tested for growth inhibition of HT-29 cells. Like stilbenes, chalcones display a number of biological properties including anti-malarial, anti-protozoal, antiinflammatory, immunomodulatory and anticancer activities. The retinoids comprise another class that shows promising results against several cancer cell lines including HT-29. Thus, a group of chalcone-retinoid hybrids was designed and synthesized in an effort to find compounds with better activity against HT-29 cells. Altogether, 20 compounds were tested. The best of the chalcone-retinoid hybrids showed moderate activity ($IC_{50}$ = 3.3 μM). Among the 20 compounds, the stilbene derivative, (Z)-1-(4-bromostyryl)-3,5-dimethoxybenzene, was most inhibitory($IC_{50}$ = 0.63 μM).

**MEDI 133**

**Synthesis and biological evaluation of coumarin-estrogen conjugates as antiproliferative agents**

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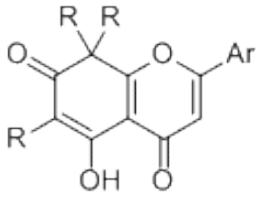
Therapeutic agents preventing the biosynthesis and physiological action of estrogen are known to be very successful in the treatment of breast cancer. Among the current cancer therapy focusing on the improvement of drug selectivity, conjugation of cytotoxic drug components to a carrier with selectivity toward the tumors or tumors tissues has proven to be an effective strategy in the development of efficient antitumor drugs. Coumarins exhibit useful and diverse biological activities, resulting in a growing interest in their synthesis and possible applications for drug discovery, e.g. 4-benzyl-3-(4'-chlorophenyl)-7-methoxycoumarin, a potent competitive aromatase inhibitor. Purpose: To design and synthesize coumarin-estradiol conjugates and determine their antiproliferative activities in various breast cancer cell lines. Methods: The National Cancer Institute (NCI) carried out the cytotoxicity studies at 5-dose concentrations in various breast cancer lines. Results: The newly synthesized coumarin-estrogen conjugates demonstrated excellent inhibitory growth activities in the human breast cancer cell lines. Conclusion: These results suggest that the conjugates show promise as potential anti-breast cancer agents.

**MEDI 134**

**Desmosdumotins as promising antitumor agents**

***Kyoko Nakagawa-Goto***[1]*, goto@email.unc.edu, Kenneth F. Bastow*[1]*, Ernest Hamel*[2]*, Po-Cheng Chang*[1]*, Tzu-Hsuan Chen*[1]*, Susan Morris-Natschke*[1]*, and Kuo-Hsiung Lee*[1]*. (1) School of Pharmacy, University of North Carolina at Chapel Hill, CB#7360, Beard Hall, Chapel Hill, NC 27599, (2) Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute at Frederick, Frederick, MD 21702*

Desmosdumotin B (**1**) showed unique in vitro cytotoxicity against the P-gp over expressing MDR tumor cell line KB-VIN, without any toxicity against non-MDR tumor cells including KB (KB/KB-VIN = 20). To explore structure activity relationships (SAR) and optimize activity, related analogs were synthesized and evaluated as in vitro inhibitors of human tumor cell growth. Analog **2** displayed enhanced KB/KB-VIN sensitivity (460-fold). This report is the first to describe compounds showing such high sensitivity. The unique activity of **1**-analogs is likely MDR-mediated, since co-treatment with verapamil partially reversed the selective toxicity of them. Interestingly, analogs with a condensed-bi-ring (B-ring) system, such as **3** (Ar = 1-naphthyl), showed significant cytotoxicity against multiple tumor cell lines, acting via strong inhibition of tubulin assembly. We will discuss the syntheses, antitumor activities and SAR findings of **1**-analogs. (Aided by NIH grants CA17625 awarded to KHL).




**1**: R = Me, Ar = Ph: Desmosdumotin B
**2**: R = Et, Ar = 4-Me-Ph
**3**: R = Et, Ar = 1-Naphthyl

**MEDI 135**

## Synthesis and cellular binding of a novel cyclic NGR peptide

***Ayele H Negussie**, Jenna L Miller, Matthew R Dreher, and Bradford Wood, Interventional Radiology, Diagnostic Radiology Department, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892*

Formation of new blood vessels is an important phenomenon for proliferation, metastasis and maintenance of tumor tissue. In addition, these tumor blood vessels carry receptors not common to the normal blood vessels such as CD13/Aminopeptidase N (APN). CD13/APN is expressed widely in angiogenic vasculature in some tumor tissue and is functionally important in angiogenesis. Therefore, targeting CD13/APN for novel anticancer therapies and delivery vehicles is an attractive research area. Cyclic Asp-Gly-Arg (NGR) has previously been shown to bind specifically to CD13/APN [1]. We have designed, synthesized and fully characterized a novel cyclic NGR peptide that does not contain a disulfide bond. For in vitro binding studies the NGR peptide was conjugated to Oregon Green dye (see figure). The peptide-dye conjugate demonstrated binding to the CD13/APN-positive HT-1080 cell line and minimal binding to the CD13/APN-negative MCF-7 cell line, thereby justifying further studies.

1. Arap. W., Pasqualini, R., and Ruoslahti, E. (1998) Science 279, 377–380

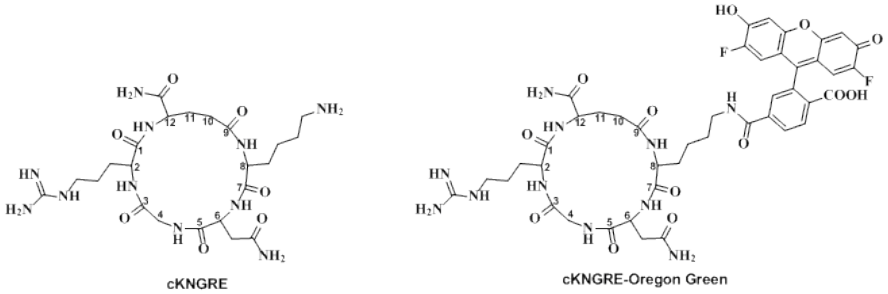



**Figure**: Cyclic NGR and its conjugate to Oregon Green dye

**MEDI 136**

## Synthesis, biochemical evaluation and molecular modeling studies of novel antimitotic and antivascular combretastatin A-4 analogs

***Niamh M. O'Boyle**, oboyleni@tcd.ie, Department of Pharmacy and Pharmaceutical Sciences, University of Dublin, Trinity College, College Green, Dublin 2, Ireland, and Mary J. Meegan, Department of Pharmacy and Pharmaceutical Sciences, University of Dublin,Trinity College, Dublin D2, Ireland*

Combretastatin A-4 (CA-4) is a natural product possessing effective anti-tubulin activity by binding at or near the colchicine-binding site of tubulin. Much effort has been invested in fixing the cis stereochemistry in CA-4 by replacing its stilbene double bond with different heterocyclic ring systems. We use the 2-azetidinone ring scaffold as a replacement for the double bond in CA-4. A series of B-lactams with different substitution patterns at the 3- and 4-positions of the 2-azetidinone ring structure was synthesised. These compounds were evaluated for their antiproliferative activity against MCF-7 and MDA-MB-231 cell lines. A number of these showed activity in the low nanomolar range. A molecular modelling study of the proposed interactions of our ligands with the tubulin was carried out using the reported tubulin-colchicine complex (3.5Å resolution). A SAR of this series of compounds was carried out to provide a useful prediction for the design of further active ligands.

**MEDI 137**

**Synthesis and evaluation of Technetium complexes as potential melanoma imaging agents**

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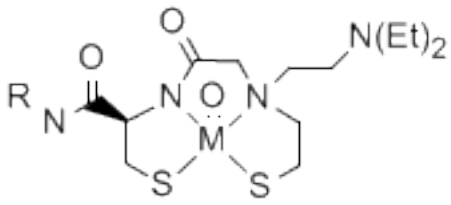
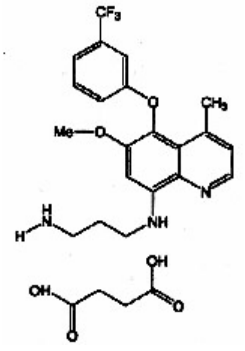
We have shown that [99mTcOAADT]-(CH2)2-NEt2) displays significant melanoma-tumor localization. To study additional structural variants of this small technetium complex, we have synthesized a series of eight derivatives with substituents on the carbon backbone at the C-5 position and have evaluated the effect of these structural modifications on in vivo melanoma uptake and localization. Structurally analogous nonradioactive oxorhenium(V) complexes have also been synthesized and characterized. In vivo assessment of the 99mTc-complexes Tc-L1–Tc-L8 in the C57B1/B16 mouse melanoma model indicates structure-related tumor localization. At 1 h post IV administration, complex Tc-L1 exhibits an in vivo tumor uptake of 4.09% ID/g, whereas Tc-L7 has tumor uptake of only 0.24% ID/g. Differences in tumor localization are attributable to variations in size and nature of the C5-substituents.




**MEDI 138**

**Bioactivity of novel substituted quinolines in murine and human tumor cell lines in vitro**

***Jean-Pierre H. Perchellet***[1]*, jpperch@ksu.edu, Elisabeth M. Perchellet*[1]*, enperch@yahoo.com, Kyle R. Crow*[1]*, crow2@ksu.edu, Aibin Shi*[2]*, aibin@ksu.edu, and Duy H. Hua*[2]*, duy@ksu.edu. (1) Anti-Cancer Drug Laboratory, Kansas State University, Division of Biology, Ackert Hall, Manhattan, KS 66506-4901, Fax: 785-532-6653, (2) Department of Chemistry, Kansas State University, Manhattan, KS 66506-3701*

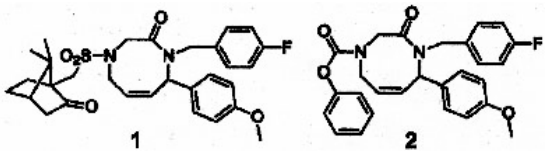



Among 11 synthetic quinoline analogs, **PQ1** succinic acid salt is the most effective antiproliferative agent, based on its ability to inhibit the metabolic activity of leukemic L1210, pancreatic Pan02, epidermoid A-431 and mammary T47D, SK-BR-3 and BT-474 tumor cells at days 2 and 4 *in vitro*. A 1.5- or 3-h treatment with **PQ1** is sufficient to inhibit the rates of incorporation of thymidine into DNA, uridine into RNA and leucine into protein over a 0.5- or 1-h period of pulse-radiolabeling in L1210 cells. Since **PQ1** does not reduce the fluorescence of the ethidium bromide-DNA complex, it does not directly bind to or destabilize double-stranded DNA. Over a 6-48 h period, **PQ1** has very little effect on the mitotic index of L1210 cells but stimulates the formation of many binucleated cells and a few micronuclei, suggesting that this compound might increase mitotic abnormality, induce chromosomal damage or missegregation, and block cytokinesis.

**MEDI 139**

## Bioactivity of novel eight-membered medium ring lactams inspired by octalactin A in murine and human tumor cell lines in vitro

***Jean-Pierre H. Perchellet***[1], *jpperch@ksu.edu, Elisabeth M. Perchellet*[2], *enperch@yahoo.com, Kyle R. Crow*[1], *crow2@ksu.edu, Keith R. Buszek*[2], *buszekk@umkc.edu, Neil Brown*[2], *brownne@umkc.edu, Ge Gao*[2], *gegao@umkc.edu, Diheng Luo*[2], *dltwb@umkc.edu, Gerald H. Lushington*[3], *glushington@ku.edu, and David VanderVelde*[3], *dvandervelde@ku.edu. (1) Anti-Cancer Drug Laboratory, Kansas State University, Division of Biology, Ackert Hall, Manhattan, KS 66506-4901, Fax: 785-532-6653, (2) Department of Chemistry, University of Missouri, Kansas City, MO 64110-2481, (3) Center for Chemical Methodologies and Library Development, University of Kansas, Lawrence, KS 66047*



http://oasys.acs.org/acs/236nm/medi/papers/viewimage.cgi?image=0&RecordType=Paper&Recordid=1186905&Hash=760fc9c5f0961f229a817c801acc2349

Pilot-scale libraries of 80 new eight-membered medium ring lactams were screened for antiproliferative activity in leukemic L1210 and HL-60, pancreatic Pan02, and mammary SK-BR-3 tumor cells *in vitro*. All compounds except three were active but structures **1** and **2** decreased the most the metabolic activity of L1210 cells at day 4 ($IC_{50}$: 470 and 640 nM, respectively). A 1.5- or 3-h treatment with **1** was sufficient to inhibit the rates of DNA, RNA and protein syntheses in L1210 cells. As **1** and **2** did not reduce the fluorescence of the ethidium bromide-DNA complex, they did not directly bind to or destabilize double-stranded DNA. Over a 12-24 h period, **1** and **2** very weakly increased the mitotic index of L1210 cells but stimulated the formation of many binucleated cells and a few micronuclei, suggesting that these compounds might enhance mitotic abnormality, induce chromosomal damage or missegregation, and block cytokinesis.

**MEDI 140**

## Antitumoral properties of cyan containing lactones derivative

***Ghazaryan Petros***[1], *ghazarpa@yahoo.com, Lusine Sahakyan Sr.*[2], *lusisahakyan@yahoo.com, and Ajcemnik Karagulyan*[1]*. (1) Department of Pharmchemistry, Yerevan State University, Alec. Manoucyan 1 str, 23, Sundukyan str, Yerevan 03741, Armenia, Fax: 03741 284478, (2) Department of Science, Center of Haematology, Yerevan 037410, Armenia*

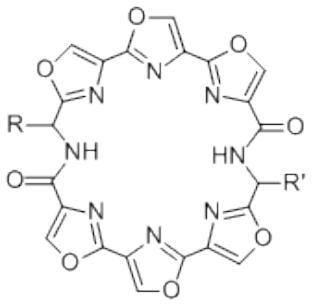
It has been established a disturbance of membranous phospholipids (PL) metabolism, in with is expressed by increase in the content of lysophosphatidylcholines (LPC), phosphatidylinosites (PI), phosphatidylserines (PS), phosphatidic acids (PA) on the background decrease of phosphatidylcholines (PC), phosphatidylethanolamines (PE), sphingomielines (SPM) in rats with sarcoma-45. The coefficient of LPC/PC increases and the PC/PA – decrease. After application of cyan-containing derivative of lactone (2-cyan-3,4,4-trimethyl-2-buten-4-olid) there is observed a marked tendency to normalization of the levels of LPC with simultaneous significant rise of PC content. Concentration of PA, PI, SPM and DPG nearly completely normalizes. The preparation has a positive effect on the activity of transport ATPase, with may certainly bring to a deficite recovery of the processes of permeability of ioms and substances of blood lymphocyte plasmatic membranes. The problem of possible pathogenetic therapy of sarcoma-45 by inclusion of cyan-containing derivatives of lactone into the complex of therapeutic means is discussed.

**MEDI 141**

**Macrocyclic polyoxazoles as selective g-quadruplex stabilizers**

***Suzanne G. Rzuczek***[1]*, srzuczek@eden.rutgers.edu, Daniel S. Pilch*[2]*, pilchds@umdnj.edu, Angela Liu*[2]*, Leroy F Liu*[2]*, Edmond J. LaVoie*[3]*, elavoie@rci.rutgers.edu, and Joseph E. Rice*[1]*, jrice@rci.rutgers.edu. (1) Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Ernest Mario School of Pharmacy, 160 Frelinghuysen Road, Piscataway, NJ 08854-8020, Fax: 732-445-6312, (2) Department of Pharmacology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854, (3) Department of Pharmaceutical Chemistry, Rutgers University, Piscataway, NJ 08854*

G-quadruplex DNA is found in the telomeric region of chromosomes as well as in the promoter region of several oncogenes. Studies suggest that stabilization of G-quadruplex structures in the telomeres indirectly inhibits telomerase, and enzyme present in >85% of human tumors but not in most normal cells, leading to cell cycle arrest, senescence, and apoptosis. We report here the synthesis, biophysical evaluation of G-quadruplex stabilization and selectivity, and cytotoxicity data for a series of 24-membered macrocyclic polyoxazoles that possess exquisite selectivity for stabilizing G-quadruplex DNA. The effect of various side chains, R and R', on selective G-quadruplex stabilization will be discussed.




**MEDI 142**

**Bone targeting dendrons**

***Rana Sanyal****, Pinar Cakir, and Amitav Sanyal, Department of Chemistry, Bogazici University, Bebek, Istanbul 34342, Turkey, Fax: 902122872467*

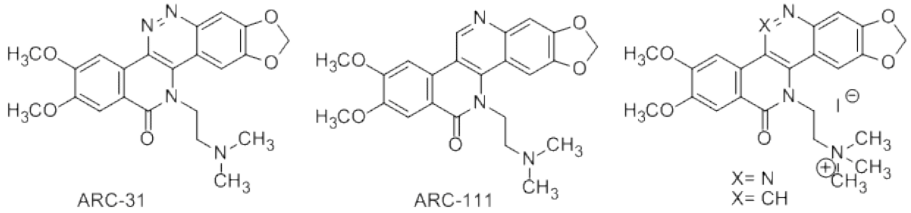
Dendrimers can be tailored to accommodate a high density and wide variety of functional groups on their surface, therefore they have emerged as promising candidates for targeted drug carriers. Segmented spherical construction of dendrimers along with their well-defined molecular structure offers an interesting architecture. While one of these segments is decorated with active drug molecules, the other one can be ornamented with targeting groups. Such a direct application of drug molecules to the diseased tissue organ will increase the effect of the therapy and decrease the side effects. This project includes new dendritic carriers developed in our group aimed towards bone targeted delivery. Synthesis of different generations of biodegradable dendritic compounds containing bone targeting molecules for targeting chemotherapy agents to bone tissue will be presented.

**MEDI 143**

**Facile formation of hydrophilic derivatives of 11-[2-(N,N-dimethylamino)ethyl]-2,3-dimethoxy-8,9-methylenedioxy-11H-isoquino[4,3-c]cinnolin-12-one (ARC-31) and its 11-deaza analog, ARC-111**

***Mavurapu Satyanarayana***[1]*, msatya@rci.rutgers.edu, Wei Feng*[1]*, wfeng@eden.rutgers.edu, Liang Cheng*[1]*, liangch@eden.rutgers.edu, Angela Liu*[2]*, Yuan-chin Tsai*[2]*, Leroy F. Liu*[2]*, and Edmond J. LaVoie*[1]*, elavoie@rci.rutgers.edu. (1) Department of Pharmaceutical Chemistry, Rutgers University, 160 Frelinghuysen Road, Piscataway, NJ 08854, (2) Department of Pharmacology, University of Medicine and Dentistry of New Jersey, Piscataway, NJ 08854*

Several 11-ethyl-2,3-dimethoxy-8,9-methylenedioxy-11H-isoquino[4,3-c]cinnoline-12-ones (e.g. ARC-31) with varied functionality at the 2-position of their ethyl substituents exhibit potent topoisomerase I (TOP1) targeting and antitumor activity. Similar results have been observed with the structurally-related analogs, 5-ethyl dibenzo[c,h][1,6]naphthyridines (e.g. ARC-111). The trimethylammonium iodide salt of both ARC-31 and ARC-111 can be readily prepared. Direct displacement of the trimethylammonium group by hydroxide, hydroxylated alkylamines and substituted ethylenediamines did provide a facile route for the preparation of 2-hydroxyethyl, several 2-(polyhydroxyalkyl)amino, as well as 2-(aminoethyl)amine derivatives. The relative TOP1-targeting activity and cytotoxicity of derivatives of both ARC-31 and ARC-111 with varied polar substituents at the 2-position of each of their ethyl substituents were determined.




**MEDI 144**

**Synthesis and structural activity relationship analysis of Sansalvamide A derivatives against drug resistant cancer cell lines**

***Robert P. Sellers****, William S. Disman, Melinda R. Davis, Stephanie Lapera, Erin Singh, Leslie D. Alexander, Robert Vasko, and Shelli R. McAlpine, Department of Chemistry and Biochemistry, San Diego State University, 5500 Campanile Drive, San Diego, CA 92182*

Sansalvamide A is an antineoplastic macrocyclic depsipeptide isolated from the marine fungus Fusarium by William Fenical in 1999. Studies have shown potent cytotoxicity against NCI's 60 cell line panel for the natural product and ten-fold inhibition over the depsipeptide for the pentapeptide derivative. A library of over 100 derivatives of the compound have been synthesized and the Structural Activity Relationships (SARs) show promising bio-potency against pancreatic, colon, breast, prostate and melanoma cancer cell-lines. Six derivatives show over 100-fold differential selectivity for cancer cell lines over normal cell lines and are over 100 times more active against pancreatic cancer cell lines than compounds used clinically to treat these cancers (e.g., 5-FU). Through use of inhibition assays and analysis of trends emerge that can be used to modify the scaffold to produce more potent compounds.

**MEDI 145**

**Structure activity relationship of nonbenzoquinone ansamycins**

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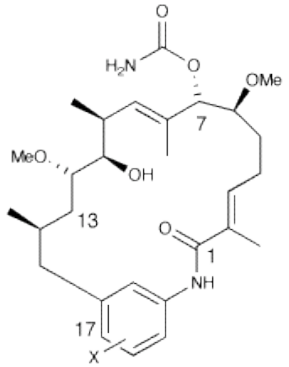
Hsp90 is an attractive target in oncology, which is involved in the correct folding of a number of the proteins implicated in cancer including Ras, Raf and Erb-2. The first in class Hsp90 inhibitors, 17-AAG and 17-DMAG semi-synthetic derivatives of geldanamycin, have been taken into clinical trials where they have demonstrated efficacy. These molecules contain a substituted benzoquinone moiety, which results from the loading of an amino hydroxy benzoic acid (AHBA) as a starter unit for the polyketide synthase. We have developed a series of non-benzoquinone ansamycins through a knock-out of the AHBA gene cluster and the feeding of alternative amino benzoic acids. A series of semisynthetic analogues have been prepared to develop a structure activity relationship. The best molecules show cytotoxicities with an approximately ten-fold improvement over the starting compounds.




**MEDI 146**

**Discovery of a boronic acid analog of chalcone as a potent anticancer proliferation agent**

*Yali Kong, yk237@georgetown.edu, Oncology, Georgetown University, 3970 Reservoir Rd, NW, NRB EP-11A, Washington, DC 20057,* ***Kan Wang****, kw88@georgetown.edu, Neuroscience, Georgetown University, 3970 Reservoir Rd, NW, Washington, DC 20057, and Milton L. Brown, mb544@georgetown.edu, Drug Discovery Program, Georgetown University Medical Center, Washington, DC 20057*

Chalcones represent a class of natural products that can be readily synthesized in efforts to improve and optimize biological activities. In this study we designed and synthesized novel boronic acid analogs of chalcones. The cytotoxicity study identified a boronic acid chalcone YK-3-237 was potent towards 16 human cancer cell lines with GI50-values in the range of 10-200 nM, and another three cell lines with GI50-values below 10 nM. Both in vitro assay and cell cycle assay excluded the involvement of this compound in either assembly or disassembly process of tubulin. Furthermore, this

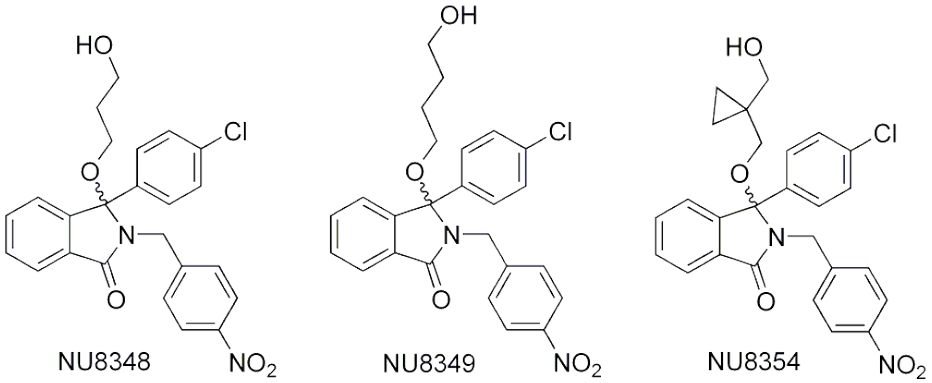
compound significantly inhibited the angiogenesis on HUVEC cell lines at 1 μM in vitro. Our result suggests that YK-3-237 has potential anti-cancer effect by a different mechanism from tubulin.

**MEDI 147**

**Isoindolinone-based inhibitors of the MDM2-p53 protein-protein interaction**

***Anna F. Watson***[1]*, anna.watson@ncl.ac.uk, Bernard T. Golding*[1]*, Roger J. Griffin*[1]*, r.j.griffin@ncl.ac.uk, Claire Hutton*[2]*, Junfeng Liu*[2]*, Xiaohong Lu*[2]*, John Lunec*[2]*, David R. Newell*[2]*, Eric Valeur*[1]*, and Ian R. Hardcastle*[1]*, I.R.Hardcastle@newcastle.ac.uk. (1) Northern Institute for Cancer Research, School of Natural Sciences - Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, United Kingdom, (2) Northern Institute for Cancer Research, Paul O'Gorman Building, Newcastle upon Tyne, NE2 4HH, United Kingdom*

The p53 tumour suppressor acts as 'the guardian of the genome' playing roles in cell cycle progression and apoptosis. In normal cells p53 activity is regulated by the MDM2 protein via a negative feedback loop. Inhibition of the MDM2-p53 protein-protein complex is expected to reactivate normal p53 pathways in cells over-expressing MDM2, resulting in anti-tumour activity. Previously we have identified small molecule inhibitors of the MDM2-p53 interaction based on an isoindolinone scaffold (NU8348 and NU8349). Further optimisation has resulted in the elucidation of structure-activity relationships for the isoindolinone pharmacophore, and the identification of compounds with improved potency, including NU8354. Resolution of the two enantiomers of NU8354 using chiral HPLC gave NU8354A ($IC_{50}$= 171 ± 15nM) and NU8354B ($IC_{50}$= 1.30 ± 0.11μM). The cellular activities of key compounds have been demonstrated with dose-dependent induction of p53 regulated genes in a variety of model systems.




**MEDI 148**

**Clicked HDAC inhibitors: A fragment-based design**

***Robert L Woodward Jr.****, Jie Shen, and Peng George Wang, Departments of Biochemistry and Chemistry, The Ohio State University, 484 West 12th Avenue, Columbus, OH 43210, Fax: 614-292-9023*

The association between histone deacetylase (HDAC) overexpression and cancer has led to the development of various inhibitors throughout the past two decades, many of which were designed

according to conserved active site features. Further analysis of the active site has revealed an additional feature which can be exploited for improved binding: two phenylalanine residues on opposite sides of the binding pocket. Accordingly, a series of inhibitors was synthesized via “click chemistry” to introduce a triazole ring so as to potentially enhance potency via π- π interactions. NIH cancer cell-line screening revealed that one of these inhibitors possesses similar potency to the clinically approved inhibitor SAHA. Thus, we have developed a method to rapidly obtain libraries of potential inhibitors, which will enable rapid incorporation of structural variations (aromatic ring type, presence of chiral centers) which have proven to enhance potency and/or introduce isozyme selectivity in other inhibitors.

**MEDI 149**

**Alkylamino- and alkylguanidinolysine analog inhibitors of lysine-specific demethylase 1**

*Stuart Hazeldine[1], Michael L. Crowley[1], Yi Huang[2], Tracey Murray-Stewart[2], Robert A. Casero[2], rcasero@jhmi.edu, and **Patrick M. Woster**[1], pwoster@wayne.edu. (1) Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, Fax: 313-577-2033, (2) The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD 21231*

Chromatin modification regulates eukaryotic gene expression, and aberrant epigenetic gene silencing contributes to tumorigenesis. The enzyme lysine-specific demethylase 1 (LSD1) has emerged as an important cellular mechanism for epigenetic control of gene expression. In particular, demethylation of the chromatin mark dimethyl lysine 4 histone H3 (H3K4me2) by LSD1 may broadly repress tumor suppressor genes and promote tumorigenesis. We reported a series of guanidine and biguanide LSD1 inhibitors that have significant effects on H3K4me2 levels and the re-expression of tumor suppressor genes. We now report alkylamino- and alkylguanidinolysine analogues designed as LSD1 inhibitors. Some analogues include “warhead” substituents that bind covalently in the catalytic site. The synthesis and inhibition kinetics of these analogues will be reported. In addition, their effects on tumor suppressor factors and chromatin marks in the HCT116 and RKO tumor cell lines alone, and in combination with deoxyazacytidine and/or trichostatin A, will be described.

**MEDI 150**

**Syntheses of halogenated copper (II) tetracarboranylphenyl porphyrins for boron neutron – capture therapy and their biological properties in EMT-6 tumor-bearing mice**

***H. Wu**[1], wuh3@mail.nih.gov, Michael S. Makar[2], Peggy L Micca[2], and Michiko Miura[2]. (1) Imaging Probe Development Center, National Heart, Lung, and Blood Institute, National Institutes of Health, 9800MCD, Rockville, MD 20850, (2) Medical Department, Brookhaven National Lab, Upton, NY 11973*

The development of tumor specific boron containing agents is playing an increasingly important role in the advance of Boron Neutron-Capture Therapy. Three halogenated carboranylphenyl porphyrins analogs were synthesized and one of these, 5, 10, 15-tris[3-o-carboranylmethoxyphenyl] - 20-[2,6-difluorophenyl] porphyrin was chelated with copper (II) and evaluated for its biodistribution and toxicity in EMT-6 tumor-bearing BALB/c mice. A dose of 220 mg/kg porphyrin (43 mg B/kg) delivered 66 ug/g B and 88 ug/g B to tumors at 1 and 2 days respectively after the last of a series of ip injections in mice. The tumor-to-blood and tumor-to-brain boron concentration ratios had reached 220:1 and 880:1

with no significant thrombocytopenia. Thus, these agents may be clinically promising porphyrin agents for boron neutron-capture therapy (BNCT). Furthermore, these agents also possess potential application in photodynamic therapy (PDT) if the copper is replaced with a photoactive metal such as zinc or tin.

**MEDI 151**

**Syntheses of monosaccharide-conjugated copper (II) tetracarboranylphenyl porphyrins for boron neutron – capture therapy and their biological properties in EMT-6 tumor-bearing mice**

***H. Wu***[1]*, wuh3@mail.nih.gov, Michael S. Makar*[2]*, Peggy L Micca*[2]*, and Michiko Miura*[2]*. (1) Imaging Probe Development Center, National Heart, Lung, and Blood Institute, National Institutes of Health, 9800MCD, Rockville, MD 20850, (2) Medical Department, Brookhaven National Lab, Upton, NY 11973*

The advance of Boron Neutron-Capture Therapy is limited by the availability of tumor specific boron agents. Glucose-conjugated boron-containing porphyrins copper (II) meso-5,15-bis[3-(o-carboranylmethoxy)phenyl]-10,20-bis[3-(â-D-glucosyl)phenyl]porphyrin (1), and galactose-conjugated copper (II) meso-5,15-bis[3-(o-carboranylmethoxy)phenyl]-10,20-bis[3-(â-D-galactose)phenyl]porphyrin (2) were synthesized and evaluated for their biodistribution and toxicity in BALB/c mice bearing EMT-6 tumors. One day after the last of a series of ip injections in mice, a dose of 200 mg/kg (31 mg/kg B) of 1 and 230 mg/kg (32.5 mg/kg B) of 2 delivered 20.2 ug/g B and 16.7 ug/g B respectively to EMT-6 tumors. Both porphyrins achieved tumor-to-blood boron concentration ratios greater than 28:1, and even higher tumor-to-brain ratios with no thrombocytopenia. Thus, these agents may be clinically promising B-10 delivery agents for boron neutron-capture therapy (BNCT).

**MEDI 152**

**Design, synthesis and discovery of novel fluorescent HDAC inhibitors that challenge current HDAC mechanisms**

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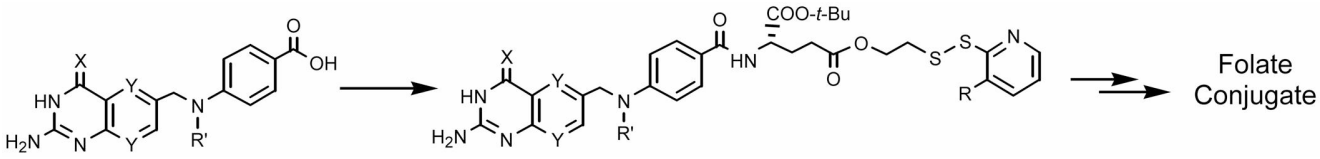
Inhibition of histone deacetylase (HDAC) represents a promising strategy for the treatment of cancer and neurological disorders. A number of HDAC inhibitors have been discovered recently, such as suberoylanilide hydroxyamic acid (SAHA) which was the first approved HDAC inhibitor by FDA for the treatment of advanced cutaneous T-cell lymphoma. However, the selectivity of HDAC inhibitors has been presenting a great challenge. The mechanism of inhibition toward tumor cells of HDAC inhibitors is also unclear. Herein, we designed and synthesized a series of novel fluorescent HDAC inhibitors using structure based design. Biological evaluation against 11 human HDAC isoforms revealed several compounds with selective nanomolar inhibition against class II HDACs. These compounds also exhibited low nanomolar IC50 toward prostate and breast cancer cell proliferation. More interestingly, the fluorescent properties of these compounds unveiled that they only localized to the cytoplasm, and not to the cell nucleus. Our studies suggest that other mechanisms might be involved in the anticancer action of HDAC inhibitors.

**MEDI 153**

## Regioselective synthesis of antifolate γ-conjugates

*Iontcho R. Vlahov[1], ivlahov@endocyte.com, **Fei You**[1], Fei_You@Endocyte.com, Mingjin Fan[1], Hari Krishna R. Santhapuram[1], and Christopher P. Leamon[2]. (1) Department of Discovery Chemistry, Endocyte Inc, 3000 Kent Ave., Suite A1-100, West Lafayette, IN 47906, (2) Department of Discovery Biology, Endocyte Inc, West Lafayette, IN 47906*

Folate γ-conjugates can efficiently deliver their cargos to diseased cells through endocytosis mediated by folate receptor (FR). One class of cytotoxic agents that may be used in such conjugates includes antifolates, which inhibit dihydrofolate reductase (DHFR). We report here the synthesis of folate receptor targeted antifolate γ-conjugates useful as cytotoxic agents.




**MEDI 154**

## Synthetic modifications of natural tubulysins and their biological activity

***Iontcho R. Vlahov**[1], ivlahov@endocyte.com, Yu Wang[1], kwang@endocyte.com, Marilynn Vetzel[2], Spencer Hahn[1], Joseph A. Reddy[2], and Christopher P. Leamon[2]. (1) Department of Discovery Chemistry, Endocyte Inc, 3000 Kent Ave., A1-100, West Lafayette, IN 47906, (2) Department of Discovery Biology, Endocyte Inc, West Lafayette, IN 47906*

Isolated from a *Myxobacteria* species, the tubulysins inhibit tubulin polymerization, leading to cell cycle arrest and apoptosis. Their exceptionally potent cytotoxicity suggests that compounds with typical tubulysin architecture might serve as novel anticancer agents.

A prominent feature in natural tubulysins is the $N^{14}$-acyloxymethyl moiety, which is one of the major elements defining the difference in both structure and activity. Here we report a general approach to alter the natural tubulysins at this position. Thus, treatment of either a single or a mixture of natural tubulysins with trifluoroacetic acid (TFA) is followed by consecutive addition of a corresponding nucleophile to introduce a new substituent, such as an alkyloxy, alkylthio, amido, acyloxy, or simply an alkyl group.

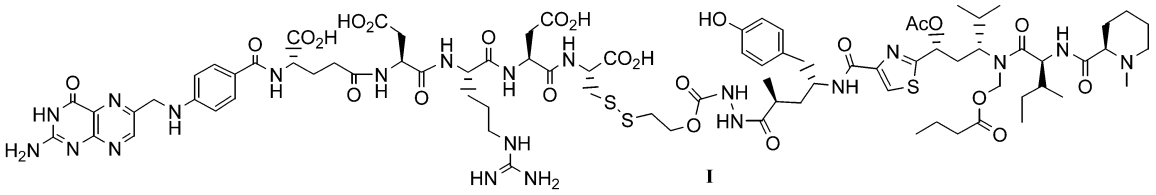
When tested on cells in culture, such tubulysin analogs inhibited the growth of KB cells in a dose-responsive fashion with an $IC_{50}$ in the lower nanomolar range.

**MEDI 155**

## Synthesis of the first releasable folate-tubulysin conjugate

*Iontcho R. Vlahov[1], ivlahov@endocyte.com, **Yu Wang**[1], kwang@endocyte.com, Joseph A. Reddy[2], Ryan Dorton[2], Marilynn Vetzel[2], and Christopher P. Leamon[2]. (1) Department of Discovery Chemistry, Endocyte Inc, 3000 Kent Ave., Suite A1-100, West Lafayette, IN 47906, (2) Department of Discovery Biology, Endocyte Inc, West Lafayette, IN 47906, IN*

The tubulysins are members of a new class of natural products isolated from a *Myxobacteria* species. Even with exceptionally potent cytotoxicity far exceeding the cell growth inhibition observed with known drugs such as epothilones, paclitaxel, and vinblastine, the natural tubulysins alone are generally considered unsuitable for commercial drug development due to very small therapeutic windows. Here we report the first synthesis of a tubulysin conjugate (**I**) containing a tubulysin hydrazide drug attached to a folate receptor targeting ligand via a disulfide-based release system. Compound **I** produced potent, dose-responsive activity both *in vitro* and *in vivo* against folate-receptor positive tumors.



**I**

**MEDI 156**

## Novel 4-phenylsulfanyl substituted tricyclic indeno[2, 1-d]pyrimidines as tyrosine kinase inhibitors and antiangiogenic agents

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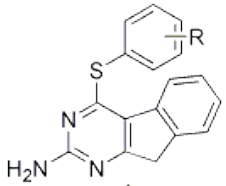
Angiogenesis plays a key role in the growth and metastasis of solid tumors. Abrogation of angiogenesis via RTK inhibition provides a new paradigm for the treatment of cancer. The most successful RTK inhibitors in cancer chemotherapy are those with multiple, rather than single RTKs inhibittion, since angiogenic pathways are redundant. Gangjee et al. designed and synthesized 4-anilino substituted tricyclic indeno[2, 1-d]pyrimidines with dual cytostatic and cytotoxic activities as antitumor agents. When the “N” of the anilino substituent was isosterically replaced by “S”, a series of 4-phenylsulfanyl substituted tricyclic indeno[2, 1-d]pyrimidines of general structure 1 were obtained. These compounds showed potent inhibitory activity against PDGFRâ and VEGFR2. The design, synthesis and RTK inhibitory activities of these compounds will be presented and discussed.



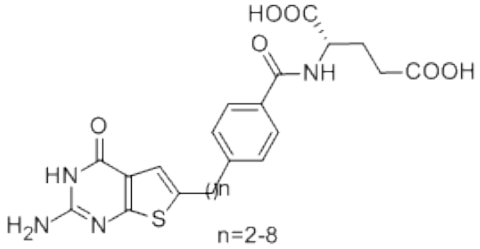
**1**

**MEDI 157**

## Classical 6-substituted thieno[2,3-*d*]pyrimidines as GARFTase inhibitors with folate receptor (FR) specificity and antitumor activity

*Aleem Gangjee[1], gangjee@duq.edu,* ***Xilin Zhou****[1], rebaccazhou@gmail.com, Yijun Deng[2], matherly@kci.wayne.edu, Larry H. Matherly[2], matherly@kci.wayne.edu, and Roy L. Kisliuk[3]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5593, (2) Barbara Ann Karmanos Cancer Institute and the Cancer Biology Program and Department of Pharmacology, Wayne State University School of Medicine, Detroit, MI 48201, (3) Department of Biochemistry, Tufts University School of Medicine, Boston, MA 02111*

Glycinamide ribonucleotide formyltransferase (GARFTase) is a folate-requiring enzyme which catalyzes the first of two one-carbon transfers in the de novo purine biosynthetic pathway. GARFTase is an important target for cancer chemotherapy. Gangjee et al. recently discovered the potent GARFTase inhibitory activity of a series of classical 6-substituted pyrrolo[2,3-*d*]pyrimidine analogues with FR specificity. In the present series, we have synthesized the thieno[2,3-*d*]pyrimidines as sulfur isosteres of our lead pyrrolo[2,3-*d*]pyrimidines. The synthesis and potent GARFTase, FR specific and antitumor activities of these analogs will be reported and discussed.




**MEDI 158**

## The synthesis and structure-activity relationships of 4-substituted cyclopent[a]pyrrolo[3,4-c]carbazole-5,7-dione analogs as potent poly (ADP-ribose) polymerase 1 (PARP-1) inhibitors.

***Allison L. Zulli****[1], azulli@cephalon.com, James L. Diebold[1], Jean Husten[2], and Robert L. Hudkins[1]. (1) Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, (2) Department of Lead Discovery and Profiling, Cephalon, Inc, West Chester, PA 19380*

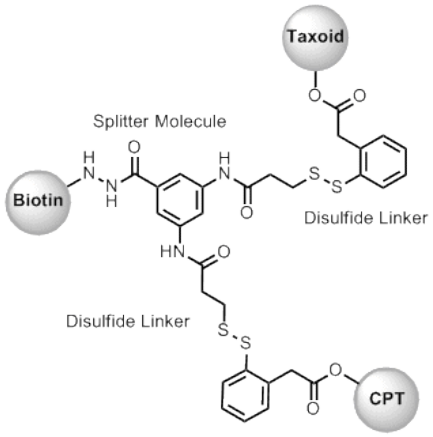
Poly (ADP-ribose) polymerase 1 (PARP-1) is a nuclear enzyme that catalyses the synthesis of poly (ADP-ribose) chains from NAD+ as part of the DNA repair process. Inhibitors of PARP have therapeutic utility in oncology through potentiation of the anti-tumor activity of radiation or DNA damaging chemotherapeutic agents. Previously we reported pyrrolocarbazole 1 as potent PARP-1 inhibitor (IC50 = 36 nM). Structural modifications around 1 to improve enzyme and cell potency led to the synthesis of a lead series of 4-substituted analogs 2. The synthesis and SAR of this series will be reported.

**MEDI 159**

**Design, synthesis and biological evaluation of a novel tumor-targeting drug conjugate bearing dual warheads**

***Edison S. Zuniga**, ezuniga@ic.sunysb.edu, Department of Chemistry, State University of New York at Stony Brook, Chemistry Building, Stony Brook, NY 11794-3400, and Iwao Ojima, iojima@notes.cc.sunysb.edu, Department of Chemistry and ICB&DD, State University of New York at Stony Brook, Stony Brook, NY 11794-3400*

We designed and synthesized a novel tumor-targeting drug conjugate with dual warheads. This novel conjugate consists of two anticancer drugs with different mechanisms of action, two self-immolative disulfide linkers, one splitter moiety, and one tumor-targeting module (biotin). We chose a taxoid (cell division inhibitor) and camptothecin (topoisomerase inhibitor) as the warheads, and biotin as the targeting module. We believe that this dual mechanism of action would make the conjugate more efficacious. It has been shown that vitamin receptors, including folate and biotin receptors, are overexpressed in cancer cells. Possessing this tumor-targeting module, the conjugate is designed to deliver both drugs specifically to cancer cells, and is internalized via receptor-mediated endocytosis. After internalization, the two active drug moieties are released through the self-immolation of the disulfide linkers triggered by glutathione to target microtubules (taxoid) and DNA (camptothecin). The design, synthesis and biological evaluation of the conjugate will be presented.



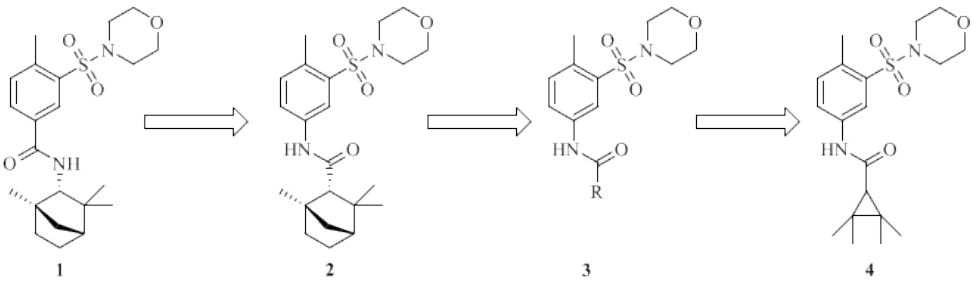

**MEDI 160**

**Novel selective CB2 agonists, Part II: Reversal of the amide linkage**

***Allan J. Goodman**[1], agoodman@adolor.com, Karin Worm[1], kworm@adolor.com, Markku Savolainen[1], Joel A. Cassel[2], Gabriel J. Stabley[2], Robert N. DeHaven[2], Christopher J LaBuda[2], Michael Koblish[2], Patrick J Little[2], and Roland E. Dolle[1]. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341*

Previous research conducted within our labs identified a series of selective $CB_2$ agonists. From this research, compound **1** was shown to bind to $CB_2$ receptors with 30 fold selectivity over $CB_1$ receptors. Reversal of the amide linkage of **1** led to compound **2** which showed similar binding to the $CB_2$ receptor to that exhibited by **1**, but the selectivity for $CB_2$ over $CB_1$ increased to 130 fold. A series of reverse amides of general structure **3** were prepared, during which compound **4** was

identified as a potent and highly selective $CB_2$ agonist. Here, we report the synthesis and *in vitro* activity of a series of $CB_2$ receptor ligands, and *in vivo* activity of compound **4**.

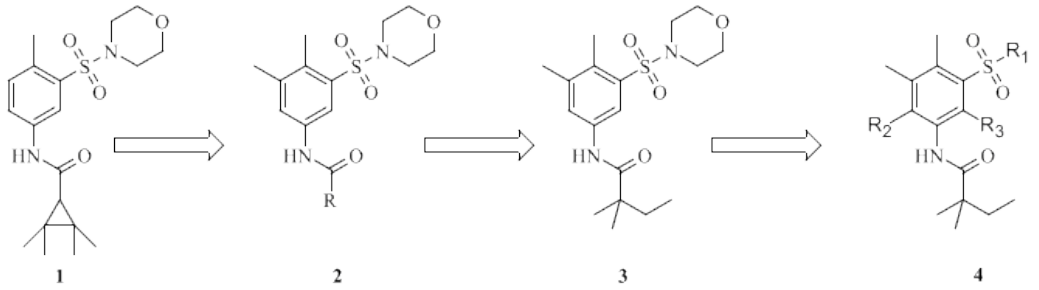



**MEDI 161**

**Novel selective CB2 agonists, Part III: Xylene derivatives**

***Allan J. Goodman***[1]*, agoodman@adolor.com, Karin Worm*[1]*, kworm@adolor.com, Ian F Sellitto*[1]*, isellitto@adolor.com, Markku Savolainen*[1]*, Joel A. Cassel*[2]*, Gabriel J. Stabley*[2]*, Robert N. DeHaven*[2]*, Christopher J LaBuda*[2]*, Michael Koblish*[2]*, Patrick J Little*[2]*, Bernice L. Brogdon*[3]*, Steven A. Smith*[3]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341, (3) Department of DMPK, Adolor Corporation, Exton, PA 19341*

In previous research we identified the aryl amide sulfonamide **1** as a potent and highly selective agonist for the $CB_2$ receptor. In an attempt to improve metabolic stability of the selective $CB_2$ ligands, a series of xylene analogs (**2**) were prepared. Initial research led to compound **3**, which was identified as a potent and selective analog with improved metabolic stability. Using a library based approach, the 'core' scaffold of compound **3** was used to investigate sulfonamide modifications (**4**). The synthesis, SAR and *in vivo* activity of compounds of general structure **4** will be presented.




**MEDI 162**

**Novel selective CB2 receptor ligands, Part VI: 2-Amido- and 2-amino-5,6,7,8-tetrahydronaphthalenes**

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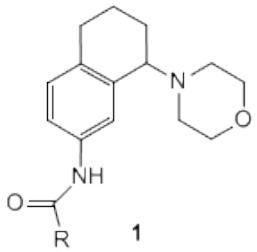
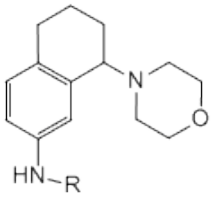
A series of 2-amido- and 2-amino- derivatives of 8-morpholin-4-yl-5,6,7,8-tetrahydro-naphthalenes **1** and **2** respectively, has been synthesized. They have been shown to be potent ligands of the $CB_2$ receptor with selectivity over the $CB_1$ receptor. The synthesis and pharmacological activity of the title compounds will be presented.




1




2

**MEDI 163**

## Thiazol-2(3H)-ylidene-1-ethanone derivatives: Identification and characterization of a novel series of potent cannabinoid ligands

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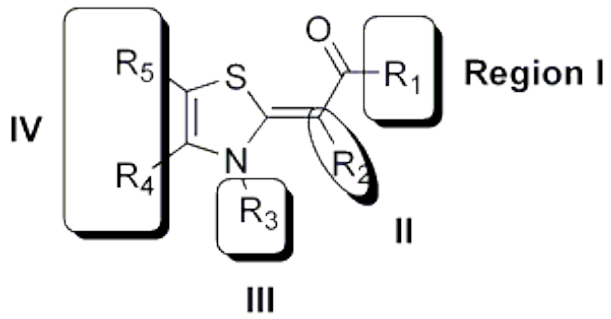
The CB1 and CB2 cannabinoid receptors, belong to the Class A rhodopsin-like GPCR family. The CB1 receptor is predominantly found in the CNS and is thought to be responsible for most of the overt pharmacological effects induced by cannabinoid receptor agonists. The CB2 receptor is primarily expressed in the periphery. Recent studies have demonstrated that CB2-selective agonists are analgesic in preclinical models of nociceptive and neuropathic pain without causing the adverse side effects associated with CB1 receptor activation. In our research efforts to design potent and highly selective CB2 agonists, the thiazole scaffold was investigated extensively. Thiazol-2(3H)-ylidene-ethanone analogs with various aryl groups (region I), pendant side chains (region II and III) and ring substitutions (region IV) were synthesized and evaluated. Numerous CB2 agonists exhibiting nanomolar potency and high selectivity versus the CB1 receptor were identified. The synthesis and preliminary SAR investigations of this new CB2-selective class of compounds will be described.



**MEDI 164**

## Novel selective CB2 receptor ligands, Part IX: Pyridine derivatives 2

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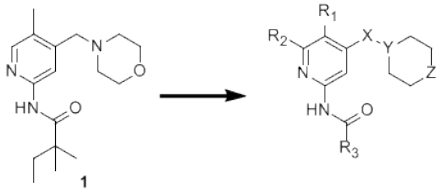
In our previous report, we described the discovery of the novel pyridine derivative, compound **1** as a potent and highly selective $CB_2$ agonist with improved pharmacological profiles. In order to further improve the $CB_2$ binding affinity, and other properties of the novel chemical series of pyridine derivative, various structural modifications around this molecule were investigated. The details of the synthesis and the biological activity of these novel pyridine derivatives will be presented.




**MEDI 165**

## Novel selective CB2 receptor ligands, Part VII: Indane and 1,2,3,4-tetrahydronaphthalene aminosulfonamides

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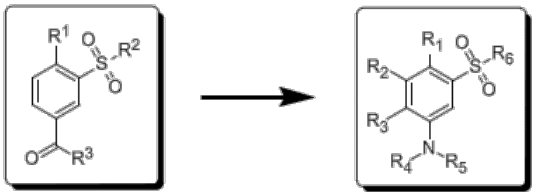
From a previous medicinal chemistry campaign, novel substituted benzene sulfonamides were identified as selective cannabinoid $CB_2$ receptor ligands. In order to improve upon the selectivity of these compounds, the central benzene template was modified to accommodate a more lipophilic bicyclic system. The synthesis, SAR and *in vivo* efficacy of this novel series of $CB_2$ ligands will be presented.



**MEDI 166**

**Novel selective CB2 receptor ligands, Part X: Substituted 2-aminopyridines**

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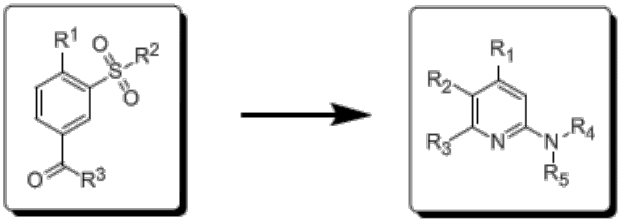
From a medicinal chemistry campaign, novel substituted benzene sulfonamides were identified as selective cannabinoid $CB_2$ receptor ligands. In order to improve the metabolic stability and bioavailability of these compounds, the benzene core was replaced by a pyridine scaffold. Herein we present a series of novel 2-amino pyridine $CB_2$ selective agonists. The synthesis, SAR and *in vivo* efficacy of these compounds will be presented.




**MEDI 167**

**(1H-Benzimidazol-2-yl)thio acetamides are CB1 receptor antagonists binding to an allosteric site**

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The cannabinoid receptor 1 (CB1) is a target of high interest in the treatment of obesity. This is because CB1 antagonists have demonstrated efficacy for weight loss in animal models and in man. [1H-benzimidazol-2-yl)thio]acetamides reversibly antagonized CB1 receptor signaling with EC50's in the range of 0.30 to 1.0 mM and are >20 fold selective for CB1 over CB2 as measured in a cAMP detection assay using CHO-CB2 cells.Equilibrium binding and kinetic dissociation experiments done using the CB1 receptor agonist CP55,940 showed that our hits are allosteric antagonists of the CB1 receptor. We hereby report the results of SAR and metabolite identification studies of this new class of CB1 antagonists.

**MEDI 168**

## Novel selective CB2 receptor ligands, Part IV: Sulfonamide replacements

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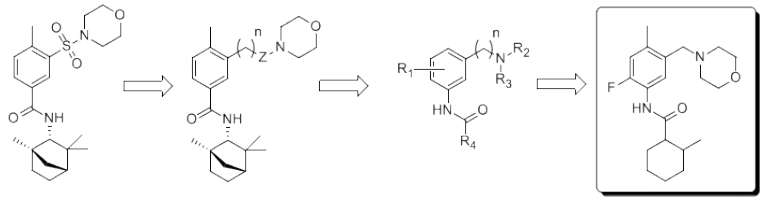
Sulfamoyl benzamides were identified as a novel series of cannabinoid receptor ligands previously. Replacing the sulfonamide functionality of the initial core structure with an amide functionality or a methylene group while varying the number of methylene spacers between the phenyl ring and the nitrogen atom was investigated. Additional structural modifications explored the SAR by varying phenyl substitution, by reversing the original carboxamide, by replacing the morpholine and by varying the amide alkyl chain. The synthesis, SAR and initial biological evaluation of these analogs will be presented.

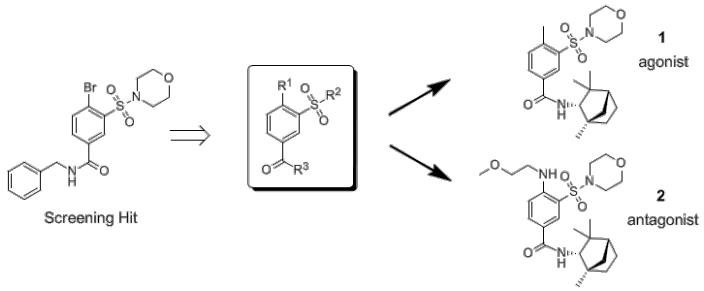


**MEDI 169**

## Novel selective CB2 receptor ligands, Part I: Amino sulfamoyl benzamides

***Karin Worm***[1]*, kworm@adolor.com, Christopher T. Saeui*[1]*, csaeui@adolor.com, Markku Savolainen*[1]*, Joel A. Cassel*[2]*, Gabriel J. Stabley*[2]*, Robert N. DeHaven*[2]*, Christopher J LaBuda*[2]*, Michael Koblish*[2]*, Patrick J Little*[2]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341*

Sulfamoyl benzamides were identified as a novel series of cannabinoid receptor ligands. Starting from a screening hit with modest affinity for the cannabinoid $CB_2$ receptor followed by a parallel synthesis campaign, compound **1**, a 30-fold selective agonist with functional activities of $EC_{50}$ $CB_2$ = 4.6 nM and $EC_{50}$ $CB_1$ = 550 nM was discovered. Introducing an amino-substituent into the system creates a series of potent and selective antagonists for the $CB_2$ receptor, e.g. **2**. Synthesis, SAR and initial biological evaluation will be presented.

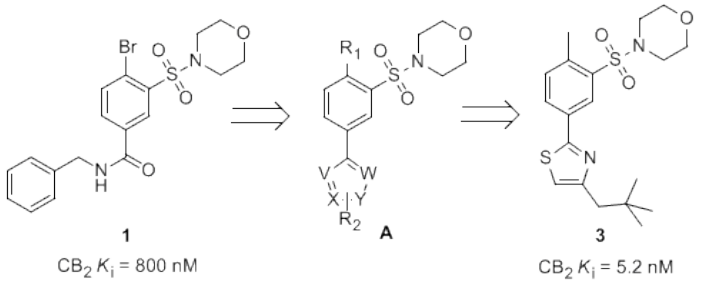


**MEDI 170**

## Novel selective CB2 receptor ligands, Part V: Biarylsulfonamides

***Christopher W. Ajello***[1]*, cajello@adolor.com, Karin Worm*[1]*, kworm@adolor.com, Bertrand Le Bourdonnec*[1]*, Heather O'Hare*[1]*, Joel A. Cassel*[2]*, Gabriel J. Stabley*[2]*, Robert N. DeHaven*[2]*, Bernice L. Brogdon*[3]*, Steven A. Smith*[3]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341, (3) Department of DMPK, Adolor Corporation, Exton, PA 19341*

In our search for a novel class of $CB_2$ agonists using high throughput screening (HTS), we found that **1** bound to the $CB_2$ receptor with a $K_i$ value of 800 nM. Based on the structure of **1**, various biaryl derivatives (formula **A**) were designed and prepared using parallel synthesis techniques. The SAR of this new class of $CB_2$ agonists will be presented.

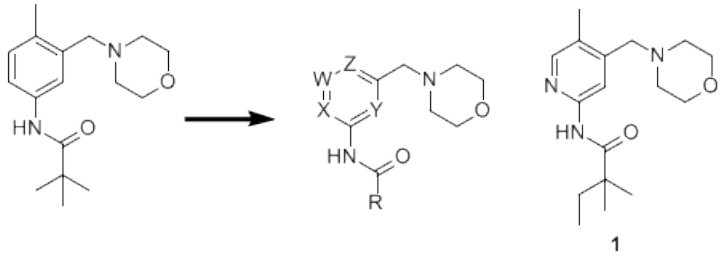



**MEDI 171**

## Novel selective CB2 receptor ligands, Part VIII: Pyridine derivatives 1

***Guo Hua Chu***[1]*, ghchu@adolor.com, Christopher T. Saeui*[1]*, csaeui@adolor.com, Karin Worm*[1]*, kworm@adolor.com, Damian G. Weaver*[1]*, dweaver@adolor.com, Allan J. Goodman*[1]*, agoodman@adolor.com, Rosalyn Green*[1]*, rgreen@adolor.com, Q. Jean Zhou*[1]*, jzhou@adolor.com, Robert L. Broadrup*[1]*, Doreen-Marie S. Dulay*[1]*, ddulay@adolor.com, Bertrand Le Bourdonnec*[1]*, Ian F Sellitto*[1]*, isellitto@adolor.com, Christopher W. Ajello*[1]*, cajello@adolor.com, Lara K. Leister*[1]*, Heather O'Hare*[1]*, Joel A. Cassel*[2]*, Gabriel J. Stabley*[2]*, Robert N. DeHaven*[2]*, Nathalie C. Conway-James*[2]*, Christopher J LaBuda*[2]*, Michael Koblish*[2]*, Patrick J Little*[2]*, Bernice L. Brogdon*[3]*, Steven A. Smith*[3]*, and Roland E. Dolle*[1]*. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341, Fax: 484-595-1551, (2) Department of Pharmacology, Adolor Corporation, Exton, PA 19341, (3) Department of DMPK, Adolor Corporation, Exton, PA 19341*

Replacement of the phenyl ring in our previous (morpholinomethyl)aniline amide cannabinoid receptor ligands with pyridine ring lead to a novel chemical series of $CB_2$ ligands. Compound **1**, 2,2-dimethyl-*N*-(5-methyl-4-(morpholinomethyl)pyridin-2-yl)-butanamide was identified as a potent and highly selective $CB_2$ agonist with improved pharmacological profiles. The details of the synthesis and the biological activity of these novel pyridine derivatives will be presented.



**MEDI 172**

## Synthesis and activity of novel 1-(3-amino-1-phenylpropyl)indolin-2-ones as selective norepinephrine reuptake inhibitors

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Norepinephrine (NE) is a major neurotransmitter in both the central and peripheral nervous system and is involved in regulation of a variety of body functions. Extracellular levels of norepinephrine can be increased by blocking its reuptake by the norepinephrine transporter (NET). Drugs that inhibit norepinephrine reuptake either selectively or in combination with serotonin or dopamine have demonstrated efficacy in the clinic for a variety of indications such as attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), pain disorders (e.g. fibromyalgia), and vasomotor symptoms (VMS). In an effort to identify new selective NRIs, we designed a novel class of 1-(3-amino-1-phenylpropyl)indolin-2-ones. These compounds showed potency inhibiting NE reuptake when tested in the human norepinephrine transporter (hNET) inhibition assay. The compounds also showed selectivity (>100) against the human serotonin and dopamine transporters. The synthesis and properties of these novel compounds are described.

**MEDI 173**

## Synthesis of curcumin mimics with multidrug resistance reversal activities

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To discover novel multidrug resistance (MDR) reversal agents for efficient cancer chemotherapy, a series of curcumin mimics with various amide moieties were synthesized and evaluated their MDR reversal activities in MDR cell line KBV20C. Among the synthesized compounds, compounds involving 4-chlorophenyl, 3,4-dichlorophenyl, and 3,5-dichlorophenyl showed potent MDR reversal activities by inhibiting drug efflux function of P-glycoprotein in KB20C cells, and almost recovered the cytotoxicity of vincristine and paclitaxel against KBV20C cell to the degree of potency against drug sensitive KB cells. The synthesis and multidrug resistance reversal activities of these compounds will be described

**MEDI 174**

**Synthesis and evaluation of potent orally active opioid receptor antagonists**

***Kevin K. Barvian****, Jason D Speake, David J Cowan, Diane M Ignar, Aaron S Goetz, Luz Helena Carballo, and Kimberly K Noble, Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709-3398*

It is well documented in the scientific literature that centrally acting opioid receptor antagonists affect feeding behavior and can cause weight loss in rodents [1]. Obesity has become a world wide epidemic and a serious risk factor for diseases such as diabetes, hypertension, arteriosclerosis, and arthritis. Because of this, we have an ongoing interest in discovering novel, brain penetrant opioid receptor antagonists/inverse agonists for the treatment of obesity in humans. We report herein on the preparation of a series of 5-phenoxybenzimidazoles that exhibit potent opioid receptor antagonist activity *in-vitro.* Further, we demonstrate that oral dosing of these compounds in both lean and diet-induced obese Long Evans rats resulted in a reduction of food intake in nocturnal feeding studies.

Reference:

1. Peptides, 2006, 25, 697–725

**MEDI 175**

**Synthesis of novel anticonvulsants as glutamate receptors antagonist**

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Epilepsy, a neurological disorder characterized by persistent seizures, currently afflicts 1 – 2% of the world's population. Although epilepsy is not well understood one possible cause is the overproduction of glutamate triggering hyperexcitation of neurons thereby producing an epileptic episode. Treatments for epilepsy includes surgery and pharmacotherapy with agents such as carbamazepine and carbatrol that have been found to produces a variety of adverse effects such as edema, nausea, aplastic anemia, and agranulocytosis. Enaminones a new class of pharmaceutical has shown superior anticonvulsant activity with increased protection indices. A series of amino acids including glutamic acid and its mono-sodium salt were chosen as pharma-reactive core units to produce the desired enaminones. These enaminones were synthesized using the reaction of amino acids with 5,5-dimethyl-1,3-cyclohexadione under microwave conditions and analyzed using SPARTAN® and Parallel Quantum Solution® (PQS). Using our novel microwave synthesis we were able to obtain the enaminones in good yields.

**MEDI 176**

## Potent dual orexin antagonists containing a 1,4-diazapane central constraint

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The hypothalamic peptides Orexin A and Orexin B are endogenous ligands for two G-protein coupled receptors, OX1R and OX2R. Dysfunction of the orexin system is implicated in the sleep disorder narcolepsy, and modulation of the orexin receptors with antagonists represents a novel strategy for the treatment of insomnia. In fact, Actelion recently reported that a dual OX1R/OX2R antagonist (ACT-078573) achieved clinical proof-of-concept in humans for the treatment of insomnia.

A novel series of potent, dual OX1R/OX2R antagonists containing a 1,4-diazepane central scaffold were discovered following a high throughput screening effort. The synthesis and structure-activity relationships of these antagonists will be discussed, along with in vivo efficacy experiments in rodents.

**MEDI 177**

## Pyridinium derivatives of histamine as novel carbonic anhydrase activators

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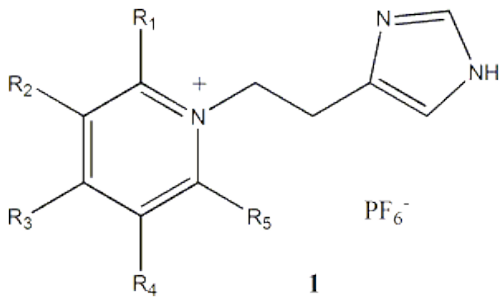
The zinc enzyme carbonic anhydrase is responsible for the reversible hydration of carbon dioxide to bicarbonate, being involved in respiration and CO2 transport between the metabolizing tissues and the lungs, pH and carbon dioxide homeostasis, electrolyte secretion, etc. Its inhibitors were exploited for more than five decades in the treatment of edema, glaucoma, obesity, cancer, epilepsy and osteoporosis. In contrast, carbonic anhydrase activators were largely unexplored until recently, when it was shown that activation of several of its isozymes can enhance synaptic efficiency, memory and spatial learning, and can constitute a conceptually new treatment for Alzheimer's disease among other cerebral dysfunctions. Building on the conclusions of our previous studies, we are reporting the synthesis of new pyridinium derivatives of histamine (1) that can act as efficient carbonic anhydrase activators, together with a complete structure-activity relationship study.

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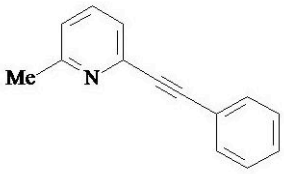
**MEDI 178**

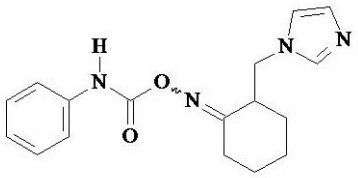
**Carbamoyloximes as novel noncompetitive mGlu5 receptor antagonists**

***György M. Keserû**, János Galambos, Katalin Nógrádi, György Domány, Attila Bielik, István Greiner, Amrita Bobok, Béla Kiss, Bernadett Benkõ, Mónika Vastag, Judit Laszy, István Gyertyán, Sándor Farkas, Krisztina Gál, and Zsolt Szombathelyi, Gedeon Richter Ltd, P.O.B. 27, Budapest H-1475, Hungary*

Although first line anxiolytics, such as benzodiazepines are effective they suffer from serious side effects that limit their clinical utility significantly. Therefore there is a large unmet need for new anxiolytics relieving symptoms quickly and without the most characteristic side effects of benzodiazepines. Recent findings pointed out an important role for the mGlu5 receptor in the mechanism of action of anxiolysis. According to the literature the first selective non-competitive mGluR5 antagonist compound, 2-methyl-6-(phenylethynyl)pyridine (MPEP) has a very broad and potent anxiolytic-like activity in rodent models of anxiety with short onset of action and without potential to induce sedation or psychotomimetic effects. Consequently, several pharma companies have started mGluR5 research programs. The high throughput screening (HTS) of our corporate compound library yielded several structural clusters. Carbamoyloximes represent one cluster of HTS hits that were transformed to promising leads. On this poster we are going to present the hit-to-lead and the subsequent lead optimization process of carbamoyloximes represented by compound 1.




MPEP
$rK_i$: 9.6 nM




1
$rK_i$: 170 nM

**MEDI 179**

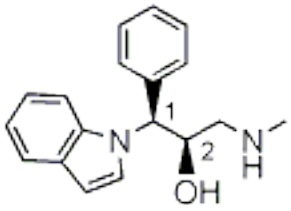
**Discovery of novel indolylphenylpropanolamine inhibitor of the norepinephrine transporter and its absolute stereochemistry**

***Callain Y. Kim**[1], kimcy@wyeth.com, Eugene J. Trybulski[1], trybule@wyeth.com, Paige E. Mahaney[1], mahanep@wyeth.com, Oliver McConnell[1], Yingru Zhang[1], Eric S. Manas[1], Douglas Ho[2], Jennifer Leiter[3], Grace H. Johnston[3], Scott Cosmi[3], and Darlene C. Deecher[3]. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, (2) Department of Chemistry, Princeton University, Princeton, NJ 08544, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Drugs that possess norepinephrine (NE) reuptake inhibition, alone or in combination with serotonin reuptake inhibition, have been approved for multiple indications including major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and pain disorders such as diabetic neuropathy. Other indications, including stress urinary incontinence (SUI) and vasomotor symptoms (VMS), are currently being assessed in clinical trials. These drugs act, either selectively or in part, by inhibiting the NE transporter, thus increasing extracellular NE concentration producing efficacy toward

a variety of CNS-related disorders associated with noradrenergic deficits. Our search for a novel and potent scaffold for this therapeutic target was initiated with a design strategy based on known potent and/or selective norepinephrine reuptake inhibitors (NRIs). In parallel, a pharmacophore-based search of our compound database was conducted. These efforts identified a novel class of NRIs, the indolylphenylpropanolamines I. Optimization strategies, along with identification of the eutomer, will be presented. As a result, compound A (1S, 2R) was selected for further study. The in vitro profile and pharmacokinetic properties of this compound will be discussed.


I




A (1S, 2R)

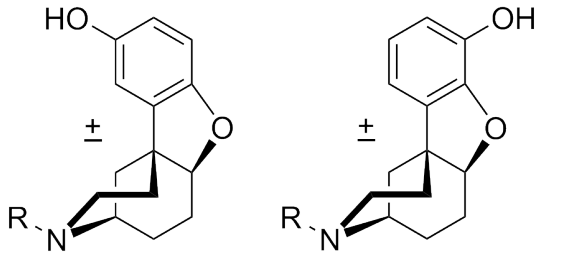
**MEDI 180**

**Synthesis and opioid binding affinity of the final pair of N-methyl substituted oxide-bridged phenylmorphans, the ortho-, para-b isomers, and their N-phenethyl analogs**

***Muneaki Kurimura***[1]*, m_kuri@research.otsuka.co.jp, A. Sulima*[2]*, AgnieszS@nhlbi.nih.gov, Akihiro Hashimoto*[3]*, ji5ngs@gmail.com, Anna K. Przybyl*[4]*, przybylanna@hotmail.com, Etsuo Ohshima*[5]*, etsuo.ohshima@kyowa.co.jp, Shinichi Kodato*[6]*, shinichi.kodato@bushu-seiyaku.co.jp, Jeffrey R. Deschamps*[7]*, deschamps@nrl.navy.mil, Christina M. Dersch*[8]*, Richard B. Rothman*[9]*, rrothman@intra.nida.nih.gov, Arthur E. Jacobson*[10]*, aej@helix.nih.gov, and Kenner C. Rice*[10]*, kr21f@nih.gov. (1) Medicinal Chemistry Group, Second Institute of New Drug Discovery, Otsuka Pharmaceutical Co., Ltd, 463-10 Kagasuno Kawauchi-cho, Tokushima, Japan, Fax: +81-88-665-6031, (2) Imaging Probe Development Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Rockville, MD 20850, (3) Achillion Pharmaceuticals Inc, New Haven, CT 06511, (4) Faculty of Chemistry, Adam Mickiewicz University, Poznan, Poland, (5) Pharmaceutical Research Center, Kyowa Hakko Kogyo Co., Ltd, Shizuoka, Japan, (6) Quality Division, Bushu Pharmaceuticals Ltd, Kawagoe, Saitama, Japan, (7) Naval Research Laboratory, Washington, DC 20375, (8) Clinical Psycho-pharmacology Sect, National Institutes of Health/NIDA, Baltimore, MD 21224, (9) Clinical Psychopharmacology Section, NIDA-IRP, NIH, DHHS, Baltimore, MD 21224, (10) Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS, Rockville, MD 20852*

In the isomeric series of 12 racemic topologically rigid *N*-methyl analogues of oxide-bridged phenylmorphans, only two racemates, **1a** and **2a**, that we have termed the *ortho*- and *para*-b-oxide-bridged phenylmorphans (*N*-methyl substituted), have remained to be synthesized. The b-isomers were very difficult to synthesize because of the highly strained 5,6-*trans*-fused ring junction that had to be formed. The successful strategy for the b-isomers required functionalization of the position *para* (or *ortho*) to a fluorine atom on the aromatic ring using an electron-withdrawing nitro group to activate that fluorine. Since we have found that the *N*-phenethyl substituted oxide-bridged phenylmorphans generally have higher affinity and are more efficacious than their *N*-methyl analogues, we have prepared and evaluated both the *N*-methyl (**1a** and **2a**) and *N*-phenethyl (**1b** and **2b**) analogues of the *ortho* and *para*-b oxide-bridged phenylmorphans. We have found that the *N*-phenethyl *ortho*- and

*para*-b isomers appeared to interact best with k-receptors (*K*i <100 nM), and had less affinity at the other opioid receptors. Further, we have preliminary evidence that the compounds are acting as k-receptor antagonists.




**1a : R = -Me** **2a : R = -Me**
**1b : R = -$(CH_2)_2$Ph** **2b : R = -$(CH_2)_2$Ph**

**MEDI 181**

**2-Aminobenzimidazoles as brain penetrating $H_1$ antagonists for the treatment of insomnia**

***Wilna J. Moree***[1]*, wmoree@neurocrine.com, Timothy Coon*[1]*, tcoon@neurocrine.com, Jinghua Yu*[2]*, jyu@isisph.com, Said Zamani-Kord*[3]*, skord@sbcglobal.net, Binfeng Li*[1]*, bli@neurocrine.com, Siobhan Malany*[4]*, smalany@trlusa.com, Mark A. Santos*[5]*, mark_santos@millipore.com, Lisa M. Hernandez*[1]*, lhernandez@neurocrine.com, Robert E. Petroski*[6]*, rpetroski@san.rr.com, Aixia Sun*[7]*, aixiasun@yahoo.com, Jenny Wen*[1]*, jwen@neurocrine.com, William A. Shirley*[8]*, w_a_shirley@hotmail.com, Sue Sullivan*[9]*, ssullivan@synteract.com, Jason Haelewyn*[10]*, jhaelewyn@celgene.com, Margaret J. Bradbury*[3]*, marg_bradbury@hotmail.com, Paul D. Crowe*[3]*, pcrowehome@gmail.com, and Graham Beaton*[1]*, gbeaton@neurocrine.com. (1) Neurocrine Biosciences, 12790 El Camino Real, San Diego, CA 92130, Fax: 858-617-7925, (2) Isis Pharmaceuticals, Inc, Carlsbad, CA 92008, (3) (4) Tanabe Research Laboratories U.S.A., Inc, San Diego, CA 92121, (5) Millipore Corporation, Temecula, CA 92590, (6) CalciMedica, La Jolla, CA 92037, (7) Takeda San Diego, San Diego, CA 92121, (8) Accelrys, Inc, San Diego, CA 92121, (9) Synteract, Inc, Carlsbad, CA 92011, (10) Celgene Signal Research, San Diego, CA 92121*

Histamine acts upon four separate G-protein coupled receptor subtypes: $H_1$, $H_2$, $H_3$ and $H_4$. The $H_1$ receptors mediate allergic responses in the periphery, while centrally they mediate the effects of histamine on arousal. Brain penetrating $H_1$ antagonists such as Benadryl have been shown to increase sleep or drowsiness in humans and have been used for the treatment of insomnia. Unfortunately, these OTC antihistamines have shown issues including mucosal side effects due to muscarinic receptor modulation as well as daytime drowsiness and hangover effects resulting from prolonged brain exposure. In this poster we describe our approach towards the development of selective and orally active, brain-penetrating $H_1$ antagonists for the treatment of insomnia with a series of 2-aminobenzimidazoles.

**MEDI 182**

**Fused bicyclic Pyrrolizinones as potent; brain penetrant $hNK_1$ antagonists**

***Gregori J. Morriello***[1]*, greg_morriello@merck.com, Robert J. DeVita*[1]*, Sander G. Mills*[1]*, Gary G. Chicchi*[2]*, Marc Kurtz*[2]*, Kwei-lan Tsao*[2]*, Julie A. DeMartino*[2]*, and Emma J Carlson*[3]*. (1) Department of*

*Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065-0900, Fax: 732-594-5350, (2) Immunology, Merck Research Laboratories, Rahway, NJ 07065, (3) Merck Sharp and Dohme Research Laboratories, Harlow CM20 2QR, United Kingdom*

Previous work on human $NK_1$ ($hNK_1$) antagonists in which the core of the structure is a substituted pyrrolidine has been disclosed. These compounds displayed good binding affinity; however, many did not exhibit the necessary brain penetration for good in vivo activity. The discovery, preparation, and structural-activity-relationships of a new class of novel 5,5-fused pyrrolizinones will be presented. Compounds of this series maintained excellent binding affinity, as in the previously reported compounds, but also displayed excellent brain penetration as observed by their good efficacy in the gerbil foot tapping assay. Several of these compounds exhibited 100% inhibition of the foot-tapping response at 0 and 24 hours with $ID_{50}$'s less than 1 mpk.

**MEDI 183**

**Synthesis and activity of novel 1- or 3-(3-amino-1-phenyl propyl)-1,3-dihydro-2H-benzimidazol-2-ones as selective norepinephrine reuptake inhibitors**

***Eugene A. Terefenko***[1]*, terefee@wyeth.com, Puwen Zhang*[2]*, zhangp@wyeth.com, Paige E. Mahaney*[2]*, mahanep@wyeth.com, Casey C. McComas*[2]*, mccomac@wyeth.com, An T. Vu*[2]*, VuA@wyeth.com, Eugene J. Trybulski*[2]*, trybule@wyeth.com, Elizabeth Koury*[3]*, Jenifer A. Bray*[3]*, and Darlene C. Deecher*[3]*. (1) Chemical and Screening Sciences, Wyeth, 500 Arcola Road, Collegeville, PA 19426, (2) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Drugs capable of selectively blocking norepinephrine (NE) reuptake are important for the treatment of disorders associated with the central nervous system. Currently, norepinephrine reuptake inhibitors (NRI), like reboxetine are prescribed for the treatment of major depressive disorder (MDD). Additionally, reboxetine has demonstrated efficacy in the treatment of fibromyalgia and lower back pain. In an effort toward identification of novel selective NRIs, we designed a new class of 1- or 3-(3-amino-1-phenyl propyl)-1,3-dihydro-2H-benzimidazol-2-ones. When tested in human norepinephrine (hNET), serotonin (hSERT), and dopamine (hDAT) transporter inhibition assays, several compounds showed potency in inhibiting NE reuptake with IC50s values ranging between 10-50 nM. Certain compounds also demonstrated selectivity (>100 fold) in blocking hNET when compared to antagonist activity for hSERT or hDAT. This poster describes the synthesis of this series of molecules and reports on their properties.

**MEDI 184**

**1- or 3-(3-Amino-2-hydroxy-1-phenyl propyl)-1,3-dihydro-2H-benzimidazol-2-ones: Novel and selective norepinephrine reuptake inhibitors**

***Eugene A. Terefenko***[1]*, terefee@wyeth.com, Puwen Zhang*[2]*, zhangp@wyeth.com, Andrew Fensome*[2]*, fensoma@wyeth.com, Paige E. Mahaney*[2]*, mahanep@wyeth.com, Callain Y. Kim*[2]*, kimcy@wyeth.com, Casey C. McComas*[2]*, mccomac@wyeth.com, Eugene J. Trybulski*[2]*, trybule@wyeth.com, An T. Vu*[2]*, VuA@wyeth.com, Elizabeth Koury*[3]*, Jenifer A. Bray*[3]*, and Darlene C. Deecher*[3]*. (1) Chemical and Screening Sciences, Wyeth, 500 Arcola Road, Collegeville, PA 19426, (2) Chemical and Screening Sciences, Wyeth Research, Collegeville, PA 19426, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Atomoxetine and reboxetine are selective norepinephrine reuptake inhibitors (NRI). Atomoxetine is currently marketed for the treatment of attention deficit hyperactivity disorder (ADHD), while reboxetine is used for major depressive disorder (MDD). Their mode of action involves the inhibition of norepinephrine reuptake, triggering an increase in extracellular norepinephrine (NE). Continuing our efforts toward identification of novel and selective NRIs, we designed a new class of 1- or 3-(3-amino-2-hydroxy-1-phenyl propyl)-1,3-dihydro-2H-benzimidazol-2-ones. These new compounds were tested for specificity using the human norepinephrine transporter (hNET), and for selectivity using human serotonin (hSERT), and dopamine (hDAT) transporters. Several compounds showed potency in the hNET reuptake assay with IC50s values ranging between 3-60 nM. Certain compounds demonstrated selectivity (>100 fold) in blocking hNET when compared to antagonism for hSERT or hDAT. Herein, we describe the synthesis of this series of molecules and their properties as selective NRIs.

**MEDI 185**

**Design, synthesis and anticancer activity assay of novel copper complex specifically inhibiting the proliferation of neuroblastoma cell**

***Haiyuan Zhang*** *and Fangyu Peng, Department of Pediatrics and Radiology, School of Medicine, Wayne State University, 3901 Beaubien Blvd, Detroit, MI 48201, Fax: 313-993-3845*

Meta-iodobenzylguanidine (MIBG) has been used as radio-imaging agent due to its specific cellular uptake through norephinephrine transporter (NET) approach into neuroblastoma cells. Herein, an active ligand (TSBG) was designed based on MIBG template. After chelating copper ion, the resulting copper complex (CuTSBG) exerted stronger antiproliferative activity on positive-NET tumor cells (BE2C and SK-N-DZ neuroblastoma cells) than on negative-NET tumor cells (U87 and PC-3 cells), which was evaluated by MTT assay. Further 64Cu Radiolabeled CuTSBG complex was used to detect different cellular uptake in above four cells. The result indicated that the uptake of 64CuTSBG in positive-NET tumor cells was also higher than that in negative-NET tumor cells. These results suggested CuTSBG complex can be specifically taken up into neuroblastoma cells through NET approach and inhibit the proliferation of neuroblastoma cells, which also suggested that MIBG can be used as a parent template for designing new anticancer drugs.

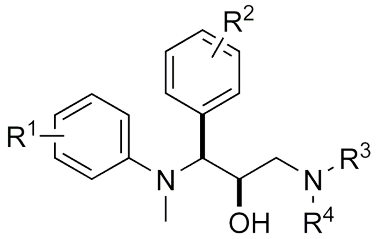
**MEDI 186**

**Arylamino-phenylpropanolamines as novel norepinephrine reuptake inhibitors**

***An T. Vu***[1]*, VuA@wyeth.com, Stephen T. Cohn*[1]*, Eugene A. Terefenko*[1]*, terefee@wyeth.com, William J. Moore*[1]*, moorew2@wyeth.com, Puwen Zhang*[1]*, zhangp@wyeth.com, Paige E. Mahaney*[1]*, mahanep@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Rebecca Dooley*[1]*, dooleyr@wyeth.com, Jenifer A. Bray*[2]*, Grace H. Johnston*[2]*, Jennifer Leiter*[2]*, and Darlene C. Deecher*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Biogenic monoamine neurotransmitters, specifically serotonin, norepinephrine and dopamine, play a crucial role in various central nervous system (CNS) activities, and monoamine deficiency has been implicated in a variety of CNS disorders. One approach to enhance monoaminergic neurotransmission is by inhibiting its reuptake after release into the synaptic cleft. Drugs that block

the norepinephrine transporter thus inhibiting norepinephrine reuptake are called norepinephrine reuptake inhibitors (NRIs), and have been used to treat major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD). Moreover, dual inhibitors of norepinephrine and serotonin transporters have recently demonstrated efficacy in other therapeutic endpoints such as neuropathic pain, stress urinary incontinence and vasomotor symptoms. In our effort to develop novel NRIs, we investigated a series of arylamino-phenylpropanolamines as a new class of NRIs. A number of compounds displayed significant norepinephrine reuptake inhibition or dual serotonin and norepinephrine reuptake inhibition, with low dopamine activity. The design, synthesis and properties of the arylamino-phenylpropanolamines will be presented.

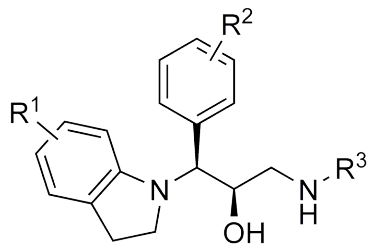



**MEDI 187**

**Indolino-phenylpropanolamines as potent and selective norepinephrine reuptake inhibitors**

***An T. Vu***[1]*, VuA@wyeth.com, Stephen T. Cohn*[1]*, Eugene A. Terefenko*[1]*, terefee@wyeth.com, Puwen Zhang*[1]*, zhangp@wyeth.com, Callain Y. Kim*[1]*, kimcy@wyeth.com, Paige E. Mahaney*[1]*, mahanep@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Lisa Nogle*[1]*, noglel@wyeth.com, Jenifer A. Bray*[2]*, Grace H. Johnston*[2]*, Jennifer Leiter*[2]*, Navin Maswood*[2]*, Scott Cosmi*[2]*, and Darlene C. Deecher*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9399, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Alterations or reductions in the levels of key monoamine neurotransmitters such as serotonin, norepinephrine and dopamine are known to play a central role in the pathophysiology of a variety of neuropsychiatric disorders. A direct strategy to elevate the local brain concentrations of these neurotransmitters is to block their reuptake through their pre-synaptic transporters. Compounds that inhibit norepinephrine reuptake are called norepinephrine reuptake inhibitors (NRIs), and have been approved for the treatment of major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD). Furthermore, dual acting serotonin and norepinephrine reuptake inhibitors (SNRIs) have recently demonstrated efficacy in other ailments such as neuropathic pain, stress urinary incontinence and vasomotor symptoms. In an effort to develop novel NRIs, we recently designed a series of indolino-phenylpropanolamines. A number of compounds were potent norepinephrine reuptake inhibitors and were selective against the serotonin and dopamine transporters. This presentation will describe the synthesis and biological evaluation of a series of indolino-phenylpropanolamines.

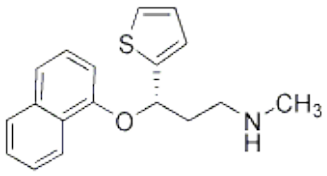


**MEDI 188**

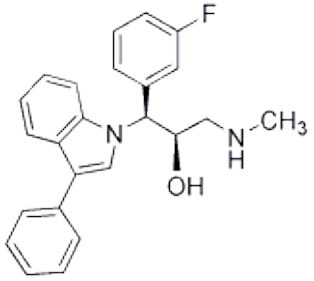
## 3-(3-Phenyl-1H-indol-1-yl)-3-phenylpropan-1-amines as selective norepinephrine reuptake inhibitors

***Fei Ye***[1]*, yef@wyeth.com, Paige E. Mahaney*[1]*, mahanep@wyeth.com, Joseph P. Sabatucci*[1]*, sabatuj@wyeth.com, Callain Y. Kim*[1]*, kimcy@wyeth.com, An T. Vu*[1]*, VuA@wyeth.com, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Jenifer A. Bray*[2]*, Grace H. Johnston*[2]*, Elizabeth Koury*[2]*, and Darlene C. Deecher*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

The aryloxypropanamine scaffold has been a standard starting point in the discovery and development of monoamine reuptake inhibitors resulting in a number of marketed drugs, e.g. Duloxetine and Atomoxetine. Drugs from this scaffold that possess norepinephrine reuptake inhibition (NRI), in some cases combined with serotonin reuptake inhibition, have been marketed for treatment of major depressive disorder and attention deficit hyperactivity disorder. In addition, NRIs have also demonstrated efficacy for neuropathic pain, lower back pain and fibromyalgia. A program targeting novel and selective NRIs resulted in the identification of the 3-(1H-indol-1-yl)-3-phenylpropan-1-amine scaffold. Further exploration of this scaffold led to the discovery of a series of 3-(3-phenyl-1H-indol-1-yl)-3-phenylpropan-1-amines as potent and selective NRIs. The synthesis and properties of these compounds will be presented.




(S)-Duloxetine

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**MEDI 189**

## Synthesis and opioid binding affinity of optically pure Benzofuro[2,3-c]pyridin-6-ols

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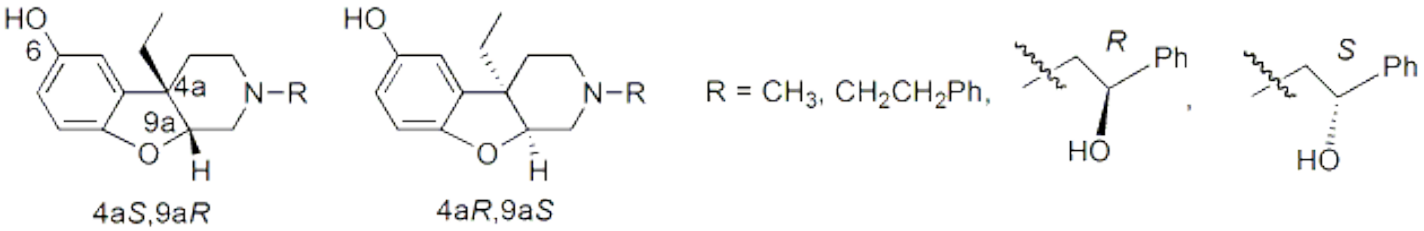
Racemic benzofuro[2,3-c]pyridin-6-ols have been found that have high affinity for mu-opioid receptors (Hutchison et al., 1989). In order to pursue our study of the topological characteristics of mu-opioid ligands, we have begun to determine the configuration of the optically pure benzofuro[2,3-c]pyridine-6-ol that is responsible for the high affinity. We have now synthesized a series of optically pure

compounds with methyl, phenethyl, 2'-hydroxy (S and R)-2'-phenethyl substituents on the nitrogen atom. The key step for synthesizing these ligands was accomplished via a high yielding multi-step synthesis of a racemic secondary amine intermediate followed by its resolution. A single crystal X-ray crystallographic study of a chiral acid salt of one of the enantiomers provided assurance of the correct structures for both optically pure amines. The target compounds were synthesized, either through direct alkylation on the amino nitrogen followed by demethylation of the phenol ether, or vice versa, depending on the stability of the intermediate under the reaction conditions. The opioid receptor binding affinities of these compounds were determined.




**MEDI 190**

**Structure activity relationship studies of spinorphin as a potent and selective human $P2X_3$ receptor antagonist**

***Kwan-Young Jung**, Hyoun Duk Moon, Ga Eun Lee, Hyun-Ho Lim, Chul-Seung Park, and Yong-Chul Kim, Department of Life Science, Gwangju Institute of Science and Technology, 1 Oryong-dong, Buk-gu, Gwangju 500-712, South Korea, Fax: 82-62-970-2484*

Spinorphin, an endogenous antinociceptive peptide (LVVYPWT), showed potent and non-competitive antagonism at the ATP-activated human $P2X_3$ receptor with an $IC_{50}$ value of 8.3 pM in a two-electrode voltage clamp (TEVC) assay with recombinant human $P2X_3$ receptors expressed in *Xenopus* oocytes. Several peptide derivatives including alanine substituted, truncated, cyclic peptides, and a retro-inverso peptide of spinorphin were evaluated for a structure-activity relationship study. It was determined that single alanine substitutions from 1st to 4th amino acids from the N-terminus of spinorphin sustained antagonistic properties at the human $P2X_3$ receptors with a nanomolar range of $IC_{50}$ values, whereas the threonine to alanine substitution resulted in an enhancing effect of the agonistic activity. The cyclic form of the LVVYPWT sequence also displayed an antagonistic effect at the human $P2X_3$ receptor, with an $IC_{50}$ value of 82.4 nM. These results suggest that the function of human $P2X_3$ receptors can be allosterically modulated by the peptide ligands.

**MEDI 191**

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

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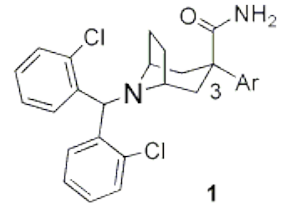
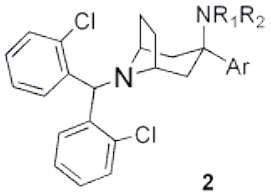
Nociceptin receptor (NOP, ORL-1), an orphan opioid receptor found in 1994, has high sequence homology to the opioid receptor family (μ, κ, and δ), however NOP does not bind classical endogenous opioid receptor ligands. Nociceptin, the NOP endogenous ligand, has been reported to mediate various physiological processes, for instance, pain, cough, anxiety, and cognition. Selective NOP agonists might have clinical potential for the treatment of related diseases without the adverse effects associated with traditional opioid receptors. In our NOP program, we have synthesized potent NOP agonists based upon 8-benzhydryl-nortropane (8-[bis(phenyl)methyl]-8-azabicyclo[3.2.1]octane) scaffold. In this poster, we will present syntheses and structure activity relationships of two series of analogs, C-3 axial amide analogs and C-3 axial *N*-substituted analogs, represented by structures **1** and **2**, respectively.




**1**

Ar = Ph, Bn, Pyridine, Heterocycles




**2**

Ar = Bn, Pyridine

**MEDI 192**

**Comparison and evaluation of the increase in delta opioid selectivity with hydroxy vs. methoxy substituted morphindoles**

***Trudy A. Smith**, Linn Thatcher, and Andrerw Coop, Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 N. Penn St, HSF2, Rm 641, Baltimore, MD 21201*

The effects of methoxy vs. hydroxy substituents at the 3- and 4- positions of indolomorphinans were evaluated to understand the effect opening the 4,5-epoxy bridge on delta selectivity. Previous studies have shown that substitution of a hydroxyl group into the 4-position of the N-CPM and N-Me series drastically decreases affinity and selectivity toward the μ, ä, and ê opioid receptors (N-CPM, Ki= 1850 ± 382, 21.8 ± 7.0, 3160 ± 205; N-Me, Ki= 2850 ± 25, 218 ± 33, >6700), respectively. To further investigate the effects of hydroxyl group on affinity and selectivity the 3,4-OMe and 3-OH indolomorphinans were evaluated. The affinities at μ, ä, and ê are: N-CPM, Ki= 1719 ±141, 19± 2, 1444± 90; N-Me, Ki= 7590±661, 41± 4, >7000, and N-CPM, Ki= 58 ±19, 0.4± 0.3, 79 ±22; N-Me, Ki= 474± 224, 4.5± 0.5, 582 ±158, respectively. The ratio of selectivity of μ/ ä for 4-OH, 3-OH, and 3,4-OMe are: N-CPM= 85, N-Me= 13; N-CPM=91, N-Me= 185; N-CPM= 145, N-Me= 105, respectively. The binding and selectivity data shows that the hydroxyl group in the 3-position has the greatest affinity and selectivity for the ä receptor. These results show that opening the 4,5-epoxy bridge retains delta selectivity, which facilitates our future goal of a mixed profile of mu agonism and delta antagonism.

**MEDI 193**

**Preparation of harmine analogs to establish SAR and improve potency of stimulation of adipogenesis**

*William J. Zuercher and **Peiling Chen**, Discovery Research, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709*

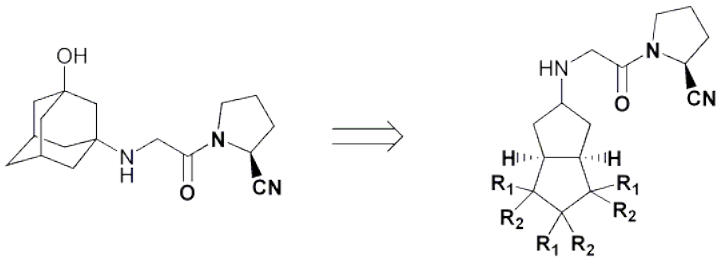
The small molecule harmine was previously identified as an insulin sensitizer. Harmine increases the expression of PPAR-gamma, consequently inducing adipogenesis. Although the adipogenic effects of harmine have been shown to proceed via inhibition of Wnt signaling, the specific molecular mechanism has not been elucidated. We undertook the preparation of structural analogs of harmine to establish SAR and improve potency in hopes of finding an optimal chemical tool for mechanistic studies and target identification efforts. We explored two main methods for formation of the beta-carboline substructure. The first method involved a six-step sequence, including an electrocyclization of a monoazahexatriene intermediate. Due to limitations of the first method, a second method was optimized which relied on Pictet-Spengler reaction and oxidative decarboxylation to form the targeted compounds.

**MEDI 194**

**Design and synthesis of dipeptidyl peptidase IV inhibitor for the treatment of type II diabetes**

*TANG Peng Cho, **YANG Fang Long**, LIN Zhi Gang, WANG Qian, WANG Yang, LI Ya Li, and ZHANG Lei, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China*

Dipeptidyl peptidase IV(DPPI-IV) inhibitors are emerging as a new class of therapetutic agents for the treatment of type 2 diabetes. The catalytic action of DPP-IV is the principle means of degradation of glucagons-like peptide-1, a key mediator of glucose-stimulated insulin secretion, and DPP-IV inhibition shows clinical benefit as a novel mechanism for the treatment of type 2 diabets. A novel series of dicyclooctane derivatives represented by general formula (1) were synthesized and evaluated as inhibitors of dipeptidyl peptidase. These compounds exhibit excellent in vitro and in vivo efficacy on animal models. The design, synthesis and inhibitory activities of these compounds will be discussed.




LAF-237 1

**MEDI 195**

**Syntheses and SAR of the novel cyclohexylamine DPP-4 inhibitors for the treatment of type 2 diabetes**

***Danqing D. Feng**, Department of Medicinal Chemistry, Merck & Co, P.O. Box 2000, 126 E. Lincoln Ave., Rahway, NJ 07065, Fax: 732-594-5790*

Abstract: The central β amino butanoyl amide moiety of sitagliptin was replaced with a cyclohexylamine group to give potent DPP-4 inhibitors. A series of novel cyclohexylamine analogs

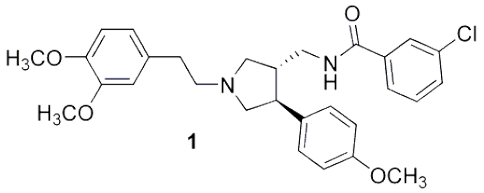
were synthesized and showed improved potencies, and excellent *in vivo* efficacy and pharmacokinetic profiles.

**MEDI 196**

**Novel pyrrolidine MCHR1 antagonists with reduced hERG binding affinity**

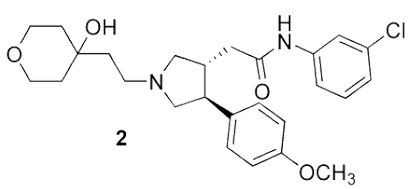
***Brian M. Fox***[1]*, bmfox@amgen.com, Reina Natero*[1]*, Kevin Richard*[1]*, Richard Connors*[1]*, rconnors@amgen.com, Philip Roveto*[1]*, proveto@amgen.com, Holger Beckmann*[2]*, holgerb@amgen.com, Katrin Haller*[2]*, and Frank Kayser*[1]*, fkayser@amgen.com. (1) Department of Chemistry, Amgen Inc, 1120 Veterans Boulevard, South San Francisco, CA 94080, Fax: 650-837-9369, (2) Amgen Research - GmbH, Amgen Inc, Regensburg 93053, Germany*

Melanin-concentrating hormone (MCH), a hypothalamic cyclic neuropeptide, plays an important role in energy homeostasis. Intraventricular injection of MCH induces hyperphagia while sub-chronic infusion causes persistent hyperphagia, hyperinsulinemia, hyperleptinemia and increased adiposity. Melanin-concentrating hormone receptor 1 (MCHR1) deficient mice do not respond to MCH infusion, are resistant to diet-induced obesity and are hyperphagic, hyperactive and hypermetabolic. Thus, it has been hypothesized that MCHR1 antagonists could be useful for the treatment of obesity. Following high-throughput screening of our small-molecule library, 1,3,4-trisubstituted pyrrolidine 1 was discovered as a potent MCHR1 antagonist possessing high hERG binding affinity. Optimization of 1 using a ligand displacement assay and an Aequorin assay led to compounds, including 2, with improved MCHR1 potency and decreased hERG binding. A stereoselective synthesis using a chiral oxazolidinone enabled us to prepare large quantities of enantiomerically pure final compounds and determine the active stereoisomer.




1

MCHR1 $IC_{50}$ = 69 nM
hERG Ki = 106 nM




2

MCHR1 $IC_{50}$ = 25 nM
hERG Ki = 8240 nM

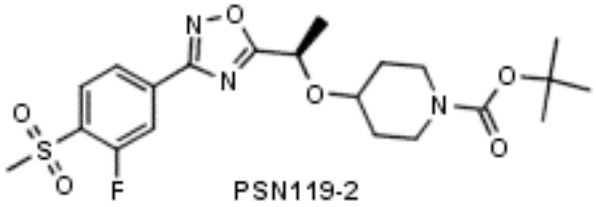
**MEDI 197**

**Discovery of PSN119-2, a novel oxadiazole-containing GPR119 agonist**

***Matthew C. T. Fyfe****, Adam J. Babbs, Lisa S. Bertram, Stuart E. Bradley, Sheila M. Doel, Smita Gadher, William T. Gattrell, Revathy P. Jeevaratnam, John F. Keily, James G. McCormack, Hilary A. Overton, Chrystelle M. Rasamison, Christine Reynet, Colin P. Sambrook Smith, Vilasben K. Shah, David F. Stonehouse, Simon A. Swain, Jonathan R. White, Peter S. Widdowson, Geoffrey M. Williams, and Martin J. Procter, Prosidion Limited, Windrush Court, Watlington Road, Oxford OX4 6LT, United Kingdom, Fax: 01144 1865 871 279*

Agonists of the recently de-orphanized G-protein coupled receptor GPR119 stimulate pancreatic insulin secretion and gastrointestinal GLP-1 release. These orally-available agents are attracting much attention as prospective antidiabetic therapies, since they may be able to simultaneously improve blood glucose control and reduce body weight. Here we describe the SAR studies leading to

the discovery of PSN119-2, a potent GPR119 agonist that stimulated insulin secretion from HIT-T15 cells ($EC_{50}$ = 18 nM) and GLP-1 release from GLUTag cells ($EC_{50}$ = 8 nM). In rats, this compound improved oral glucose tolerance, delayed gastric emptying, and reduced food intake, thus supporting the premise that GPR119 agonists could be effective oral antidiabetic agents that have the added potential to cause weight loss.

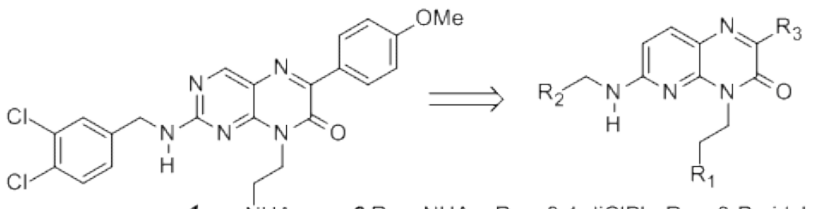



**MEDI 198**

**Potent, selective, and metabolically stable stearoyl-CoA desaturase (SCD) inhibitors for the potential treatment of obesity and diabetes**

***Dmitry O. Koltun***[1]*, dmitry.koltun@cvt.com, Eric Q. Parkhill*[1]*, Natalya I. Vasilevich*[2]*, Andrei I. Glushkov*[2]*, Timur M. Zilbershtein*[2]*, Aleksey V. Ivanov*[2]*, Andrew G. Cole*[3]*, acole@pharmacop.com, Ian Henderson*[3]*, Nathan A. Zautke*[4]*, Sandra A. Brunn*[4]*, Nevena Mollova*[5]*, Kwan Leung*[5]*, Richard Lawn*[6]*, Jeffrey W. Chisholm*[4]*, and Jeff Zablocki*[1]*, jeff.zablocki@cvt.com. (1) Department of Bioorganic Chemistry, CV Therapeutics, 3172 Porter Dr, Palo Alto, CA 94304, (2) Department of Chemistry, ASINEX Ltd, Moscow 123367, Russia, (3) Department of Chemistry, Pharmacopeia Drug Discovery, Inc, Princeton, NJ 08543, (4) Department of Pharmacological Sciences, CV Therapeutics, Inc, Palo Alto, CA 94304, (5) Department of Pre-Clinical Development, CV Therapeutics, Inc, Palo Alto, CA 94304, (6) Department of Discovery Research, CV Therapeutics, Inc*

Based on studies with knockout mice, antisence oligonucleotides, and small molecule inhibitors, stearoyl-CoA Desaturase (SCD) has recently emerged as a therapeutic target for the potential treatment of obesity, metabolic syndrome, and diabetes. SCD has been linked to a number of metabolic functions including: regulation of body weight, energy balance, plasma and liver triglyceride levels, glucose production, and peripheral insulin resistance. We herein report SCD inhibitors that are not based on previously described series, but rather came from an independent screen of a large compound collection. After some structural refinement of the initial hit (**1**, SCD $IC_{50}$ 240 nM in HEPG2 assay), we discovered a number of compounds that are highly potent (e.g. **2** and **3**, Δ9 SCD $IC_{50}$ 4 nM and 3 nM, respectively), selective against Δ5 and Δ6 desaturases, and have the desired metabolic stability. Structure-Activity Relationships (SAR) in the series will be discussed along with in vivo PK data for selected compounds.




***1***

***2*** $R_1$ = NHAc, $R_2$ = 3,4-diClPh, $R_3$ = 3-Pyridyl

***3*** $R_1$ = $CONH_2$, $R_2$ = 3-$CF_3$Ph, $R_3$ = 4-MeOPh

**MEDI 199**

## Piperazine sulfonamides as potent inhibitors of the 11beta-HSD1

***Jianchang Li***[1]*, jcli@wyeth.com, Wei Li*[1]*, Charlie Wu*[1]*, CWu@wyeth.com, Jason Xiang*[1]*, jxiang@wyeth.com, Vipin Suri*[2]*, Steve Tam*[1]*, STam@wyeth.com, John C. McKew*[1]*, JMcKew@wyeth.com, Eddine Saiah*[1]*, esaiah@wyeth.com, Tarek S. Mansour*[3]*, mansout@wyeth.com, May Tam*[2]*, mstam@wyeth.com, Yuzhe Xing*[2]*, YXing@wyeth.com, Xin Xu*[4]*, XXu@wyeth.com, and James Tobin*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, 200 CambridgePark Drive, Cambridge, MA 02140, (2) Cardiovascular and Metabolic Diseases, Wyeth, Cambridge, MA 02140, (3) Department of Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (4) Drug Safety and Metabolism, Wyeth Research, Andover, MA 01810*

Abstract:

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

We now report novel piperazine sulfonamides as potent 11beta-HSD1 inhibitors. The IC50 of these sulfonamides was measured in a cell-based assay and many of them reached nM range. Detailed SAR and their synthesis of these inhibitors will be discussed and the cell-based assay results will be presented. In addition, we will also present positive ex vivo results.

**MEDI 200**

## Synthesis of anthocyanin analogs as alpha-glucosidase inhibitors

***Zhitao Li****, Paul DeWitt, and Kathleen Leger, Department of Chemistry, Binghamton University, Binghamton, NY 13902*

Anthocyanins are an important class of glycosylated natural products. Some anthocyanins showed very interesting bioactivities like anti-tumor and anti-diabetic properties. A library of anthocyanins has been made by reduction of glycosylated flavonols, which are made through Algar-Flynn-Oyamada reaction and consequent glycosylation reactions. These compounds were then evaluated for their alpha-glucosidase inhibition activities as a part of research to develop novel anti-diabetic reagents.

**MEDI 201**

## 5-Aryl substituted 2-aminothiazolinones as 11â-HSD1 inhibitors via direct palladium/ligand catalyzed arylation

***Qingyian Liu***[1]*, qingyian@amgen.com, Anil Guram*[1]*, Nianhe Bruce Han*[1]*, Christopher Fotsch*[1]*, Chester Yuan*[1]*, Emilio Bunel*[1]*, Clarence Hale*[1]*, Michelle Chen*[1]*, Rod Cupples*[1]*, Jenne Fretland*[2]*, Dean Hickman*[1]*, and Ming Wang*[1]*. (1) Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA 91320, (2) Amgen, Inc, Thousand Oaks, CA 91320*

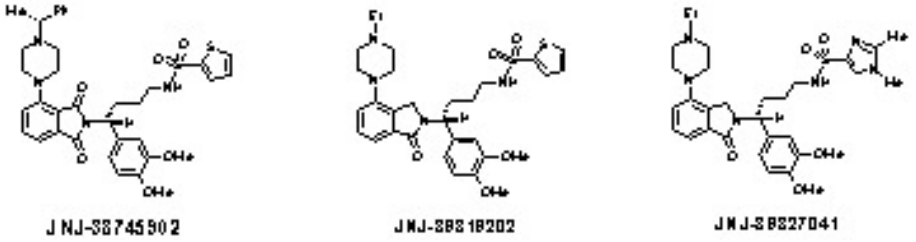
11ß-HSD1, which is expressed mainly in the liver and adipose tissue, is the enzyme that converts cortisone to cortisol. Studies in preclinical species and in humans suggest that the selective inhibition of 11ß-HSD1 may serve as a new therapy for type 2 diabetes and other aspects of the metabolic syndrome. In this poster, we report the discovery of a series of 5-aryl substituted 2-aminothiazolinones as potent and selective 11ß-HSD1 inhibitors. Some of the compounds showed good oral bioavailability in rats. A palladium/ligand catalyzed arylation reaction was developed for convenient access to a range of 5-aryl compounds from common precursor 5-methylthiazolinones.

**MEDI 202**

**Urotensin-II receptor antagonists with piperazino-phthalimide and piperazino-isoindolinone structures: Assessment of potency, selectivity, and in vitro ADME properties**

***Diane K. Luci***[1]*, dluci@prdus.jnj.com, Edward C. Lawson*[1]*, elawson@prius.jnj.com, Shyamali Ghosh*[1]*, sghosh1@prdus.jnj.com, William Kinney*[1]*, Jenson Qi*[2]*, jqi@prdus.jnj.com, Charles E. Smith*[2]*, Yuanping Wang*[3]*, Lisa K. Minor*[3]*, Barbara Haertlein*[2]*, Tom Parry*[2]*, Bruce P. Damiano*[2]*, and Bruce E. Maryanoff*[3]*, bmaryano@prdus.jnj.com. (1) Research & Early Development Chemistry, Johnson & Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, P.O. Box 0776, Spring House, PA 19477-0776, Fax: 215-628-4985, (2) Research & Early Development Biology, Johnson & Johnson Pharmaceutical Research and Development, Spring House, Fax: 215-628-4985, PA 19477-0776, (3) Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776*

Nonpeptide urotensin-II (U-II) receptor antagonists have potential for treating metabolic and cardiovascular disorders, such as renal failure, diabetes, and chronic heart failure. We modified a phthalimide-based antagonist from high-throughput screening (HTS) into analogue JNJ-38745902 (Figure), which has good in vitro and in vivo potency (iv). However, this compound also exhibited CyP450 inhibition and a poor ADME profile. An optimization strategy involving simplified derivatives with lower molecular weight was executed. Replacing the N-(alpha-methylbenzyl) group with methyl, ethyl, or isopropyl gave good potency in rat and human U-II FLIPR assays. Eliminating one ring carbonyl, as with isoindolinone JNJ-39319202, gave good potency, as JNJ-39319202 was 70-fold more potent in the human U-II FLIPR assay than its corresponding phthalimide. The isoindolinone scaffold led to compounds with better Lipinski parameters, decreased CyP450 inhibition, and good in vitro ADME profiles, relative to compounds with the phthalimide scaffold, as exemplified by JNJ-39327041.

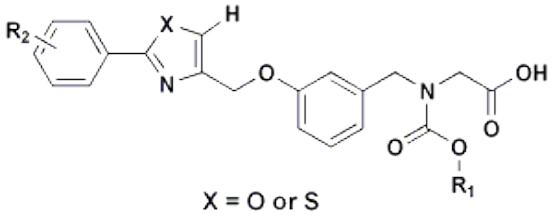


**MEDI 203**

## Discovery and structure-activity relationships of potent and selective PPARalpha activators

***Xiang-Yang Ye***[1], *xiang-yang.ye@bms.com, Stephanie Y. Chen*[1], *Hao Zhang*[2], *hao.zhang@bms.com, Shiwei Tao*[1], *Jun Li*[1], *jun.li@bms.com, Lawrence J. Kennedy*[1], *Yan Shi*[3], *Andres Hernandez*[1], *Sean Chen*[1], *Pratik V. Devasthale*[1], *Wei Wang*[1], *Kenneth T Locke*[4], *Kevin O'Malley*[4], *Litao Zhang*[4], *Raiajit Srivastava*[5], *Bowman Miao*[5], *Daniel S. Meyers*[5], *Hossain Monshizadegan*[5], *Debra Search*[5], *Denise Grimm*[5], *Rongan Zhang*[5], *Thomas Harrity*[5], *Lori K. Kunselman*[5], *Michael Cap*[5], *Jodi Muckelbauer*[6], *Chiehying Chang*[7], *Stanley Krystek Jr.*[6], *stanley.krystek@bms.com, Vinayak Hosagrahara*[8], *Lisa Zhang*[8], *Pathanjali Kadiyala*[9], *Carrie Xu*[9], *Michael A. Blanar*[5], *Robert Zahler*[1], *Ranjan Mukherjee*[5], *Peter T. Cheng*[1], *and Joseph A. Tino*[1]. *(1) Discovery Chemistry, Bristol-Myers Squibb, P.O. BOX 5400, Princeton, NJ 08543-5400, Fax: 609-818-3460, (2) Discovery Chemistry, Bristol-Myers Squibb Co, Princeton, NJ 08543-5400, (3) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research and Development, Princeton, NJ 08543-5400, (4) Lead Evaluation, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (5) Department of Biology, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (6) Macromolecular Crystallography & CADD, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (7) CADD, Bristol-Myers Squibb Co, Princeton 08543, (8) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Co, Princeton 08543, (9) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton 08543*

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors and members of the nuclear hormone receptor superfamily. PPARα, a subtype highly expressed in liver, skeletal muscle and heart, modulates genes regulating lipid homeostasis. Herein, we wish to present a series of potent and selective PPARα activators (structure shown below) incorporating 2-aryl-4-oxazolylmethoxy and 2-aryl-4-thiazolylmethoxy moieties into an oxybenzylglycine framework. Through judicious variation of substituents R1 and R2, a wide range of selectivity (PPARα vs. PPARγ) can be achieved. Systematic SAR (structure-activity relationship) studies led to the discovery of several potent and selective PPARα activators, whose in vivo pharmacology as well as ADME profile will be discussed in detail.




**MEDI 204**

## Synthesis and biological evaluation of azole acid analogs as novel, potent dual PPAR alpha/gamma activators

***Hao Zhang***[1], *hao.zhang@bms.com, Pratik Devasthale*[1], *Wei Wang*[1], *Denis Ryono*[1], *Dennis Farrelly*[2], *Liqun Gu*[2], *Kevin Omalley*[2], *Thomas Harrity*[2], *Michael Cap*[2], *C Chu*[2], *Lori Kunselman*[2], *Nathan Morgan*[2], *Lisa Moore*[2], *Neil Flynn*[2], *Vinayak Hosagrahara*[3], *Lisa Zhang*[3], *Pathanjali Kadiyala*[4], *Carrie Xu*[5], *Arthur Doweyko*[6], *Chiehying Chang*[6], *Jodi Muckelbauer*[6], *Aneka Bell*[7], *Robert Zahler*[1], *Narayanan Hariharan*[2], *and Peter T. Cheng*[1], *peter.t.cheng@bms.com. (1) Discovery Chemistry,*

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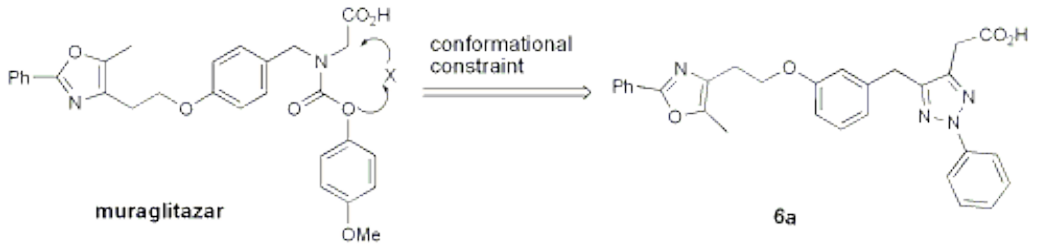
As part of our effort to identify novel potent and efficacious PPARalpha/gamma dual activators with different PPARalpha and PPARgamma activities, we explored a number of different structural variations of the oxybenzylglycine PPARalpha/gamma dual activator muraglitazar. Bioisosteric modification of the oxybenzylglycine moiety of muraglitazar, e.g. the replacement of the glycine carbamate with heterocyclic rings, resulted in the discovery of a novel series of azole-acids as PPARalpha/gamma ligands. Analogs from this series showed varying degrees of PPARalpha and PPARgamma functional activity; in particular, analogs such as 6a showed excellent binding affinity and functional activity at both PPARalpha and PPARgamma. In diabetic/dyslipidemic db/db mice, compound 6a decreased levels of fasting plasma glucose (-36%) and triglycerides (-50%) at 10 mg/kg/day in a 14-day study.




**MEDI 205**

**Diverse isoxazole glutamate analogs arise from a common intermediate**

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Since Krogsgaard-Larsen's pioneering development of AMPA in 1980, isoxazoles have played a useful role in delineating selectivity among proteins that bind glutamate in the CNS. We previously reported an improved preparation of AMPA analogs, including a catalytic asymmetric route. Subsequent binding studies indicate that there exists a distinct SAR distinguishing Receptors and Transporters, specifically the AMPA receptor from the Sytem Xc- transporter, which relates to the size and distance of a lipophilic group in the C-5 position from the functionalized isoxazole. Further investigation of this observation has lead us to examine routes to C-3 carboxy analogs of ibotenate, homo-ibotenate, and homo-AMPA, as well as investigate bioisosteres which are not limited to amino acids, all originating from a common intermediate. Our recent progress on this endeavor from both chemistry and biology perspectives will be described.

**MEDI 206**

## Discovery of new HIV protease inhibitors and prodrug strategies for enhancing their oral bioavailability

***David A. DeGoey**, William J. Flosi, David J. Grampovnik, Charles A. Flentge, Larry L. Klein, Clinton M. Yeung, Lynn Colletti, Tatyana Dekhtyar, Warren M. Kati, Hongmei Mo, Yaya Liu, Rita Ciurlionis, Michelle A. Long, Kennan C. Marsh, James M. Schmidt, Sue J. Swanson, Jeffrey F. Waring, Akhteruzzaman Molla, and Dale J. Kempf, Global Pharmaceutical Research and Development, Abbott Laboratories, Department R4CQ, Building AP52, 200 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-938-2756*

Currently marketed HIV protease inhibitors (PIs) have some important limitations, such as adverse effects on serum lipids and unconjugated bilirubin, and limited pharmacokinetics. We employed new preclinical in vivo models for PI off-target activities developed in our program to guide our identification of new PIs with lower potential for these side effects. Most HIV PIs are large, lipophilic, peptidomimetic compounds that have low aqueous solubility and poor oral bioavailability. To overcome the limitation of solubility on oral bioavailability, we evaluated the use of solubility enhancing prodrugs. While standard prodrug approaches failed to provide PK enhancements for our series, oxymethylphosphate (OMP) and oxyethylphosphate (OEP) prodrugs provided high levels of aqueous solubility and improved oral bioavailability. We developed chemistry to introduce these prodrugs efficiently and applied this approach to other HIV PIs, demonstrating the potential to reduce the pill burden for these therapies.

**MEDI 207**

## Acyl guanidine inhibitors of BACE

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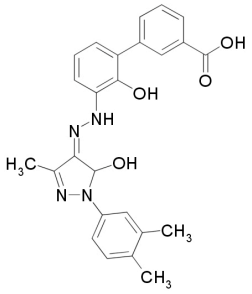
The production of the amyloidogenic beta amyloid 1-42 protein fragment from amyloid precursor protein (APP) is hypothesized to initiate the pathology characteristic of Alzheimer's disease. Beta-secretase (BACE) and gamma-secretase are responsible for the liberation of beta amyloid 1-42, and hence inhibition of these enzymes would be of potential therapeutic benefit. A series of acyl guanidines has been advanced from initial screening hits to afford single-digit nanomolar in vitro and cellular potency vs. BACE. The optimization efforts within this series of compounds will be presented.

**MEDI 208**

**Discovery of Eltrombopag: An oral therapy for the treatment of thrombocytopenia**

***Kevin J. Duffy**, Oncology Center of Excellence for Drug Discovery, GlaxoSmithKline, 1250 S. Collegeville Rd., Collegeville, PA 19426*

Thrombopoietin (TPO) is the cytokine primarily responsible for the differentiation of hematopoietic stem cells along the megakaryocyte lineage and thus ultimately the production of platelets in vivo. The utility of various recombinant forms of thrombopoietin in ameliorating thrombocytopenias has been extensively studied as has its ability to boost platelet levels in healthy donors. However, the development of neutralizing antibodies has led to the termination of the clinical development of recombinant forms of TPO. Recently, small-molecule, oral therapeutics have been developed to stimulate the TPO receptor and initiate megakaryocyte hematopoiesis. In this presentation I will discuss the high-throughput screening strategies employed to discover agonists of the signaling pathways involved in megakaryocytopoiesis and the process that ultimately lead to the discovery of Eltrombopag (SB-497115-GR/Promacta®/Revolade™). The development of a common pharmacophore for the interaction of several, distinct chemical series with the TPO receptor will also be discussed and how the various structure-activity relationships from these multiple series contributed to the design of Eltrombopag. In late 2007, an NDA was filed with the FDA for the short-term treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP) and data from the supporting clinical trials will also be presented.




Eltrombopag

**MEDI 209**

**Beta-secretase as a therapeutic target for Alzheimer's disease**

***Jordan Tang**, Protein Studies Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, OK 73104, Fax: 4052717249*

Beta-secretase (memapsin 2, BACE1) is the protease that initiates the cleavage of amyloid precursor protein leading to the production of amyloid-beta (Abeta). Since an excess level of Abeta in the brain is the major factor of Alzheimer's disease (AD), beta-secretase is an attractive target for the development of inhibitor drugs to treat this disease. Such a therapy would be expected to modify the progression of the disease, in contrast to the existing AD drugs that only relieve the symptoms. The catalytic mechanism and inhibition of this class of protease is well known and the gene deletion of beta-secretase is well tolerated in mice. Therefore, the research on this protease and the development of its inhibitors has been actively pursued and the recent inhibitors contain many

targeted characteristics of a drug. The current knowledge base will likely lead to beta-secretase inhibitor drugs in the clinics. This discussion will focus on the characteristics of beta-secretase, its in vivo regulation in Abeta production and the therapeutic strategy to achieve Abeta reduction using a beta-secretase inhibitor.

**MEDI 210**

**Development of antiviral therapy of HIV infection: From AZT to Darunavir**

***Hiroaki Mitsuya**, Experimental Retrovirology Section, HIV & AIDS Malignancy Branch, National Cancer Institiute, 9000 Rockville Pike, Building 10, Room 5A11, Bethesda, MD 20892, Fax: 301-402-0709*

Upon the discovery of the first human pathogenic retrovirus HTLV, no attempt was made to explore antiretroviral therapy, since it was believed that once cells were infected by retrovirus, drugs would do nothing to the progress of retrovirus-associated diseases. The first three dideoxynucleoside reverse transcriptase inhibitors including AZT made changes. Thus far, a number of agents have benn added to our armamentarium to fight with AIDS. One new area in the development of antiretroviral agents is predictive modeling, which maximizes our chances of success. I will discuss an approach of combining mutagenesis-based data and molecular modeling, a novel strategy for structural insights for drug design. We recently discovered that darunavir and a group of agents block the dimerization of HIV protease, an essential step in the replication cycle of HIV. Further improved approaches to explore new treatment modalities should make it possible to control HIV diseases more effectively.

**MEDI 211**

**Structure-based design of aspartyl protease inhibitors: From treatment of drug-resistant HIV to Alzheimer's disease**

***Arun K. Ghosh**, Departments of Chemistry and Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, Fax: 765-496-1612*

Aspartyl proteases are implicated in the pathogenosis of a host of human diseases. As a consequence, aspartyl proteases have increasingly become important drug-design targets. Highly active antiretroviral therapy (HAART) with HIV protease inhibitors and reverse transcriptase inhibitors continues to be the major treatment regimen for HIV/AIDS. One of the major challenges of HAART-therapy is the emergence of multi-drug-resistant HIV-1 variants. Our structure-based design strategies targeting protein backbone led to a number of exceedingly potent HIV-1 protease inhibitors including darunavir, a recently FDA approved inhibitor for the treatment of drug-resistant HIV. Another aspartyl protease, memapsin 2 (beta-secretase, BACE-1), has become an important drug-design target for the treatment of Alzheimer's disease. Our structure-based design has led to the development of a number of potent and selective inhibitors of memapsin 2. This presentation will feature novel design-concepts, general strategies and tools for HIV-1 protease and beta-secretase inhibitors.

**MEDI 212**

## PET in neuroscience and drug development

***Christer Halldin**, Department of Clinical Neuroscience, Karolinska Institutet, Psychiatry Section, Karolinska Hospital, Stockholm, Sweden, Fax: 46-8-5177-1753*

PET provides a new way to image the function of a target and by elevating the mass, to pharmacologically modify the function of the target. The main applications of PET radioligands in brain research concern human neuropsychopharmacology and the discovery and development of novel drugs to be used in the therapy of psychiatric and neurological disorders. A basic problem in PET brain receptor studies is the lack of useful radioligands with ideal binding characteristics. Prerequisite criteria, such as high affinity and selectivity, need to be satisfied for a radioligand to reveal target binding sites in vivo. During the past decade over a hundred neurotransmitters have been identified in the human brain. Most of the currently used drugs for the treatment of psychiatric and neurological disorders interact with central neurotransmission. Molecular biological techniques have now revealed the existence of hundreds of novel targets for which little or no prior pharmacological or functional data existed. Due to the lack of data on the functional significance of these sites, pharmacologists are now challenged to find the physiological roles of these receptors and identify selective agents and possible therapeutic indications. During the past decade various 11C- and 18F-labeled radioligands have been developed for labeling some of the major central neuroreceptor systems. There is still a need to develop pure selective PET tracers for all the targets of the human brain. This presentation will review recent examples in neuroreceptor radioligand development and the clinical potential of in vivo imaging of neurotransmitter systems. The review will focus on studies with PET radiotracers in neuropsychopharmacological drug development. Drug research now benefits from the fast development of functional imaging techniques such as PET.

**MEDI 213**

## Translational applications of molecular imaging with PET

***Yu-Shin Ding**, Dept. of Diagnostic Radiology, Yale University School of Medicine, 15 York St, New Haven, CT 06510*

Modern PET research is enriched and strengthened by the integration of many disciplines, and advances in radiotracer chemistry have played a pivotal role in driving the field in new directions in studies of human physiology. At the heart of this development is the rapid incorporation of simple short-lived positron-emitting building blocks into organic compounds that can be used to map specific biochemical processes and the movement of drugs in living systems. This presentation will describe how we characterize radiotracers in animals, how we apply tracers to study neuroscience, and how we translate a promising radioligand from pre-clinical investigation in non-human primates to clinical research in humans.

**MEDI 214**

## Imaging agents for neurodegenerative diseases

***H Kung**, Department of Radiology and Pharmacology, University of Pennsylvania, 3700 Market St, Philadelphia, PA 19104*

Neurodegenerative diseases are increasingly important in providing medical care for aging population. Parkinson's disease (PD) and Alzheimer's disease (AD) are two common neurodegenerative diseases. Advances in developing targeted imaging agents for positron emission tomography (PET) and single photon computed tomography (SPECT) have led to improvements in early diagnosis and monitoring disease progression by imaging methods. The first imaging agent for PD is 18F-6-fluoro-dopa is a false precursor, or substrate, for aromatic amino acid decarboxylase. All of the other dopamine transporter imaging agents are derivatives of tropane, a core structure of cocaine; they include 11C-CFT, 18F- or 123I-FP-CIT, 123I-β-CIP, 123I-altropane and 99mTc-TRODAT. Radiolabeled tetrabenazine derivatives, such as 11C-DTBZ, will target vesicular monoamine transporters inside the dopamine neurons. They may provide an alternative strategy in imaging the integrity of dopamine system as related to PD.

Formation of Abeta plaques in the brain is a hallmark of patients with AD and there is an underlying relationship between accumulation of Abeta in the brain and AD. Recently, radiolabeled tracers for binding Abeta plaques have been developed. Several Abeta specific binding agents which are derivatives of benzothiazole, stilbene or other related heterocyclic derivatives containing an electron-donating group on one of the aromatic rings, have been reported. They are simple, relatively small, neutral and lipophilic molecules displaying high binding affinity to Abeta aggregates (Ki at the range of 0.1-20 nM), they are suitable candidates as Abeta plaque-selective imaging agents. More importantly, they also showed ability to penetrate the intact blood-brain barrier, an essential pre-requisite for a useful plaque-imaging agent. These target-site-specific imaging agents may be useful for early detection and monitoring the progression and effectiveness of treatment of AD.

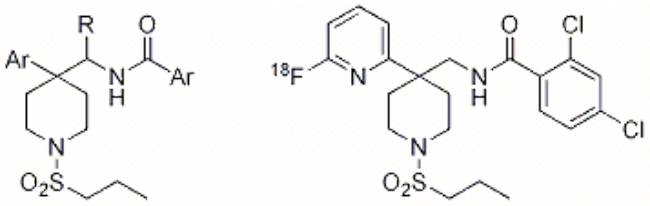
**MEDI 215**

## Synthesis and characterization of glycine transporter (GlyT1) PET ligands

***Terence G. Hamill**[1], terence_hamill@merck.com, Andrew S. R. Jennings[2], Richard T. Lewis[2], Andrew Pike[2], Steven Thomas[2], Suzanne Wood[2], Leslie Street[2], Shil Patel[1], David Wisnoski[3], david_wisnoski@merck.com, Scott E. Wolkenberg[4], scott_wolkenberg@merck.com, Craig Lindsley[3], Zhijian Zhao[3], Stephen M. Krause[1], Christine Ryan[1], Maria Michener[1], David Williams[1], Zhizhen Zeng[1], Patricia Miller[1], Kerry Riffel[1], Waisi Eng[1], Raymond E. Gibson[1], Cyrille Sur[1], Richard Hargreaves[1], and H Donald Burns[1]. (1) Department of Imaging Research, Merck Research Laboratories, WP44D-2, West Point, PA 19486, (2) The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Harlow, Essex CM20 2QR, United Kingdom, (3) Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, (4) Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486*

Glycine transporters, which belong to the Na+/Cl- - dependent family of neurotransmitter transporters, are thought to regulate the synaptic levels of glycine, an amino acid inhibitory neurotransmitter that is a co-agonist for the NMDA receptor complex. Two glycine transporters, GlyT1 and GlyT2, have been identified. GlyT1 is found throughout the mammalian brain and has been shown to co-localize with NMDA receptors. Because hypofunction of the glutamatergic system has been suggested as a factor

behind schizophrenia, increasing synaptic glycine levels by inhibiting its uptake by GlyT1 antagonists may be a useful therapy for schizophrenia. Having a PET tracer to determine central GlyT1 occupancy of therapeutic compounds would be an important tool to guide the selection of clinical doses for Phase IIa proof of concept studies. A series of PET tracers based on aryl amide 1 labelled with either carbon-11 or fluorine-18 were synthesized and evaluated as potential GlyT1 PET tracers. [18F]2, a potent, selective GlyT1 inhibitor, has excellent properties as a CNS receptor ligand and has been identified as a potential clinical PET tracer for imaging GlyT1. The in vitro and in vivo preclinical characterization of tracers leading to [18F]2 will be presented.




1 [18F]2

**MEDI 216**

**Quantitative imaging in drug discovery using positron emission tomography**

***Steven M. Larson**, Nuclear Medicine Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021*

PET/CT imaging in oncology is rapidly expanding because of the benefits of evaluating the function as well as the structure of human tumors. These clinical benefits have greatly increased availability of PET/CT for patients' studies throughout the United States. In addition high-resolution animal imaging PET scanners have been developed, for experimental imaging including studies of the pharmacology of cancer drugs based on radiotracer methods.

At Memorial Sloan-Kettering cancer center we have applied these techniques to study small molecules, peptides, and radiolabeled antibodies in living animals and humans. We have imaged the pharmacodynamics of these drugs; e.g. the effect of HSP 90 inhibitors and signal transduction targeting drugs on nucleoside phosphorylation, glycolysis and expression of key biomolecules of her2 and AR. In this lecture we will present an overview of applications to cancer pharmacology and immunology in animals and man.

**MEDI 217**

**Schizophrenia: Overview and treatment strategies**

***Judith A. Siuciak**, Neuroscience Department, Bristol-Myers Squibb Co, 5 Research Parkway, Wallingford, CT 06492*

Schizophrenia is a complex psychiatric disorder that is characterized by three major categories of symptoms: positive, negative and cognitive. Although current pharmacotherapies are effective treatments for psychosis, there remains a need for drugs with improved efficacy towards negative symptoms and cognitive impairment, as well as reduced side effects. The dopamine hypothesis has

been the leading theory on the pathophysiology of schizophrenia for decades and drug development has focused largely around this neurotransmitter. Second generation agents included actions on other monoamine neurotransmitters such as serotonin. However, contemporary theories have implicated deficits in cortical glutamate transmission as contributing to the disease and have formed the basis for several new approaches. Finally novel approaches which target second messenger pathways are being explored. The growing understanding of the neurochemical abnormalities underlying this disorder have led to the pursuit of a wide variety of pharmacological agents with novel mechanisms.

**MEDI 218**

**Discovery of mGlu2/3 receptor agonists as a novel approach for the treatment of schizophrenia**

***James Monn**, Discovery Chemistry Research and Technologies, Eli Lilly and Company, Lilly Corporate Center, Drop 0510, Indianapolis, IN 46285*

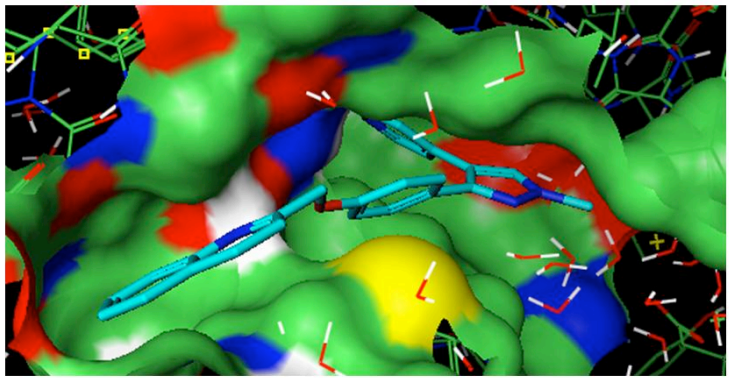
Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system and is fundamental in the regulation of neuronal excitability and plasticity. Aberrant glutamate neurotransmission has been associated with pathophysiologic states associated with both psychiatric (e.g. anxiety, depression, schizophrenia) and neurologic (e.g. Parkinson's, Huntington's, epilepsy, stroke) conditions. The actions of glutamate are mediated via molecular families of ligand-gated ion channel-forming (ionotropic, iGlu) receptors and G-protein coupled, (metabotropic, mGlu) receptors. The mGlu receptors are comprised of eight members (mGlu1-8) and belong to the class C family of GPCRs. Our group has focused on the identification of novel orthosteric agonists acting at mGlu2 and mGlu3 receptors for the treatment of psychiatric disorders. From this work we discovered LY404039, a potent and selective mGlu2 / mGlu3 receptor agonist (mGlu2 EC50 = 23 nM; mGlu3 EC50 = 48 nM). Preclinical evaluation of LY404039 in rodent behavioral models revealed potent antipsychotic-like effects following oral administration; however, low plasma exposure following oral dosing in humans hindered the clinical progression of this molecule. To overcome this pharmacokinetic limitation, a prodrug of LY404039, LY2140023, was subsequently discovered. LY2140023 is a L-methionine amide of LY404039 and is a substrate for human peptide transporter 1 (PepT1). In humans, LY2140023 was found to produce substantially higher plasma concentrations of LY404039 following oral dosing when compared to LY404039, enabling its clinical progression to a critical proof-of-concept study in schizophrenic patients. In a double-blind, placebo-controlled, positive comparator-controlled clinical trial, LY2140023 treatment led to statistically significant improvement in the PANSS-total scores when compared to those patients in the study receiving placebo. However, LY2140023 treatment did not separate from the placebo-treatment group with respect to multiple adverse event parameters. These results provide important clinical evidence that activation of mGlu2/3 receptors represents a new approach for the treatment of schizophrenia.

**MEDI 219**

**Development of multiple structural lead options utilizing structure based drug design to identify a PDE10 clinical candidate to treat schizophrenia**

***Patrick R Verhoest**, CNS Chemistry, Pfizer, 8220-4168 Eastern Point Road, Groton, CT 06340*

PDE10A is a dual substrate cyclic nucleotide phosphodiesterase that has expression in the spiny neurons of the striatum. Inhibiting PDE10 in rodents leads to increases in cyclic nucleotides in the striatum and a behavioral anti-psychotic phenotype. Structure based drug design was utilized to identify and develop the SAR of multiple lead options. The design and optimization of the pyrazole series and the quinazoline series into molecules with drug-like properties will be discussed. The structure of the clinical candidate PF-2545920 along with its' preclinical rational and Phase I single dose PK will be disclosed.



**MEDI 220**

**Glycine transporter 1 (GlyT1) inhibitors for the treatment of schizophrenia**

***Scott E. Wolkenberg****, Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 4, WP14-1, West Point, PA 19486, Fax: 215-652-6345*

Scott E. Wolkenberg for the Merck GlyT1 Team

Departments of Medicinal Chemistry, Neuroscience Research, Drug Metabolism, Imaging, Clinical Pharmacology, and Clinical Drug Metabolism

Merck and Co., Inc., West Point, PA; Upper Gwynedd, PA;

Neuroscience Research Centre, Merck Sharp and Dohme, Terlings Park, Harlow, UK

Inhibitors of Glycine Transporter 1 (GlyT1) represent a promising new approach for the treatment of schizophrenia. Glycine is a co-agonist at the N-methyl-D-aspartate (NMDA) glutamate receptor, and increasing synaptic concentrations of glycine through inhibition of GlyT1 potentiates NMDA receptor signaling. Because glycine acts as a potentiator of glutamatergic signaling, GlyT1 inhibitors may offer advantages over direct NMDA receptor agonists. By addressing NMDA hypofunction, GlyT1 inhibitors provide the potential to treat the cognitive deficits and negative symptoms of schizophrenia that are insufficiently addressed with currently available treatments. High throughput screening of the Merck

sample collection provided numerous hits, and a 4,4-disubstituted piperidine was selected for further optimization based on its modular structure and attractive properties. Structure-activity studies initially focused on improving selectivity versus off-target ion channels and eliminating susceptibility to P-glycoprotein (P-gp) transport. Optimization of in vivo efficacy was guided by an in vivo occupancy assay utilizing a novel GlyT1 radioligand. Extensive studies were pursued to improve the pharmacokinetic profile of the lead including the use of in vivo cassette dosing experiments. As a result of this optimization, a development candidate was identified which has advanced to clinical testing. This work also led to the discovery of a clinically validated PET tracer that was used to determine occupancy of the clinical candidate in both preclinical species as well as humans.

**MEDI 221**

**Glycine transporter-1 (GlyT-1) inhibitors for the treatment of schizophrenia: From tools to PETs**

***Roderick A. Porter**, Neurosciences CEDD Dept of Medicinal Chemistry, GlaxoSmithKline, Harlow, United Kingdom*

GlaxoSmithKline is committed to identifying novel therapies for the treatment of schizophrenia. One of our approaches is to address NMDA receptor hypofunction that has been associated with this crippling disease. The NMDA receptor contains multiple binding sites including an allosteric modulatory site sensitive to glycine and D-serine. NMDA receptors are co-localized with GlyT-1, which is involved in the regulation of synaptic glycine levels. While large doses of the co-agonists glycine and D-serine have shown encouraging responses in small scale clinical trials, synaptic glycine levels may be modulated more effectively by GlyT-1 inhibitors. Early GlyT-1 inhibitors, based on glycine, such as sarcosine (N-methylglycine) or glycyldodecylamide, showed only weak target activity. While detailed SAR studies have identified more potent analogues, the strategy of GSK has been to focus on non-glycine based approaches.

In this presentation activity to identify potent, selective novel non-glycine based GlyT-1 inhibitors will be reviewed. Topics to be covered will include SAR summaries, the importance of early pharmaceutical development input, the potential of protein modelling in GlyT-1 inhibitor research and the role of tissue binding in guiding optimisation of in vivo activity. Finally, work to identify [11C]931145, a compound currently under evaluation as a PET ligand for supporting clinical progression of GlyT-1 inhibitors, will be summarised.

**MEDI 222**

**Development of selective α7 NNR agonists for the treatment of schizophrenia**

***Daniel Yohannes**, daniel.yohannes@targacept.com, Drug Discovery, Targacept, Inc, 200 East 1st St, Suite 300, Winston-Salem, NC 27101, and Anatoly Mazurov, anatoly.mazurov@targacept.com, Department of Medicinal Chemistry, Targacept, Inc, Winston-Salem, NC 27410*

The National Institute of Mental Health recently took the lead in organizing a government/academic/industry cooperative initiative called Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). MATRICS identified cognitive dysfunction in schizophrenia (CDS) as a core feature of the illness that contributes significantly to the diminished quality of life of schizophrenia patients. With the need for a therapy to treat CDS and the established

evidence of a link between α7 neuronal nicotinic acetylcholine receptors (NNRs) and schizophrenia, the α7 NNR subtype has emerged as a therapeutic target that may be relevant to cognitive dysfunction as well as the positive symptoms (hallucinations, delusions, thought disorder) of schizophrenia.

To investigate the limits of the α7 NNR binding site, we initiated virtual and synthetic diversification of the quinuclidine scaffold, a common pharmacophoric element of this NNR subtype. Its basic nitrogen, in occupying a bridgehead position within an azabicyclic system, allocates maximal electrostatic interaction combined with minimal steric demand. The cationic center is a core for selective ligands around which hydrophobic fragments, hydrogen bond acceptors and hydrogen bond donor moieties can be assembled in a defined order. Exploration of 2-substituted quinuclidin-3yl-amides, carbamates, and ureas led to the discovery of a new pharmacophoric element – namely, a pyridylmethyl group, which appears to interact with the receptor as a hydrogen bond acceptor and improve selectivity, potency and metabolic stability of the optimized α7 ligand. Diversification of the hydrogen bond acceptor and π-electron rich pharmacophoric elements resulted in the discovery of new ligand classes for this receptor subtype. TC-5619 was thus identified as a potent and selective α7 NNR agonist whose preclinical profile competes favorably with other compounds targeting the α7 NNR. Importantly, TC-5619 has demonstrated therapeutic potential in animal models of positive *and* cognitive symptoms associated with schizophrenia along with favorable pharmacokinetic and safety profiles.

**MEDI 223**

**AZ10419369 a translational tool for 5-HT1B receptors**

***M. Edward Pierson***[1]*, edward.pierson@astrazeneca.com, Jan Andersson*[2]*, Jan.Andersson@ki.se, Svante Nyberg*[3]*, svante.nyberg@astrazeneca.com, J. Söderström*[3]*, johan.soderstrom@astrazeneca.com, Dennis J. McCarthy*[1]*, dennis.mccarthy@astrazeneca.com, Sjoerd J. Finnema*[2]*, sjoerd.finnema@ki.se, Katarina Varnäs*[2]*, katarina.varnas@ki.se, Akihiro Takano*[2]*, akihiro.takano@ki.se, Per Karlsson*[2]*, per.karlsson@karolinska.se, Balázs Gulyás*[2]*, Balazs.Gulyas@ki.se, Mark E. Powell*[1]*, mark.powell2@astrazeneca.com, J. Richard Heys*[4]*, William Potts*[1]*, william.potts@astrazeneca.com, Donna Maier*[1]*, donna.maier@astrazeneca.com, Amy Medd*[1]*, amy.medd@astrazeneca.com, Cynthia D. Sobotka-Briner*[1]*, cynthia.sobotka-briner@astrazeneca.com, Nicholas Seneca*[5]*, nicholasseneca@mail.nih.gov, Lars Farde*[2]*, lars.farde@ki.se, and Christer Halldin*[2]*, christer.halldin@ki.se. (1) AstraZeneca Pharmaceuticals, PO Box 15437, Wilmington, DE 19850, (2) Department of Clinical Neuroscience, Karolinska Institutet, S-17176 Stockholm, Sweden, (3) Clinical Neuroscience, AstraZeneca Pharmaceuticals, S-151 85 Södertälje, Sweden, (4) CNS Discovery, AstraZeneca Pharmaceuticals, Wilmington, DE 19850, (5) Molecular Imaging Branch, National Institute of Mental Health, Bethesda, MD 20892*

The 5-HT1B receptor is a potential pharmacological target in the treatment of depression. We report the use of [11C]AZ10419369 (5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4H-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide), a novel high affinity radioligand, for in vivo visualization of 5-HT1B receptors. [11C]AZ10419369 was prepared by N-methylation of the N-H precursor, using carbon-11 methyl triflate in >99% radiochemical purity and specific activity of >6000 Ci/mmol. Regional brain uptake patterns of [11C]AZ10419369 were characterized by PET measurements in primates. After iv injection of [11C]AZ10419369, 3-4% was in brain after 7.5 minutes. The highest uptake of radioactivity was in the occipital cortex and basal ganglia, and lowest in the cerebellum in accord with autoradiographic studies performed using [3H]AZ10419369. In primates and guinea pigs pre-treated with the selective 5-HT1B receptor antagonists, binding of radiolabeled AZ10419369 was

reduced in a dose-dependent manner, consistent with specific binding to 5-HT1B receptors. These data support [3H] and [11C]AZ10419369 as a suitable radioligand for imaging 5-HT1B receptors and determining receptor occupancy of test compounds.

**MEDI 224**

**Synthesis, characterization and in vivo imaging in nonhuman primates of a series of carbon-11 reboxetine analogs as norepinephrine transporter (NET) PET imaging agents**

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**Objectives:** The NET is a molecular target for the treatment of depression, anxiety disorder, and attention-deficit/hyperactivity disorder (ADHD). The development of radioligands to map the NET by positron emission tomography (PET) presents opportunities to define the functional status and pharmacology of the NET in the living human brain. The objective of this study was to investigate the regional uptake, specificity and binding kinetics of a series of carbon-11 labeled reboxetine analogs, (2S,3S)-2-[α-(2-(methyl)phenoxy)benzyl]morpholine (**1**), (2S,3S)-2-[ α-(2-(methylthio)phenoxy)benzyl]morpholine (**2**), (2S,3S)-2-[α-(2-(methylthiophenylthio)phenylmethyl]morpholine (**3**), and (2S,3S)-2-[ α -(2-methoxyphenylthio)phenylmethyl]morpholine (**4**) using PET imaging.

**Methods and results:** In vitro binding in cells transfected to express human NET, SERT and DAT gave Ki's (nM) = 1 (**1**), 2 (**2**), 0.8 (**3**), and 0.6 (**4**) (vs [$^{3}$H]nisoxetine), 94 (**1**), 91 (**2**), 10 (**3**)and 13 (**4**) (vs [$^{3}$H]citalopram) and 328, (**1**), 6506 (**2**), 4054 (**3**), and 1440 (**4**) (vs [$^{125}$I]RTI-55). The in vivo regional brain uptake of [$^{11}$C] (**1**), (**2**), (**3**), and (**4**) were determined in anesthetized and awake rhesus monkeys after administration of ~15 mCi. [$^{11}$C] (**1**), (**2**), (**3**), and (**4**) showed high uptake in NET rich regions (thalamus, locus ceruleus, anterior cingulate and cerebellum) and displayed favorable kinetics with a peak uptake at 22.5-60 min. Blocking studies carried out with the NET ligand desipramine (0.125 & 0.25 mg/kg) 30 min prior to injection of [$^{11}$C] (**1**), (**2**), (**3**), and (**4**) showed significant reduction of the radioactivity from the NET rich regions proving NET specificity.

**Conclusions:** This preliminary studies demonstrate that [$^{11}$C] (**1**), (**2**), (**3**), and (**4**) show fast kinetics and in vivo specificity, selectivity for CNS NET and could be useful for assessing alterations in brain NET. Research supported by NIMH and Wyeth Ayerst.

**MEDI 225**

**Tools for monitoring therapeutic interventions in neurodegenerative diseases**

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Hemispheric cortical surface mapping of 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([F-18]FDDNP) binding is a powerful tool for assessment and visualization of the rate of brain pathology deposition. With several hundred patients performed to date, including severe and moderate AD subjects, patients with mild cognitive impairment (MCI), presenilin-1 and presenilin-2 patients as well as patients with other forms of dementias (e.g., fronto-temporal dementias, Down syndrome, prion diseases and viral dementias) significantly greater accumulation of [F-18]FDDNP is observed in brain areas expected to have amyloid, NFTs or prion aggregates. In AD the distribution of [F-18]FDDNP accumulation correlates well with behavioral measures (e.g., MMSE scores) and follows known patterns of pathological distribution seen in autopsy in the same patients and in brain specimens by Braak and Braak. The imaging approach permits monitoring of disease progression and also monitoring of therapeutic interventions in the same patient or in groups of patients. Prion deposition in Gerstmann-Sträussler-Scheinker (GSS) disease can be equally monitored. A strong correlation of [F-18]FDDNP binding, cell losses in hippocampus and decreased glucose utilization ([F-18]FDG PET) in several neocortical regions was found in the same AD and MCI subjects. Therefore a battery of molecular imaging probes for the assessment of specific biochemical and cellular events in the living human brain are currently available.

**MEDI 226**

**Strategies for developing and labeling radiopharmaceuticals for imaging estrogen receptor presence and function in breast cancer**

***John A. Katzenellenbogen****, School of Chemical Sciences, University of Illinois, 600 S. Mathews Ave., Urbana, IL 61801, Fax: 217 333 7325*

Elevated levels of steroid receptors are found in certain tumors, and these receptors serve as key targets for endocrine therapies involving hormone antagonists and endogenous hormone depletion treatments that can often be very effective, with minimal side effects. We have designed high affinity steroid receptor ligands, labeled with the positron-emitting radionuclide fluorine-18, for positron emission tomographic imaging of estrogen and progesterone receptors in breast tumors and androgen receptors in prostate cancers. This non-invasive determination of receptor levels in the tumors provides valuable information in selecting both breast and prostate cancer patients most likely to benefit from endocrine therapy. In addition, a hormone challenge test which images hormone-induced changes in tumor metabolism is proving highly predictive of response to endocrine therapies in breast cancer. We have also investigated ways in which steroid receptor ligands might be labeled with the more widely available radionuclide, technetium-99m.

**MEDI 227**

**PET Radioligand discovery and development for mGluR5 receptors**

***Victor W. Pike****, Fabrice G. Siméon, Sami S Zoghbi, H. Umesha Shetty, Amira K. Brown, and Robert B. Innis, Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Rm B3 C346A, 10 Center Drive, Bethesda, MD 20892, Fax: 301 480 5112*

Brain mGluR5 receptors have become of interest as a therapeutic target for several neuropsychiatric disorders, including cocaine addiction and Fragile X. An ability to image and quantify mGluR5 receptors in living human brain with positron emission tomgraphy (PET) and a suitable radioligand

would permit unique investigations of the role of mGluR5 receptors in these disorders. Furthermore, such a radioligand could be useful for establishing the therapeutic doses of mGluR5-targetted developmental drugs to be used in clinical trials, through receptor occupancy studies. Here we describe the discovery and development of a successful PET radioligand for imaging mGluR5 receptors in human brain.

**MEDI 228**

**Progesterone receptor biology**

***Francesco J DeMayo**, Jaewook Jeong, Heather L Franco, Jinrong Wang, Sophia Y. Tsai, Ming-Jer Tsai, and John P. Lydon, Molecular and Cellular Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, Fax: 7137901275*

Progesterone Receptor (PR) action regulates signaling pathways in the uterus which are critical to ensure normal uterine function. Utilizing genetically engineered mice in combination with high-density DNA microarray analysis, we have identified and evaluated Hedgehog, Bone morphogenic protein (BMP), and Wnt signaling pathways as being regulated by PR. Conditional ablation of Indian Hedgehog (Ihh) in the uterus demonstrated that this morphogen coordinates the proliferation and vascularization of the endometrium through the actions of the orphan nuclear receptor Chicken Ovalbumin Upstream Promoter Transcription Factor II (COUP-TFII) in the stroma cells. In the pre implantation uterus, the P4- Ihh-COUP-TFII axis functions to regulate the ‘window of receptivity' in the uterus. This pathway is also important for the regulation of Estrogen Receptor sensitivity in the uterine epithelium and Epidermal Growth Factor Receptor expression in the stroma. In the post-implantation uterus, this axis regulates the expression of the growth factor BMP2. Conditional ablation of BMP2 in the uterus functions to regulate post-implantation differentiation of the uterine stroma to allow for decidualization. BMP2 accomplishes these goals by regulating PR signaling as well as the expression of members of the Wnt signaling family. These pathways identified in the mouse are conserved and functional in the human endometrium and may shed light on the mechanisms leading to endometrial dysfunction. Disruption of progesterone signaling in the uterus is associated with endometrial diseases such as infertility, endometriosis, and endometrial cancer.

**MEDI 229**

**Structural characterization of the progesterone receptor**

***Jeffrey D. Bray**, jeffrey.d.bray@gsk.com, Urogenital Biology/Cardiovascular and Urogenital Center for Excellence in Drug Discovery, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Rd, King of Prussia, PA 19406, Fax: 610-270-5681, and Kevin Madauss, GlaxoSmithKline, Research Triangle Park, NC 27709*

The Progesterone Receptor (PR) is a member of the nuclear receptor family of ligand-activated transcription factors. The effects of PR ligands are mediated through a complex regulation of gene expression networks resulting in physiological changes. PR-dependent transcriptional specificity depends on the ligand type, the PR isoform, and the potential cofactors available in a cell. The PR isoforms, designated PR-A, -B, and -C, have demonstrably unique cell and promoter based functions, partially explained by their primary protein structure. The PR isoforms are generated from unique transcriptional starts in the same PGR gene. All isoforms contain a DNA binding domain and a C-terminus ligand binding domain that contains a ligand-dependent activation function domain

(designated AF-2). Our crystallographic and structural analyses of PR complexed with ligands have provided insights into the mechanism of action based on these ligand-induced conformational changes. Currently, ways to pharmacologically exploit these new understandings are being pursued.

**MEDI 230**

**Steroidal specific progesterone receptor modulators (SPRM), strategy of compound finding and basic clinical results**

***Walter Elger**, Berlin, Germany*

Asoprisnil (J 867; benzaldehyde, 4-[(11b, 17b)-17-methoxy-17-(methoxymethyl)-3 oxoestra-4, 9-dien-11-yl]-, 1-oxime) is the prototype of a novel class 11b-benzaldoxime-substituted selective progesterone receptor modulators (SPRMs) and the first-in-class SPRM to reach an advanced stage of clinical development for the treatment of uterine fibroids and endometriosis. This compound was screened in a drug discovery program aimed to identify progesterone receptor (PR) ligands with predominant agonist but also some antagonist activities. The screening program included a range of receptor binding studies and a hierarchy of in vivo tests. A series of 11b-benzaldoxime-substituted steroidal compounds exhibiting mixed PR agonist/antagonist effects were synthesized and characterized. The 11b-benzaldoxime-substituted SPRMs showed high progesterone (PR) binding affinities, reduced glucocorticoid receptor (GR) affinities compared with the antiprogestin mifepristone, marginal androgen receptor (AR) binding affinities and no binding to estrogen receptors (ER). Animal tests in guinea pigs (luteolysis inhibition assay) and rabbits (McPhail test) constituted the secondary screening tests. A mosaic of progesterone agonist and antagonist effects were found in various models. The most agonistic compounds were selected for further evaluation in animal models with respect to labor induction and endometrial effects. Unlike progesterone antagonists, asoprisnil and related compounds showed marginal effects on labor and parturition in guinea pigs. Proof-of-concept studies in non-human primates revealed endometrial antiproliferative effects of selected compounds, including asoprisnil and J1042, in the presence of amenorrhea and follicular phase estradiol concentrations. Asoprisnil was selected for further clinical development. It shows promising results in the treatment of uterine leiomyomata and endometriosis. The preclinical strategies will be discussed on the basis of the clinical findings.

**MEDI 231**

**Indole sulfonamides as potent nonsteroidal progesterone receptor modulators.**

***Kuo-Long Yu**, Thomas J. Bleisch, Christian A. Clarke, Jeffery A. Dodge, Rachelle J. Galvin, Andrew G. Geiser, Scott A. Jones, Jose E. Lopez, Charles W. Lugar, Chahrzad Montrose-Rafizadeh, Brian S. Muehl, Nita J. Patel, Timothy I. Richardson, and Ying K. Yee, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-0715*

There is accumulating evidence indicating that the sex hormones progesterone and estrogen are essential for the growth of uterine fibroids in women. Several steroidal progesterone receptor antagonists and modulators (PRMs) have been shown to reduce the size of fibroids and relieve symptoms in this patient population. Often steroidal PRMs are not receptor selective which results in adverse effects. It has been hypothesized that a non-steroidal PRM with better receptor selectivity could have a better safety profile. We have discovered a novel series of indole sulfonamides as potent PRMs with excellent receptor selectivity against glucocorticoid, mineralocorticoid , and

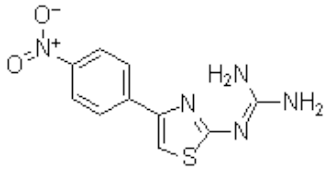
androgen receptors. The design, synthesis and biological profile of these indole sulfonamides will be presented.

**MEDI 232**

**Discovery, synthesis and SAR evaluation of new 3-(thiazol-2-yl)oxazolidin-2-one progesterone receptor modulators leading to the discovery of WAY-257027 (PRA-027).**

***Andrew Fensome***[1]*, fensoma@wyeth.com, Ronald C. Bernotas*[1]*, bernotr@wyeth.com, Thomas J. Commons*[1]*, commonT@wyeth.com, Gavin D. Heffernan*[1]*, hefferg@wyeth.com, Ronald L. Magolda*[1]*, magoldr@wyeth.com, Michael Marella*[1]*, marellm@wyeth.com, Casey C. McComas*[1]*, mccomac@wyeth.com, Andrea Olland*[1]*, Eugene J. Trybulski*[1]*, trybule@wyeth.com, Ray J Unwalla*[1]*, unwallr@wyeth.com, Michael B. Webb*[1]*, James Wilhelm*[1]*, Scott Wolfrom*[1]*, Richard P. Woodworth*[1]*, WOODWOR@wyeth.com, Richard C. Winneker*[2]*, Matthew Yudt*[2]*, Zhiming Zhang*[2]*, William Adams*[3]*, Andrea Adams*[3]*, Christine Huselton*[3]*, Cheryl Mugford*[3]*, Ov Slayden*[4]*, and Jay E. Wrobel*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484-865-9398, (2) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426, (3) Biotransfomation Division, Drug Safety and Metabolism, Wyeth Research, Collegeville, PA 19426, (4) Division of Reproductive Sciences, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR*

The Progesterone Receptor (PR) has been the target of drug discovery and development for the past few decades. Whilst PR agonists have been widely used in women's health care, PR antagonists have received relatively little utility in the clinic. Recently, steroidal agents, such as mifepristone (RU-486) and asoprisnil have shown efficacy in reducing the symptoms of uterine fibroids in clinical trials.

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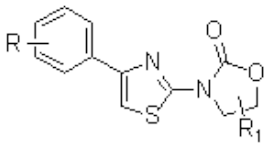


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As part of our PR modulator program, we conducted a virtual screen of the Available Chemicals Directory, using a PR ligand-binding domain model. One of the more interesting leads was the 2-(thiazol-2-yl)guanidine **1**, a potent PR antagonist in the T47D cell alkaline phosphatase assay ($IC_{50}$ = 5 nM), which was selected for optimization. This presentation will highlight the discovery and development of the 3-(thiazol-2-yl)oxazolidin-2-one PR modulator scaffold **2**, from the initial screening lead. We will also be disclosing the structure and characterization of WAY-257027, which has advanced into Phase 1 clinical trials for the treatment of uterine fibroids.

**MEDI 233**

**An overview of purinergic signalling.**

***Geoffrey Burnstock****, Autonomic Neuroscience Centre, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, England, Fax: 020 7830 2949*

A seminal article by Drury and Szent-Györgi in 1929 described potent extracellular actions of purines on the heart and blood vessels. Then, in 1970, evidence was presented for ATP as a neurotransmitter in nonadrenergic, noncholinergic nerves supplying the gut and in 1972 the word “purinergic” was coined and the purinergic neurotransmission hypothesis was proposed (Burnstock, 1972). This concept met with considerable resistance for many years, because ATP had been established as an intracellular energy source involved in various metabolic cycles, and it was thought that such a ubiquitous molecule was unlikely to be involved in extracellular signalling. However, purinergic signalling is now widely accepted (see Burnstock, 2007). Later, it was established that ATP was a cotransmitter with classic transmitters in both the peripheral and central nervous systems and that purines were also powerful extracellular messengers to non-neuronal cells, including exocrine and endocrine, secretory, endothelial, musculoskeletal, immune, and inflammatory cells. Separate membrane receptors for adenosine and ATP were recognised in 1978 and later P2 receptors were divided into P2X and P2Y receptors on the basis of pharmacology, transduction mechanisms and molecular cloning (see Ralevic and Burnstock, 1998). Currently 4 subtypes of P1 receptor, 7 subtypes of ionotropic P2X receptors, many of which can form heteromultimers as well as homomultimers, and 8 subtypes of metabotropic P2Y receptors, some responsive to pyrimidines as well as purines. It is recognised that there is both short-term purinergic signalling in neurotransmission, mechanosensory transduction, secretion and vasodilatation and long-term (trophic) purinergic signalling in cell proliferation, differentiation, motility and death involved in development and regeneration. Plasticity of purinoceptor expression occurs in development, ageing and in a wide range of pathological conditions and there is an emerging therapeutic potential for purinergic compounds (Burnstock, 2006).

**MEDI 234**

**Development of P2Y2 agonists for ophthalmic and respiratory diseases**

***Ben Yerxa**, Research and Development, Inspire Pharmaceuticals Inc, 4222 Emperor Boulevard, Suite 200, Durham, NC 27703-8030, Fax: 919-941-9177*

The P2Y2 receptor, which is expressed on the apical side of most wet surface epithelia, is activated by exogenous nucleoside triphosphates such as ATP and UTP. Activation leads to stimulation of salt, water and mucin release in a coordinated fashion and is believed to be an important mucosal defense mechanism. In the lung, P2Y2 agonists also stimulate cilia beat frequency, thereby increasing overall mucocilary clearance. On the ocular surface, rehydration of the mucosa leads to reduced epithelial surface damage due to dryness. A new class of stable P2Y2 agonists, dinucleoside polyphosphates, was developed as novel treatments for cystic fibrosis lung disease and ocular surface disease associated with dry eye. Exploration of the SAR of symmetrical and unsymmetrical dinucleotides lead to the discovery and development of two clinical candidates, diquafosol and denufosol, both of which are in Phase 3 clinical development.

**MEDI 235**

**Development of a direct-acting reversible P2Y12 antagonist**

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*Abstract text not available.*

**MEDI 236**

**Dual P2X3/P2X2/3 purinergic receptor antagonists: Novel treatments for inflammatory and neuropathic pain**

***Michael P. Dillon**, Department of Medicinal Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304, Fax: (650) 354-2442*

Purinergic receptors are a family of ligand gated ion channels whose endogenous ligand is ATP. Homomeric P2X3 and heteromeric P2X2/3 receptors are selectively localized at the peripheral and central terminals of non-myelinated afferent nerve fibers and, along with ATP, have been implicated in the transmission of sensory signals. Blockade of these signals with antagonists offers the potential to treat a broad range of pain conditions. HTS of the Roche compound collection identified a hit series of P2X3 antagonists similar in structure to the antibacterial trimethoprim.

This presentation will describe the SAR and optimization of this series resulting in the discovery of RO-4 a highly potent and selective dual P2X3/P2X2/3 antagonist. In vivo efficacy in a number of preclinical models demonstrating the therapeutic potential of this mechanism in a number of pain conditions will also be presented.

**MEDI 237**

**P2X7 Antagonists in a rheumatoid arthritis animal model**

***Mark Furber**, Department of Medicinal Chemistry, AstraZeneca, Bakewell Road, Loughborough Leics. LE11, United Kingdom, Fax: Fax: (+44) 01509 645512*

Purinergic receptors are believed to play a pivotal role in the modulation of inflammatory and immune responses. The P2X7 receptor is a ligand gated ion channel present on a variety of inflammatory and immunomodulatory cells and is involved in the processing and release of IL1b and IL18, cytokines implicated in the pathogenesis of rheumatoid arthritis. This presentation will inform the audience on the identification of a series of potent selective small molecule P2X7 antagonists and the strategies used for their optimisation. Data will be presented from a study of the effect of AZ11657312 on disease progression and histological outcome in an SCW model of arthritis.

**MEDI 238**

**Molecular recognition in P2Y nucleotide receptors**

***Kenneth A. Jacobson**, Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0810, Fax: 301-480-8422*

Eight subtypes of P2Y receptors that respond to extracellular nucleotides (ADP, ATP, UDP, UTP, and UDP-sugars) are providing new opportunities for drug development through the modulation of immune, neuronal, and cardiovascular function. Agonists selective for $P2Y_1$, $P2Y_2$, $P2Y_6$ and $P2Y_{14}$ receptors and various nucleotide antagonists have been identified and used as pharmacological

probes. Analogues in which the ribose moiety is substituted by conformationally-locked ring systems, such as the bicyclo[3.1.0]hexane “methanocarba” modification, display enhanced potency and selectivity. Selective non-nucleotide antagonists are reported for $P2Y_1$, $P2Y_2$, $P2Y_6$ , $P2Y_{11}$ , $P2Y_{12}$ and $P2Y_{13}$ receptors. Competitive $P2Y_1$ receptor antagonists are promising leads for antithrombotic therapy. In silico quantitative predictions are explored to facilitate lead optimization. Molecular modeling of the $P2Y_6$ receptor correctly predicted conformational features of docked nucleotides, which were validated experimentally. Introduction of a methanocarba ring constrained in the South conformation enhances potency of nucleotide analogues exclusively at the $P2Y_6$ receptor.

**MEDI 239**

**Histamine H3 receptor as a therapeutic drug target for multiple CNS disorders**

***John Renger**, Depression & Circadian Disorde, Merck, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-1658*

Impaired cognitive performance particularly reduced attention and working memory, is a symptom of a wide variety of neurological disorders including Alzheimer's disease, attention-deficit hyperactivity-disorder (ADHD), and Parkinson's disease. Enhancement of various "wake-active" neurotransmitter systems, such as acetylcholine, norepinephrine, and dopamine are known to be at least moderately beneficial therapeutic approaches for normalizing these cognitive deficits in patients, as has been shown by the clinical utility of cholinesterase inhibitors and dopamine/ norepinephrine transport inhibitors such as donepezil and methylphenidate to treat these diseases. The release of the neurotransmitter histamine has long been known to be correlated with increased central nervous system arousal. Exogenous addition of histamine to the sleeping brain of mammals has been further shown to cause increased wakefulness. The identification and characterization of the histamine H3 receptor as a presynaptic negative regulator of neurotransmitter release revealed a potential therapeutic mechanism for the enhancement of release of wake-associated neurotransmitter histamine as well as acetylcholine, norepinephrine and others. Since the cloning of the H3 receptor there have been efforts to create pharmacological tools, both agonists and antagonists, which have been successfully identified and characterized against the receptor. Some of these compounds are demonstrating compelling preclinical effects in a wide variety of animal behavioral models including obesity, sleep-wake modification, cognition, and schizophrenia. This presentation will review the histamine H3 receptor and its pharmacology as well as its role in normal brain function and the recent progress which is being made in targeting this receptor for multiple therapeutic uses.

**MEDI 240**

**Discovery of new histamine H3 receptor antagonists: From a complex natural product to small molecule leads**

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We are interested in developing H3 antagonists as potential wake promoting agents and recently described a new series of H3 antagonists derived from the natural product Conessine, a known H3 antagonist. While compounds from this series showed excellent potency and selectivity for the H3 receptor, their pharmacokinetic (PK) profiles and structural complexity prompted us to study other chemical scaffolds.

We have examined a number of structurally simplified compounds as potential antagonists of the H3 receptor. Several compounds from these new series retained the potency and selectivity of our earlier compounds while exhibiting improved PK characteristics as well as potent in vivo efficacy. A detailed summary of the development of these compounds will be presented.

**MEDI 241**

**Design principles for building better histamine H3 receptor antagonists**

***Marlon D. Cowart**, Neuroscience Research, R4MN, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064*

Histamine H3 receptors in CNS play an important role in negatively modulating the release of key neurotransmitters, including histamine and acetylcholine. H3 antagonists induce release of these transmitters, and are especially potent and effective in overcoming deficits in preclinical models assessing components memory, cognition, and attention. Much interest in the field has targeted improving the drug-likeness of candidates while maintaining the in vitro and in vivo potency and efficacy required of any candidate to potentially advance to clinical investigation. Principles will be detailed that in multiple series greatly increased selectivity for H3 versus hERG channels, rationalized receptor occupancy versus behavioral efficacy in key in vivo models, and improved PK profiles, highlighting specific example compounds.

**MEDI 242**

**Discovery and characterization of novel histamine H3 antagonists**

***Michael A. Letavic**, Neuroscience, Johnson & Johnson Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121*

The histamine H3 receptor is a pre-synaptic auto- and hetero-receptor that has high receptor density in the central nervous system. As such, the histamine H3 receptor controls the release of histamine and a variety of other neurotransmitters in the brain. Activation of the histamine H3 receptor leads to a decrease in the levels of histamine, promoting sleep, and antagonism of the H3 receptor increases the levels of histamine and is expected to promote wakefulness. Histamine H3 antagonists are also expected to improve cognition via an increase in the level of several other neurotransmitters, including acetylcholine and norepinephrine. Our efforts towards the identification and pharmacological characterization of novel histamine H3 antagonists have led to several new chemotypes that are high affinity histamine H3 antagonists. Several of these compounds readily penetrate the CNS and efficiently occupy the histamine H3 receptor, providing tools for characterization of the pharmacology of the H3 receptor in pre-clinical models. The medicinal chemistry, in-vitro biology and pre-clinical in-vivo evaluation of a variety of novel histamine H3 chemotypes will be discussed in detail.

**MEDI 243**

**Identification and optimization of a novel series of histamine H3 receptor antagonists**

***David M. Wilson**, Department of Medicinal Chemistry, Neuroscience Centre of Excellence for Drug Discovery; GlaxoSmithKline, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW, United Kingdom*

The biological effects of histamine are mediated through a family of four 7-transmembrane G-protein coupled receptors (H1, H2, H3, H4). Antagonists of the histamine H1 and H2 receptors, which are extensively used in the treatment of allergic rhinitis and gastric acid disorders respectively, have achieved unquestionable success as small molecule drug therapies. In contrast, the clinical importance of the histamine H3 receptor remains unknown which is in part due to the poor developability characteristics of the early antagonists. However, following the cloning of the receptor in 1999 and the discovery of more developable, non-imidazole based antagonists, there has been considerable renewed interest in the target. Antagonists of the histamine H3 receptor have been proposed as potential therapies for a number of disorders including Alzheimer's disease, schizophrenia, attention deficit hyperactivity disorder, obesity, narcolepsy and allergic rhinitis.

Our initial lead was 3-(cyclopropylmethyl)-7-[(phenylmethyl)oxy]-2,3,4,5-tetrahydro-1H-3-benzazepine which was identified as a novel H3 chemotype with encouraging antagonist activity at the human recombinant receptor. The optimisation of this benzazepine template to a highly potent, orally bioavailable and CNS penetrant series of antagonists suitable for further pre-clinical evaluation will be presented.

**MEDI 244**

**Design, synthesis, and evaluation of novel quinazolinone class of histamine H3 receptor inverse agonists**

***Nagaaki Sato**, Tsuyoshi Nagase, Takashi Mizutani, Shiho Ishikawa, Etsuko Sekino, Takahide Sasaki, Takashi Fujimura, Sayaka Ito, Yuko Mitobe, Yasuhisa Miyamoto, Ryo Yoshimoto, Takeshi Tanaka, Akane Ishihara, Norihiro Takenaga, Shigeru Tokita, and Takehiro Fukami, Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical CO.,LTD, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan*

The histamine H3 receptor, mainly located in the CNS, is a presynaptic autoreceptor that inhibits the release and synthesis of histamine. This receptor has been implicated in the regulation of a variety of CNS functions such as wakefulness, memory process, and feeding; therefore, histamine H3 inverse agonists have been suggested to have potential as drug therapies for the treatment of various CNS disorders. Inspired by promising background information, we initiated screening of in-house chemical collections against the human H3 receptor (hH3) and identified novel quinazolinone derivative 2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-5-(trifluoromethyl)-4(3H)-quinazolinone. The subsequent structural modifications resulted in a series of potent and selective H3 inverse agonists. The synthesis, SAR, and biological profiles of the quinazolinone class of H3 inverse agonists will be presented.

**MEDI 245**

**An overview of ligand gated ion channels**

***Stephen F Traynelis**, Pharmacology, Emory University School of Medicine, Rollins Research Center, 1510 Clifton Road, Atlanta, GA 30322-3090, Fax: 404 727 0357*

The brain utilizes transmembrane proteins that respond to extracellular neuroactive substances. Different ligands bind to various channels to trigger opening of an ion permeable pore across the membrane. Depending on the physical and electrical properties of this pore, cations or anions can flow down their electrochemical gradient to alter membrane potential in cells of the central nervous system. Ligand-gated channels therefore couple the energy of ligand binding to channel opening within a single macromolecular complex. There are numerous sites on channels at which drugs could act. In addition, there are numerous functional properties of channels that drugs could target. For example, drugs could bind to the ligand recognition pocket, the ion channel pore, or distinct sites that modulate channel function, ion permeation, or agonist affinity. Functionally, ligand-gated channels typically activate during exposure to agonist by opening a conduction path across the membrane for varying duration. Following closure of the pore, activating ligands can unbind, and the duration of both of these events could be targets for modulation by drugs. In summary, each of these functional properties could be considered a therapeutic target for ion channel modulation.

**MEDI 246**

**Discovery of TRPV1 antagonist ABT-102 for treatment of pain**

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TRPV1 (transient receptor potential vanilloid subtype 1) is a non-selective cation channel that is considered to be one of the key therapeutic targets for pain. Both TRPV1 agonists and antagonists were shown to alleviate pain, however the antagonist approach has been the major focus of the drug discovery effort. Systematic optimization of the lead aryl-benzyl urea class of TRPV1 antagonists by improving pharmacological and pharmaceutical properties led to ABT-102, which in low nanomolar concentrations blocked the activation of TRPV1 receptor by a number of stimuli such as capsaicin, heat (>$42^0$C) and extracellular pH<6. This presentation will discuss the process of identification of ABT-102, its pharmacokinetic properties and in vivo pharmacology in preclinical pain models.

**MEDI 247**

**NR2B subtype selective NMDA receptor antagonists**

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*J. Liverton[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3, West Point, PA 19486, (2) Molecular Pharmacology, Merck Research Laboratories, West Point, PA 19486, (3) Stroke and Neurodegeneration, Merck Research Laboratories, West Point, PA 19486, (4) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

The N-methyl-D-aspartate (NMDA) receptor is a ligand-gated ion channel that is present throughout the mammalian CNS and is activated by the excitatory amino acid, glutamate. This receptor plays a fundamental role in a number of physiological processes and may be an avenue for the treatment of such disease states as stroke, Parkinson's disease and neuropathic pain. Agents that block the NMDA channel have been shown to alleviate pain in human clinical trials, however the low therapeutic index over side effects such as loss of motor coordination make such compounds unattractive for chronic therapy.

The NMDA receptor is made up of a combination of NR1 subunits (a-h) and at least one of four NR2 subunits (A-D) which are heterogeneously distributed throughout the brain. The reduced level of NR2B subunits in the cerebellum suggests that NR2B-selective agents may show an enhanced therapeutic window vs. locomotor side effects. This hypothesis has been borne out in several animal studies with a number of NR2B-selective compounds. Our interest has been in identifying selective antagonists of the NR2B-containing NMDA receptor with good oral bioavailability, CNS penetration and selectivity versus other ion channels. The biological profiles of unique structural classes of selective NR2B antagonists will be presented.

**MEDI 248**

**Positive allosteric modulators of the alpha 7 nicotinic acetylcholine receptor.**

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The alpha 7 nicotinic acetylcholine receptor (nAChR) is a calcium permeable, ligand-gated ion channel that modulates synaptic transmission in the hippocampus, thalamus, and cerebral cortex, which are three of the key regions of the central nervous system (CNS) involved in learning and memory. Several lines of evidence suggest a link between the alpha 7 nAChR and brain disorders including schizophrenia, Alzheimer's disease, and traumatic brain injury. Previously disclosed work described a novel molecule, PNU-120596, that acts as a powerful positive allosteric modulator (PAM) of the alpha 7 nAChR. PNU-120596, discovered as part of a high throughput screening effort, increased agonist-evoked calcium flux mediated by an engineered variant of the human alpha 7 nAChR. The SAR around the PNU-120596 template was refined by independent examination of the aryl portion, heteroaryl portion, and the linker group resulting in compounds with enhanced potency and an improved pharmacokinetic profile. This presentation will summarize the synthesis, biological activity, and emerging SAR from this class of PAMs.

**MEDI 249**

**Spirofuropyridines as alpha-7 neuronal nicotinic receptor agonists**

***Glen E. Ernst****, William E. Frietze, Donald W. Andisik, Timothy M. Piser, Jeffrey S. Smith, Kathy L. Neilson, Rebecca A. Urbanek, Thomas R. Simpson, James M. Woods, Hui Xiong, Lindsay Hinkley, Amy Chang, Christopher R. Holmquist, Eifion Phillips, James M. Hulsizer, G. Scott Lehr, Chad S. Elmore, J. Richard Heys, Peter N. Dorff, David Gurley, Simon G. Sydserff, John Gordon, and Michael Balestra, CNS Discovery, AstraZeneca Pharmaceuticals, Wilmington, DE 19850*

The alpha-7 neuronal nicotinic receptor is a calcium-permeable, ligand-gated ion channel which regulates synaptic transmission in several brain regions associated with memory and learning. In vivo administration of alpha-7 antagonists are known to produce significant working memory deficits across several species, while agonists have displayed cognition-enhancing effects. Alpha-7 agonists are considered to be candidates for the treatment of cognitive deficits in schizophrenia (CDS). Our medicinal chemistry efforts have identified a series of spirofuropyridines as alpha-7 agonists. The spirofuropyridines have demonstrated potent and selective in vitro binding at the alpha-7 receptor, and have shown efficacy in animal models of cognition. We will describe the design, SAR and synthesis of spirofuropyridine alpha-7 agonists.

**MEDI 250**

**Oxidation at C(41) is not necessary for potent antifungal activity in amphotericin B**

***Daniel S. Palacios****, Thomas M Anderson, and Martin D Burke, Department of Chemistry, University of Illinois, Champaign-Urbana, 600 S Mathews, Urbana, IL 61801*

Amphotericin B (AmB) is clinically indispensable for the treatment of systemic mycoses. It is hypothesized that AmB exerts its antifungal activity by self-assembling within fungal cell membranes to create an ion channel complex which disrupts the transmembrane ion gradient. A salt bridge between an amine and a carboxylic acid is proposed to be the main interaction stabilizing this channel. A flexible degradative synthesis was developed to allow access to derivatives lacking either one or both of these chemical groups. It was then demonstrated that removal of these groups does not alter the solution-phase structure of the AmB skeleton. These derivatives were assayed against S. cerevisiae and C. albicans and it was found that contrary to the current model for AmB's mechanism of action the derivative lacking the carboxylic acid was equipotent to AmB. Thus, the nature of the AmB channel and its role in antifungal activity must be reevalulated.

**MEDI 251**

**Hydrophobicity-oriented enzymology for polyketide biosynthesis**

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Modular polyketide synthases (PKSs) are giant biosynthetic machines in which the multifunctional enzymes catalyze programmed metabolic pathways by assembly-line arrays. Typically, the building

blocks of polyketides are alpha-carboxylated acyl-CoAs such as malonyl-CoA and methylmalonyl-CoA. Different decarboxylative mechanisms are involved in chain initiation and elongation steps to release redundant carboxyl groups and increase the hydrophobicity of final products. Here we present the enzymatic study of the PKS for curacin A, a highly hydrophobic anticancer lead compound isolated from the marine cyanobacterium, Lyngbya majuscula. In this pathway, three novel decarboxylation-associated enzymatic mechanisms have been disclosed. First, the chain initiation is catalyzed by a GNAT-like domain with unprecedented decarboxylase/S-acetyltransferase activity. Second, an on-assembly-line modification can introduce a pendent carbon into C-2 position and remove the carbonyl oxygen to increase the hydrophobicity. This so-called “beta-branching” modification is mediated by a HMG-CoA synthase-like gene cassette. Third, a decarboxylative chain termination is catalyzed by the sulfotransferase and thioesterase, which can generate a terminal olefin group in the final product. All these enzymes can be engineered as biosynthetic tools to optimize the physico-chemical properties of medicinal polyketide-related compounds.

**MEDI 252**

**Discovery of an intranasal CGRP antagonist for migraine**

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Calcitonin Gene Related Peptide (CGRP), a naturally occurring 37 amino-acid peptide, has been implicated in the pathogenesis of migraine. Clinical trials have demonstrated that intravenous administration of a CGRP receptor antagonist is accompanied by the alleviation of pain in migraineurs. Intranasal delivery would seem ideally suited for the treatment of migraine as it can be expected to deliver a faster onset of action over traditional oral formulations without the need for the patient to self-inject and offers the opportunity to treat even those patients with vomiting. Our medicinal chemistry effort has focused on the identification of a potent CGRP antagonist which is suitable for intranasal delivery. Early chemistry leads suffered from modest potency, significant CYP3A4 inhibition, and poor aqueous solubility. We will detail the optimization of these leads to give a molecule with outstanding potency, a clean predictive toxicology profile, and remarkable aqueous solubility. The compound also has good intranasal bioavailability and shows dose-dependent activity in validated in vivo and ex vivo migraine models.

**MEDI 253**

## Discovery of (R)-3-amino-1-(3-pyridinyl)-pyrrolidine, a neuronal nicotinic receptor agonist for the treatment of chronic pain

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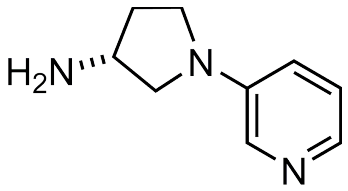
The antinociceptive properties of nicotine were first demonstrated more than seventy-five years ago, however the poor pharmacokinetic properties and adverse side effects of nicotine have limited its therapeutic potential. Recent evidence suggests that the analgesic activity of nicotine and other nicotinic ligands is derived primarily from agonist activity at the α4β2 neuronal nicotinic receptor (NNR) subtype, whereas gastrointestinal and cardiovascular side effects are related to activation of ganglionic α3-containing NNRs. Efforts to discover compounds with improved safety and tolerability profiles for the treatment of pain have therefore focused on enhancing selectivity for the α4β2 subtype. We have identified a novel series of 3-aminopyrrolidine derivatives that possess potent in vitro NNR activity and are effective in a variety of preclinical chronic pain models. The synthesis and SAR of this series of compounds, culminating in the discovery of (R)-3-amino-1-(3-pyridinyl)-pyrrolidine, will be presented.




**MEDI 254**

## Spirocyclic piperidine amides as potent, nonpeptide inhibitors of human mast cell tryptase

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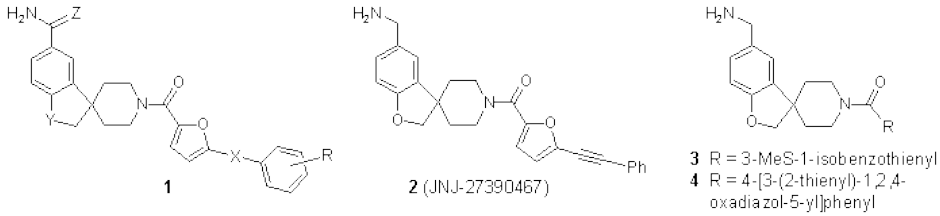
The serine protease tryptase is released from mast cells at sites of inflammation. Thus, tryptase inhibitors have potential for treating inflammatory disorders, such as asthma, allergic rhinitis, and inflammatory bowel disease. We explored a series of spirocyclic piperidine amide derivatives (**1**) as tryptase inhibitors and identified **2** (JNJ-27390467) as a potent, selective inhibitor of human β-tryptase (Ki = 3.7 nM). This compound has ~700-fold selectivity vs. inhibition of trypsin, and greater selectivity vs. inhibition of 12 other serine proteases. In pharmacokinetics studies in dogs and rats, **2** showed

excellent oral bioavailability of 66% and 100%, respectively, and **2** was orally efficacious in sheep and guinea pig models of asthma. The X-ray co-crystal structure of **2**•tryptase revealed an interesting induced-fit binding mode, involving the phenylethynyl group and a hydrophobic pocket formed by amino acid side chains from two adjacent monomers of the tetrameric protein. An extensive SAR investigation of the N-acyl portion of **2** led to potent tryptase inhibitors **3** and **4** (IC50 < 10 nM), with excellent selectivity vs. trypsin. An X-ray co-crystal structure of **3**•tryptase was determined.




**MEDI 255**

**First time disclosure of a novel series of CCR1 antagonists: From library hit to optimized lead**

***J. Robert Merritt**, Medicinal Chemistry, Pharmacopeia Inc, 3000 Eastpark Blvd., Cranbury, NJ 08512*

Monocyte infiltration is implicated in a variety of diseases including multiple myeloma, rheumatoid arthritis and multiple sclerosis. CCR1 is a chemokine receptor that upon activation, particularly by MIP1-alpha and RANTES, mediates monocyte trafficking to sites of inflammation. High through-put screening of our combinatorial collection identified potent CCR1 antagonists. This presentation details the optimization of this compound series to a potent, orally bioavailable lead.

**MEDI 256**

**Activation and inhibition of latent serine proteases, complement factors B and C2**

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The innate immune response involves a tightly regulated complement activation cascade to effect recognition/destruction/removal of foreign organisms and modified cells. Protracted/dysfunctional activation causes inflammatory diseases. Classical, lectin and alternative pathways of complement activation intersect at cleavage of C3 by two C3 convertases. Their catalytic cores, B and C2, are inactive zymogens that require activation by classical (C1s), lectin (MASP2) or alternative (D) serine proteases. We find that B and C2 are each catalytically active serine proteases at pH>9, processing C3 or 2-10 residue chromogenic C3-derived peptides. Activity is attributed to a pH-accessible conformation that provides clues to serine protease catalysis. We investigated influences on kinetics of catalysis by B and C2, determined substrate preferences, and identified small molecule inhibitors that also inhibit C3 convertases, block MAC formation, and inhibit cell lysis. Such compounds may be useful leads to modulators of complement activation in inflammatory diseases.

**MEDI 257**

## Discovery of hydroxyisoquinolines as novel and potent 11-β-HSD-1 inhibitors for the treatment of type 2 diabetes

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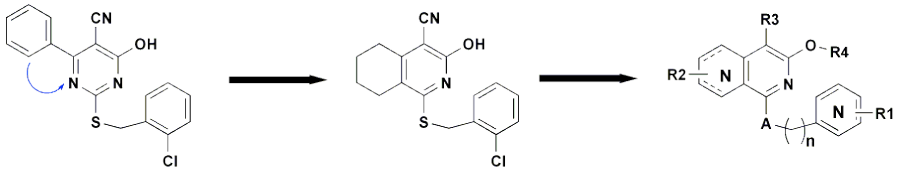
Hydroxypyrimidine 1 was identified as an inhibitor of 11-β-HSD-1 through high-throughput screening of the BMS compound collection. Structurally, 1 contains a unique (in the field of 11-β-HSD-1 inhibitors) hydroxylpyrimidine functionality which appears to act as a novel H-binding pharmacophore and has good cross species 11-β-SD-1 inhibitory activity for mouse, cynomologus monkey, and human enzyme (IC50 nM: 58, 53, 27, respectively). Constraining the phenyl moiety onto pyrimidine core and replacing one of the pyrimidine nitrogens with carbon led to tetrahydrohydroxyisoquinoline 2. Tetrahydrohydroxyisoquinoline 2 showed improved activity over 1 against 11-β-HSD-1 enzyme as well as selectivity over 11-β-HSD-2. We have examined the effects of structural variations of the hydroxyisoquinoline core and peripheral substituents on activity and development liabilities. The SAR leading to the discovery, optimization, and biological properties of this series, as well as structural studies with inhibitors bound to the enzyme, will be described.




**MEDI 258**

## NanoMedicinal chemistry: Prostate cancer chemotherapy

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NanoMedicinal Chemistry is a relatively new area of research aimed at identifying, synthesizing and developing new nanometer-sized synthetic (non-natural) chemical systems suitable for therapeutic use. Here we present the results of our analysis of the NanoMedicial chemistry approach towards prostate cancer chemotherapy, and our initial attempts to utilize this approach for the development of advanced chemotherapy agents against hormone-refractory prostate cancer. Since the direct synthesis of functional nanometer-sized molecules with favorable therapeutic profile represents significant challenge, the effort was focused on the modification of nanomolecules with macrocyclic structures to enhance the desired effect against the known biological targets. Additional consideration was given to the review of nanomolecular systems made of several interlinked molecules with pre-established activity capable of dissociative cleavage in biological objects. The Discovery Chemistry Project is sponsored by the IPP program, US Department of Energy; Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC under contract DE-AC05-00OR22725.

**MEDI 259**

**Resveratrol, its structural analogs and novel compounds for prostate cancer treatment**

***Andrey V. Sosnov**, sva@iihr.ru, Chemical Diversity Research Institute, 2a Rabochaya St., Khimki, Moscow Region 114401, Russia, and Andrei A. Gakh, gakhaa@ornl.gov, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6242*

Prostate cancer is the most frequently diagnosed cancer in men in the United States. We attempted to develop chemical agents which show specific activity against androgen-independent prostate cancer cells by comparative analysis of publicly available NSC screening data for 60 different cell lines using Modular Chemical Descriptor Language (MCDL) approach. Screening of 5200 new compounds was performed using the DU145 cell line. Several promising chemo-types were identified for the synthesis of inhibitors with increased potency and selectivity. We also investigated resveratrol and its structural analogs due to earlier reports that some of these analogs exhibit much higher anti-cancer activity than the parent compound, and could conceivably have specific activity against prostate cancer cells. Results of our preliminary analysis of resveratrol analogs in grape-based products are also presented. The Discovery Chemistry Project is sponsored by the IPP program, US Department of Energy; Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC under contract DE-AC05-00OR22725.

**MEDI 260**

**Cardiometabolic syndrome: The role of sphingolipids**

***Sotirios Karathanasis**, Bioscience, AstraZeneca, AstraZeneca R&D Molndal, SE-431 83 Molndal, Sweden*

Cardiometabolic Syndrome (CMS) is a condition of visceral adiposity, insulin resistance, increased triglyceride and decreased plasma HDL levels. It is a very prevalent condition in USA and around the world. Epidemiological evidence suggests that CMS is a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease. Although the molecular aetiology of CMS is not clearly understood, in vitro and in vivo studies suggest that lipid overload driven “lipotoxic” pathways are responsible for at least some of the pathophysiology observed in this disorder. In this presentation I will present data suggesting that lipid overload driven de novo sphingolipid biosynthesis contributes to T2DM and atherosclerosis.

**MEDI 261**

## Bile acid reabsorption inhibitors: On the way to novel hypolipidemic drugs

***Heiner Glombik**, TD Mertabolism, Medicinal Chemistry, Sanofi-Aventis, Industry Park Hoechst, Building G 878, Frankfurt/Main 65926, Germany, Fax: 49-69-305-942329*

The enterohepatic circulation of bile acids is a major regulator of serum cholesterol homeostasis. Upon biosynthesis from cholesterol in the liver, bile acids are secreted with bile into the lumen of the small intestine to aid in the digestion and absorption of fat and fat-soluble vitamins. In the terminal ileum the bile acids are nearly quantitatively reabsorbed by a Na+-dependent transport system (IBAT or ASBT), are then transported with portal blood to the liver and taken up by a second Na+-/bile acid cotransporter (LBAT) to be resecreted into bile. Via FXR activation in the liver, bile acids inhibit the rate-limiting enzyme for the conversion of cholesterol into bile acids: cholesterol–7alpha-hydroxylase. By interruption of the enterohepatic circulation of bile acids this feedback inhibition is reduced, leading to upregulation of hepatic LDL-receptors with a concomitant decrease of serum LDL-levels. Specific inhibitors of the IBAT belonging to different chemotypes have been identified in recent years for this purpose. To exert a profound systemic effect these compounds do not need to be available systemically but can act from the luminal side of the small intestine. This principally offers the advantage to avoid the well-known adverse side effects of other hypolipidemic drugs like statins which are due to metabolism and drug-drug interactions in the liver. This also implies the need to follow other than standard procedures in compound optimization and drug development, and the concept of low absorption drugs was established. The presentation is going to address some mechanistic and therapeutic principles of the approach, and an overview will be given on the molecular target, the discovery of specific inhibitors and respective optimization strategies.

**MEDI 262**

## Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes

***Philip D Lambert**, Pharmacology, Sirtris Pharmaceuticals, 200 Technology Square, Suite 300, Cambridge, MA 02139, Fax: 617-252-6924*

Calorie restriction extends healthy life span through improvements on cardiovascular and metabolic systems. These beneficial effects are likely mediated through activation of the sirtuin, SIRT1. The discovery program at Sirtris has identified multiple novel and potent NCEs from several distinct chemical scaffolds that activate SIRT1 by binding to the SIRT1 enzyme–peptide substrate complex at an allosteric site. These small molecules are currently being investigated as novel treatments for diabetes using in vitro and in vivo models with a goal to initiate additional clinical testing in the future. In diet-induced obese and genetically obese mice, these compounds improve insulin sensitivity, lower glucose concentration, and increase mitochondrial capacity. In Zucker fa/fa rats, hyperinsulinaemic-euglycaemic clamp studies demonstrate that SIRT1 activators improve whole-body glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver. A lead molecule, SRT501, is currently being evaluated for safety and PK in Phase I clinical trials.

**MEDI 263**

## Discovery of the cholesteryl ester transfer protein inhibitor anacetrapib

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The atherosclerosis related conditions of coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease are major causes of morbidity and mortality. Epidemiological evidence suggests an inverse correlation between high density lipoprotein-cholesterol (HDL-C) levels and CHD. There are a number of approaches to increasing HDL-C in humans and cholesteryl ester transfer protein (CETP) inhibition is one such approach. CETP catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL. It also mediates the reciprocal net transfer of triglycerides from the apoB lipoproteins to HDL. It is established that pharmacological inhibition of CETP in humans will result in increased HDL-C, although any beneficial effect of this inhibition on coronary heart disease has yet to be confirmed. This presentation will outline the medicinal chemistry program leading to the discovery of anacetrapib - a potent CETP inhibitor which has been shown to raise HDL-C and lower LDL-C in clinical studies.

**MEDI 264**

## Role of malonyl-CoA and CPT1c in regulating global energy homeostasis

***M. Daniel Lane****, Department of Biological Chemistry, Johns Hopkins Medical School, 725 N. Wolfe Street, WBSB 512, Baltimore, MD 21205, Fax: 410-955-0903*

Malonyl-CoA, the enzymatic product of acetyl-CoA carboxylase (ACC) and an intermediate in fatty acid synthesis, functions as a mediator of global energy balance via the CNS/hypothalamus. The activity of ACC is regulated through phosphorylation by AMP-activated protein kinase, whose activity is determined by the [AMP]/[ATP] ratio in the cell. The level of malonyl-CoA in the hypothalamus is an indicator of energy surplus and controls the expression of the orexigenic (NPY and AgRP) and anorexigenic (POMC/&alpha MSH and CART) neuropeptides. Fluctuations in the levels of these neuropeptides control food intake and modulate peripheral (notably skeletal muscle) energy expenditure. CPT1c is a brain-specific outer mitochondrial membrane protein that binds malonyl-CoA and appears to regulate energy balance by transmitting the ‘malonyl-CoA signal' in the CNS to the orexigenic and anorexigenic neuropeptide systems. The mechanism by which this signal is transmitted is still unknown.

**MEDI 265**

## Efficient lead optimization guided by free-energy calculations

***William L Jorgensen**, Department of Chemistry, Yale University, New Haven, CT 06520-8107*

Drug development is being pursued through computer-aided structure-based design. For de novo lead generation, the BOMB program builds combinatorial libraries in a protein binding site using a selected core and substituents, and QikProp is applied to filter all designed molecules to insure that they have drug-like properties. Monte Carlo/free-energy perturbation simulations are then executed to refine the predictions for the best scoring leads including ca. 1000 explicit water molecules and extensive sampling for the protein and ligand. FEP calculations for optimization of substituents on an aromatic ring and for choice of heterocycles is now common. Alternatively, docking with Glide is performed with the ZINC database to provide leads that are then optimized via the FEP-guided route. Successful application has been achieved for HIV reverse transcriptase and macrophage migration inhibitory factor (MIF); micromolar leads have been rapidly advanced to extraordinarily potent inhibitors.

**MEDI 266**

## Integrating bioprospection and structure based drug design against tropical infectious diseases

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Infectious diseases continue to impede social and economic progress in the developing countries, disproportionately affecting poor and marginalized populations. The available chemotherapy is extremely limited with drugs that were predominantly developed in the first half of last century, presenting significant risk due to side effects. Additionally, the widespread upsurge of parasite strains resistant to the available drugs has been alarming, whereas the development of new alternatives for treatment and prevention has been minimal, therefore representing a challenge for the Medicinal Chemistry of developing countries. In this talk we will present our integrated experimental approach to this goal, which includes cloning and overexpression of parasitic enzymes, their crystallization and X-ray crystallography studies, rational drug design, synthesis and extensive screening and testing of both synthetic and natural products compounds obtained from the Brazilian biodiversity. In the past years, a dozen different proteins from tropical parasites had their structures elucidated in our lab, related to Chagas disease, leishmaniasis, schistosomiasis, sleeping sickness, nagana and malaria. Also, in an on-going program to screen natural products libraries in the search for new potential inhibitors, a series of promising compounds were identified and subsequently improved by structure based drug design, QSAR techniques and conventional and combinatorial chemistry. We will conclude by focusing on the enzyme GAPDH from *T.cruzi*, of which we have 10 different crystal structures, offering a unique view of the catalytic mechanism and inhibitory pathways of this enzyme.

**MEDI 267**

**Virtual screening for drug discovery**

***Diane Joseph-McCarthy**, Computational Science, Infection, AstraZeneca, 35 Gatehouse Drive, Waltham, MA 02451, Fax: 781-839-4640*

Ligand-based and target-based virtual screening techniques are commonly used to generate new leads during the drug discovery process. Where possible it is beneficial to employ both approaches to a given target. Case studies involving the use of ligand-based methods, target-based methods, and a combination of the two will be presented. The results in terms of hit rates and the types of hits obtained will be compared. Various docking and scoring methods and their applicability to different types of targets and small molecules will also be discussed.

**MEDI 268**

**Ligand recognition by thyroid hormone and estrogen receptors: Structural studies and molecular dynamics simulations.**

*Leandro Martínez[1], Milton T. Sonoda[2], Munir S. Skaf[1], and **Igor Polikarpov**[2], ipolikarpov@if.sc.usp.br. (1) Universidade Estadual de Campinas - UNICAMP, (2) Instituto de Física de São Carlos, Universidade de São Paulo, Av. Trabalhador São Carlense, 400, São Carlos, SP 13560-970, Brazil, Fax: +55-16-3373-9881*

Nuclear receptors are ligand-inducible transcription factors that share structurally related DNA-binding (DBD) and ligand-binding (LBD) domains. Hormone binding to nuclear receptors is mediated by repositioning of helix 12 and conformational changes in LBDs, which have profound effects on NR interactions with the cognate DNA response elements and co-regulating proteins, hence provoking profound changes in gene transcription activation and repression. Mechanistic details of this complex molecular event continue to be elusive. To shed more light on molecular basis of NR:ligands interactions we undertook studies of structure and dynamics of thyroid hormone (TR) and estrogen (ER) nuclear receptors. Here we will discuss our recent crystallographic results on TR complexes with TRƒ"-selective ligands and molecular dynamics simulations of ligand dissociation from ER and TR.

**MEDI 269**

**Comparison of the rhodopsin and beta2 adrenergic receptor structures as templates for GPCR modeling**

***Andrew J. Tebben**, Percy Carter, Qihong Zhao, and Roy Kimura, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000*

Much of the GPCR modeling undertaken in the past several years has been derived from the rhodopsin crystal structure. While this has proven to be a viable template structure, the models often require significant manipulation to accommodate ligands in the binding site and produce results consistent with mutagenesis and SAR studies. Recently a new structure has become available, the ƒ"2 adrenergic receptor crystallized with the inverse agonist carazolol. It is potentially a more relevant template as it has higher homology to many receptors of interest and the size of the co-crystallized

ligand is closer to that of many small molecule GPCR agonists and antagonists. To assess the utility of this new structure, models have been built from both it and the rhodopsin template. These models were evaluated in the context of receptor mutagenesis and SAR. Based on these results, the ƒ"2 adrenergic template appears to be superior, particularly for antagonist modeling.

**MEDI 270**

**Design, synthesis and evaluation of new antifolates for malaria**

***Jose Daniel Figueroa-Villar***[1]*, figueroa@ime.eb.br, Marta Gonçalves dos Santos*[1]*, martags@ime.eb.br, Luzineide Wanderley Tinoco*[2]*, lwtinoco@nppn.ufrj.br, Cristiane Diniz Ano Bom*[1]*, Tanos Celmar Costa França*[1]*, and Leandro Araújo de Lima*[1]*. (1) Department of Chemistry, Medicinal Chemistry Group, Military Institute of Engineering, Praça General Tiburcio 80, Rio de Janeiro 22290-270, Brazil, Fax: 5521-2546-7059, (2) Núcleo de Pesquisas de Produtos Naturais, Federal University of Rio de Janeiro, Rio de Janeiro 21941-590, Brazil*

Malaria is one of the most dangerous parasitic diseases caused by protozoan species, killing about a million people worldwide every year. One of the major problems regarding malaria chemotherapy is resistance development as a consequence of drug pressure on the parasites. Also, effective antimalarial drugs are expensive for treatment of patients in third world countries. In this work we have used molecular modeling methodologies to design and evaluate cheap new 2,4-diaminopyrimidines as inhibitors of mutant Plasmodium falciparum dihydrofolate reductase (PfDHFR). The planned compounds were synthesized and tested as selective ligands for PfDHFR using NMR and enzyme kinetics. The most effective compound was able to kill in vitro 94% of the parasites at a 3,2 nM concentration, thus being 5 times more effective than pyrimethamine on pyrimethamine-resistant P. falciparum.

**MEDI 271**

**The role of co-crystals in pharmaceutical science**

***Michael J. Zaworotko****, Department of Chemistry, University of South Florida, 4202 E Fowler Ave, CHE 205, Tampa, FL 33620-5250, Fax: 813-974-3203*

Abstract:

(150 words)

The emerging field of crystal engineering facilitates the generation of a wide range of new crystal forms of compounds without the need to invoke covalent bond breakage or formation, i.e. it enables discovery of new compositions of matter even for long known molecules that would otherwise be difficult to patent and fine tune in terms of physical properties. This contribution will focus upon the role of cocrystals in pharmaceutical science with emphasis upon the following:

- A historical perspective of this long known but little studied class of compounds;

- How to design co-crystal formers using crystal engineering and prepare them using “green” methodologies;

- Examples of new co-crystals that include some long known natural products and how they fine tune physical properties of clinical relevance;

- The use of cocrystals for synthesis of new molecular species, i.e. cocrystal-controlled solid state synthesis.

**MEDI 272**

**Pharmaceutical co-crystals in action**

***Matthew L. Peterson**, TransForm Pharmaceuticals, 29 Hartwell Avenue, Lexington, MA 02421*

The composition of a pharmaceutical formulation and the process by which a dosage form is made can dramatically affect the performance of a resulting drug product. Pharmaceutical co-crystals are becoming important materials for the improvement of the physico-chemical and in vivo performance of pharmaceutical compounds. Enhancements in crystal engineering of pharmaceutical substances and characterization capabilities have increased the drive to translate understanding of crystal form into rational formulation design. Two key aspects of innovation in dosage form design are (1) the discovery and selection of the right crystal form of the drug, and (2) the ability to study materials through manufacture, storage and use of a product. The latter includes the study of interactions of formulations with simulated gastrointestinal fluids, especially in the case of oral formulations of water-insoluble compounds. In this presentation, examples will be presented from the development of pharmaceutical co-crystals into orally bioavailable compositions.

**MEDI 273**

**Serendipity in drug development: Discovery of and development of stable co-crystals**

***Narayan Variankaval**, Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065*

This presentation will present the serendipitous discoveries of crystal forms in Merck and their implications in drug development. Two cases will be discussed - (a) crystalline HCl salts of an MC4R agonist and (b) co-crystalline complexes of a PDE-IV compound with tartaric acid and other dicarboxylic acids. In each case, emphasis will be placed on the nature of the isolation process and, more importantly, structure-property-function relationships that enabled these forms of the active ingredient to be successfully formulated into drug products. In some of these cases, crystal structures were solved either from single-crystals or from high resolution powder diffraction data using simulated annealing algorithms. The role played by serendipity in a time of high-throughput approaches for crystal form screening will be highlighted throughout.

**MEDI 274**

**Synthesis and applications of pharmaceutical co-crystals: A materials science view**

***Paul A. Meenan**, Groton/New London Laboratories, Pfizer Inc, 558 Eastern Point Road, Groton, CT 06340*

The field of co-crystals has elicited significant interest in the pharmaceutical industry recently with the potential to utilize this technology as means of enhancing physicochemical properties such as solubility and dissolution; in addition to enhancements to particle properties that could aid drug product development, .e.g. improving both chemical and physical stability and indeed as a method to induce crystallization of materials that traditionally would have been isolated as an oil or an amorphous material. There is also considerable ongoing debate as to the theoretical definition of a co-crystal, how a co-crystal can be reliably synthesized, manufactured and characterized, coupled with the intellectual properties ramifications therein. This presentation will outline some of our recent research efforts (in-house & external) into the synthesis of co-crystals, and will outline different techniques that can be utilized to characterize co-crystals.

**MEDI 275**

**Co-(operative?)-crystal structures**

***Jack Gougoutas***[1]*, Jack.Gougoutas@gmail.com, John DiMarco*[2]*, john.dimarco@bms.com, Michael A Galella*[2]*, michael.galella@bms.com, and Mary F. Malley*[3]*, mary.malley@bms.com. (1) Department of Crystallography, Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000, (2) Analytical R & D, Bristol-Myers Squibb Research and Development, Princeton, NJ 08543-4000, (3) Department of Analytical R & D, Bristol-Myers Squibb, Princeton, NJ 08543-4000*

Most of the ~390,000 crystal structures described in the latest release of the Cambridge Structural Database (2008, as529be) were assembled/grown in some suitable solvent(s). Nevertheless, about half of these "small-molecule" structures crystallized in "NEAT" arrangements assembled ONLY from the "compound of interest" - sometimes in more than one conformational, tautomeric or stereochemical form within the lattice.

The other half of the known structures in the database contain one or more "extraneous chemical components/impurities" as an INTEGRAL and NECESSARY part of the observed crystal structure of the "compound of interest".

Although water and/or solvent(s) of crystallization are the most common "extraneous lattice components" (hydrates/solvates), many examples demonstrate that stable 3d arrangements/crystal structures can be assembled with the aid of a surprisingly wide variety of "extraneous chemical compounds" (co-crystals). If Nature co-operates in our designs, some choices of "extraneous components" may lead to improved physical and/or biological properties of novel co-crystals.

**MEDI 276**

**In silico prediction of blood-brain barrier permeation.**

***Anna Seelig****, Anna.Seelig@unibas.ch, Biophysical Chemistry, University of Basel, Klingelbergstrasse 70, Basel CH-4056, Switzerland, Fax: +41 61 267 21 89, Sarah Guethe, sarah.guethe@unibas.ch, Biophysical Chemistry, Biozentrum, University of Basel, Basel CH-4056, Switzerland, and Grégori Gerebtzoff, gregori.gerebtzoff@roche.com, F. Hoffmann-La Roche Ltd, Basel CH-4070, Switzerland*

To predict membrane barrier permeation by drugs we developed an algorithm that determines the molecular axis of amphiphilicity and the cross-sectional area, ADcalc, perpendicular to this axis.

Starting from the conformational ensemble of each molecule the three-dimensional, membrane-binding conformation was determined as the one with the smallest cross-sectional area, ADcalcM, and the strongest amphiphilicity. The calculated and the measured cross-sectional areas correlated linearly. The calculated cross-sectional areas were then used together with the calculated octanol-water distribution coefficients, LogD7.4, of 55 compounds (with known ability to permeate the blood-brain barrier) to establish a calibration diagram for the prediction of blood-brain barrier permeation. A limiting cross-sectional area (ADcalcM = 70 Å2) and an optimal range of octanol-water distribution coefficients ( 1.4 ≤ LogD7.4 < 5.0) was obtained. The calibration diagram was validated with an independent set of 43 compounds yielding a prediction accuracy of 86%.

**MEDI 277**

**Blood-brain barrier permeability considerations for CNS-targeted compound design**

***Stephen Hitchcock**, Medicinal Chemistry, Amgen, One Amgen Center Drive, Thousand Oaks, CA 91320*

In order to account for the limitations imposed by blood-brain barrier permeability, a further refinement of the concept of drug-likeness is required for compounds intended to modulate central nervous system (CNS) targets. This presentation will center on criteria and processes that can be applied to the de novo design of individual compounds and libraries to increase the odds of structures residing within CNS-accessible chemical space. Application of these principles to the identification and optimization of CNS-targeted leads will be discussed.

**MEDI 278**

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

***Lorin A. Thompson III**[1], lorin.thompson@bms.com, Lawrence R. Marcin[2], Kenneth M. Boy[1], boyk@bms.com, Jianliang Shi[2], Mendi A. Higgins[2], Jason M. Guernon[1], jason.guernon@bms.com, Richard E. Olson[2], Andrew C. Good[2], andrew.good@bms.com, Catherine R. Burton[2], Donna M. Barten[3], Jodi K. Muckelbauer[2], Jeremy H Toyn[2], Kimberley A. Lentz[2], James E. Grace[2], John J Herbst[2], Anthony M. Marino[2], Jere E. Meredith[2], Charlie F. Albright[2], charlie.albright@bms.com, and John E. Macor[1]. (1) Neuroscience Chemistry, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492-7660, (2) Research and Development, Bristol-Myers Squibb, Wallingford, CT 06492-7660, (3) Neuroscience Biology, Bristol-Myers Squibb, Wallingford, CT 06492-7660*

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

**MEDI 279**

**Design of CNS penetrant bradykinin antagonists**

***Scott D. Kuduk**, Department of Medicinal Chemistry, Merck & Co., Inc, WP14-3, Sumneytown Pike, Post Office Box 4, West Point, PA 19486*

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 of these disease states. The inducible BK B1 receptor is expressed at high levels in injured tissue and is also present in the central nervous system implying the potential for a central mode of action. A series of antagonists has been optimized to possess sub-nanomolar affinity for the human B1 receptor and acceptable pharmacokinetic properties suitable for clinical evaluation. A particular challenge during this optimization was to design compounds that were not substrates for the efflux transporter P-glycoprotein, and thus exhibited adequate levels of brain exposure to target central B1 receptors.

**MEDI 280**

**Recent design advances in compound brain penetration**

***Ronald L. Magolda**, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543*

Modern medicinal chemistry involves integrating with SAR several diverse components that include physical properties, ADME, and safety. In the discovery of drugs to treat neurological diseases there is the added requirement of compound localization into the brain. Much like the “Lipinski Rules”, several general principles have evolved to increase the chances of compound brain penetration. Generally, these principles are better at predicting when a compound will not get into the brain as opposed to when it would get into the brain. To lower this risk of predicting brain penetration of compounds, several tools, both old and new, are being applied to guide drug design. This presentation will provide a survey of the current state-of the-art tools that guide medicinal chemists to increase their chances to get brain penetration. Several examples and some case studies within Wyeth will be provided that will outline the scope and limitations of such tools.

**MEDI 281**

**Brain unbound fraction: Application to drug discovery**

***J. Cory Kalvass**, Drug Disposition, Eli Lilly, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285*

According to the “free drug hypothesis”, brain unbound fraction is informative for CNS drug discovery for at least two reasons: 1) only unbound drug concentration equilibrates between plasma and brain and 2) unbound drug concentration at the site of action drives pharmacological activity. In this presentation, several case studies are used to illustrate the value of brain unbound fraction in

assessing brain penetration and for understanding concentration-effect relationship of CNS-active drug candidates.

**MEDI 282**

**Developing a stable complex between photoactivated rhodopsin and the G protein transducin**

***Kris Palczewski**, Department of Pharmacology, Case Western Reserve University, USA, 10900 Euclid Ave., Cleveland, OH 44106-4965*

Rhodopsin is the predominant membrane protein of disk membranes in rod outer segments of retinal rod cells, the specialized neurons that detect photons and communicate with secondary neurons about the presence of light. Rhodopsin, a member of the GPCR superfamily, is comprised of a membrane-embedded chromophore, 11-*cis*-retinal that is covalently bound to the apoprotein opsin at Lys296 (in bovine opsin) located in transmembrane helix VII *via* a protonated Schiff base linkage. Upon absorption of a photon, isomerization of the chromophore to an all-*trans*-retinylidene conformation induces changes in the rhodopsin structure, ultimately converting it from an inactive to an activated signaling state that allows it to signal intracellularly through heterotrimeric G proteins. Activation of rhodopsin relays the activating changes to the retinal G protein, transducin, initiating the biochemical cascade of reactions in a process termed phototransduction. Phototransduction represents a model system for G protein-coupled receptor (GPCRs) signaling. The structures of key phototransduction proteins such as rhodopsin (Rho), photoactivated Rho (Rho*), $G\alpha\beta\gamma$ protein (transducin, Gt-GDP), arrestin, regulators of G-protein signaling (RGS) proteins and other regulatory proteins have been solved and subsequently improved; however, a comprehensive understanding of phototransduction and other GPCR signaling requires further structural work on complexes of the individual components.

**MEDI 283**

**NIH support for structure-based drug design for GPCR targets**

***Peter C. Preusch**, Ph.D., Chief, Biophysics Branch, Division of Cell Biology and Biophysics, National Institute of General Medical Sciences, National Institutes of Health, 45 Center Drive, MSC 6200, Bethesda, MD 20892-6200, Fax: 301-480-2802*

NIH supports several programs that will enable the structure-based design of drugs targeting G-protein coupled receptors (GPCRs) in the near future. These include: i) on-going support for research projects in computational chemistry and drug design; ii) the recently restructured program of Centers for Structure-Based Drug Design Related to AIDS; iii) the recently announced Drug Docking and Screening Resource; iv) the on-going program of support for the Structural Biology of Membrane Proteins; and v) the NIH Structural Biology Roadmap. A notable accomplishment of the Roadmap program was the solution of the beta-2 adrenergic receptor in November, 2007. This program has been extended for FY2008-2013 (total cost $45 million) with the goal of solving structures of complex membrane proteins and of complexes formed between membrane proteins and their partners, such as GPCR-G-Protein complexes. This presentation will cover the goals, funded projects, outcomes, and funding opportunities of the above programs.

**MEDI 284**

**Proteome scale prediction of GPCR ligand-protein complexes**

***Jeffrey Skolnick*** *and Michal Brylinski, Center for the Study of Systems Biology, Georgia Institute Of Technology, School of Biology, 250 14th ST NW, Atlanta, GA 30318*

The TASSER protein structure prediction algorithm has been applied to predict the tertiary structures of all putative GPCRs in the human proteome. Comparison of the blind prediction with the recently solved beta-adrenergic receptor structure reveals that the model has a root-mean-square deviation, RMSD, from native of 2.28 Å in the transmembrane region, whereas the RMSD of the best template, rhodopsin, is 3.7 Å, with significant errors in the ligand binding region. Using the predicted structure, the ability of a flexible ligand docking algorithm, QDOCKX, to improve the geometry of the ligand-protein complex is examined. Then, FINDSITE (a new ligand binding site/ligand identification algorithm) is applied to identify known drug molecules and their corresponding targets. By screening the entire GPCR proteome, the ability to prioritize lead molecules with putative enhanced specificity is assessed.

**MEDI 285**

**Are GPCR 3-D models useful in structure-based drug design?**

***Didier Rognan****, Bioinformatics of the Drug, CNRS UMR 7175-LC1 - Université Louis Pasteur, 74, route du Rhin, 67400 Illkirch, France, Fax: +33-3-90244310*

G Protein-coupled receptors (GPCRs) have been under the spotlight of drug discovery for many decades for their key role in many biochemical signalling pathways and their outstanding druggability. Until recently, most drug discovery programs have been capitalizing on previous knowledge and semi-empirical rules to find and/or optimizing new lead compounds. The first high-resolution X-ray structure of a GPCR (bovine rhodopsin) in 2000 has brought GPCR drug discovery into the world of structure-based design and a considerable number of studies based on GPCR homology models have been reported afterwards. Notably, the possibility to propose 3-D atomic coordinates for a GPCR lined up with the development of virtual screening technologies aimed at identifying putative hits from large compound libraries. After nearly a decade of structure-based approaches to identify GPCR ligands, we will review existing achievements in predicting binding sites and ligands from 3-D models. Several key issues in GPCR modelling will be addressed and strengths/limitations of pure structure-based approaches illustrated by concrete examples.

**MEDI 286**

**Structure and dynamics of the human beta 2 adrenergic receptor**

***Brian K. Kobilka****, Department of Molecular and Cellular Physiology, Stanford University, Beckman Center, Stanford University Medical School, Stanford, CA 94305, Fax: 650-725-8021*

G protein coupled receptors (GPCRs) are remarkably versatile signaling molecules. The beta 2 adrenoceptor (beta2AR) is a prototypical Family A GPCR that mediates physiologic responses to

adrenaline and noradrenaline. The function of the beta2AR can be modulated by a spectrum of synthetic ligands ranging from full agonists to inverse agonists. We have used crystallography to determine the three-dimensional structure of the beta2AR, and fluorescence spectroscopy to map ligand-induced conformational changes and characterize the structure of beta2AR dimers. I will discuss what we these studies have taught us about the structural basis of beta2ARs function.

**MEDI 287**

**Caging the farnesyltransferase inhibitor L-744,832 with the photoremovable protecting group bromohydroxyquinoline**

***Daniel A Abate Pella**, abate006@tc.umn.edu, Department of Chemistry, University of Minnesota, 207 Pleasant St SE, Minneapolis, MN 55455, Amanda J DeGraw, degraw@chem.umn.edu, Department of Chemistry, Univeristy of Minnesota, Minneapolis, MN 55455, and Mark D. Distefano, diste001@umn.edu, Departments of Chemistry and Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455*

Mutant Ras proteins are responsible for 30% of human cancers, and farnesylation is a key step that activates their oncogenicity. Here we report the successful caging of the farnesyltransferase inhibitor L-744,832 with the photolabile protecting group bromohydroxyquinoline (BHQ). BHQ is an attractive caging group for biological studies because it requires light of low energy to uncage, as opposed to other uncaging approaches which are more damaging to biological systems. We have synthesized an activated form of BHQ, bromohydroxyquinoline chloride, in six steps starting from 2-aminophenol. Utilizing the caged farnesyltransferase inhibitor, we demonstrated the photolysis of BHQ upon its exposure to light and characterized its kinetics of uncaging. Applications of this system to study biological processes are under way.

**MEDI 288**

**Synthesis and antitumor activities of the beta-carboline derivatives**

***Yuri A. Nikolyukin**, PortaScience Inc, 1 Wittendale Dr., Suite E, Moorestown, NJ 08057, Fax: 856-231-9822*

Novel 3,4-substituted β-carbolines 1 have been prepared via oxonium cations and evaluated in vitro for their antitumor activity.

Several compounds have demonstrated significant inhibition at 60 human tumor cell lines with average cytotoxic activity ($GI_{50}$) in a range of 18.5 to 2.9 μM. Synthesis and structure-activity relationship in the series 1 will be presented.

**MEDI 289**

**Designed antimicrobials from host defense peptides using multivalent and combinatorial library strategies**

***Zhigang Liu*** *and Neville R. Kallenbach, Department of Chemistry, New York University, 100 Washington Square East, Rm1001, New York, NY 10003*

As natural effectors of innate immunity, host defense peptides (HDPs) exhibit rapid killing and a broad spectrum of activity against Gram-positive and -negative bacteria, fungi, and viruses. HDPs have thus inspired a variety of designs for antimicrobial therapeutics. We have employed two strategies aimed at identifying potent antimicrobial agents for the ultimate therapeutic treatment of MDR infections. The first derives from the application of the principle of multivalency to create antimicrobial agents using a variety of scaffolds to link short RW peptides to afford multivalent constructs with different topology. In the second strategy, we designed and screened several combinatorial libraries based on a 1,3,5-triazine scaffold to mimic the hydrophobic and charge patterns detected in the pharmocophore metioned above. In present poster, a set of compounds have been identified from these strategies with potent antimicrobial activity and low hemolytic activity. These provide a set of new antimicrobial leads that open possible routes to novel antimicrobials with more drug-like pharmaceutical properties than natural peptides.

**MEDI 290**

## SAR study on novel benzimidazoles as potential broad-spectrum antibacterial agents targeting FtsZ

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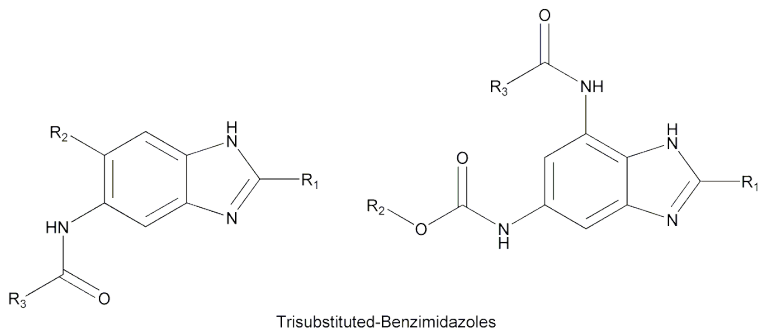
FtsZ, a prokaryotic homologue of tubulin, is shown to be essential for bacterial cell division. It polymerizes at the mid cell to form a Z-ring that coordinates the bacterial cytokinesis. As FtsZ is highly conserved protein and plays a vital role in cell division in all bacteria, we hypothesized that FtsZ-inhibitors can be developed into broad-spectrum antibacterial agents with novel mechanism of action. Accordingly, we designed and synthesized a library of novel trisubstituted-benzimidazoles through newly developed polymer-assisted solution phase method. A number of these compounds exhibited promising antibacterial activities against Mtb H37RV strain. Polymerization assay confirmed that these compounds inhibited Mtb-FtsZ assembly. We also screened those benzimidazoles against other Gram-positive bacterial strains including VRE and MRSA. Synthesis, antibacterial activities and SRA of novel benzimidazoles will be presented.




Trisubstituted-Benzimidazoles

**MEDI 291**

**Structure-guided optimization of bacterial ATPase inhibitors: From hit-to-lead**

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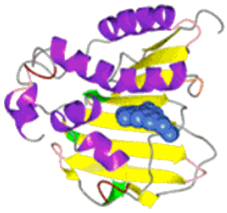
Successful replication of chromosomal DNA in bacteria is in part dependent upon two essential enzymes, DNA gyrase (GyrA/GyrB) and topoisomerase IV (ParC/ParE). These ATP-dependent enzymes maintain the correct topological state of DNA during replication. The discovery, design, and synthesis of dual target inhibitors of GyrB/ParE is described. Crystallographic fragment-based screening was used to discover new scaffolds, which were elaborated using structure-guided methods to create analogues with increased activity. Further development of these compounds could lead to novel antibacterial agents.



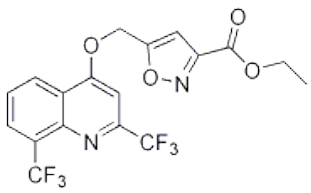
Structure of E. faecalis GyrB with dual target ligand

**MEDI 292**

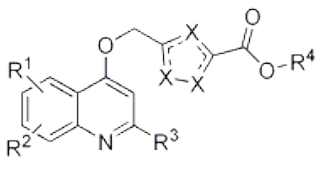
**Synthesis and biological activity of antituberculosis agents based on a quinoline core**

***Annamaria Lilienkampf***[1]*, lilienka@uic.edu, Jialin Mao*[2]*, jmao4@uic.edu, Baojie Wan*[2]*, Yuehong Wang*[2]*, Scott G. Franzblau*[2]*, and Alan P. Kozikowski*[1]*, kozikowa@uic.edu. (1) Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, (2) Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612*

Up to one-third of the world's population is infected by *Mycobacterium tuberculosis*, which results in 1.6 million deaths each year from tuberculosis (TB). However, no new TB drugs have been introduced over the last 40 years. The significant emergence of multidrug-resistant TB, and the frequent co-infection with HIV, has made TB a pressing target for drug discovery. Continuing our previous research of mefloquine-based isoxazole derivatives **1**, we have identified new potent anti-TB agents **2**, based on a quinoline core. The synthesis, biological activity and SAR of these novel anti-TB agents will be discussed.



**1** MIC 0.9 μM



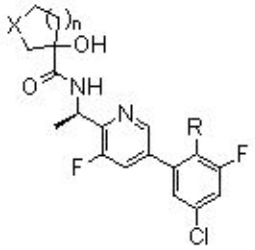
**2** X = C, O, N, S

**MEDI 293**

## Bradykinin B1 receptor antagonists: SAR studies in the hydroxycycloalkyl series

***Christina Ng Di Marco***[1], *christina_ng@merck.com, Robert M. DiPardo*[1], *Ronald K. Chang*[1], *ronald_chang@merck.com, Kathy L. Murphy*[2], *Richard W. Ransom*[2], *Duane R. Reiss*[2], *Cuyue Tang*[3], *Thomayant Prueksaritanont*[4], *Douglas J. Pettibone*[2], *Mark G. Bock*[1], *and Scott D. Kuduk*[1], *scott_d_kuduk@merck.com. (1) Department of Medicinal Chemistry, Merck & Co., Inc, WP14-3, Sumneytown Pike, Post Office Box 4, West Point, PA 19486, (2) Neuroscience Drug Discovery, Merck Research Laboratories, West Point, PA 19486, (3) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (4) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

The investigation of novel mechanistic pathways for the treatment of chronic pain and inflammation is of significant importance. The G-protein coupled bradykinin $B_1$ receptor is one such potential target which has been shown to be involved in these disease states. Not only is the $B_1$ receptor rapidly upregulated in the periphery at the site of trauma, it has also been shown to be constitutively expressed in the CNS, implicating a central pathway for mediating pain. Accordingly, a bradykinin $B_1$ receptor antagonist program has been undertaken with the goal of developing a small molecule, non-peptidic, orally active, and CNS penetrant compound suitable for a clinical proof of concept study. The first development candidates from these efforts have been previously disclosed. Our progress towards the identification of a structurally diverse backup compound with an improved pharmacological and metabolic profiles will be presented.

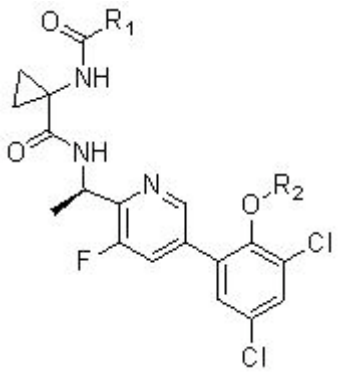



**MEDI 294**

## Bradykinin $B_1$ receptor antagonists with high oral bioavailability and minimal PXR activity

***Robert M. DiPardo***[1], *bob_dipardo@merck.com, Ronald K. Chang*[1], *Christina N. Di Marco*[1], *Jenny M. Wai*[1], *Dong-Mei Feng*[2], *Kathy L. Murphy*[3], *Richard W. Ransom*[3], *Duane R. Reiss*[3], *Cuyue Tang*[4], *Thomayant Prueksaritanont*[5], *Douglas J. Pettibone*[3], *Mark G. Bock*[2], *and Scott D. Kuduk*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3, Sumneytown Pike, PO Box 4, West Point, PA 19486, (2) Department of Medicinal Chemistry, Merck & Co., Inc, West Point, PA 19486, (3) Neuroscience Drug Discovery, Merck Research Laboratories, West Point, PA 19486, (4) Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (5) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

The quest for improved treatments of chronic pain and inflammation continues to be an area of intense research. Human bradykinin $B_1$ receptor antagonists embody a novel approach to the treatment of these disease states. The inducible BK $B_1$ receptor is expressed at high levels in injured tissue and is also present in the central nervous system implying the potential for a central mode of action. The design and synthesis of a novel class of human bradykinin $B_1$ antagonists featuring difluoroethyl ether and isoxazole carboxamide moieties will be presented. Several of these compounds displayed good pharmacokinetic properties, efficient ex vivo receptor occupancy, and low potential for P450 induction via activation of the pregnane-X receptor (PXR) pathway.




**MEDI 295**

**Hydroxy amides and keto amides as a primary pharmacophore in soluble epoxide hydrolase inhibitors**

***Sampath-kumar Anandan****, Zung N Do, Bhasker Aavula, Heather K Webb, Richard Gless, and Dinesh V Patel, Chemistry, Arete Therapeutics, 3912 Trust Way, Hayward, CA 94545, Fax: 510-785-7061*

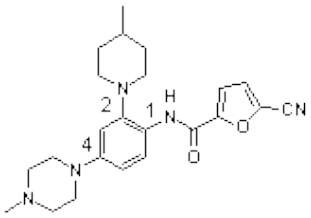
Soluble epoxide hydrolase (sEH) has shown potential as a pharmaceutical target in a number of disease indications including hypertension, stroke, end organ protection, and inflammatory disease. In humans, sEH metabolizes endogeneously produced epoxides of arachidonic acids (epoxyeicosatrienoic acids or EETs) to their corresponding diols (dihydroxyeicosatrienoic acids or DHETs). EETs produce vasodilation in various vascular beds such as renal, coronary, intestinal and cerebral vasculature. Hydrolysis of EETs by sEH to the corresponding DHETs significantly diminishes this activity, suggesting that inhibition of the mammalian sEH is a promising new therapy in the treatment of hypertension and vascular inflammation. Several 1, 3-disubstituted ureas including (adamantylureido)dodecanoic acid (AUDA) are reported to be potent inhibitors of sEH. From the X-ray crystal structure, the urea functionality of these inhibitors has been invoked in the binding at the active site of the sEH enzyme. However, the urea based sEH inhibitors suffer from poor solubility and oral bioavailability. Therefore, there remains a need for identifying novel sEH inhibitors with improved biological availability and stability. This poster reports our finding that $\alpha$-hydroxy amide and $\alpha$-keto amide can replace the urea as a primary pharmacophore to afford good in vitro potency against sEH enzyme.

**MEDI 296**

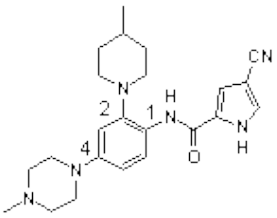
**Structure-based optimization of a novel class of arylamide FMS inhibitors**

***Shelley K. Ballentine****, Sanath K. Meegalla, Carl R. Illig, Jinsheng Chen, Mark J. Wall, Kenneth J. Wilson, Renee L. DesJarlais, Yanmin Chen, Carsten Schubert, Ioanna Petrounia, Carl S. Crysler, Christopher J. Molloy, Margery A. Chaikin, Carl L. Manthey, Bruce E. Tomczuk, and Mark R. Player, Johnson and Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, Spring House, PA 19477*

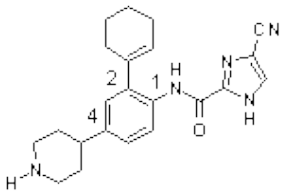
The macrophage colony-stimulating factor (CSF-1) is the primary growth factor for the macrophage lineage, which specifically binds to its exclusive receptor FMS, a type III tyrosine kinase receptor expressed in macrophages and their progenitor cells. The activation of FMS due to the binding of CSF-1 initiates an intracellular signaling cascade resulting in differentiation and activation of these cells. As macrophages are known to play an important role in the inflammatory process, the inhibition of macrophage proliferation by CSF-1 might be of therapeutic value in intercepting an inflammatory process. This hypothesis has also been validated by various animal studies. CSF-1-deficient mice are reported to be resistant to collagen-induced arthritis. In a collagen induced arthritis mouse model, CSF-1 was shown to increase the severity of disease while a neutralizing anti-CSF-1 antibody had the opposite effect. Our discovery efforts led to the identification of potent FMS inhibitors 1A and 1B and to the demonstration of the anti-inflammatory activity of 1B in a model of rat collagen-induced arthritis. Despite the excellent potency and in vivo efficacy of this series, the 1,2,4-phenylenetriamine core structure of 1A and 1B was considered a liability due to the potential for it to form reactive quinonediimine metabolites, which could result in idiosyncratic drug reactions (IDRs). Herein we describe the optimization of 1,2,4-phenylenetriamine-containing series of FMS inhibitors into a series with equivalent potency by incorporation of carbocyclic substituents represented by the compound 1C. Structure-based modeling provided the framework to efficiently effect this transformation and restore potencies to previous levels.



**1A** $IC_{50}$ = 0.001 μM



**1B** $IC_{50}$ = 0.0008 μM



**1C** $IC_{50}$ = 0.0008 μM

**MEDI 297**

**Thienyl aminohydantoins as potent BACE1 inhibitors**

***Michael S. Malamas****[1], malamam@wyeth.com, Jim Erdei[1], erdeij@wyeth.com, Iwan Gunawan[1], Keith Barnes[2], Matthew Johnson[2], Albert Robichaud[1], robicha@wyeth.com, Jim Turner[3], Yu Hui[4], Yun Hu[4], Rajiv Chopra[4], Kristi Fan[1], and Jonanthan Bard[3], bardj@wyeth.com. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Albany Molecular Research, Albany, NY, (3) Neuroscience, Wyeth Research, Princeton, NJ 08543, (4) N/A*

The deposition of amyloid beta-peptide (Ab) in the brain is one of the major events in the pathogenesis of Alzheimer's Disease (AD). Ab*f*n peptide results from the sequential cleavage of

APP, a type I transmembrane glycoprotein, first at the N-terminus by b-secretase enzyme (BACE-1), followed at the C-terminus by one or more g-secretases, as part of the b-amyloidogenic pathway. Although, the cause of AD remains mainly unknown, a large body of evidence suggests that Ab production affects the deterioration of the brain in AD patients. Thus, processes that limit Ab production, prevent aggregation, and enhance clearance may offer effective treatments for AD. BACE-1 inhibition is considered a prominent therapeutic target for treating AD by diminishing Ab peptide in AD patients.

The design and development of thienyl aminohydantoins as inhibitors of beta-secretase (BACE1) was based on our potent BACE1 inhibitor WAY-258131 (previously reported). X-ray crystallography and molecular modeling studies assisted our design efforts that ultimately produced potent and selective inhibitors (FRET assay IC50 = 10 nM; ELISA cell-based assay EC50 = 80 nM). We have identified key ligand-protein interactions at S2' region that contribute to the compound potency and selectivity. These new BACE1 inhibitors are useful biological tool towards the understanding of APP processing, and the development of disease-modifying AD therapeutics.

**MEDI 298**

**Pyrazinyl aminohydantoins as potent BACE1 inhibitors**

***Michael S. Malamas***[1]*, malamam@wyeth.com, Jim Erdei*[1]*, erdeij@wyeth.com, Keith Barnes*[2]*, Matthew Johnson*[2]*, Albert Robichaud*[1]*, robicha@wyeth.com, Ping Zhou*[1]*, zhoup@wyeth.com, Yinfa Yan*[1]*, yany1@wyeth.com, William R. Solvibile*[1]*, solvibw@wyeth.com, Jim Turner*[3]*, Yu Hui*[4]*, Yun Hu*[4]*, Rajiv Chopra*[4]*, Kristi Fan*[1]*, and Jonanthan Bard*[3]*, bardj@wyeth.com. (1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, (2) Albany Molecular Research, Albany, NY, (3) Neuroscience, Wyeth Research, Princeton, NJ 08543, (4) N/A*

Alzheimer's Disease (AD) is a neurodegenerative disorder associated with accumulation of amyloid plaques and neurofibrillary tangles in the brain. Amyloid beta peptide is the major constituent of the plaques and is generated by sequential proteolytic cleavage of amyloid precursor protein (APP) by beta and gamma-secretases. First, BACE-1 (beta-site APP cleaving enzyme 1) cleaves APP at the N-terminus by beta-secretase enzyme (BACE-1), followed at the C-terminus by one or more gamma-secretases, as part of the beta-amyloidogenic pathway. Although, the cause of AD remains mainly unknown, a large body of evidence suggests that Ab production affects the deterioration of the brain in AD patients. Reduction of Ab-peptide by BACE-1 inhibition is considered a prominent therapeutic approach to treat AD.

In this paper, we used the HTS hit WY-24454 (FRET; IC50 = 40 uM) as the starting point to generate pyrazinyl aminohydantoins. More specifically, we have used the pyrazinyl moiety to explore the S2' region of the BACE1 protein binding pocket. Our rational drug design was supported by X-ray crystallography and molecular modeling studies. Several compounds have demonstrated excellent in vitro potency in a FRET assay (IC50 = 8 nM) and in an ELISA cell-based assay (EC50 = 70 nM). These new pyrazinyl aminohydantoins BACE1 inhibitors represent excellent biological tools towards the understanding of APP processing, as well as the development of disease-modifying AD therapeutics.

**MEDI 299**

**Synthesis and evaluation of bifunctional inhibitors of cytochrome P-450 3A**

***Charles A. Flentge***[1], *chuck.a.flentge@abbott.com, John T. Randolph*[1], *john.randolph@abbott.com, Peggy P. Huang*[1], *Larry L. Klein*[2], *Kennan C. Marsh*[3], *kennan.marsh@abbott.com, John E. Harlan*[1], *and Dale J. Kempf*[2]*. (1) Global Pharmaceutical Research and Development, Abbott, 200 Abbott Park Road, D-R4CQ AP-52, Abbott Park, IL 60064, Fax: 847-938-2756, (2) Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, (3) Exploratory Sciences, Dept. 4EK, Abbott Laboratories, Pharmaceutical Products Division, Abbott Park, IL 60064*

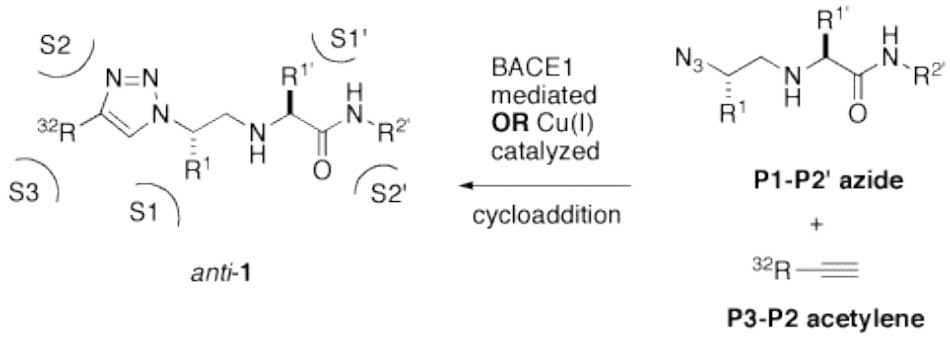
The HIV protease inhibitor ritonavir (RTV) is a potent inhibitor of the metabolizing enzyme cytochrome P-450 3A (CYP3A) and is clinically useful in HIV therapy in its ability to enhance human plasma levels of other HIV protease inhibitors. A novel series of CYP3A inhibitors was designed around the structural elements of RTV important to CYP3A inhibition. Compounds were evaluated for their abilities to inhibit CYP3A-mediated oxidation of 7-benyloxyquinoline. Potent analogs exhibit inhibition properties comparable to RTV (IC50 = 50 nM). In vivo, compounds were evaluated orally by co-administration with lopinavir (LPV) (5 mg/kg each) in dogs. A compound was identified that was superior to RTV in its capacity to enhance the plasma level of LPV. Importantly, these compounds are structurally less complex than RTV and they have no activity towards HIV aspartyl protease. The compounds described may be useful for enhancing the pharmacokinetics of drugs that are metabolized by CYP3A.

**MEDI 300**

**Triazole-linked reduced amide isosteres: A novel approach for the discovery of BACE1 inhibitors**

*Paul R. Carlier*[1]*, pcarlier@vt.edu,* ***Christopher J. Monceaux***[2]*, cmoncea@vt.edu, Yasuji Matsuoka*[3]*, ym56@georgetown.edu, and Chiho Hirate-Fukae*[3]*, ch296@georgetown.edu. (1) Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, Fax: 425-984-8099, (2) Department of Chemistry, Virginia Tech, Blacksburg, VA 24061, (3) Department of Neurology, Georgetown University, Washington, DC 20057*

BACE1 is the aspartic protease responsible for amyloidogenic processing of the amyloid precursor protein, and BACE1 inhibitors have thus attracted tremendous interest as therapeutic agents for Alzheimer's disease. A key feature of our design strategy is replacement of the P2 amide in reduced amide isostere BACE1 inhibitors with a 1,2,3-triazole unit. This modification will allow both enzyme-mediated inhibitor synthesis ("in situ click chemistry") as well as concurrent microtiter plate copper-catalyzed synthesis/screening, We will describe synthesis of the requisite P3-P2 acetylenes and P1'-P2' azides, their assembly to the corresponding triazoles **1**, and their BACE1 inhibitory properties.




*anti*-**1**

**MEDI 301**

## Identification and optimization of potential Cruzain inhibitors

***Bryan T. Mott***[1]*, mottb@mail.nih.gov, Anton Simeonov*[1]*, David J. Maloney*[1]*, Ajit Jadhav*[1]*, Craig J. Thomas*[1]*, craigt@nhgri.nih.gov, Jim Inglese*[1]*, Rafaela Ferreira*[2]*, Brian K Shoichet*[2]*, shoichet@cgl.ucsf.edu, and Christopher P. Austin*[1]*. (1) NIH Chemical Genomics Center, National Institutes of Health, 9800 Medical Center Dr, Bethesda, MD 20892-3370, (2) Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA 94143-2550*

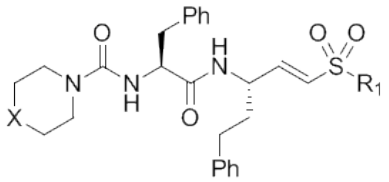
Chagas disease, a main cause of heart failure in Latin American countries, is caused by the protozoan parasite Trypanosoma cruzi. Cruzain is a cysteine protease native to T. cruzi found to serve a key role in survival of the parasite, making it an attractive target for small molecule inhibitors. A combination of quantitative high-throughput screening (qHTS) efforts at the NIH Chemical Genomics Center (NCGC) and computerized docking studies at UC San Francisco has identified two structural classes – triazine nitriles and benzamidoacetates - with potency in the low-micromolar range. Synthetic efforts are currently underway to optimize the potency of both lead series, with the goal of establishing low-nanomolar potency chemical probes. These probes could ultimately facilitate the development of a therapeutic for Chagas disease, as no effective treatment currently exists. Assay and screen design, qHTS data, and results from early rounds of synthesis are presented, along with plans for future synthesis and directions.

**MEDI 302**

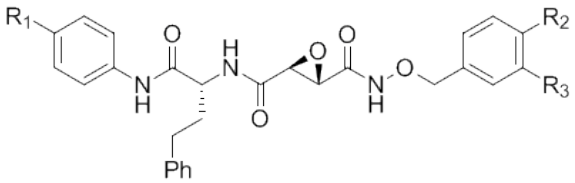
## Effects of hydrophobicity on trypanocidal activity of cysteine protease inhibitors

***George P. Nora***[1]*, gnora@scripps.edu, William R. Roush*[1]*, Cory D. Emal*[2]*, Alejandro Alvarez-Hernandez*[2]*, Meredith Miller*[2]*, acs.officers@umich.edu, Yen Truong*[2]*, Elizabeth Hansell*[3]*, joey@cgl.ucsf.edu, Patricia S. Doyle*[4]*, and James H. McKerrow*[5]*, jmck@cgl.ucsf.edu. (1) Department of Chemistry, Scripps Florida, 5353 Parkside Drive RF-2, Jupiter, FL 33458, (2) Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, (3) Sandler Center for Basic Research in Parasitic Diseases, University of California, San Francisco, San Francisco, CA 94158, (4) Department of Pathology, UCSF, San Francisco, CA 94158-2330, (5) Sandler Center for Basic Research in Parasitic Diseases, University of California San Francisco, San Francisco, CA 94158*

Chagas' disease, or American trypanosomiasis, affects 16-18 million people in Central and South America, causing about 13,000 deaths per year. This disease is caused by a chronic infection of the flagellate protozoan Trypanosoma cruzi, which is typically transmitted to humans through the bite of the triatomid beetle, or ‘kissing bud', during a blood meal. We have demonstrated that vinyl sulfonyl and E-64-related epoxysuccinyl scaffolds exhibit in vivo activity against T. cruzi are in the process of improving these inhibitors of T. cruzi. In the process of expanding our library of vinyl sulfonyl inhibitors, we recognized the possibility that inhibitor hydrophobicity (as calculated by clog P) might play a large role in determining the effectiveness of inhibitors of T. cruzi. This poster will demonstrate the importance of this physical parameter within the vinyl sulfonyl inhibitor series and the successful extension of this concept to the epoxysuccinyl-based cysteine protease inhibitor series.



vinyl sulfonyl inhibitors



E-64-related epoxysuccinyl scaffold

**MEDI 303**

## Design and synthesis of novel inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1)

***Maulik R Patel**, Maria Pino, Blase Billack, and Tanaji T Talele, Department of Pharmaceutical Sciences, College of Pharmacy & Allied Health Professions, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439*

Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that signals the presence of DNA damage by catalyzing the addition of ADP-ribose units to DNA, histones, and various DNA repair enzymes and by facilitating DNA repair. PARP has been gaining increasing interest as a therapeutic target for many diseases and especially for cancer. A structure-based drug design strategy has been applied on PARP-1 enzyme for finding novel heterocyclic templates which could fit into nicotinamide binding pocket of the catalytic fragment of PARP-1. This computational study eventually led to the identification of nitrogen containing heterocyclic-3-carboxamide templates. These initial templates were systematically modified in order to develop series of compounds as potential PARP-1 inhibitors. The synthesis, structure-activity relationship, and biological activity of these compounds will be discussed in the poster.

**MEDI 304**

## Dual acting histone deacetylase-topoisomerase II inhibitors

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Malignant tumors are multifactorial and are frequently linked to defects in more than one signaling pathways. Therefore multi-targeting therapy might be more beneficial, not only to eliminate cancer cells but also to combat emergence of drug resistance. At this front, we are designing novel single agents that simultaneously inhibit topoisomerase and histone deacetylase (HDAC) activities. Both HDAC inhibitors and anthracyclines are clinically validated drugs for cancer treatment. Anthracyclines act primarily by stabilizing DNA-topoisomerase II cleavable complex through intercalation between DNA base pairs. However, DNA is non-covalently associated with histone proteins. HDAC inhibitors, which induce hyperacetylation of histones, could increase the accessibility of DNA within chromatin and consequently potentiate the anticancer activities of topoisomerase inhibitors. These compounds are expected to act across various stages of cancer cell cycle, thereby targeting larger population of cells, resulting in superior anti-proliferative activity. Design, synthesis and biological activity of the dual-acting inhibitors will be presented.

**MEDI 305**

## Inhibitors of SHP2, a protein tyrosine phosphatase

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Tyrosine phosphatases play an important role in regulating the phosphorylation status of signaling proteins, thereby controlling cellular growth, proliferation and differentiation. Whilst the modulation of kinase activity is a clinically proven therapeutic strategy for blocking signaling pathways, the design of inhibitors of protein tyrosine phosphatases (PTPs) has received considerably less attention. PTP inhibitor design is a new area in the field of drug development. Chemical genetic studies of most PTPs are not yet possible because of the lack of specific inhibitors.

SHP2, a non-receptor protein tyrosine phosphatase, is a signal-enhancing component of growth factor, cytokine, and extra-cellular matrix receptor signaling, and plays an important role in cell cycle. SHP2 binds directly to EGFR, PDGFR, Met receptor, IRS-1 and 2, src, FRS1 and 2, and Gab 1 and 2. It has been found that Shp2 dephosphorylates Gab1 and partially dephosphorylates EGFR indicating that Gab1 and EGFR can be the substrates for SHP2. RasGAP has been found to be a downstream target of SHP2 since SHP2 dephosphorylates RasGAP to facilitate Ras activation. This suggests that SHP2 is a great target for cancer therapy since, inhibiting the dephosphorylation of Gab1 by SHP2 may ultimately stop the PI3K/MAPK/ERK signaling cascade, thereby preventing the alteration of gene expression. Therefore, the search for small molecules that can restore the basal state of SHP2, by interacting with the PTP catalytic domain, represents an exciting and novel area for anti-cancer drug development. Based on the hits obtained from HTS screening of a library of 20000 compounds, we have designed and synthesized a small library of putative SHP2 phosphatase inhibitors. The microwave assisted parallel synthesis and SAR studies of a library of 4(1H)-Quinolinones will be presented.

**MEDI 306**

## Inhibition profile of polyaminobenzamides and their isosteres against histone deacetylase isoforms

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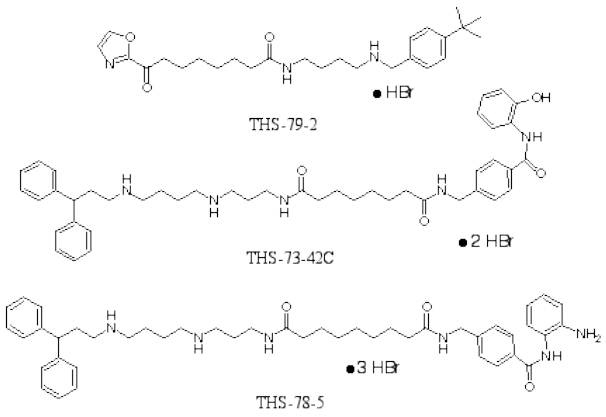
Chromatin remodeling plays a key role in epigenetic regulation of gene expression, including numerous genes that mediate tumorigenesis. Aberrant histone deacetylase (HDAC) activity promotes chromatin condensation and inhibits expression of tumor suppressor factors; by contrast, HDAC inhibition results in tumor growth inhibition. Traditional HDAC inhibitors lack isoform specificity, and can produce toxicity to non-cancerous cells. We reported polyaminohydroxamic acid (PAHA) and polyaminobenzamide (PABA) HDAC inhibitors with reduced toxicity, higher affinity for chromatin and

the potential for uptake by the polyamine transporter. Specific interaction of the polyamine moiety with the HDAC rim region could also improve isoform specificity. PAHAs were potent HDAC inhibitors, but poor substrates for the transporter. PABA derivatives were also potent HDAC inhibitors, and were internalized by the polyamine transporter. We now report the synthesis of additional PABAs and isosteric homologues, their activity against HDACs 1, 3, 6 and 8, and their effects on cultured tumor cells.




**MEDI 307**

**Role of the chlorine atom in a series of 3-chloroindole-7-yl-based FXa inhibitors**

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A consistent feature of many of the most potent neutral FXa inhibitors is the presence of a chlorine or other halogen atom that binds at the base of the S1 pocket, however few studies have critically and quantitatively examined the reasons for this apparent preference over the methyl-containing analogs. Here we study a FXa inhibitor series with an indole-based P1 moiety both experimentally and computationally to explore the increased binding energy of the chlorinated versus methylated compounds. The results suggest that the increased affinity of the chlorinated series results from a) the higher hydrophobicity of chloro- versus methyl-containing compounds and b) stronger interactions of the 3-chloro- versus 3-methyl indoles with Gly219 backbone. Tyr228 interacts with both analogs without special preference. Similar calculations for other series are discussed, resulting in a generalized understanding of the role of chlorine at the base of the S1 pocket in FXa and other trypsin-like inhibitors.

**MEDI 308**

## Semisynthetic route to enzyme inhibitors from natural products

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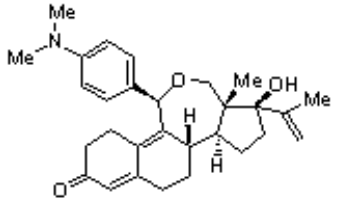
The camptothecins are a class of topoisomerase I inhibitors which also have the ability to inhibit HIF-1a. The parent compd. camptothecin, isolated from Camptotheca acuminata, consists of a planar, pentacyclic ring system with considerable scope for refinement using classical QSAR methods. Camptothecin exhibited significant anti-tumor activity in in vivo studies initiating human clin. trials, however due to high toxicities and low water soly.; it failed to receive FDA approval. Two derivs. of camptothecin however,topotecan and irinotecan, are now FDA approved drugs used in the treatment of ovarian and colon cancer resp. In an effort to identify new analogs of this class with improved biol. profiles, a no. of C-5 aminoalkyl derivs. were synthesized using microwave enhanced methodol. The analogs were screened using a variety of biol. assays, and a 5-fluoroethyl analog with potent HIF inhibitory activity was identified.

**MEDI 309**

## Synthesis and SAR study of novel pseudo-steroids as potent and selective progesterone receptor modulators.

***Nareshkumar Jain***, *George Allan, Olivia Linton, Pamela Tannenbaum, Xin Chen, Jun Xu, Peifang Zhu, Joseph Gunnet, Keith Demarest, Scott Lundeen, and Zhihua Sui, Johnson & Johnson Pharmaceutical Research & Development LLC, 665 Stockton Drive, Exton, PA 19341*

There exist numerous proven and potential applications for progesterone antagonists (PA) in women's health care. Mifepristone (RU-486), one of the most widely prescribed PAs is of limited clinical use due to lack of selectivity for the progesterone (PR) over the glucorticoid receptor (GR). The resulting undesirable side effect profile has provided the stimulus to search for more selective PAs. These efforts have lead to the discovery of a variety of both steroidal and nonsteroidal entities in recent years. Herein we report the synthesis and SAR of a novel series of pseudosteroids with an improved selectivity of PR over GR. The synthesis of these novel 7-pseudo-steroids 1 has been achieved from trenbolone via an efficient 14-step sequence with overall yields of 10-15%. Various substitutions were incorporated at both the aromatic side chain as well as the D ring.



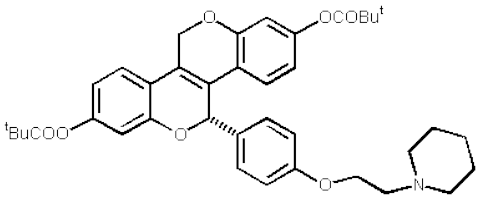

1-(Pseudo-steroids)

**MEDI 310**

## Bisbenzopyran derivatives as delective estrogen receptor modulators with unique pharmacological profiles

***Nareshkumar Jain**, Ramesh M. Kanojia, Fuyong Du, Guo Jian-Zhong, Emmanuel Pacia, Muh-Tsann Lai, Amy Musto, George Allan, DoWon Hahn, Scott G. Lundeen, and Zhihua Sui, Johnson & Johnson Pharmaceutical Research & Development LLC, 665 Stockton Drive, Exton, PA 19341*

Selective estrogen receptor modulators (SERMs) are compounds that act as estrogen agonists on selected targets while being estrogen antagonists on others. Raloxifene, the only second-generation SERM on the market, is being used for treatment and prevention of osteoporosis in postmenopausal women. However, raloxifene exacerbates hot flushes and vaginal dryness in postmenopausal woman, and hence is limited in its clinical use. It is our ongoing effort to identify third-generation SERMs that retain raloxifene's beneficial properties as well as to alleviate hot flushes and improve cognition. We have discovered a novel bisbenzopyran SERM 1, which possesses such biological profile in preclinical studies. It relieves hot flushes and improves vaginal dryness while retaining all the beneficial effects of raloxifene. A systematic SAR study of this novel scaffold will be presented.



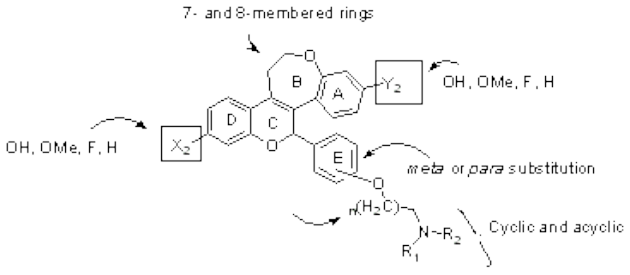

*1*

**MEDI 311**

## Identification and structure-activity relationships of novel chromene-derived selective estrogen receptor modulators

***Nareshkumar Jain**, Jiayi Xu, Ramesh M. Kanojia, Fuyong Du, Guo Jian-Zhong, Emmanuel Pacia, Muh-Tsann Lai, Amy Musto, George Allan, DoWon Hahn, Scott Lundeen, and Zhihua Sui, Johnson & Johnson Pharmaceutical Research and Development, LLC, 665 Stockton Drive, Exton, PA 19341*

As part of a program aimed at the development of selective estrogen receptor modulators (SERMs), novel chromene scaffolds of benzopyranobenzoxapanes were discovered. Substitutions at A ring, D ring and side chain substitutions along with chirality were the determinants for the receptor binding affinity as well as potency in ER modulated MCF-7 or Ishikawa cell-based functional assays. Many compounds showed low nanomolar binding affinity and displayed antagonist activity in the functional assays with IC50s in low nanomolar range. Various compounds with appropriate side chain substitutions demonstrated strong inhibitory activity in uterotropic assays in rats per oral route. A systematic SAR study of this novel scaffold will be discussed.

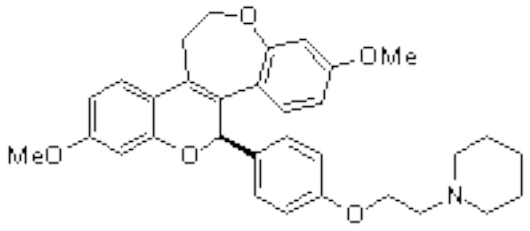


**MEDI 312**

**Discovery of a Chromene-based novel SERM for treatment of postmenopausal syndrome**

***Nareshkumar Jain****, Fuyong Du, Michael Reuman, Jiayi Xu, Guo Jian-Zhong, Emmanuel Pacia, Muh-Tsann Lai, Amy Musto, George Allan, DoWon Hahn, Scott Lundeen, Ronald Rusell, David Ritchie, Martin Cousineau, Sean Peng, and Zhihua Sui, Johnson & Johnson Pharmaceutical Research & Development LLC, 665 Stockton Drive, Exton, PA 19341*

The clinical significance of the selective estrogen receptor modulators (SERMs) is well documented. The intensive research is currently directed at discovery of the “ideal SERM”, an agent that is antiestrogenic in breast and endometrial tissue, but pro-estrogenic in the vasculature and brain, which would be of use as a preventative in breast and uterine cancer and an alternate attractive HRT. Compound 1-(R) is a backup development candidate of the bisbenzopyran lead compound in our SERM program. This compound has shown promising preclinical profile with excellent pharmacokinetic properties. The identification and profiles of this novel SERM will be discussed.




**1**-(*R*)

**MEDI 313**

**Design, synthesis and biochemical evaluation of novel estrogen-receptor conjugates for the treatment of hormone-dependent breast cancer**

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The human hormone estradiol can play a key role in the development and progression of breast tumours. The cause of disease can be affected through the binding of different estrogen-receptor (ER) ligands, which mimic the binding of estradiol, in the ER or by gaining control over intracellular concentrations of estradiol. In this study, the design, synthesis and biological evaluation of structurally related triarylethylene-heterocycle linked compounds containing the modified tamoxifen-type triarylethylene pharmacophore with potential application as selective estrogen receptor modulators (SERMS) was investigated. These SERMS, or estrogen receptor antagonists target the ER and thus act as carrier prodrugs of other selected cytotoxic drugs. A number of bioactive agents have been covalently linked to different SERM scaffolds and the resulting conjugates have been tested in vitro for their antiproliferative activity, cytotoxicity and binding ability to ERα and ERβ. A number of synthesised compounds displayed high ER binding affinities and potent antiproliferative activity.

**MEDI 314**

## Synthesis and SAR of novel 7-membered heterocyclic estrogen receptor ligands

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Although Hormone Replacement Therapy (HRT) has been employed for many years in the prevention of a variety of post-menopausal disorders, there are inherent risks associated with its use. These arise from the indiscriminate effects of estrogen on the body's tissues and include increased risk of both breast and uterine carcinomas. Tamoxifen (Nolvadex®), the first of a class of compounds known as Selective Estrogen Receptor Modulators (SERMs), is a potent treatment for breast cancer due to its strong antagonist properties in breast tissue. However, Nolvadex's strong uterotropic properties limit its use as an HRT agent. Raloxifene (Evista®), a second generation SERM, is a much better HRT candidate since it functions as an antagonist in both breast and uterine tissue but as an agonist in bone and cardiovascular tissue. Unfortunately, Evista's tendency to exacerbate hot flashes, a condition experienced by 75% of post-menopausal women, has limited demand for this HRT option. Thus the search for a third generation SERM that has raloxifene's beneficial properties with an improved side effect profile has been the subject of intense research efforts in recent years.

During routine screening of intermediates for the androgen receptor modulator program, a novel structure was discovered that, while devoid of androgen binding activity, displayed estrogen receptor affinity in the low micromolar range. A structure based design program was initiated and through systematic modification of this lead, molecules with low nanomolar affinity for the alpha subtype of the estrogen receptor have been prepared. The synthesis and SAR of these potential third generation SERM leads are discussed.

**MEDI 315**

## Synthesis and SAR of novel spirofuran potassium channel openers

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While not a life-threatening condition, urinary incontinence (UI) is a disease that can profoundly affect a patient's quality of life. Overactive bladder (OAB), characterized by symptoms of increased urinary frequency, urgency and involuntary loss of urine, accounts for between 40 and 70% of all diagnosed UI cases. Oversensitivity of the bladder with unexpected and involuntary contraction unrelated to urine volume is the primary cause of OAB. Currently muscarinic receptor antagonists are the most widely prescribed agents for OAB though the prevalence of mechanism-based side effects has severely limited patient compliance. Bladder-selective potassium channel openers (KCOs) could offer a novel therapy for OAB that would circumvent the shortcomings of muscarinic agents and a number of promising reports of such compounds have emerged in recent years. As part of our efforts in this arena, we initiated a structure based design program centered on a novel spirofuranyl amine template, culminating in the discovery of a compound with good in vitro potency and effects in vivo in a rat model of OAB. The synthesis and SAR of these potential KCOs are discussed.

**MEDI 316**

**Natural and enantiomeric progesterone derivatives for the treatment of traumatic brain injury**

***Christopher J. MacNevin***[1]*, cmacnev@emory.edu, Dennis C. Liotta*[1]*, dliotta@emory.edu, Donald G. Stein*[2]*, dstei04@emory.edu, and Iqbal Sayeed*[2]*, isayeed@emory.edu. (1) Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, (2) Emory University School of Medicine Brain Research Laboratory, Emory University School of Medicine, Atlanta, GA 30322*

Traumatic brain injury (TBI) affects nearly 1.5 million Americans each year and is a significant health concern worldwide. Pre-clinical and clinical research findings have revealed that the hormone progesterone (PROG), when acutely administered, can dramatically reduce cerebral edema, inflammation, tissue necrosis, and programmed cell death following TBI. The use of PROG as a therapeutic suffers from a number of practical limitations, including most notably its poor solubility and its potential for generating unwanted side effects. Several chemically novel derivatives of PROG and its enantiomer (ent-PROG) have been synthesized and screened using a whole animal model of TBI. All new derivatives demonstrated improved solubility relative to PROG and select compounds have shown equivalent effectiveness to PROG in reducing cerebral edema after TBI.

**MEDI 317**

**Design, synthesis and biological evaluation of 6-substituted-4-azasteroids as tissue selective androgen receptor modulators**

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The androgen receptor is a member of the nuclear receptor superfamily. The androgen receptor is found in many tissues; including the prostate, seminal vesicle, smooth muscle and bone. It is responsible for mediating the physiological actions of the endogenous steroidal androgens testosterone and dihydroxytestosterone (DHT). A tissue selective androgen receptor modulator (SARM) which has anabolic action on bone with little side effects on skin and reproductive tissues is desirable for the treatment of osteoporosis. A class of 6-substituted-4-azasteroids have been identified as SARMs. The synthesis and biological evaluation of this class of compounds will be described.

**MEDI 318**

**Fused imidazole heterocycles as antagonists of the gonadotropin releasing hormone (GnRH) receptor**

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Antagonism of the Gonadotropin Releasing Hormone (GnRH) receptor is utilized as a means to control certain sex hormone related disorders such as prostate cancer, endometriosis, and precocious puberty in children. In our effort to develop small molecule GnRH receptor antagonists, we previously identified several active 4-(1-piperazinyl)benzimidazoles with pendant 1,2-alkyl imidazoles . To further explore the structure-activity relationships (SAR) of these compounds, we envisioned that fusing the alkyl functionalities of the imidazole ring into various bicyclic heterocycles would be useful. Thus, fused imidazo heterocycles including: imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines, imidazo[1,2-a]pyrazines, and imidazo[1,2-c]pyrimidines were prepared and analyzed using a panel of in vitro assays. These included binding inhibition assays performed on recombinant cells expressing either rat or human GnRH receptors and cell-based functional assays (human inositol phosphate release inhibition and rat LH release inhibition). Herein, the preparation of the fused imidazo heterocycles will be described and their activity versus the lead compounds will be discussed.

**MEDI 319**

**Design, synthesis and biological evaluation of 16-substituted-4-azasteroids as tissue-selective androgen receptor modulators**

***Helen J. Mitchell***[1]*, helen_mitchell2@merck.com, William P. Dankulich*[1]*, william_dankulich@merck.com, Chang Bai*[2]*, Thomayant Prueksaritanont*[3]*, Azriel Schmidt*[2]*, Fang Chen*[2]*, Donald B. Kimmel*[2]*, and Robert S. Meissner*[1]*, robert_meissner@merck.com. (1) Department of Medicinal Chemistry, Merck Research Laboratories, 770 Sumneytown Pike, West Point, PA 19486, (2) Department of Molecular Endocrinology, Merck Research Laboratories, West Point, PA 19486, (3) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486*

The androgen receptor is a member of the nuclear receptor superfamily and is responsible for mediating the physiological action of endogenous androgen ligands such as dihydrotestosterone (DHT) and testosterone. A selective androgen receptor modulator (SARM) that is osteoanabolic and has little or no undesirable side effects is desirable for the treatment of osteoporosis. A novel series of 16-substituted-4-azasteroids has been identified as potential tissue-selective androgen receptor modulators. These ligands display potent hAR binding with varying levels of agonist activity, along with attractive physical properties and good pharmacokinetics in dogs. An analog demonstrating a tissue-selective osteoanabolic profile will be identified.

**MEDI 320**

**Proline bis-amides as potent dual orexin receptor antagonists with in vivo efficacy**

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The orexin receptors (OX1R and OX2R) are G-protein coupled receptors expressed mainly in the brain. These receptors are believed to be involved in the regulation of the sleep-wake cycle and other behaviors in animals and humans. Activation of these two receptors by two endogenous peptides, orexin A and orexin B, promotes wakefulness in animals. Hence, blockade of orexin signaling by a small molecule antagonist may offer a new treatment for insomnia patients. Clinical evidence for this hypothesis was demonstrated in 2007 with the release of data from a Phase II insomnia trial from Actelion Pharmaceuticals (1).

Analysis of potential leads from an orexin antagonist screen resulted in the identification of a novel series of dual orexin receptor antagonists containing a proline bis-amide core structure. Several project objectives were achieved using this series of compounds including initial in house studies demonstrating in vivo activity. Data will be presented demonstrating in vivo effects in a pharmacodynamic model of orexin-induced locomotor activity in the rat as well as small molecule antagonist effects in rat sleep.

1.Dingemanse, J.; Dorffner, G.; Hajak, G. ; Benes, H.; Danker-Hopfe, H.; Polo, O.; Saletu, B.; Barbanoj, M. J.; Pillar, G.; Penzel, T.; Chiossi, E.; Hoever, P. Proof-of-concept study in primary insomnia patients with almorexant (ACT-078573), a dual orexin receptor antagonist, World Sleep Congress Poster Presentation, Cairns, Australia, September 3-6, 2007.

**MEDI 321**

## 2-(4-Dialkylaminophenyl)-4-piperazinylbenzimidazole antagonists of Gonadotropin Releasing Hormone (GnRH): In vitro optimization for human and rat activity

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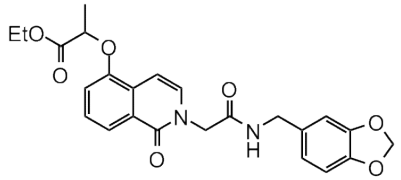
Gonadotropin releasing hormone (GnRH) plays an important role in the stimulation and release of sex hormones. As such, small molecule GnRH antagonists could play a role in the treatment of sex hormone dependent diseases, such as endometriosis, hirsutism, and cancers of the reproductive organs. Additionally, small molecule antagonists could offer potential dosing and compliance advantages over the currently available peptide based therapies. We recently reported on a series of potent, orally bioavailable 2-(4-t-butylphenyl)-4-(1-piperazinyl)benzimidazole-based GnRH receptor antagonists. In particular, we were interested in addressing chemical modifications of the t-butyl functionality, with regard to potency and potential metabolic liabilities. Interestingly, replacement of the t-butyl group with a diethylamino function led to compounds with nanomolar affinity for the human receptor but micromolar affinity for the rat receptor in vitro. Since in vivo evaluation was to be performed in rats, we were challenged with optimizing for both species. Herein, we report our successful optimization of a series of potent dialkylaniline-based GnRH antagonists for both the rat and human receptor.

**MEDI 322**

## Synthesis of small molecule inhibitors of the orphan nuclear receptor steroidogenic factor-1 (NR5A1) based on isoquinolinone scaffolds

***Joshua Roth***[1]*, joshroth@scripps.edu, Franck Madoux*[2]*, fmadoux@scripps.edu, Peter Hodder*[3]*, hodderp@scripps.edu, and William R. Roush*[1]*. (1) Department of Chemistry, Scripps Florida, 5353 Parkside Drive, RF-2, Jupiter, FL 33458, (2) The Scripps Research Institute Molecular Screening Center, Scripps Florida, Jupiter 33458, (3) The Scripps Research Institute Molecular Screening Center and Department of Molecular Therapeutics, Scripps Florida, Jupiter 33458*

Three synthetic routes were developed for structure activity relationship (SAR) studies of high throughput screen-derived isoquinolinone inhibitors of the orphan nuclear receptor steroidogenic factor-1 (NR5A1). Nuclear receptors, several of which are important targets for treatment of human diseases, are transcription factors that regulate gene expression through the binding of endogenous ligands. When natural ligands are not known for nuclear receptors, they are termed “orphan” nuclear receptors. Selective small-molecule biological probes will aid in efforts to determine the pharmacology and therapeutic potential of this sub-set of receptors. Different aspects of the SAR surrounding the initial lead compounds, 1 and 2, including analogs with improved SF-1 inhibitor potency, lower cellular toxicity, and improved NR selectivity will be presented.

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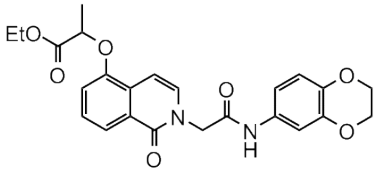


2

**MEDI 323**

## Synthesis of [$^{11}$C]fallypride, a PET tracer for D2/D3 receptors.

***Mingzhang Gao****, Min Wang, Barbara E. Glick-Wilson, Bruce H. Mock, and Qi-Huang Zheng, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-202, Indianapolis, IN 46202, Fax: 317-278-9711*

Fallypride [5-(3-fluoropropyl)-2,3-dimethoxy-*N*-[(2*S*)-1-(2-propenyl)-2-pyrrolidinyl]methyl-benzamide] is a well-known dopamine D2/D3 antagonist with high affinity (*Ki* 30 pM for D2 receptor sites). [$^{18}$F]Fallypride is a commonly used PET tracer for D2/D3 receptors. [$^{11}$C]Fallypride has a potential advantage in back-to-back same-day PET studies. Synthesis and preliminary evaluation of [$^{11}$C]Fallypride have appeared in the literature, however, there are gaps in synthetic detail among them, and certain key steps gave poor yields or were difficult to repeat in our hands. Wishing to study this compound in this laboratory, we investigated an improved synthesis of [$^{11}$C]Fallypride. The precursor 5-(3-fluoropropyl)-2-hydroxy-3-methoxy-*N*-[(2*S*)-1-(2-propenyl)-2-pyrrolidinyl]methyl-benzamide and the standard compound Fallypride were synthesized from 2-hydroxy-3-methoxy-5-(2-propenyl)benzoic acid methyl ester in 7 and 5 steps with 16% and 22% overall chemical yields, respectively. The direct methylation of precursor hydroxyl-Fallypride with methyl iodide also provided authentic standard in 31% yield. The target tracer [$^{11}$C]Fallypride was prepared by *O*-[$^{11}$C]methylation of hydroxyl-Fallypride with [$^{11}$C]$CH_3OTf$ and isolated by HPLC method in 50-60% radiochemical yields and 4-6 Ci/μmol specific activity at end of bombardment (EOB).

**MEDI 324**

## A redox- and light-responsive MRI contrast agent

***Chuqiao Tu*** *and Angelique Y Louie, Department of Biomedical Engineering, University of California, Davis, CA 95616*

The ability to non-invasively monitor redox activity in a living system would provide a foundation for detailed studies of metabolism in relation to disease processes and therapies. Here we report the synthesis and characterization of a novel redox- and light-responsive, T1-weighted magnetic resonance imaging (MRI) contrast agent which is combination of a Gd(III) containing moiety, a spacer and a spiropyran(SP)/merocyanine(MC) motif. The agent exhibits obvious change in r1 relaxivity and signal intensity in MRI when mixed with NADH or irradiated with visible light in both solution and cells in culture. The agent also gives out strong fluorescence which can be influenced by NADH or light irradiation. This novel MRI contrast agent may have unique potential to respond to NADH related biochemical activities and promising for direct, non-invasive investigation of metabolic activities and cell signaling in vivo.

**MEDI 325**

## Synthesis and anti-HIV activity of fatty acyl derivatives of Stavudine

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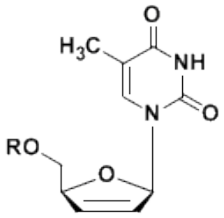
Stavudine is a nucleoside reverse transcriptase inhibitor anti-HIV drug. About half of the unmodified drug is eliminated by urine due to hydrophilic nature of the compound. Fatty acids, 12-azidododecanoic acid, 12-thiaethyldodecanoic acid, and 12-bromododecanoic acid, were previously reported to be moderately active against HIV-infected T4 lymphocytes. We investigated whether esterification of Stavudine with fatty acids can result in enhanced potency by improving uptake of the prodrug into infected cells and releasing the active moieties. Evaluations of anti-HIV-1 activity against cell-free and cell-associated virus revealed that the anti-HIV activity of 5′-substituted derivatives is clearly dependent on the nature of the 5′-substituents. From all derivatives of Stavudine, the azidododecanoyl analog (KKH-2) was the most potent, displaying $IC_{50}$ value that was about half of that of Stavudine against cell-free virus. None of the compounds were significantly cytotoxic ($EC_{50}$ >100 μg/mL).




Stavudin (d4T)

| | R |
|---|---|
| **KKH-1** | $Me(CH_2)_{12}CO$- |
| **KKH-2** | $N_3(CH_2)_{11}CO$- |
| **KKH-3** | $EtS(CH_2)_{11}CO$- |
| **KKH-4** | $Br(CH_2)_{11}CO$- |

"Support for this subproject (MSA-03-367) was provided by CONRAD, Eastern Virginia Medical School under a Cooperative Agreement (HRN-A-00-98-00020-00) with the United States Agency for International Development (USAID). The views expressed by the authors do not necessarily reflect the views of USAID or CONRAD."

**MEDI 326**

**Optically pure synthesis of IDX899: An aryl phosphinate-indole (API) as novel NNRTI with potent anti-HIV activity and enhanced barrier to resistance**

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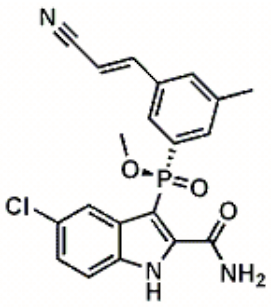
Background: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are key component in HIV-therapy in the so-called Highly Active Antiretroviral Therapy (HAART), a combination of two nucleoside HIV reverse transcriptase inhibitors (NRTIs) and one NNRTI or one protease inhibitor (PI). However, the emergence of mutants and the cross-resistance of these mutants across this class of drugs require the development of second generation of NNRTI with higher barrier to resistance. Methods: Our efforts to discover new NNRTI led to the identification of a new class of inhibitors: Aryl Phosphinate Indoles (API). Racemic and optically pure synthetic routes of those NNRTIs were developed and the compounds were evaluated for anti-HIV activity against wild type (WT), single mutant (K103N, Y181C) and double mutant (K103N/Y181C) in enzyme- and cell-based assay. Results: The synthesis of API was investigated and several routes were identified starting from 3-halogenoindole either in halogen/lithium exchange chemistry or in palladium cross-coupling reaction as key steps. A Structure Activity Relationship (SAR) study of about 300 compounds revealed that arylmethylphosphinate at position 3 of the indole and a 3,5-disubstituted phenyl ring are essential to achieve high activity towards mutants. Among them, IDX899 showed in vitro nM activity against WT and mutants and best pharmacokinetic properties. Synthetic efforts were focused in optimisation of optically pure synthesis of phosphinate IDX899. Conclusion: SAR study of new NNRTI Aryl Phosphinate Indoles led to highly potent IDX899; an inhibitor of wild type and resistant HIV-1 RT. Optically pure syntheses of IDX899 were developed and optimised. An ongoing phase I/II clinical trial is evaluating the safety, tolerability and antiviral activity of IDX899.




IDX899

**MEDI 327**

**Structural and mechanistic basis of penicillin-binding protein inhibition by lactivicins**

***Tom Brown Jr.***[1]*, tom.brown@chem.ox.ac.uk, Pauline Macheboeuf*[2]*, Delphine Fischer*[1]*, Astrid Zervosen*[3]*, André Luxen*[3]*, Bernard Joris*[4]*, Andréa Dessen*[2]*, desseb@ibs.fr, and Christopher J.*

*Schofield[1], christopher.schofield@chemistry.oxford.ac.uk. (1) Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom, (2) Institut de Biologie Structurale Jean-Pierre Ebel Commissariat à l'énergie atomique, Centre National de La Recherche Scientifique – Université Joseph Fourier, Grenoble, Grenoble F-38027, (3) Centre de Recherches du Cyclotron, B30, Université de Liège, Liège B-4000, Belgium, (4) Centre d'Ingénierie des Protéines, Institut de Chimie, B6a, Université de Liège, Liège B-4000, Belgium*

β-lactam antibiotics, including penicillins and cephalosporins, inhibit penicillin-binding proteins (PBPs), which are essential for bacterial cell wall biogenesis. Pathogenic bacteria have evolved efficient antibiotic resistance mechanisms, including mutations to PBPs that are resistant to β-lactam inhibition. Lactivicin (LTV) is the only natural β-lactam inhibitor that does not contain a β-lactam ring. LTV and an analogue, phenoxyacetyllactivicin (PLTV), were synthesized and assayed for activity versus penicillin-resistant bacterial strains. Crystallographic analyses of complexes with *Streptococcus pneumoniae* PBP1b revealed that LTV and PLTV inhibition involves opening of both cycloserine and γ-lactone rings. In PBP1b complexes, the ring-derived atoms from LTV and PLTV show a notable structural convergence with those derived from a complexed cephalosporin, cefotaxime. The structures imply that derivatives of LTV will be useful in the search for new antibiotics with activity against β-lactam–resistant bacteria.

**MEDI 328**

**Discovery of a potent anti-Lassa fever virus drug**

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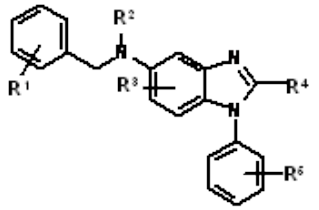
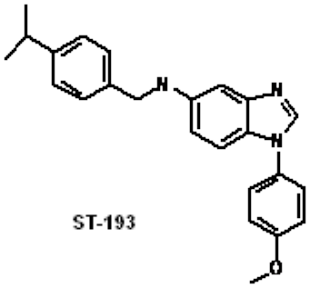
Lassa fever virus, along with several other arenaviruses, is categorized as a Category A priority pathogen by the CDC and NIAID. The virus is currently endemic in West Africa with a mortality rate of 15-20% among hospitalized patients. A pseudotyped virus assay was utilized to screen a small-molecule library of about 400,000 compounds and identified a benzimidazole derivative with inhibitory activity against Lassa virus. A preliminary structure-activity relationship study indicated that electron-donating groups ($R^1$ and $R^5$) on the phenyl rings increase potency, while their positions also affect activity. Subsequent optimization identified a potent inhibitor (ST-193) with $IC_{50}$ of 1.6nM. The compound has undergone a series of evaluations, including tolerability, pharmacokinetics, toxicity, and efficacy. ST-193 shows superiority to ribivarin in a lethal Lassa fever guinea pig model. The drug is now in pre-clinical stage of development.





## MEDI 329

### Seven-membered ring sugar nucleosides: Synthesis and first antiviral evaluation of a novel class of modified nucleosides

***Frédéric Leroy**, Tony Bouisset, Dominique Chaves, David Dukhan, Gilles Gosselin, Jean-Christophe Meillon, and Richard Storer, IDENIX Laboratoire, Cap Gamma, 1682, rue de la Valsière BP50001, 34189 Montpellier, France*

In the last few years there has been an increasing interest in base- and sugar-modified nucleosides as potential antiviral agents. As such, we are interested in the study of a new family of sugar-modified nucleosides, including a seven-membered carbohydrate ring. Thus far, only one report relating to their preparation has been published. In the present study, the two fastest and most convenient syntheses leading to these seven-membered ring sugar nucleosides will be described. Analogues 1 and 2 including Adenine and Cytosine as the heterobase: The presentation will also disclose on the first biological evaluations of these nucleosides against hepatitis C virus infections.

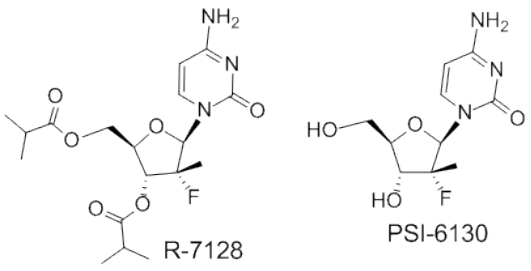

1 2

## MEDI 330

### Beta-D-2'-Deoxy-2'-fluoro-2'-C-methyluridine (PSI-6206) phosphoramidates: Potent liver targeting nucleoside inhibitors of HCV RNA replication

*Michael J. Sofia, Peiyuan Wang, Jinfa Du, Holly Micolochick Steuer, Congrong Niu, Bruce S. Ross, Suguna Rachakonda, Phillip A. Furman, Michael J. Otto, and **Dhanapalan Nagarathnam**, Pharmasset, Inc, 303A College Road East, Princeton, NJ 08540, Fax: 609-613-4150*

HCV infection is a major health issue with over 170 million carriers worldwide. Recently, we demonstrated potent clinical antiviral activity with R-7128, a prodrug of PSI-6130 (Beta-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine). Cell metabolism studies have shown that PSI-6130-monophosphate is partially converted to its uridine metabolite, PSI-6206-monophosphate via cytidylate deaminase. The nucleoside, PSI-6206, by itself is not an inhibitor of HCV, however, PSI-6206-triphosphate is a potent inhibitor of HCV NS5B polymerase. Further studies have shown that PSI-6206 is not a substrate for phosphorylation, but, PSI-6206-monophosphate can be converted to the triphosphate derivative via YMPK and NDPK. Based on these findings, we explored phosphoramidates of PSI-6206 in an effort to overcome the deficient first phosphorylation step. Systematic lead optimization in this area yielded potent HCV inhibitors, which that demonstrated as much as a 100-fold increase in potency over PSI-6130 in the HCV replicon assay.




R-7128 PSI-6130

**MEDI 331**

**Synthesis and SAR studies of antifungal 5(6)-substituted benzotriazole derivatives**

***Pallav D Patel**, Maulik R Patel, Andrew Warren, Stacia Nicholson, Blase Billack, and Tanaji T Talele, Department of Pharmaceutical Sciences, College of Pharmacy & Allied Health Professions, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439*

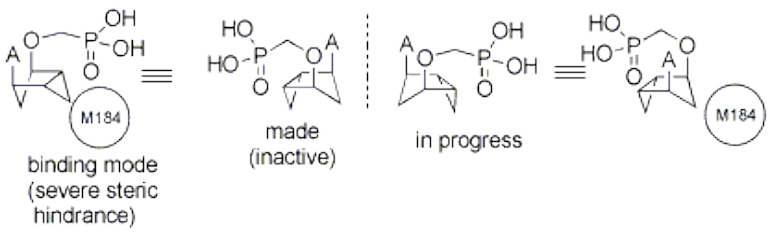
In an effort to develop potent antifungal agents, series of fluconazole analogs where one of it's 1,2,4-triazole ring was replaced with 5(6)-substituted benzotriazoles and 4(7)-azabenzotriazole, was prepared and evaluated for antifungal activity against Candida spp., and Aspergillus spp. in vitro. Several of these analogs were found to be superior to fluconazole. The synthesis, SAR, molecular docking, and antifungal evaluation of these analogs will be discussed in the poster.

**MEDI 332**

**Probing the interaction of HIV reverse transcriptase with conformationally locked threosyl nucleoside phosphonates: A stereochemical approach**

***Hisao Saneyoshi**, saneyoshih@ncifcrf.gov, Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, Frederick, MD 21702, B. Christie Vu, cvu@ncifcrf.gov, HIV Drug Resistance Program, CCR, NCI, NIH, Frederick, MD 21702, Stephen H. Hughes, hughes@ncifcrf.gov, HIV Drug Resistance Program, NCI, NIH, Frederick, MD 21702, Paul L Boyer, NCI/HIV Drug Resistance Program, NCI-FCRDC, Frederick, Frederick, MD 21702, Stefan G Sarafianos, Department of Molecular Microbiology and Immunology, University of Missouri-Columbia, School of Medicine, Columbia, MO 65212, and Victor E. Marquez, marquezv@dc37a.nci.nih.gov, Laboratory of Medicinal Chemistry, Center for Cancer Reserch, NCI-Frederick, Frederick, MD 21702*

Nucleoside phosphonates are an important category of antiviral agents, which can bypass the inefficient, and rate-limiting first phosphorylation step. A nucleoside phosphonate can be further phosphorylated by cellular kinases to produce the required triphosphate congener. Recently, Herdewijn et al. reported that deoxy-L-threosylphosphonate nucleosides are effective anti-HIV agents. This innovative report inspired us to synthesize nucleoside phosphonates of conformationally locked carbocyclic nucleosides to probe their interactions with the active site of HIV-1 RT. We synthesized a conformationally locked, carbocyclic nucleoside phosphonate version of the active L-threosyl analogue built on a rigid bicyclo[3.1.0]hexane template from chiral cyclopentene monoacetate. The structure of the precursor was confirmed by X-ray crystallography. However, the compound was inactive against HIV-1 possibly due to a steric clash with M184. The synthesis of the D-enantiomer, which according to modeling should avoid this clash, is in progress and results with this compound will be presented.



**MEDI 333**

## Design and synthesis of 1-Beta-D-arabinofuranosyladenine prodrugs as antiviral agents

***Wei Shen***[1]*, wshen@tsrlinc.com, John Hilfinger*[2]*, jhilfinger@tsrlinc.com, Jae-Seung Kim*[3]*, Summer Laviolette*[3]*, Jie Zhang*[3]*, Stefanie Mitchell*[3]*, Phil Kish*[3]*, Paul Kijek*[3]*, Julie M. Breitenbach*[4]*, Brian G. Gentry*[4]*, and John C. Drach*[4]*, jcdrach@umich.edu. (1) Department of Chemistry, TSRL, Inc, 540 Avis drive, Ann Arbor, MI 48108, (2) TSRL, Inc, Ann Arbor, MI 48108, (3) Department of Biopharmaceutics and Analytical, TSRL, Inc, Ann Arbor, MI 48108, (4) Department of Biologic and Materials Sciences, University of Michigan, Ann Arbor, MI 48109*

1-Beta-D-arabinofuranosyladenine (vidarabine) is an antiviral drug with activity against herpes viruses, poxviruses, and certain rhabdoviruses, hepadnarviruses, and RNA tumour viruses. However it is more toxic and less metabolically stable than other current antivirals such as acyclovir and ganciclovir. It is readily deaminated by adenosine deaminase to ara-hypoxanthine (ara-H). This metabolite possesses weak antiviral activity, but is at least 10-fold less potent than vidarabine. We now present preliminary work on design and synthesis of prodrugs for vidarabine. The synthesis was based on a facile method to selectively protect 2'- and 3'-hydroxyl group of vidarabine as the levulinate ester. Thus, TBDMSi was used to protect the 5'-hydroxyl group of vidarabine followed by levulinate esterification of 2'- and 3'-hydroxyl groups. Removal of TBDMSi group with TBAF and acetic acid provided 2'- and 3'-hydroxyl protected vidarabine as dilevulinate ester without detectable 3' to 5' ester migration. Parallel synthesis strategy was then applied to selectively couple different L- and D-amino acids, lipid acid or phosphoramidates with the 5'-hydroxyl group of vidarabine. The levulinate group was readily removed with hydrazone in pyridine-acetic acid buffer within 10 to 20 minutes without affecting the ester bond on 5'-hydroxyl group. This strategy provided a low cost method for synthesizing libraries of prodrugs with large quanties (around 100 mg for each) at relatively high yield. These compounds were evaluated for oral bioavailabity and their bioavailabilities were improved comparing to the parent drug. *In vitro* the prodrugs had $IC_{50}$ values against vaccinia and cow pox viruses comparable to vidarabine alone. These compounds also had enhanced enzymatic stability further illustrating good potential for oral delivery. Results of the detailed evaluation of the compounds will be reported. Supported by grant 1 R43 AI071400 from N.I.H.

**MEDI 334**

## Novel potent pyrazole based inhibitors of the HCV NS5B RNA-dependent RNA polymerase

***Martin J Slater****, Gianpaolo Bravi, Anne G Cheasty, John A Corfield, Rebecca H Fenwick, Richard M Grimes, David Harrison, C David Hartley, Richard L Jarvest, Katrina J Medhurst, Malcolm L Meeson, Jacqueline E Mordaunt, Fereshteh Mirzai, Nigel R Parry, Pritom Shah, Pia A Thommes, Claire S Wilkinson, and Emily Williams, Infectious Diseases Chemistry Stevenage, GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom, Fax: 44-1438-768232*

The HCV NS5B gene encodes the viral RNA-dependent RNA polymerase (RdRP) which is responsible for the replication of the viral genome. It is a clinically validated and tractable target of considerable interest.

The HSV NS5B polymerase has a structure similar to other polymerases. These can be likened to a right hand, with ‘finger', ‘palm' and ‘thumb' domains clearly distinguished. Several classes of inhibitors directed against HCV NS5B have been described, which inhibit the enzymatic activity and viral

replication in the HCV replicon system. These compounds bind to distinctive sites on the polymerase molecule and thus have been termed ‘palm', ‘thumb', ‘primer-grip' or ‘finger-loop' binders, etc.

We have previously reported the identification of two distinct series with different binding modes in the palm site of the polymerase; thiadiazines and acylpyrrolidines. As part of our ongoing search for novel chemotypes capable of inhibiting the NS5B polymerase of HCV, we have now developed a pyrazole based series which bind at the thumb site of the polymerase and are complementary to the palm site binders. The design and optimisation of the pyrazole series utilized structure-based design, parallel use of NS5B enzyme and HCV replicon assays. Structure-activity relationships leading to molecules with nanomolar EC50 potencies in the HCV replicon (1a and 1b) and their pharmacokinetic profiles in the rat will be described.

**MEDI 335**

**1,2,3-Triazoles as 8-azapurine nucleoside analogs**

*Christopher L. Boswell, Whitney H. Mudd, Joshua B. Knight, Danielle L. Jordan, and **Erland P. Stevens**, Department of Chemistry, Davidson College, PO Box 7120, Davidson, NC 28035, Fax: 704-894-2709*

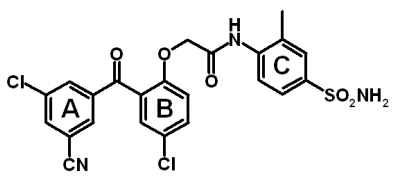
1,2,3-Triazoles were prepared through cycloadditions of enol ethers with azides bearing a protected ribosyl or similar group. Deprotection of the sugar unit and further functionalization of the triazole ring afforded triazole nucleoside analogues. Synthetic details and preliminary activity data against selected viruses will be presented.

**MEDI 336**

**Lead optimization studies of GW8248X, a novel benzophenone NNRTI for the treatment of HIV-I**

***Matthew D. Tallant**, Mark P. Edelstein, Robert G. Ferris, George A. Freeman, Pek Y. Chong, Huichang Zhang, Harry B. Marr, Dan Todd, Daniel G. Lang, and Maggie S. McIntyre, Infectious Diseases CEDD, GlaxoSmithKline Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709*

GW8248X is a novel benzophenone NNRTI (Non-nucleoside reverse transcriptase inhibitor) with excellent activity against HIV-1 and clinically relevant viral mutations, the prodrug of which showed significant antiviral activity in Phase I studies. Unfortunately GW8248X has extremely low aqueous solubility as well as microMolar activity against hERG. As such, a backup effort was initiated and herein we describe efforts focused on replacement of the sulfonamide as well as the “A-ring” chlorine in an attempt to improve drug-like properties. The synthesis and SAR studies within this chemical series led to the identification of GSK3986A which exhibits good activity against a wide panel of HIV mutant viruses as well as improved hERG and aqueous solubility properties.




GW8248X

**MEDI 337**

**Synthesis and biological activity of A-33853 and its analogs**

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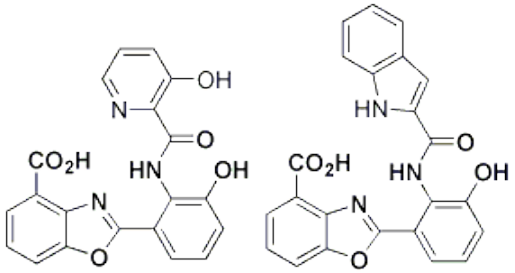
A benzoxazole natural product, antibiotic A-33853 is produced by submerged aerobic fermentation of a new Streptomyces sp. NRRL 12068. A-33853, its diacetyl and triacetyl derivatives have shown promising antibacterial and antiviral activities[1]. Structure of A-33853 has been elucidated through X-ray diffraction studies of its tetraacetyl derivative. The biological data shows that antibiotic A-33853 is a very attractive lead compound for the development of novel antibacterials. The parent natural product and a number of it derivatives were synthesized and evaluated for their activity against Bacillus anthracis, the causative agent of anthrax. The synthesized compounds show low micromolar activities. Synthesis and SAR of a number of novel derivatives of the natural product are presented.
[1]. Michel, K. H.; Boeck, L. D.; Hoehn, M. M. The discovery, fermentation, isolation, and structure of antibiotic A-33853 and its tetraacetyl derivative. J. Antibiot. 1984, 37, 441-445.




A-33853

**MEDI 338**

**Metalloform-selective inhibitors of methionine aminopeptidase with antibacterial activity**

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All bacteria express methionine aminopeptidase (MetAP) from a single essential gene, which removes the N-terminal methionine residue from nascent proteins, and therefore, MetAP is a promising target to develop novel antibiotics. Several chemical classes of MetAP inhibitors have been discovered, but none of them have shown significant antibacterial activity. Divalent metals are required for enzyme catalysis. Although Co(II), Mn(II), Fe(II), Zn(II) and Ni(II) can all activate purified MetAP, it is not clear which of the metals is actually used by MetAP inside bacterial cells. One of the challenges in the development of MetAP inhibitors as therapeutic agents is to define the metal ion used by cellular MetAP and to discover MetAP inhibitors that can effectively inhibit this metalloform.

Our research group has recently discovered several non-peptidic MetAP inhibitors that show remarkable potency and selectivity towards different metalloforms of MetAPs by high throughput screening. Evaluation of these inhibitors on inhibition of purified enzymes and inhibition of bacterial cell growth revealed the possible metal used by cellular MetAP and discovered MetAP inhibitors with significant antibacterial activity when tested on Gram-positive and Gram-negative bacteria. They provide not only valuable new research tools for defining the relevant metal for MetAP inside cells, but also novel leads for obtaining antibacterial drugs.

**MEDI 339**

**Cell-based optimization of novel benzamides as antimalarials**

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Malaria is an immense health threat and places a large economic burden on infected countries. Malaria directly causes about 2 million deaths each year. Due the growing problem of drug resistance to the current antimalarial drugs, new chemical entities are needed to fill a drying development pipeline.

Here we report our effort to develop novel antimalarials from a cell-based screening strategy. The starting point is our in house compound collection, which were screened against a cell-based proliferation assay of plasmodium falciparum. A novel benzamide scaffold was structurally modified to remove human kinase activity while maintaining antimalarial properties. SAR for this series of compounds will be disclosed, focusing on optimization of cellular potency against wild-type and drug resistant parasites and improvement of physiochemical and pharmacokinetic properties. The lead compounds in this series show good potency in vitro and good oral exposure levels in vivo.

**MEDI 340**

**Antileishmanial betulin derivatives**

*Sami Alakurtti*[1]*, Nina Sacerdoti-Sierra*[2]*, Charles L. Jaffe*[2]*, Salme Koskimies*[3]*, and* ***Jari Yli-Kauhaluoma***[1]*, jari.yli-kauhaluoma@helsinki.fi. (1) Division of Pharmaceutical Chemistry, University of Helsinki, Faculty of Pharmacy, P. O. Box 56 (Viikinkaari 5 E), FI-00014 Helsinki, Finland, Fax: 358-9-19159556, (2) Hadassah Medical School, Hebrew University, Jerusalem 91120, Israel, (3) VTT, Technical Research Centre of Finland, FI-02044 Espoo, Finland*

Betulin (lup-20(29)-ene-3,28-diol) is an abundant naturally occurring triterpene, and it is found predominantly in bushes and trees forming the principal extractive (up to 30% of dry weight) of the bark of birch trees. Betulin and its derivatives such as betulinic acid have many interesting pharmacological properties, such as cytotoxic activity against many tumour cell lines and anti-HIV activity with a new mechanism of action. Several synthetic betulin derivatives that have been chemically modified at the positions C-3 and C-28 of the lupane skeleton were produced, and the anti-leishmanial inhibition activity of compounds was evaluated at 50 μM against Leishmania donovani and Leishmania tropica. Betulonic acid had the best anti-leishmanial activity with

remarkable 98% inhibition at 50 μM giving a GI50 value of 14.6 μM. In conclusion, carbonyl or carboxyl groups seem to have beneficial effect in anti-leishmanial inhibition activity, and these compounds represent important leads for further optimization.

**MEDI 341**

**Design, synthesis and evaluation of 6-6 fused bicyclic nonclassical *Pneumocystis jirovecii(pj)* and *Toxoplasma gondii(tg)* dihydrofolate reductase(DHFR) selective inhibitors**

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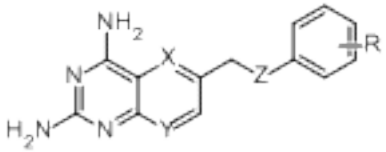
*P. jirovecii* and *T. gondii* are pathogens that cause often fatal opportunistic infections in immunocompromised patients, particularly AIDS patients. Inhibiting dihydrofolate reductase (DHFR) of these pathogens could provide a treatment for the infections. Current therapies are only partially successful, due to the lack of selectivity of agents for the pathogen DHFR. The absence of any animal models for human *Pneumocystis jirovecii* pneumonia and the lack of crystal structures of *pj*DHFR and *tg*DHFR make the design of such analogs more difficult. Using analog design, we have synthesized 6-6 fused bicyclic nonclassical compounds of general structure 1 as potential inhibitors of DHFR from *P. jirovecii* and *T. gondii*. The design, synthesis and biological evaluation of these inhibitors will be presented.




1

**MEDI 342**

**HIV-1 Integrase inhibitors derived from 2,3-dihydro-6,7-dihydroxy-1H-isoindol-1-ones and 4,5-dihydroxy-1H-isoindole-1,3(2H)-diones**

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Integrase (IN) is a crucial enzyme in the life cycle of human immunodeficiency virus type 1 (HIV-1) that has recently been validated as an antiviral target by the FDA approval of the IN inhibitor MK-0518 (raltegravir) for the treatment of HIV/AIDS. Several chemical families of highly potent IN inhibitors have been reported, which are believed to function by chelating catalytically essential divalent metal

ions. Recently we reported that the 2,3-dihydro-6,7-dihydroxy-1H-isoindol-1-one ring system provides the basis for IN inhibitors with good inhibitory potency and strand transfer (ST) selectivity in Mg2+. Addition of one oxo-group to the isoindole-1-one ring system provided the 4,5-dihydroxy-1H-isoindole-1,3(2H)-dione based series of potent IN inhibitors. Further structural investigation on these two ring systems lead to highly potent IN ST inhibitors with sub-micromolar inhibitory potency and good selectivity for ST versus 3'-P (3'-processing) in vitro. Substituents on the benzyl amide portion of the molecules significantly affect the inhibitory potency in vitro. Antiviral assays using HIV-1 vectors show that many of the compounds block HIV-1 replication in cultured cells but exhibit relatively low therapeutic indices.

**MEDI 343**

**Mechanism elucidation of dendrimeric antimicrobial peptides**

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The development and derivation of new antibacterial agents have been based on antimicrobial peptides (AMPs) because of their potential ability to overcome antibiotic-resistant bacterial strains. Our recent studies indicate that a multivalent strategy of polymerized AMPs can enhance the potency of monomeric peptides based on repeating sequences of arginine and tryptophan. A dendrimeric display of these amino acids have been the most effective scaffold. In the present study, biological assays, cytotoxic assays and spectroscopic studies were carried out under physiological conditions to clarify the mechanism of this new class of antibacterial agents.

**MEDI 344**

**Synthesis and structure activity relationships of 2-triazole substituted analogs of 5'-O-[N-salicyl(sulfamoyl)]adenosine: Potent antitubercular agents that target siderophore biosynthesis**

***Amol Gupte**, Helena I. Boshoff, Clifton E. Barry, and Courtney C. Aldrich, Center for Drug Design, University of Minnesota, Academic Health Center, Minneapolis, MN 55455*

Tuberculosis (TB) is a leading cause of bacterial infectious disease mortality in the world and the development of multi- and extensively drug resistant strains of Mycobacterium tuberculosis demands the development of new chemotherapeutic agents. Recently, 5„S-O-[N-(Salicyl)sulfamoyl]adenosine (Sal-AMS, 1) was described as a potent antitubercular agent, whose mechanism of action is due to inhibition of MbtA that catalyzes the first step in siderophore biosynthesis of this organism. A study of the structure activity relationships is detailed targeting the C-2 position of the purine. Installation of an azido group at the C-2 position enabled preparation of a series of substituted 1,2,3-triazoles 2 via the copper catalyzed azide alkyne cycloaddition (CuAAC) reaction. A systematic series of aryl and alkyl groups positioned on the triazole were investigated. The overall trends from this series of analogues will be discussed. Significantly, analogues were identified that exhibited improved physiochemical and pharmacological properties over the parent compound.

## MEDI 345

### Leveraging chemistry in the attack on M. tuberculosis resistance and persistence

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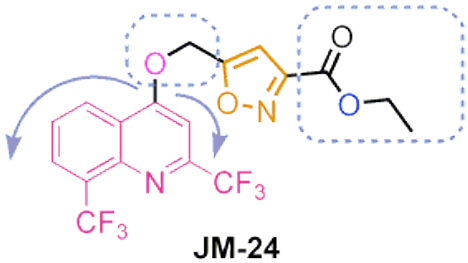
The current antitubercular drug arsenal is >40 years old and is asked to combat an epidemic. Two significant hurdles stem from M. tuberculosis (Mtb) drug resistance and persistence. Phenomenologically understood, drug resistance continues to escalate, highlighted by the absence of a viable treatment for extensively drug-resistant strains. Persistence - the development of tolerance to drug therapy – is ill defined in terms of its basic biology and is intertwined with resistance by prolonged therapeutic regimens to expunge persistent mycobacterial sub-populations. The chemical exploration of inhibitors of mycobacterial targets pertinent to resistance and persistence will be described. 5-substituted triclosan analogs will be discussed in terms of their structure-based design, synthesis, and biological evaluation against drug-sensitive and drug-resistant strains of Mtb. Efforts will also be described towards the design of small molecule inhibitors of the glyoxylate shunt, supported by genetic data to be relevant to the persistent phase of tuberculosis.

## MEDI 346

### From serendipity to rational antituberculosis drug discovery on mefloquine-based ligands

***Jialin Mao***[1], *jmao4@uic.edu, Hai Yuan*[2], *Annamaria Lilienkampf*[2], *lilienka@uic.edu, Yuehong Wang*[1], *Baojie Wan*[1], *Richard B. van Breemen*[3], *breemen@uic.edu, Alan P. Kozikowski*[2], *kozikowa@uic.edu, and Scott G. Franzblau*[1]. *(1) Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, (2) Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612, (3) Department of Medicinal Chemistry & Pharmacognosy, University of Illinois College of Pharmacy, Chicago, IL 60612-7231*

JM-24 [5-(2,8-bis-trifluoromethylquinolin-4-yloxymethyl)-isoxazole-3-carboxylic acid ethyl ester], as a promising lead candidate against M. tuberculosis, had excellent in vitro antituberculosis activity (MABA MIC=0.39ug/ml) and showed in vivo efficacy in BALB/c mice at the dosage of 400mg/kg p.o.. In vitro metabolism indicated that JM-24 had two metabolic soft spots. Therefore, we separated our chemistry work into two categories: 1) achieving better in vitro anti-TB activity and 2) removing the metabolic soft spots to achieve better in vivo efficacy. Medicinal chemistry efforts included modifications at the ester terminal and the ether linker. The detailed structure-activity relationships and the proposed biotransformation pathway will be presented and discussed.




**JM-24**

**MEDI 347**

**Structure activity relationship (SAR) investigations of tetrahydroquinolines as BKCa agonists**

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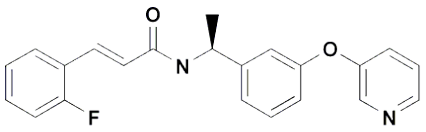
BKCa (also known as MaxiK) is a large-conductance calcium-activated potassium channel that is believed to be an important regulator of neuronal excitability and synaptic transmission. It has been postulated that BKCa constantly monitors the electrical and metabolic state of the cell based on its unique gating mechanism. BKCa is activated by the combination of membrane voltage and intracellular calcium. Activation of BKCa results in a large potassium ion efflux that causes the cell to be rapidly hyperpolarized, thereby reducing the neuronal excitability and decreasing the intracellular calcium load. BKCa is expressed in the trigeminovascular pain (TNC) pathway and it is known that during a migraine attack there is increased neuronal firing in this pathway. We have developed a series of substituted tetrahydroquinoline analogs as BKCa agonists. Using these BKCa agonists, we have performed slice electro-physiology studies in the TNC to show that BKCa agonism reduces spontaneous and evoked neuronal firing in this pathway. Based on these results, BKCa agonists may be a unique way to treat migraine headaches. Herein we discuss the SAR and in vitro efficacy of this series.

**MEDI 348**

**Design and synthesis of novel cinnamamides as KCNQ2 potassium channel openers**

***Li-Qiang Sun****, Yong-Jin Wu, Jie Chen, Huan He, John E. Starrett Jr., Charlie Conway, Christopher G. Boissard, Rick L. Pieschl, Valentin K. Gribkoff, Joanne Natale, Ronald J. Knox, David G. Harden, Mark W. Thompson, William Fitzpatrick, David Weaver, Frederic Machet, and Steven I. Dworetzky, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702*

A novel series of cinnamamides was synthesized and the effect of these compounds on mKCNQ2, a voltage-gated potassium channel, expressed in mammalian cells, was determined through high-throughput library screening using a thallium flux assay. The results of the SAR studies in this series led to the identification of several lead KCNQ2 openers. The two most active compounds emerging from the series, 1 and 2, were chosen for further evaluation of their effects on mKCNQ2 currents heterologously expressed in HEK 293 cells using whole-cell patch-clamp to confirm their activities. Compound 1 was subsequently tested on rat hippocampal slices and in both Diabetic and Chung models. This KCNQ2 opener showed significant activity in reducing neuronal hyperexcitability and was active in both Diabetic and Chung neuropathic models. Thus, the KCNQ2 opener may have therapeutic potential for the treatment of CNS disorders characterized by neuronal hyperexcitability, such as migraine, epilepsy, and neuropathic pain.

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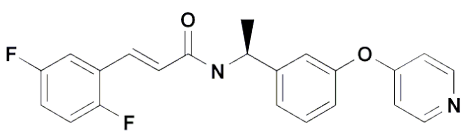


2

**MEDI 349**

## Ligand based design and synthesis of imidazolidine-2,4-dione analogs for their use as inhibitors of hyperexcited neuronal voltage-gated sodium channels

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Hyperexcited neuronal voltage-gated sodium channels (VGSCs) play an integral role in seizure activity, a characteristic symptom of epilepsy. The state dependent inhibition of hyperexcited VGSCs is feasible with phenytoin ($IC_{50}$ 40 ìM) and other imidazolidine-2,4-dione analogs. Implementation of ligand-based drug design techniques predicted that selected changes to the structure of our lead compounds, including phenytoin, would provide for increased inhibition of hyperexcited neuronal VGSCs. Three molecular regions of phenytoin were identified for modification and analogous design to probe the binding pocket located at Site 2 in the VGSC. Promising molecular entities predicted by our comformational molecular field analysis (CoMFA) were synthesized. These synthesized entities were summarily tested by BTX-3[H] displacement assay (40 ìM at Site 2). Six of the developed compounds demonstrated inhibition, greater than that of phenytoin, ranging from 57% to 86%.

**MEDI 350**

## Diethylstilbestrol and other non-steroidal estrogens: Novel class of store-operated calcium channel modulators

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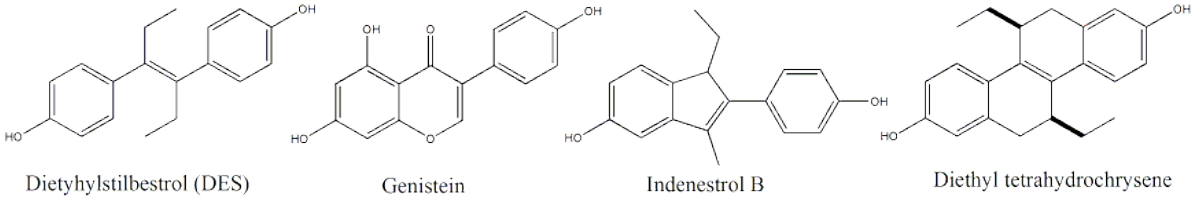
We demonstrated that non-steroidal estrogens with trans-stilbene moiety comprise the novel class of store-operated calcium influx inhibitors, with diethylstilbestrol (DES) being the most potent and specific. Compounds structurally similar to DES such as stilbene derivatives, tetrahydrochrysenes and indenestrols (rigid analogs of DES) as well as dietary isoflavonoids and flavonoids (e.g. genistein) also block store-operated calcium influx into human platelets; all this compounds have similar IC50= 1 uM . Unsubstituted para- hydroxyls in phenyl rings, ethyl side chains and conjugated double bond between phenyl rings enhance activity. Substituted tetrahydrochrysenes have the activity similar to DES, indenestrols have activity similar to isoflavonoids. There is no correlation between the estrogenic activity of the compound and its ability to inhibit calcium influx. Flavonoids are less active than isoflavonoids and glycosylated compounds are inactive. The ability of dietary polyphenols to inhibit calcium influx and activation of platelets can contribute to their antithrombotic cardiovascular benefits.



**MEDI 351**

## Design and synthesis of peptidomimetics as EphB2 inhibitors

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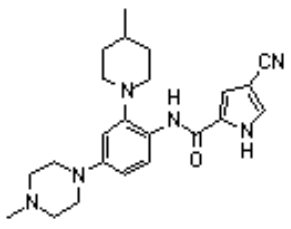
Based on crystal structure of EphB2 and Ephrin B2, peptidomimetics using β-D-glucose as a scaffold were designed to target the protein-protein interaction between EphB2 and Ephrin B2. All compounds were evaluated by SPR assay on Biacore 3000. Among the compounds tested, compound 1 was shown to be the most promising lead compound. In an effort to improve the binding affinity, we postulate the solubility of the synthesized peptide mimetics could be one of the factors that resulted in the lower binding affinity between the ligand and Eph receptor. A series of new compounds based on compound 1 were synthesized to test this hypothesis. Another possibility to improve the binding affinity is through the use of divalent binding to the Eph receptor dimers. A short PEG linker was used to attach two small molecular ligands at both ends in an attempt to prepare a dimeric Eph antagonist with improved affinity and solubility. However, Biacore SPR studies on these new compounds showed no obvious correlations between their affinity and aqueous solubility.

**MEDI 352**

## Discovery of novel FMS kinase inhibitors as anti-inflammatory agents

***Sanath K. Meegalla****, Carl R. Illig, Jinsheng Chen, Mark J. Wall, Kenneth J. Wilson, Shelley K. Ballentine, M. Jonathan Rudolph, Reneé L. DesJarlais, Yanmin Chan, Carsten Schubert, Ioanna Petrounia, Carl S. Crysler, Christopher J. Molloy, Margery A Chaikin, Carl L. Manthey, Mark R. Player, and Bruce E. Tomczuk, Johnson and Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, Spring House, PA 19477*

The colony stimulating factor-1 receptor (CSF-1R, also known as M-CSFR, or FMS) is the exclusive receptor for its ligand, colony stimulating factor-1 (CSF-1 or macrophage colony stimulating factor, M-CSF). The binding of CSF-1 to the extracellular domain of FMS induces the dimerization and trans-autophosphorylation of several cytoplasmic tyrosine residues. High expression of FMS is limited principally to monocyte/macrophages, oocytes, trophoblasts, mammary epithelium (during lactation), and to cells of the macrophage lineage, while CSF is the predominant growth factor for macrophage lineage cells including osteoclasts. Recent studies have demonstrated a direct correlation between tumor-associated macrophage numbers and tumor progression and between synovial macrophage numbers and disease severity in rheumatoid arthritis. Further, osteoclasts mediate bone erosions leading to pain and fracture in metastatic bone disease and deformity in rheumatoid arthritis. Hence the inhibition of FMS appears to be of therapeutic value in treating diseases such as rheumatoid arthritis and metastatic cancer to the bone where osteoclasts and macrophages are pathogenic. This hypothesis is also well-supported by the biological studies conducted with CSF-1 deficient mice. Herein we describe the identification of a potent FMS inhibitor (1) that served as a proof-of-concept candidate in a collagen-induced model of arthritis in mice . .




(1) FMS $IC_{50}$ - 0.0008 μM

**MEDI 353**

WITHDRAWN

**MEDI 354**

**Discovery of pyrazolodihydropyrimidine Kv1.5 blockers**

***John Lloyd***[1]*, john.lloyd@bms.com, Karnail Atwal*[1]*, Wayne Vaccaro*[1]*, Tram Huynh*[1]*, Heather J. Finlay*[1]*, heather.finlay@bms.com, Alexander Kover*[1]*, Joseph Prol*[1]*, Lin Yan*[1]*, Rao Bhandaru*[1]*, Christine Huang*[2]*, Mary Lee Conder*[1]*, Tonya Jenkins-West*[1]*, Hong Shi*[1]*, Lucy Sun*[1]*, Huabin Sun*[1]*, Danshi Li*[1]*, and Paul Levesque*[1]*. (1) Bristol-Myers Squibb Pharmaceutical Research and Development, P. O. Box 5400, Princeton, NJ 08543-5400, Fax: 609-818-3331, (2) Pharmacological Candidate Optimization, Bristol-Myers Squibb Pharmaceutical Research and Development, Princeton, NJ 08543-5400*

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects over 2.2 million patients in the United States alone. Current treatments have focused on non-selective ion channel inhibitors which affect both atrial and ventricle refractory period. Recent literature suggests that greater safety and efficacy in the treatment of AF may be achieved by targeting atrial specific ion channels. The ultra-rapid potassium current (IKur) is a potassium current conducted by the Kv1.5 channel that is functionally expressed in the atrium but not the ventricle in human hearts. Early work showed that nifedipine (**1**) demonstrated weak activity in blocking Kv1.5. Directed screening was conducted on a collection of structurally related calcium channel blockers and the pyrazolodihydropyrimidine (**2**) was identified with an IC50 of 1 uM. Subsequent modifications resulted in the identification of BMS-394136 which showed significantly improved *in vitro* potency, selectivity over other ion channels and atrial selective effects *in vivo*.

**MEDI 355**

**Pyrrolo[2,1-f][1,2,4]triazine-based dual inhibitors of HER1 and HER2 kinases**

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HER1(EGFR) and HER2 (ErbB2) are cell-surface growth factor receptor tyrosine kinases that are known to play a crucial role as signal transducers and have been implicated in a number of cancers. Frequent co-expression of HER1 and HER2 in a variety of tumor types and their capacity to form heterodimers with other members of the EGFR family, provide a strong rationale for simultaneous

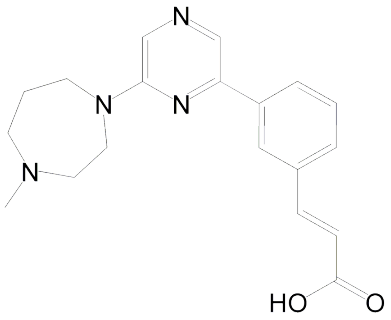
targeting of the two receptors. Efforts at Bristol-Myers Squibb on a series of pyrrolotriazine-based HER1/HER2 inhibitors will be described. Modeling studies suggested that the pyrrolotriazine ring binds in the adenine pocket of the ATP binding site and makes several key interactions with the hinge region similar to ATP. Depending on the chemical constituency, the aniline group at 4-position of the pyrrolotriazine can occupy a lipophilic kinase selectivity pocket whereas, an amino-substituted C5 group is directed into the highly conserved ribose-phosphate pocket where it can interact with conserved residues involved in phosphate binding. SAR was developed by introducing a wide range of substituents at C4 and C5 positions to optimize the potency of enzyme inhibition and incorporate desirable pharmaceutical properties. Structure-activity relationships will be described along with in vivo evaluation of a lead compound in tumor xenograft models.

**MEDI 356**

**Hit to lead account of the discovery of a new class of inhibitors of Pim-2 kinase**

***Anthony S. Prokopowicz III****, Tina Morwick, Charles L. Cywin, Kevin Qian, Wang Mao, John P. Wolak, Charlene Peng, Mohammed A. Kashem, Jun Li, Lian Wang, and Scott Jakes, Department of Research, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877-0368*

In-house genomics analysis of the NF-κB signaling pathway characterized Proviral Integration Site in Murine Leukemia Virus 2 (Pim-2) as a potential inflammation target. Subsequent screening of our compound collection identified a series of cinnamic acids as potent and selective Pim-2 inhibitors. The SAR for this series is described, and a cocrystal structure is presented highlighting a unique binding mode compared to other classical ATP-site kinase inhibitors.




**MEDI 357**

**Aminobenzimidazole derivatives as selective and orally bioavailable inhibitors of Aurora B kinase**

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Aurora kinases are promising oncology drug targets due to their critical role in the proper regulation of the cell cycle. Aurora kinases (A and B) belong to a family of serine/threonine kinases and are expressed from prophase through cytokinesis. They play essential roles in the regulation of centrosomes, the mitotic spindle checkpoint function, and cytokinesis. Reported herein is the evolution of a non-selective pyridinyl pyrimidine urea screening hit into a series of pyridinyl pyrimidine aminobenzimidazole derivatives as highly selective and orally bioavailable inhibitors of Aurora B kinase. Synthesis and SAR of these compounds will be presented.

**MEDI 358**

**Discovery of pf-4254644 as a highly potent and exquisitely selective c-met inhibitor**

***Hong Shen**, Mitchell Nambu, Michelle Tran-Dube, Catherine Johnson, Michele McTigue, Max Parker, Shinji Yamazaki, Helen Zou, James G. Christensen, and J. Jean Cui, PGRD La Jolla Laboratories, Pfizer, Inc, 10770 Science Center Dr, San Diego, CA 92121*

c-Met/HGF signaling plays an important role in human oncogenesis and tumor progression, and are attractive targets for oncology application. 6-[1,2,4]Triazolo[4,3-b][1,2,4]triazin-3-ylmethyl-quinoline has been identified as a class of potent and exquisitely selective c-Met inhibitors at Pfizer. However, this class of compounds is susceptible to metabolism. 6-[1,2,4]Triazolo[4,3-b]pyridazin-3-ylmethyl-quinolines demonstrated good pharmaceutical properties but with reduced potency. PF-4254644, 6-{(S)-1-[6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl]-ethyl}-quinoline, is a highly potent and exquisitely selective c-Met inhibitor, discovered using structure based drug design and medicinal chemistry lead optimization. PF-4254644 had low nM potency against c-Met in both in vitro cell assays and in vivo target modulation studies, demonstrated effective tumor growth inhibition in c-Met dependent tumor models, and exhibited good oral PK properties. PF-4254644 demonstrated over 1000-fold selectivity against a diverse array of >100 different tyrosine and serine-threonine kinases.

**MEDI 359**

**Molecular modeling the interaction between the chemical ligands and Cyclin-Dependent Kinase**

*Shana Stoddard, Milton Jackson, Stephen Bacon, and **Huajun Fan**, Department of Chemistry, Prairie View A&M University, PO Box 519, Mail Drop 2215, Prairie View, TX 77446-0519, Fax: 936-261-3117*

CDKs are crucial regulators of the eukaryotic cell cycle whose activities are controlled by associated cyclins. CDK5 is a subfamily of Ser/Thr protein kinases that controls cell differentiation and morphology. In this study, we will apply the computational modeling tools and structure-based methods to investigate the drug-receptor interaction, and identify, design and screen the suitable candidates for CDK5 receptor. Many factors could contribute and affect the docking outcomes of potential drug candidate with the binding site. Besides docking various database at the binding site of various crystal structures, quantum mechanic modeling at the active site will be investigated to provide vital information how the drug binds to the receptor and forces that controls the interaction and binding energies. We report here the particular conformation and substituents on the drug

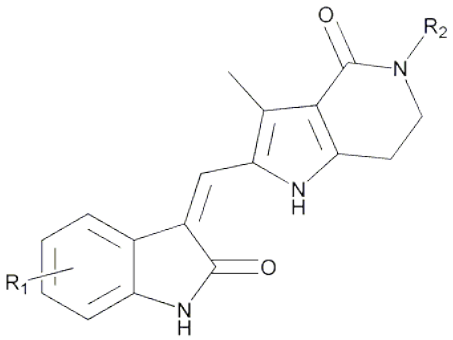
candidates that could impact the docking score, which can be used to identify the potential candidates for the CDKs.

**MEDI 360**

**Pyrrolo[3,2-c]pyridine-4-one-2-indolinone derivatives as tyrosine kinase inhibitors**

*TANG Peng Cho, **YANG Fang Long**, SU Yi Dong, XIAO Lu, LI Ya Li, ZHANG Lei, ZHOU Ying, and HU Bing, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China*

Receptor tyrosine kinases (RTKs) have been implicated as therapeutic targets for the treatment of human diseases including cancers, inflammatory diseases. A series of Pyrrolo [3,2-c] pyridine-4-one 2-indolinone derivatives as tyrosine kinase inhibitors were designed and synthesized. They were found to inhibit the tyrosine kinase activity associated with vascular endothelial growth factor receptor 2(VEGF-R2). Their biological evaluation results and structure-activity relationship will be discussed.



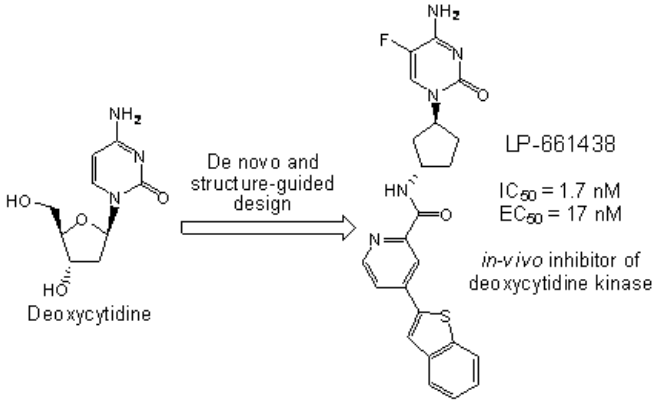

**MEDI 361**

**Lead optimization and structure-based design of deoxycytidine kinase inhibitors with potent in vitro and in vivo activity**

***Theodore C. Jessop**[1], tjessop@lexpharma.com, James E. Tarver Jr.[1], Ann Marie DiGeorge Foushee[2], Kanchan G. Jhaver[2], Jerry A. Taylor[1], Xiaolian Xu[1], Qinghong Fu[1], Marianne Carlsen[1], Min Shen[1], Xuan-Chuan Yu[2], Ziye Liu[2], Maricar L. Miranda[2], Amr NourAlDeen[2], Xiang-Qing Yu[2], Leslie W. Tari[3], ltari@triusrx.com, Michael J. Hunter[4], Issac D. Hoffman[4], Alan G. E. Wilson[2], Stephen J. Anderson[2], Tamas Oravecz[2], Terry R. Stouch[1], tstouch@lexpharma.com, David J. Augeri[1], and Kenneth G. Carson[1]. (1) Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540, (2) Lexicon Pharmaceuticals, Corporate Headquarters, The Woodlands, TX 77381, (3) Trius Therapeutics, Inc, San Diego, CA 92121, (4) ActiveSight, San Diego 92121*

A potent and selective inhibitor (LP-661438) of deoxycytidine kinase was discovered that displayed good bioavailability and in-vivo enzyme inhibition in mice. De novo design of deoxycytidine kinase inhibitors afforded cytidine-like analogs with the ribose ring replaced by a substituted cyclopentane. Frequent in-vivo mouse pharmacokinetic studies of these analogs allowed simultaneous optimization of pharmacokinetics and potency. X-ray crystallography of an unrelated ligand (identified by HTS) bound to deoxycytidine kinase revealed a new hydrophobic binding pocket formed by a major conformational change of the enzyme. This structural information enabled rapid advances of the cyclopentyl-cytosine series and culminated in the design and synthesis of LP-661438. This molecule

was a potent inhibitor of deoxycytidine kinase ($IC_{50}$ = 1.7 nM, $EC_{50}$ = 17 nM) and inhibited the incorporation of tritiated deoxycytidine in mouse and human primary cells. Finally, oral administration of LP-661438 to mice blocked incorporation of tritiated deoxycytidine in a dose dependent manner.




**MEDI 362**

**Synthesis and biological activity of 2-desamino-4-substituted anilino-6-substituted phenylmethyl pyrrolo[2,3-*d*]pyrimidines as inhibitors of receptor tyrosine kinases**

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Receptor tyrosine kinases (RTKs) have been identified as modulators of angiogenesis based on their function(s) in the cellular signaling cascades that control cell proliferation and growth. Primary tumors recruit new blood vessels for growth and migration to distal sites in the body. Several tumors have dysfunctional, hyperactive growth factor RTKs which include PDGFR, FGFR, VEGFR, IGFR and EGFR among others, which result in abnormal signaling. Several RTK inhibitors have been designed as therapeutic agents for the treatment of cancer such as erlotinib, sunitinib and sorafenib. Gangjee *et al.* designed and synthesized 2-amino-4-substituted anilino-6-substituted phenylmethyl pyrrolo[2,3-*d*]pyrimidines as inhibitors of multiple RTKs. These analogs demonstrated that variation of substituents in the 6-benzyl as well as the 4-anilino moiety controlled both the potency and specificity of inhibition of various RTKs. The 2-amino moiety was maintained in these analogs. Using these analogs as the leads, we have synthesized the 2-desamino-4-substituted anilino-6-substituted phenylmethyl pyrrolo[2,3-*d*]pyrimidines to evaluate the importance of the 2-amino moiety on the potency and selectivity of RTK inhibition. A remarkable difference in the biological activities was seen for the 2-desamino compounds compared to the 2-amino series. The synthesis and RTK inhibitory activities of these compounds will be presented and discussed.

**MEDI 363**

**Synthesis of selective and potent ERK inhibitors utilizing a protein kinase/small-molecule inhibitor complementary pair method**

***Christopher A. LeClair**[1], leclairc@mail.nih.gov, Jose P. Vaqué[2], Adrian G. Turjanski[2], J. Silvio Gutkind[2], and Craig J. Thomas[1]. (1) NIH Chemical Genomics Center, NHGRI, National Institutes of*

*Health, 9800 Medical Center Drive, Rockville, MD 20850, (2) Oral and Pharyngeal Cancer Branch, NIDCR, National Institutes of Health, Bethesda, MD 20892*

The use of kinase-specific inhibitors in the treatment of cancer is of great interest due to the prevalent connection between constitutive protein kinase activation and oncogenic cell transformation. Unfortunately, the vast size of the protein kinase superfamily coupled with the highly conserved nature of the kinase active site makes the discovery and design of inhibitors a formidable endeavor. Shokat et al. have developed an engineered kinase/inhibitor complementary pair method for kinase substrate identification. Focusing on the family of MAPKs, we utilized this method for investigation of the MAPK/ERK signal transduction pathway by inhibiting ERK. With substrate hydrophilicity of great importance, we modified Shokat's most potent and selective serine/threonine kinase inhibitor, a C3-1'-naphthylmethyl PP1 analogue. Molecular modeling of the inhibitor within the modified ERK binding pocket conveyed potential derivatization sites. Synthesis of various analogues provided ERK inhibitors with improved hydrophilicity while maintaining selectivity and potency comparable to the C3-1'-naphthylmethyl PP1 analogue.

**MEDI 364**

**The synthesis of AB/A'B' subunit of angelmicin B, a potent protein tyrosine kinase inhibitor**

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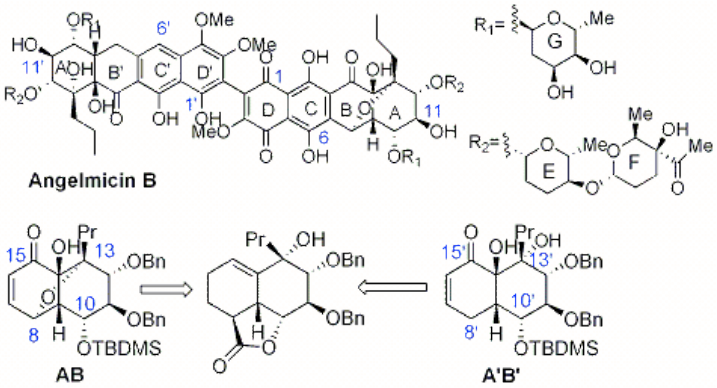
Angelmicin B (hibarimicin B) has been shown to be a highly specific inhibitor of *v-Src* type protein tyrosine kinase ($IC_{50}$: 23 μM). It has also been shown to inhibit the growth of tumor cells and to induce differentiation in human myeloid leukemia cell lines HL-60 ($IC_{50}$: 57 nM). The complexity and the intriguing bioactivity make it an important synthetic target. We have previously described a Ring Closing Eneyne Metathesis/Intramolecular Diels-Alder, and tandem alkoxy radical fragementation-etherification sequence for the synthesis of AB subunit synthon. Herein we present the application of the methodoly to an A'B' subunit.

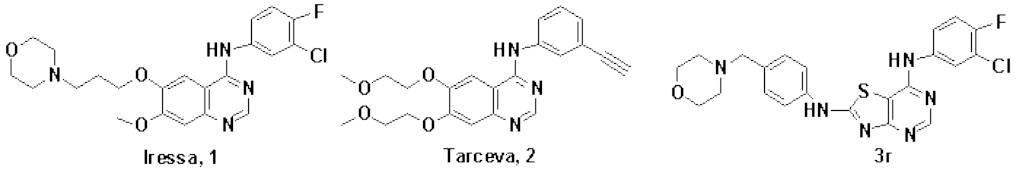


**MEDI 365**

## Synthesis and evaluation of 2,7-diamino-thiazolo[4,5-d]pyrimidines analogs as antitumor EGFR tyrosine kinase inhibitors

***Ronghui Lin**, Sigmond Johnson, Peter Connolly, Steven Wetter, Eva Binnun, Terry Hughes, William Murray, Niranjan Pandey, Sandra Moreno-Mazza, Mary Adams, Angel Fuentes-Pesquera, and Steven Middleton, Johnson & Johnson Pharmaceutical Research & Development L.L.C, 1000 Route 202, Raritan, NJ 08869, Fax: 908-526-6469*

The epidermal growth factor receptor (EGFR) is a member of cellular trans-membrane tyrosine kinases, which is over-expressed in a significant number of human tumors. EGFR-dependent aberrant signaling is associated with cancer cell proliferation, apoptosis, angiogenesis, and metastasis. A number of small molecules of EGFR kinase inhibitors have been evaluated in clinical trails of cancers. For example, anilinoquinazoline-containing compounds Gefitinib (Iressa, **1**) and Erlotibib (Tarceva, **2**) have been developed and approved for the chemotherapeutic treatment of patients with advanced non-small-cell-lung cancer (NSCLC). Herein a series of 2,7-diamino-thiazolo[4,5-d]pyrimidines analogues were synthesized as novel EGFR tyrosine kinase inhibitors. Representative compounds (e.g. compound **3r**) showed potent and selective EGFR inhibitory activities and inhibited *in vitro* cellular proliferation in human tumor cells. The synthesis and preliminary biological evaluation of these thiazolopyrimidine compounds will be presented.




**MEDI 366**

## Design, synthesis, and SAR of new (2-aminothiazol-5-yl)-pyrimidines as potent p38 MAP kinase inhibitors

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Inhibiting the p38 MAP kinase pathway in vivo is known to be highly efficacious in controlling the release of various proinflammatory cytokines, most notably TNF&alpha and IL-1&beta. As a result, the pursuit of small molecule p38 inhibitors has garnered significant attention within the pharmaceutical industry due to the potential to effectively treat significant inflammatory diseases such as rheumatoid arthritis with p38 inhibitors. We wish to report the design, synthesis, and structure-activity relationships (SAR) of a new class of (2-aminothiazol-5-yl)-pyrimidines as p38 MAP kinase inhibitors. Results from X-ray crystallographic studies using these inhibitors will also be utilized to rationalize SAR findings within this series.

**MEDI 367**

## Development of a potent and specific ligand for the Src SH3 domain

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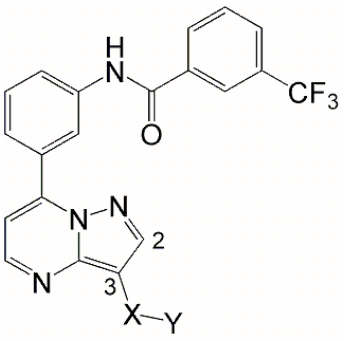
The Src family of tyrosine kinases are SH2 and SH3 domain containing proteins involved in the transmission of extracellular signals from the plasma membrane to targets in the cytoplasm and nucleus. Elevated levels of kinase activity have been directly associated with a variety of cancers including human breast and colon cancer. Due to the role of the SH3 domain in regulating protein-protein interactions, work is being done to develop potent and specific ligands for the Src SH3 domain. VS-12 (a 12-mer peptide) with a $K_d$ of 1.3 μM was previously reported as the best ligand for the Src SH3 domain. We developed a peptide ligand with $K_d$ of 0.02 μM by tethering VS-12 tethered to a six-residue extension. The new ligand is highly specific for the normal Src SH3 domain over other neuronal Src SH3 domain and Lck SH3 domain. This approach may be generalized in designing selective ligands for regulatory domains of other kinases.

**MEDI 368**

## Investigation of pyrazolo[1,5-a] pyrimidines as inhibitors of B-Raf kinase

***Nancy Torres***[1]*, torresn@wyeth.com, Dan M. Berger*[1]*, bergerd@wyeth.com, Greg Ciszewski*[1]*, Ariamala Gopalsamy*[1]*, Kyung-Hee Kim*[1]*, kimk@wyeth.com, Jeremy I. Levin*[1]*, Dennis W. Powell*[1]*, Vlad Aron Buklan*[2]*, Karen Collins*[2]*, Eileen Frommer*[2]*, Donald Wojciechowicz*[2]*, Robert Mallon*[2]*, Yongbo Hu*[1]*, James Wilhelm*[1]*, and Weixin Xu*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (2) Oncology Research, Wyeth Research, Pearl River, NY 10965, (3) Chemical & Screening Sciences, Wyeth Research, Cambridge, MA 02140*

The RAS-RAF-MEK-ERK signal transduction pathway (ERK pathway) plays a key role in tumorigenesis and cancer progression. A V600E mutation of the B-Raf isoform induces a constitutive activation of this kinase in the ERK pathway that increases cell proliferation and cell survival. Mutant B-Raf has been associated with several types of cancer, in particular with malignant melanomas. Several drugs targeting components of the ERK pathway, including small molecule inhibitors of B-Raf, are currently in clinical trials. In this poster, we present our study of B-Raf SAR at C-3 on a pyrazolo[1,5-a] pyrimidine scaffold (**1**). Aryl, heteroaryl, and alkynyl substituents (**X**) were elaborated with water-solubilizing groups (**Y**) in an effort to enhance potency and pharmacological properties. Crystallographic studies of an active lead in this series will also be presented.



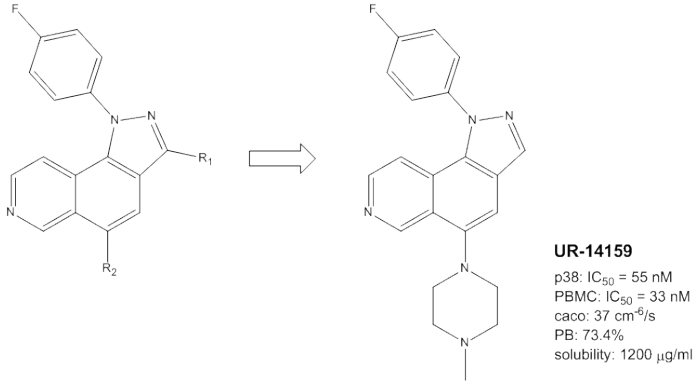

**1**

**MEDI 369**

## Novel tricyclic pyrazole inhibitors of p38 map kinase

***Marina Virgili**, Carmen Almansa, and Fernando L. Cavalcanti, Innovation & Drug Discovery, Palau Pharma S.A, Av Cami reial 51-57, E-08184 Palau-Solita i Plegamans, Spain, Fax: +34 938646606*

Since the discovery of p38 mitogen activated protein (MAP) kinase, a key enzyme involved in the production of the pro-inflammatory cytokines TNF&alpha and IL-1&beta, numerous groups have centered their efforts in finding small-molecule p38 inhibitors as potential therapeutic agents for the treatment of chronic inflammatory diseases. In the context of our p38 program, herein we report the discovery of a novel tricyclic pyrazole scaffold. Adequate modification of the central ring through a selective bromination reaction and subsequent derivatization allowed us to identify a series of highly potent compounds. Several derivatives represented by UR-14159 showed high in vitro potency (radiometric and cellular assays), good oral activity in vivo (inhibition of LPS-induced TNF&alpha production in mice), good in vitro ADME properties, good kinase selectivity and high solubility.



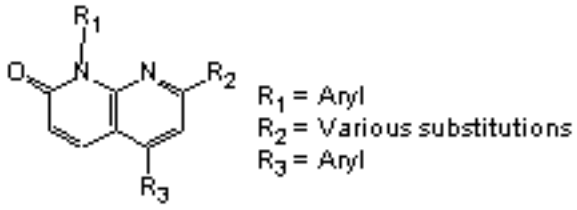

**MEDI 370**

## Design, synthesis and biological activity of a novel series of naphthyridinone derivatives as potent p38α MAP kinase inhibitors for the treatment of rheumatoid arthritis

***Ginger XuQiang Yang**[1], ginger_yang@merck.com, John Stelmach[1], Zao Hu[1], zao_hu@merck.com, HIroo Koyama[1], hiroo_koyama@merck.com, Ranjit C Desai[1], ranjit_desai@merck.com, Meng-Hsin Chen[1], Swaminathan Natarajan[1], Daniel J. Miller[1], Stephen O'Keefe[2], O'neill Edward[2], Kaushik Mitra[3], kaushik_mitra@merck.com, Denise Visco[4], Karen Owens[1], Dennis M. Zaller[2], Jim B Doherty[1], and Soumya P. Sahoo[1], soumya_sahoo@merck.com. (1) Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-9556, (2) Department of Immunology, Merck Research Laboratories, Rahway, NJ 07065, (3) Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, (4) Department of Laboratory Animal Resources, Merck Research Laboratories*

Tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β) are proinflammatory cytokines implicated in many inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis. P38α is a mitogen activated protein (MAP) kinase that plays an essential role in the signal transduction pathways leading to the synthesis of TNFα and IL-1β. Thus, inhibition of p38 MAP kinase has remained a popular drug development target for orally active small molecules.

This presentation will describe the synthesis, SAR exploration and biological activity of this novel class compounds as p38 MAP kinase inhibitors.




**MEDI 371**

**Discovery and synthesis of a new class of potent fluorescent roscovitine analogs**

***Venkata M Yenugonda***[1]*, vmy2@georgetown.edu, Simeng Suy*[1]*, suys@georgetown.edu, Bogdan Stoica*[2]*, stoicab@georgetown.edu, Alan I Faden*[2]*, fedena@georgetown.edu, and Milton L. Brown*[1]*, mb544@georgetown.edu. (1) Drug Discovery Program, Georgetown University Medical Center, 3970 Reservoir Road NW, Washington, DC 20057, Fax: 2026877659, (2) Department of Neuroscience, Georgetown University Medical Center, Washington, DC 20057*

Activation of cell cycle pathways involving cyclin dependent kinases (CDK) associated with uncontrolled cell division typical for cancer as well as cell death in post-mitotic neurons as observed in neurodegenerative diseases. The molecular pathways responsible for CDK activation in both cancer and neuronal cell death need to be investigated, especially in vivo. Development of potent and selective CDK inhibitors that provide a diagnostic “readout” would be of major importance. In order to achieve these aims we designed and synthesized fluorescently tagged variants of some of the most specific and potent CDK inhibitors. These new compounds provide an opportunity to assess their in vivo ability to reach desired molecular targets, and study their intracellular localization. Here we report a strategy for the selective and efficient synthetic incorporation of a low-molecular-weight fluorophores into Roscovitine and Purvalanol B (CDK inhibitors) at specific positions that do not diminish their cellular activity.

**MEDI 372**

**Design and synthesis of oxazolo pyrimidine based library target kinase**

***Qiang Yu*** *and Xiangzhong Li, CGeneTech, Inc, 7128 Zionsville Road, Indianapolis, IN 46268*

A novel scaffold, Oxazolo-pyrimidine, was developed based on computational aid drug design. A focused library aimed kinase targets was synthesized accordingly.

**MEDI 373**

**$N^4$-(3-bromophenyl)-7-(substitutedbenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamines as novel potent multiple receptor tyrosine kinase inhibitors**

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The concept of blocking the growth of solid tumors by inhibiting blood supply via the inhibition of angiogenesis is now well established. In an attempt to develop small molecule receptor tyrosine kinase (RTK) inhibitors, Gangjee *et al.* modeled the ATP from IRK into VEGFR-2 (SYBYL 6.7) to produce a pharmacophore model, on the basis of which a series of potent RTK inhibitors: 6-arylmethyl pyrrolo[2,3-*d*]pyrimidines were designed. To determine the effect of transposing the substituent from the 6-position to the 7-position on activity against RTKs, a series of 7-arylmethyl pyrrolo[2,3-*d*]pyrimidines was designed. The biological activities indicate that most of these analogs function as dual RTK inhibitors (VEGFR-2, PDGFR--*β*). Some of the analogs were 3-fold better PDGFR kinase inhibitors than the standard compound used in this assay. The design, synthesis and RTK inhibitory activities of 7-arylmethyl pyrrolo[2,3-*d*]pyrimidines with a variety of substituted aryl groups will be presented in this report.

**MEDI 374**

**Synthetic peptides regulate the paracellular transport of dextrans across Caco-2 cell monolayers**

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The paracellular route is a selective transport pathway, limited to small, hydrophilic molecules that diffuse through the intercellular spaces sealed by the tight junctions. A strategy typically used to enhance paracellular permeability is tight junction modulation. We synthesized a series of peptides derived from zonula occludens toxin (ZOT), a protein secreted by Vibrio cholerae that transiently and reversibly opens epithelial tight junctions. The permeability inducer AT-1002 enhanced FITC-dextran (FD) transport across Caco-2 cell monolayers 17-, 5.6-, and 1.4-fold for FD-4, FD-20, and FD-70, respectively. The permeability inhibitor, AT-1001, inhibited the effect of AT-1002 on FD-4 and FD-20 by 93% and 316%, respectively. These results suggest AT-1002 may enhance drug permeability through the paracellular pathway. Furthermore, the results indicate AT-1001 can prevent the permeability of molecules across a compromised epithelial barrier.

**MEDI 375**

## AT-1001, a tight junction modulator peptide, inhibits epithelial permeability induced by TNF-α and IL-4

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Overproduction of cytokines is observed in disease states such as inflammatory bowel disease (IBD). Crohn's disease patients have increased levels of tumor necrosis factor (TNF)-α, while interleukin (IL)-4 is increased in patients with ulcerative colitis. Elevated cytokine levels are associated with increased intestinal permeability. Herein, we investigated the effect of AT-1001, a permeability inhibitor 8-mer synthetic peptide, on TNF-α and IL-4 induced permeability of Lucifer yellow in vitro. We found that AT-1001 reduced TNF-α induced permeability after 24 and 72 hours in Caco-2 cell monolayers by 40% and 50%, respectively. Additionally, AT-1001 reduced the IL-4 induced permeability after 24 hours in T84 cell monolayers by 86%. Our data suggest that AT-1001 inhibits TNF-α and IL-4 induced permeability, and demonstrates potential as a therapeutic agent for the treatment of IBD.

**MEDI 376**

## Dihydropyrimidines are potent and selective Rho-kinase inhibitors

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Rho kinase (ROCK) inhibitors are potential therapeutic agents for cardiovascular diseases ranging from hypertension to atherosclerosis. Our chemistry effort has been focused around the initial lead dihydropyrimidine 1, which suffered from poor oral bioavailability, moderate Rho kinase potency, and potent P450 inhibition. Lead optimization efforts resulted in the identification of 2 which represents an improvement in all three properties. The SAR and X-Ray cocrystal structure of an advanced compound will be described.

**MEDI 377**

## Structure-activity relationship study on vitamin D receptor antagonist TEI-9647 analogs

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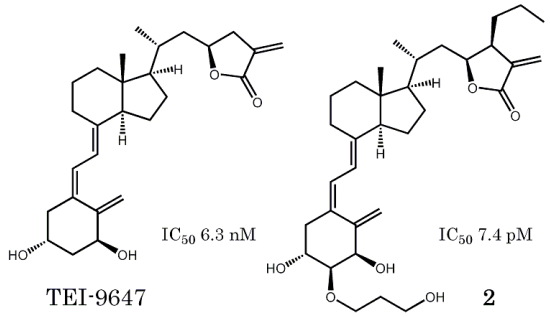
1alpha,25-Dihydroxyvitamin $D_3$ (**1**) regulates various biological actions, for example, calcium and phosphorus homeostasis as well as cellular proliferation and differentiation, through interaction with its specific nuclear receptor, vitamin D receptor (VDR). We reported modification at the 2alpha position of **1** increased its biological activity and we found a couple of super-agonists of VDR.

Introducing 2alpha-methyl, 2alpha-(3-hydroxypropyl), or 2alpha-(3-hydroxypropoxy) group into **1** showed 2- to 4-fold higher binding affinity for the VDR compared to **1**. 1alpha-Hydroxyvitamin $D_3$-26,23-lactone (TEI-9647) having an alpha-methylene-gamma-lactone structure on the CD-ring side chain is the first VDR antagonist reported in 1999. The unique structure and unprecedented biological profiles with considerable attention as a potential remedy for Paget's disease prompted us to investigate the structure-activity relationship of TEI-9647 based on our experience in our VDR-agonist studies to search for more potential anti-D molecules. We introduced the above three A-ring motifs to the TEI-9647 skeleton to improve the binding affinity for the VDR, and we also focused on the influence of the structure, including stereochemistry, of the lactone moiety on biological activity. We synthesized 2alpha-substituted 24-alkyl-, 24,24-dimethyl-, and 24,24-ethano-TEI-9647 analogs. Among these synthetic analogs, (24*S*)-2alpha-(3-hydroxypropoxy)-24-propyl-TEI-9647 (**2**) exhibited 850-fold more potent antagonistic activity ($IC_{50}$ 7.4 pM) than that of TEI-9647 ($IC_{50}$ 6.3 nM). We have succeeded in the development of highly potent VDR antagonists based on the C24- and C2alpha-functionalization of TEI-9647.




**MEDI 378**

**Identification of allergens from inside and outside latex gloves**

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Natural rubber latex (NRL) allergy is commonly found in two distinct populations, those who undergo multiple surgeries and health care workers. Although allergic reactions are found in both populations, two distinct patterns of allergies arise from this exposure to the latex glove. Patients who undergo multiple surgeries are solely exposed to the outside of the glove while health care workers are only exposed to the inside of the latex gloves. This research sought to find differences between allergens on the inside and outside of a latex rubber glove. Samples were isolated by solubilization in borate buffer and separated using PAGE-SDS electrophoresis 10-20% gels. Two distinct bands were found for samples collected from the outside of the gloves while the inside of a latex glove had only one band. Differences between these allergens may give insight into the specific patterns of infections.

**MEDI 379**

**Studies on bioactive triterpene glycosides of sea cucumbers**

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Stichopus variegatus Semper distributed abundantly in South China Sea, especially in Hainan sea area. Up to date, only few chemical works have been performed on these sea cucumbers.Guided by Pyricularia oryzae bioassay model, the anticancer and antifungal constituents of Stichopus variegatus Semper have been investigated by various chromatography methods including LPLC, MPLC, HPLC on silica gel,ODS RP C-18 and Zorbax SB C-18 respectively. Ten compounds were isolated and structures of seven glycosides were elucidated by chemical and spectral analysis (IR, EI-MS, ESI-MS,HRESI-MS, 1H NMR, 13C NMR, 1H-1H COSY, DQF-COSY, TOCSY, HMQC, HMBC, NOESY), three compounds are new glycosides.

These compounds showed moderate cytotoxity in vitro against human tumor cell lines such as A-549,P-388,HL-60 and so on. One compound showed strong antifungal activity against Candida albicans with MIC80 3.4(ug/ml), C. neoformans with MIC80 6.8(ug/ml), C. parapsilosis with MIC8013.6(ug/ml), C. tropicalis with MIC80 3.4(ug/ml) .

**MEDI 380**

**Photoactive molecular tools to profile heat shock proteins in cells**

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Heat shock proteins (HSPs) are important therapeutic targets and potential biomarkers for many disorders including cancer and neurodegenerative diseases. Here we present a simple conjugate of adenine, benzophenone, and biotin that can selectively photolabel HSPs in Jurkat cell lysates. Recombinant HSP70 protein was used to determine the photolabeling efficiency. Furthermore, mass spectrometric analyses were conducted to deduce the site of photocrosslinking. Structural basis of the observed selectivity will be discussed.

**MEDI 381**

**Cellular delivery of cryptophanes for xenon biosensing**

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Cryptophane-A has generated considerable interest as a host molecule based on its high affinity for xenon. This avidity for xenon has motivated the design of cryptophane-A biosensors for $^{129}$Xe nuclear magnetic resonance (NMR) spectroscopy. Here, we report the cellular delivery and toxicity of three

cryptophane biosensors. First, cryptophanes were delivered using two cationic cell penetrating peptides into several human cancer and normal cell lines. In order to increase specificity of delivery, an RGD peptide targeting $\alpha_v\beta_3$ integrin receptor was attached. Labeling the peptides with Cy3 made it possible to monitor cellular delivery using fluorescence microscopy. Cellular toxicity, as determined by MTT assay, was only slightly elevated at the micromolar cryptophane concentrations required for 129Xe NMR biosensing experiments.

**MEDI 382**

**Design, synthesis and structure activity relationship of 1,3,6-trisubstituted-2-carboxy-quinol-4-ones as selective endothelin-A receptor antagonists**

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Endothelin-1 (ET-1) is a member of novel family of vasoconstrictor, which consists of 21 amino acid residues with two intra-chain disulphide linkages. ET-1 is recognized as the major isoform of relevance in human physiology and pathophysiology. It is involved with variety of conditions including systemic and pulmonary hypertension, congestive heart failure, renal failure, cancer, preterm labor and cerebrovascular disease. ET-1 exerts its biological effects through the stimulation of 2 subtypes of receptors, endothelin receptor subtype A (ET-A) and endothelin receptor subtype B (ET-B) receptors. ET-A receptors mediate most of the actions of ET-1 associated with these pathological conditions suggesting a selective ET-A receptor antagonist would be useful as a therapeutic agent for chronic treatment of these pathological conditions. A series of 6-alkoxy substituted-3-carboxybenzyl-N-benzyl-quinol-4-ones were designed and synthesized as potential ET-A selective inhibitors. Preliminary in vitro studies of these compounds showed them to be selective ET-A antagonists with 6-hydroxy analog, a prototype compound of the series, being able to prevent preterm labor (PTL) in the pregnant mouse model. These compounds may serve as the pharmacological tools to determine the role of ET-A in PTL. Results of the biological testing will be discussed in terms of structure activity relationship related to the binding affinity of these compounds for ET-A and ED50 to prevent PTL.

**MEDI 383**

**Revisiting bioisosterism**

***Hugo O. Villar**, Shahin Saneinejad, and Mark R. Hansen, Altoris, Inc, 7660-H Fay Ave #347, La Jolla, CA 92037*

The concept of bioisosterism is well established in medicinal chemistry. Bioisosterism refers to substructures of compounds that share similar steric, electronic and other physicochemical characteristics and which can substitute for each other with the result of producing substantially the same bioactivity.

We compiled a collection of over 100 bioisosteres from the literature and computed a series of physicochemical properties that are related to their steric, entropic or electronic characteristics. Multivariate statistical techniques were applied to determine which subset of the properties can be

responsible for the observed similarity among bioisosteric pairs that have been found to behave similarly across multiple targets. While certain substructures can substitute for each other for a given target, for a different target the substitution may not result in a similar end-point.

**MEDI 384**

**Study on the maturation of dendritic cells induced by phenylethanoid glycosides purified from the seeds of Plantago asiatica L**

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In this study, the effects of acteoside and isoacteoside purified from the seeds of Plantago asiatica L. on the maturation of murine bone marrow DCs were investigated. Immature DCs generated from the bone marrow cells were cultured in the presence of rmIL-4 and rmGM-CSF, and then stimulated with acteoside, isoacteoside or LPS (positive control; 1 μg/mL). It was observed by the inverted microscope that DCs treated by acteoside and isoacteoside displayed a more mature morphology with long protrusions, while untreated-DCs displayed shorter protrusions. It was found by the determination of flow cytometry that compared with untreated-DCs, acteoside and isoacteoside increased the co-expression of CD11c and I-A/I-E molecules on DCs surface, while the uptaking FITC-dextran of DCs treated by acteoside and isoacteoside was restrained. The antigen presenting ability of DCs treated by acteoside and isoacteoside to naïve T lymphocytes was also examined by the lymphocyte proliferation of mixed lymphocyte reaction (MLR), and the results showed an improved ability, compared with untreated DCs. This research demonstrated that acteoside and isoacteoside purified from the seeds of Plantago asiatica L. both could promote the maturation of murine DCs in vitro, which may provide experimental basis of pharmacodynamics for clinical application of acteoside and isoacteoside.

Keywords: dendritic cells; acteoside; isoacteoside; Plantago asiatica L.; flow cytometry

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**MEDI 385**

**Isolation and characterization of immunomodulatory phytosterols from juzen-taiho-to.**

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Phytosteol mixtures have been reported to possess promising immunomodulatory activities for the treatments of many disorders, including cancer and cardiovascular diseases (1-3). The identification of active constituents in those mixtures, however, has been hampered by various difficulties; e.g., (i) phytosterol mixtures are notoriously difficult to separate, and (ii) activity often disappears during

fractionation. Using a fractionation guided by real-time PCR of ICAM1, we recently isolated three phytosterol constituents from Juzen-Taiho-to (JTT), an Oriental herbal formulation with immunostimulatory activity (4). Remarkably, these phytosterols synergistically stimulated monocytes (THP1 cells). Our presentation will outline the purification, structural characterization, and the evaluation of synergistic immunomodulation of these phytosterols.

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4. Juzen-taiho-to (Shi-Quan-Da-Bu-Tang): Scientific Evaluation and Clinical Applications Taylor & Frances: Boca Raton FL., 2005; Vol. 5.

**MEDI 386**

**Development of benzylpiperazines as subtype selective muscarinic ligands.**

***Richie Bhandare*** *and Daniel J Canney, Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 3307 N Broad Street, Philadelphia, PA 19140*

Muscarinic acetylcholine receptors (mAChRs) are divided into five subtypes (M1-M5). The physiological roles of these subtypes range from controlling smooth muscle tone (bronchioles, gastrointestinal and genitourinary tracts) to neurotransmitter release. This wide range of effects affords therapeutic opportunities for muscarinic ligands that include Alzheimer's Disease, Parkinson's Disease, peptic ulcer disease, COPD, urinary incontinence, and as anti-spasmodic agents. Kaiser et al reported M3 selective ligands prepared by making a nonselective ligand (benactyzine) more rigid. Canney and coworkers used a similar approach to prepare a related series of muscarinic ligands. Molecular modifications of these lead compounds have been made based on the recent SAR data and molecular modeling techniques. The purpose of the present work was to design a series of novel benzylpiperazines as muscarinic ligands and evaluate their selectivity for muscarinic receptors in radioligand binding assays (CEREP). The, design, synthesis and preliminary testing of these novel ligands will be reported.

**MEDI 387**

**Five-substituted 4,5-dihydro-3,3-diethyl-2(3H)-furanones as subtype selective muscarinic ligands**

***Rong Gao*** *and Daniel J. Canney, Dept of Pharmaceutical Sciences, Temple University, 3307 North Broad Street, philadelphia, PA 19140*

Five subtypes of muscarinic receptors (M1-M5) have been identified and cloned. Subtype-selective ligands would be valuable pharmacological tools with which to better characterize the receptors. A series of 5-substituted 4,5-dihydro-3,3-diethyl-2(3H)-furanones are reported to exhibit low affinity for muscarinic subtypes. Molecular modification of these lead molecules has been undertaken in an effort to design higher affinity, more selective ligands. Thus, the furanone was coupled to the amine-containing moiety via an amide or methylene linker. Synthesis of the amide series involved the Prins reaction of an olefinic ester to the corresponding lactone followed by Jones' oxidation. The acid chloride (thionyl chloride) is treated with the appropriate amine to afford the target amide-based ligands. The methylene-linked ligands are also prepared from the lactone described above by treating it with tosyl chloride followed by reaction with the appropriate amine. The design, synthesis and evaluation (radioligand binding; CEREP) of target compounds will be reported.

**MEDI 388**

**Development of Riccardin C analogs as novel LXR ligands**

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Liver X receptors (LXRα and β) play critical roles in cholesterol metabolism via controlling the related gene expression. LXR is also involved in cardiovascular diseases, inflammation, diabetes, and therefore, LXR is one of the significant molecular targets for the development of drugs for such diseases. We reported that Riccardin C, a natural product isolated from Blasia pusilla, has LXRα-selective agonistic activity (N. Tamehiro et al. FEBS Lett. 2005, 579, 5299-5304). In this study, we developed novel Riccardin C analogs as LXR ligands. First, we examined the total synthesis of Riccardin C utilizing ring-closure Suzuki-Miyaura coupling as a key step. Several cyclic analogs were synthesized, based on the established synthetic methods. Then, the acyclic analogs of Riccardin C were designed by the consideration of its estimated three-dimensional structure. Among synthesized acyclic analogs, some compounds exhibited LXRα agonistic activity.

**MEDI 389**

**Discovery and structure-activity relationships of substituted tetrahydroisoquinoline as liver X receptor (LXR) agonists**

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The liver X receptors (LXRs) are oxysterol-activated nuclear hormone receptors. There are two LXR subtypes, LXR*ƒ*Ñ and LXR*ƒ*", which play a key role in regulating cholesterol homeostasis. LXR agonists have been shown to stimulate Reverse Cholesterol Transport (RCT) by regulating multiple cholesterol efflux and absorption pathways. In rodent models they have been shown to increase RCT and decrease atherosclerosis. As a result, LXR agonists are potential agents to treat cardiovascular diseases. Using high-throughput screening, we have identified a novel series of tetrahydroisoquinoline LXR agonists as exemplified by the lead compound 1. Investigation of the structure-activity relationships resulted in the identification of compounds with improved potency compared to the HTS lead.

**MEDI 390**

**Aryl ether and aryl aniline derivatives as potent H3 antagonists**

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The histamine H3 receptor plays an important role in the synthesis and release of histamine and several other neurotransmitters in the central nervous system (CNS). Consequently, H3 antagonists have attracted great interest as potential treatments for a diverse set of disorders in which these neurotransmitters are thought to play a role.

Previous reports form our laboratories described a new series of H3 antagonists in which a lipophilic phenethylamino group was critical to activity at the H3 receptor. We have incorporated this structural motif in new series of aryl ethers and anilines which also act as potent antagonists of the H3 receptor. The design, synthesis and in-vivo profiles of these compounds will be presented.

**MEDI 391**

**Synthesis and structure activity relationship of novel spiro-isobenzofuranone derivatives as potent, brain penetrable and selective histamine H3 receptor inverse agonists**

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The $H_3$ receptor modulates the release and synthesis of histamine as a presynaptic autoreceptor. Antagonists/inverse agonists of the $H_3$ receptor have been suggested to have potential as drug therapies for various central nervous system (CNS) disorders. *N*-methyl-*N*-(2-piperidin-1-ylethyl)-4-(2-naphthyl)piperidine-1-carboxamide (**1**) was identified as a lead compound, which had an $IC_{50}$ value of 110 nM for the human $H_3$ receptor ($hH_3$) upon screening of Merck sample collections. After the modification of the left hand moiety of **1**, *trans*-*N*-methyl-*N*-(2-piperidin-1-ylethyl)-3*H*-spiro[3-oxo-2-benzofuran-1,1'-cyclohexane]-4'-carboxamide (**2**) was identified as a markedly potent analogue.

Compound **2** showed an $IC_{50}$ value of 0.72 nM at $hH_3$, a 150-fold improvement over **1**. **2** displayed excellent selectivity over other histamine receptor subtypes and 60 CNS receptors. **2** and its analogues appeared to be ideal $H_3$ PET tracer candidates based on their overall profile. Evaluation of **2**-based tracers in the MRL imaging research group is ongoing. The synthesis, SAR, and profiles of this novel class of $H_3$ inverse agonists will be presented.

**MEDI 392**

**Preclinical characterization of histamine H3 antagonists with serotonin reuptake inhibitor activity**

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Serotonin reuptake inhibitors are among the most widely prescribed agents for the treatment of depression. While often effective, these agents generally fail to treat all the symptoms of the disease. For example, many patients report sleep disorders and mild cognitive impairments that are associated with depression and in some cases serotonin reuptake inhibitors are actually reported to induce fatigue and excessive sleepiness. Attempts to overcome the fatigue and sleepiness associated with depression and thereby improve the efficacy of serotonin reuptake inhibitors have included the use of wake-promoting agents such as modafinil. One alternative approach is to combine a serotonin reuptake inhibitor with other wake-promoting agents, for example histamine H3 antagonists. The histamine H3 receptor controls the release of histamine and a variety of other neurotransmitters in the brain and antagonism of the H3 receptor promotes wakefulness in pre-clinical models. Histamine H3 antagonists are also expected to improve cognition. Given our experience with the discovery of novel histamine H3 antagonists, we hypothesized that we may be able to combine histamine H3 antagonism with serotonin reuptake inhibition in a single molecule and therefore obtain an improved therapy for the treatment of depression. Our efforts towards this end will be discussed in detail.

**MEDI 393**

**Synthesis, SAR and biological evaluation of novel quinazolinone class of histamine H3 receptor inverse agonists**

***Tsuyoshi Nagase****, Takashi Mizutani, Shiho Ishikawa, Etsuko Sekino, Takahide Sasaki, Takashi Fujimura, Sayaka Ito, Yuko Mitobe, Yasuhisa Miyamoto, Ryo Yoshimoto, Takeshi Tanaka, Akane Ishihara, Norihiro Takenaga, Shigeru Tokita, Nagaaki Sato, and Takehiro Fukami, Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical CO.,LTD, 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan*

Histamine neurons are exclusively localized in the tuberomammillary nucleus of the posterior hypothalamus and project widely thorough the central nervous system (CNS). The histamine H3

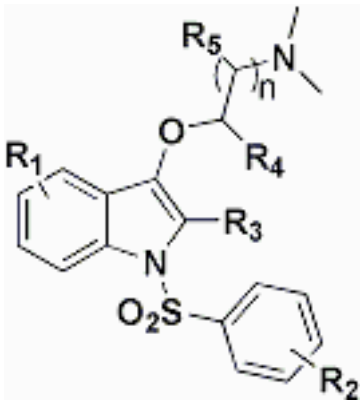
receptor, mainly located in the CNS, is a presynaptic autoreceptor that inhibits the release and synthesis of histamine. The histamine H3 receptor also modulates the release of other neurotransmitters as a presynaptic heteroreceptor. Histamine H3 receptor antagonists/inverse agonists have been shown to increase the level of the neurotransmitters and have the potential as therapeutic agents for treatment of various CNS disorders. Screening of in-house chemical collection against the human H3 receptor (hH3) resulted in the identification of novel quinazolinone derivatives. Optimization of key in vitro parameters resulted in the identification of 2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-5-(trifluoromethyl)-4(3*H*)-quinazolinone (**1**) as a potent, selective, brain penetrable and orally active H3 receptor inverse agonist. Subsequently, our efforts were focused on the improvement of the H3 activity of **1**. Structurally constrained analogues of **1** were synthesized and evaluated, resulting in the discovery of more in vivo potent derivatives. This presentation will be focused on the synthesis, SAR, and biological profiles of the structurally constrained quinazolinone derivatives.

**MEDI 394**

**Novel centrally acting 5-HT6 receptor ligands as potential antiobesity agents**

***Ramakrishna V. S. Nirogi****, Anand V. Daulatabad, Parandhama Gudla, Mohammad Shaik, Anil K Shinde, and Rama Sastry Kambhampati, Discovery Research - Medicinal Chemistry, Suven Life Sciences Ltd, Serene Chambers, Road No 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India, Fax: 91-40-23541152*

Intensive research is being focused on the development of new anti-obesity agents in order to control the epidemic of obesity. 5-HT6R antagonists work through reducing the food intake by activation of satiety center and also possibly through induction of catabolism. 5-HT6R antagonists from Biovitrum, Epix and Dr. Esteve's lab have entered into clinical trials for obesity. We at Suven have developed a novel series of N-aryl sulfonyl 3-(amino)alkoxy indole derivatives as highly potent and selective 5-HT6R ligands. A Set of selected compounds were tested in male Wistar rats for their effect on food intake (day and night time) and body weight. They were also tested in the DIO model using C57BL mice along with effect on fat mass and clinical chemistry. Lead compound at 30 mg/Kg p. o. dose exhibited significant reduction in food intake and body weight gain as compared to the control group. It also exhibited significant reduction in fat mass and triglyceride levels. The synthesis, in-vitro binding data along with SAR and in-vivo efficacy data of the lead molecule will be presented.



**MEDI 395**

## Biphenyl derivatives with potent H3 antagonist activity

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Selective antagonists of the histamine H3 receptor are the focus of growing interest lately due to the central role this receptor plays in modulating the production and release of numerous neurotransmitters in the central nervous system (CNS). Such compounds may have utility in treatment of diseases in which wakefulness, attention and/or cognitive function are compromised.

Among several new scaffolds examined in our search for new H3 antagonists, we have identified several biphenyl derivatives that are potent and selective antagonists of the H3 receptor. Herein, we summarize the discovery and development of these compounds, including an examination of their structure activity relationships, pharmacokinetic profiles and in vivo activity.

**MEDI 396**

## Novel indolizine compounds as potent inhibitors of phsophodiesterase IV: Syntheses and structure-activity relationship

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Phospodiesterases (PDEs) are a family of enzymes that regulate cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) via degradation of them to the corresponding 5'-monophosphate counterparts. Among the eleven PDE isoenzymes identified, the cAMP-specific PDE IV (PDE4) is shown to be the predominant isoenzyme that presents in inflammatory cells and is widely considered to be responsible for Asthma and other chronic or acute inflammatory diseases. Inhibition of PDE4 can significantly increase the intracellular c-AMP concentration and thus lead to the attenuation of some inflammatory processes. Therefore, PDE4 has been becoming a promising therapeutic target for some common serious inflammation diseases such as Asthma and chronic obstructive pulmonary diseases (COPD). We have discovered a series of indolizine compounds (1) that showed very potent activities in inhibiting this enzyme. The syntheses, biological activities and preliminary SAR of these novel indolizine compounds will be disclosed.

**MEDI 397**

**Synthesis and optimization of pyridopyrazinones as PDE5 inhibitors**

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As part of our ongoing efforts to identify a long-acting, selective PDE5 inhibitor suitable for chronic use in multiple indications, we discovered a series of pyridopyrazinones. We describe the synthesis and the initial elucidation of structure-activety relationships of this series focusing on improvements in PDE5 potency, selectivity versus PDE6 and PDE11 and physicochemical properties.

**MEDI 398**

**Discovery and optimization of a potent and selective new class of PDE4 inhibitors**

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The modulation of transcription factors, along with the subsequent increase or decrease of transcription of certain genes, is a sought after means of cell cycle control, and may lead to the alteration of numerous disease states. Recently, the NIH Chemical Genomics Center developed a cell based quantitative high throughput screen in search of small molecule modulators of CREB (cAMP response element-binding) proteins. A promising series of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines were uncovered as possible lead structures. Upon examination of these compounds in follow-up assays against likely protein candidates within the CREB signaling pathway, these molecules were found to be potent and selective inhibitors of phosphodiesterase 4 (PDE4). A synthetic pathway for the basic scaffold was developed and an initial library of substituted thiadiazines was prepared to optimize for both potency and selectivity. Data collected from this study allowed for the design and synthesis of a second, more potent library of compounds.

**MEDI 399**

**Design, synthesis, and evaluation of polyphenolic inhibitors of plasminogen activator inhibitor-1**

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Plasminogen activator inhibitor-1 (PAI-1) is an endogenous serine protease inhibitor, elevated levels of which have been implicated in acute and chronic conditions, including sepsis, myocardial infarction, cancer, atherosclerosis, and type 2 diabetes. It is believed that development of therapeutic agents that are potent and selective inhibitors of PAI-1 will be beneficial in the treatment of these conditions. A variety of polyphenolic compounds have been synthesized and found to be potent inhibitors of PAI-1. The synthesis and structure-activity relationships of these compounds will be presented.

**MEDI 400**

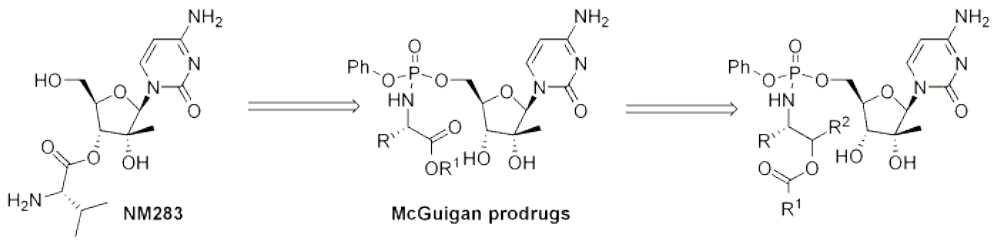
**Identification of novel phosphoramidate prodrugs for the treatment of HCV**

***Monica Donghi***[1]*, monica_donghi@merck.com, Barbara Attenni*[1]*, Cristina Gardelli*[1]*, Michael Rowley*[1]*, David B. Olsen*[2]*, Malcolm MacCoss*[3]*, Joseph F. Leone*[3]*, Sergio Altamura*[4]*, Annalise Di Marco*[5]*, Fabrizio Fiore*[5]*, Claudio Giuliano*[5]*, Ralph Laufer*[5]*, Vincenzo Pucci*[5]*, and Frank Narjes*[1]*. (1) Department of Medicinal Chemistry, IRBM/MRL Italy, Via Pontina km 30,600, Pomezia (RM) 00040, Italy, (2) Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, (4) Biochemistry, IRBM, 00040 Pomezia (Roma), Italy, (5) Department of Pharmacology, IRBM/MRL Italy, Pomezia (RM) 00040, Italy*

Hepatitis C virus has infected an estimated 170 million individuals. The current standard of care (interferon-a/ribavirin-combination) is poorly tolerated and has a suboptimal response particularly in patients infected with HCV genotype 1.

Amongst the viral enzymes, the NS5B polymerase is essential for HCV virus replication. The NS5B inhibitor NM283 showed moderate efficacy in Phase IIb trials (a mean 1.2 log10 reduction in HCV RNA was observed upon dosing 800 mg qd). The main impediment for a higher drop in viral load using NM283 is poor initial 5'-phosphorylation.

Here we illustrate our efforts towards the optimization of 2'-methyl-cytidine prodrugs employing a kinase-bypass approach based on 5'-phosphoramidate prodrugs (McGuigan).



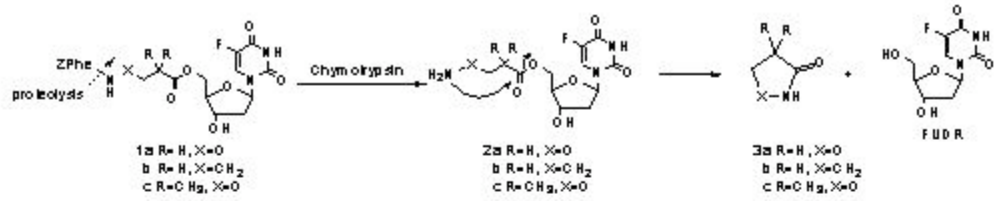

We will describe a novel class of phosphoramidate prodrugs based on aminoalcohols, the synthetic approach, the SAR and the in vivo and in vitro studies.

**MEDI 401**

## 3-Aminoxypropionate as a novel linker system for cyclization activation in prodrug design

***Yiyu Ge***[1]*, geyy007@hotmail.com, Xinghua Wu*[2]*, xhwu@eden.rutgers.edu, Dazhi Zhang*[1]*, and Longqin Hu*[1]*, LongHu@rutgers.edu. (1) Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, (2) Department of Pharmaceutical Chemistry, School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020*

Protease-activated prodrugs can be designed to improve target-specificity of anticancer agents used in the treatment of cancer. An efficient linker system is critical for drug activation and release at the targeted tumor site. Here we report a new linker system in the form of 3-aminoxypropionate designed to introduce hydroxylamine functionality to the activation and release of active drug molecules through intramolecular cyclization. It was found that the model Linker-Drug conjugate 2a bearing hydroxylamine in the linker system released the active drug 21 times faster than the corresponding amine conjugate 2b at pH=7.4, 37 ¢ªC (t1/2=1.1 h vs 23 h). The rate of cyclization is pH dependent. The drug release from conjugate 2a was 20 times slower with a half-life of 22.6 h at pH=6.0, 37 ¢ªC. Under the same conditions, only 4.5% of the drug was released from the corresponding amine conjugate 2b after 48 h incubation. The introduction of two methyl groups $\alpha$ to the ester linker (conjugate 2c) facilitated cyclization process and increased the cyclization rate by nearly 2 fold at pH=7.4, 37 ¢ªC (t1/2=39 min vs 1.1 h). The designed linker system 2c was successfully applied to a model prodrug of FUDR. The model prodrug 1c was activated by $\alpha$ chymotrypsin at pH=7.4, 37 ¢ªC with t1/2 of 36.5 min. The results suggest that the designed 2-aminoxypropionate is a good linker system for protease-activated prodrugs.



**MEDI 402**

## A prodrug approach for A2A receptor mediated anticancer immunotherapy: Design, synthesis and therapeutic effect on tumor cells

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It is a long-held dream that cancer patients use their own immune system to inhibit tumor growth. Unfortunately, malignant tumor cells often escape immune surveillance. Recently, it was found that adenosine, which is over expressed extracellularly within hypoxic tumor tissue, switches off T-cell immune function via an A2 Adenosine receptor mediated pathway. This key discovery points to the potential clinical application of A2AR antagonists. Both the natural antagonist caffeine and KW6002, a synthetic A2A receptor antagonist, have been used to prove this concept, the latter showing promising therapeutic effect on tumors in mice. However, existing A2AR antagonists were designed for CNS applications and are typically of poor solubility due to their high lipophilicity. Herein, we report a prodrug approach aiming to improve drugs' solubility and tumor specificity by the incorporation of an enzymatically cleavable carrier. A detailed account of design philosophy, synthetic methodology and in vivo experiments will be described.

**MEDI 403**

## Optimization of fibrin-binding peptides as targeting vectors for thrombus-specific MRI-contrast agents

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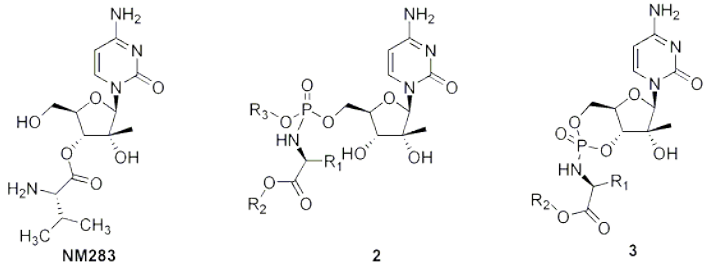
There remains a need for a high resolution, non-invasive bright spot imaging method to identify and assess thrombi (blood clots), which are implicated in a number of fatal diseases such as heart attack and stroke. Fibrin is an attractive imaging target: it is present in all thrombi at high levels providing high sensitivity, but it is not present in blood plasma resulting in high specificity. A class ($X_3$CPYGLC$X_3$) of fibrin-binding cyclic peptides was discovered via Phage display, resulting in the identification of a lead peptide, EP-769. The optimization of EP-769 focused on improving fibrin affinity and other biological properties. This process ultimately led to the gadolinium derivatized peptide EP-2104R, which recently completed a positive proof-of-concept phase II study for MRI-detection of thrombosis. Design, synthesis and optimization of the fibrin-binding peptides as well as their application towards fibrin-targeted MRI-contrast agents for detection of thrombus will be discussed.

**MEDI 404**

## A prodrug approach for the treatment of HCV infection

***Malte Meppen***[1]*, malte_meppen@merck.com, Frank Narjes*[1]*, narjes@irbm.it, David B. Olsen*[2]*, Barbara Pacini*[1]*, barbara_pacini@merck.com, Joseph F. Leone*[3]*, Malcolm MacCoss*[3]*, Michael Rowley*[1]*, Sergio Altamura*[4]*, Annalise DiMarco*[4]*, Fabrizio Fiore*[4]*, Claudio Giuliano*[4]*, Odalys Gonzalez-Paz*[4]*, Ralph Laufer*[4]*, Vincenzo Pucci*[4]*, and Cristina Gardelli*[1]*. (1) Department of Medicinal Chemistry, IRBM/MRL Italy, Via Pontina Km 30,600, Pomezia (Rome) 00040, Italy, (2) Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, (4) Department of Pharmacology, IRBM/MRL Italy, Pomezia (RM) 00040, Italy*

The NS5B RNA-dependent RNA-polymerase enzyme is essential for HCV virus replication and is an attractive target for drug discovery. A compound targeting the polymerase is the nucleoside derivative **NM283**, developed by Idenix which until recently has been in Phase IIb trials. **NM283** shows moderate efficacy in man displaying a 1.2 log-drop in viral load at 800 mg qd. The main impediment for a more pronounced log-drop in viral load by using this nucleoside, however, is the rate limiting 5'-phosphorylation. We describe our efforts toward the optimisation of 2'-methyl-cytidine prodrugs as inhibitors of HCV NS5B, employing a kinase-bypass approach (5'-phosphoramidate) for a more efficient formation of the active triphosphate. Phosphoramidate prodrugs such as **2** have been described; we on the other hand disclose the synthesis of novel, cyclic prodrugs **3** and their SAR. As a proof of concept study, dosing of our prodrug derivatives **3** in preclinical species validated the effectiveness of the kinase-bypass effect in vivo, resulting in higher liver triphosphate-levels with respect to **NM283**.



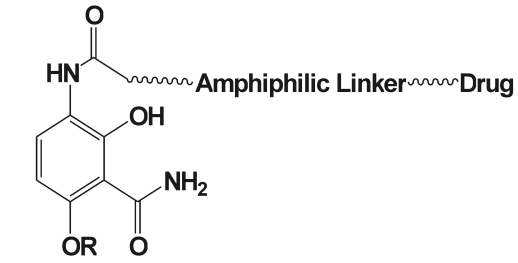

**MEDI 405**

## Targeting drugs to bone

***Natali B. Richter***[1]*, nbrich01@louisville.edu, Kathleen Hamilton*[2]*, Michael Voor*[3]*, Jeff Falcone*[2]*, Jian Cai*[4]*, Qian Xu*[5]*, Kevyn Merten*[6]*, K. Grant Taylor*[1]*, and William M. Pierce Jr.*[4]*. (1) Department of Chemistry, University of Louisville, Louisville, KY 40292, (2) Department of Physiology and Biophysics, University of Louisville, Louisville, KY 40292, (3) Department of Orthopaedic Surgery, University of Louisville, Louisville, KY 40292, (4) Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY 40292, (5) Department of Mechanical Engineering, University of Louisville, Louisville, KY 40292, (6) Pradama, Inc, Louisville, KY 40292*

Because of the unique mineral content of bone, molecules that have an affinity for hydroxyapatite might be utilized to act as “drug carriers” to target bone in a tissue-specific manner. Previous structure-activity relationship studies revealed the hydroxyapatite-binding properties of an aromatic

amine based on the A ring of tetracycline. Novel drug conjugates employing this bone-targeting moiety have been designed and synthesized. As shown below, drugs were tethered to the bone-targeting domain of the molecule via an amphiphilic linker. Preliminary in vivo and in vitro biological efficacy studies of some of the conjugates have shown potential for development into new treatments for bone diseases.




**Bone-targeting domain**

**R = $CH_3$ or $CH_2C_6H_5$**

**MEDI 406**

**Development of synthetic methodology suitable for the radiosynthesis of combretastatin A-4 and combretastatin A-1 along with their corresponding prodrugs**

***Madhavi Sriram**, John Hall, Anupama R. Shirali, Benson Nguyen, Rajsekhar Guddneppanavar, J Freeland Ackley, Rogelio Siles, Mallinath B. Hadimani, Christopher J. Jelinek, Phyllis Arthasery, and Kevin G. Pinney, Department of Chemistry and Biochemistry and The Center for Drug Discovery, Baylor University, One Bear Place # 97348, Waco, TX 76798, Fax: 254-710-4272*

Therapeutic strategies that selectively target tumor vasculature are attracting increasing attention in cancer therapy. Combretastatin-A4 (CA4) and combretastatin-A1 (CA1) are known tubulin depolymerizing agents that cause rapid shutdown of tumor vasculature. Both of these compounds in prodrug form (Zybrestat$^{TM}$ and OXi4503 respectively) are in human clinical development as vascular disrupting agents (VDAs). Pharmacokinetic and biodistribution studies are aided by the availability of radiolabeled drug candidates. We have developed an efficient synthetic methodology to facilitate the preparation of both Zybrestat$^{TM}$ and OXi4503 in high specific activity radiolabeled form. A key synthetic step allows the introduction of a $^{14}$C-methyl group at a relatively late stage in the overall synthesis without concomitant isomerization of the stilbene molecular core. In addition, alternative synthetic routes will be presented that may also prove useful for the radiosynthesis of selected combretastatin derivatives. The actual work described utilizes carbon-12, however the chemistry is readily adaptable to carbon-14.

**MEDI 407**

**Synthesis of new carbon-11 labeled nimesulide analogs as potential PET SAER radiotracers for imaging of breast cancer aromatase**

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

Aromatase is a particularly attractive target in the treatment of estrogen receptor positive breast cancer and the development of enzyme-based cancer imaging agents for biomedical imaging technique positron emission tomography (PET). A novel series of nimesulide analogues have been recently developed as potential selective aromatase expression regulators (SAERs) in breast cancer cells. New carbon-11 labeled nimesulide analogues were designed and synthesized as potential PET SAER radiotracers for imaging of aromatase in breast cancer. Unlabeled nimesulide analogues and their desmethylated precursors were synthesized from 2-amino-5-nitrophenol in multiple steps with moderate to excellent yields. The target tracers *N*-(2-(benzyloxy)-4-nitrophenyl)-*N*-[$^{11}$C]methylmethanesulfonamide, *N*-[$^{11}$C]methyl-*N*-(2-(4-methylbenzyloxy)-4-nitrophenyl)methanesulfonamide, *N*-(2-(4-fluorobenzyloxy)-4-nitrophenyl)-*N*-[$^{11}$C]methylmethanesulfonamide, *N*-(2-(biphenyl-2-ylmethoxy)-4-nitrophenyl)-*N*-[$^{11}$C]methylmethanesulfonamide, and *N*-[$^{11}$C]methyl-*N*-(2-(naphthalene-1-ylmethoxy)-4-nitrophenyl)methanesulfonamide were prepared from their corresponding precursors *N*-(2-(benzyloxy)-4-nitrophenyl)methanesulfonamide, *N*-(2-(4-methylbenzyloxy)-4-nitrophenyl)methanesulfonamide, *N*-(2-(4-fluorobenzyloxy)-4-nitrophenyl)methanesulfonamide, *N*-(2-(biphenyl-2-ylmethoxy)-4-nitrophenyl)methanesulfonamide, and *N*-(2-(naphthalene-1-ylmethoxy)-4-nitrophenyl)methanesulfonamide with [$^{11}$C]$CH_3OTf$ under basic condition (NaH) through *N*-[$^{11}$C]methylation and isolated by HPLC method in 30-50% radiochemical yields.

**MEDI 408**

**Synthesis and biological evaluation of a radiolabeled dansylhydrazone derivative as an imaging agent for apoptosis**

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Apoptosis is an important process involved in the etiology, pathogenesis, and response to therapy of a variety of diseases. To develop a small molecule-based tracer for in vivo apoptosis imaging, a dansylhydrazone derivative (DFNSH) was synthesized in 93% yield in less than 30 minutes. The biological evaluation showed that DFNSH selectively binds to paclitaxel-induced apoptotic cancer cells and is localized within the cytoplasm of cells. [18F]-DFNSH was synthesized and isolated in 50-60% radiochemical yields. The straightforward preparation of fluorine-18 labeled DFNSH makes it a promising tracer for PET imaging of apoptosis.

**MEDI 409**

**Class B G-protein coupled receptors as targets for protein-based virtual screening**

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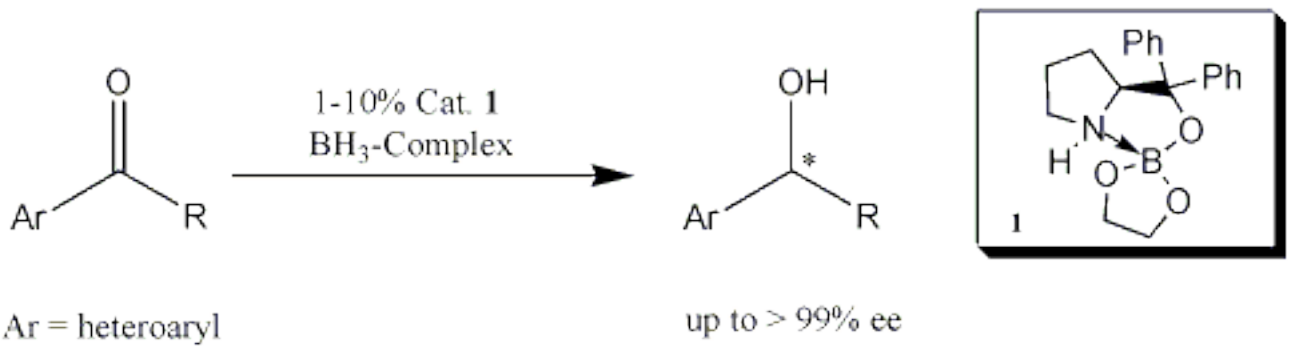
The aim of the present study is to evaluate whether homology models of the transmembrane (TM) domain of secretin-like (Class B) G-Protein coupled receptors (GPCRs) are accurate enough for retrospective structure-based virtual screening. A detailed computational workflow to derive TM domain models based on GPCR templates is described. The models are then optimised and evaluated for their ability to explain site-directed mutagenesis data and ligand structure-activity relationships. They are then validated in stringent retrospective virtual screening experiments.

**MEDI 410**

**Highly enantioselective reduction of heterocyclic aromatic ketones with borane and the spiroborate ester derived from (S)-diphenyl prolinol**

***Melvin De Jesus***[1]*, me_dejesus@hotmail.com, Cindybeth Vazquez*[2]*, cindyvazquez8@hotmail.com, Lorianne Bermudez*[2]*, ennairolis7@hotmail.com, Irisbel Guzman*[1]*, irisg23@hotmail.com, Viatcheslav Stepanenko*[1]*, the3spiritslava@hotmail.com, Wildeliz Correa*[3]*, and Margarita Ortiz*[1]*, mr_ortiz@webmail.uprh.edu. (1) Department of Chemistry, University of Puerto Rico at Humacao, CUH Station,100 Rd 908, Humacao, PR 00791-4300, Fax: 787-850-9422, (2) Department of Chemistry, University of Puerto Rico, Humacao, Humacao, PR 00791, (3) Department of Chemistry, University of Puerto Rico, Humacao, PR 00791*

Enantiopure alcohols are very important precursors in the synthesis of pharmaceutical and other biologically active products. The asymmetric reduction of prochiral ketones into non-racemic alcohols continues generating tremendous academic and industrial attention. Recently, we have developed the novel spiroborate ester 1, derived from (S) – diphenyl prolinol and ethylene glycol, as a highly effective catalyst for the asymmetric borane-mediated reduction of ketones. The synthesis of optically pure alcohols containing furanyl and other heterocyclic fragments using 1-10 mol % of catalyst 1 in high chemical yields and excellent enantioselectivity will be described.




**MEDI 411**

**Introduction of the oxetan-3-yl group into aromatic and heteroaromatic systems**

***Matthew Duncton****, M. Angels Estiarte, Donogh J. R. O'Mahony, Darlene Tan, Russell Johnson, Matthew Cox, Carl Kaub, William T. Edwards, John Kincaid, and Michael G. Kelly, Renovis, Inc, Two Corporate Drive, South San Francisco, CA 94080, Fax: 650-266-1505*

The oxetan-3-yl module has recently been described as a priviledged motif within medicinal chemistry. However, few methods for the introduction of this group have been described in the

chemical literature. In this paper, we describe a number of different strategies for incorporation of an oxetan-3-yl moiety in to aromatic and heteroaromatic systems.

**MEDI 412**

**Synthesis and biological evaluation of tannic acid and related tannins**

***Jennifer J. Vogel***[1]*, jvogel5@emich.edu, Maria M. Puscau*[1]*, mpuscau@emich.edu, Seo J. Oh*[1]*, soh@emich.edu, Mark Warnock*[2]*, Jacqueline M. Cale*[2]*, Daniel A. Lawrence*[2]*, and* ***Cory D. Emal***[1]*, cemal@emich.edu. (1) Department of Chemistry, Eastern Michigan University, 225 Mark Jefferson, Ypsilanti, MI 48197, (2) Internal Medicine, University of Michigan, Ann Arbor, MI 48109*

Tannic acid (decagalloyl glucose, $C_{76}H_{52}O_{46}$) is naturally occurring polyphenol, commonly found in the fruits and barks of various trees, and consists of multiple digallate esters arranged around a central glucose ring. Challenges concerning the regiospecific synthesis of the pendant digallate esters present in tannic acid will be discussed. In addition, the biological activity of inhibitors based on digallate-containing gallotannins and digallate analogs will be presented.

**MEDI 413**

**Microwave-assisted synthesis of human nesfatin: An efficient tool for synthesis of long and challenging peptide sequences.**

***Fernando Ferrer***[1]*, fernando.ferrer@amylin.com, Dorene Wood*[1]*, and Ved P Srivastava*[2]*. (1) Amylin Pharmaceutical, Inc, Department of Chemistry, 9360 Towne Centre Dr, San Diego, CA 92121, Fax: 858 3341161, (2) Amylin Pharmaceutical, Inc, CA 92121*

Microwave-assisted synthesis has become increasingly advantageous in solid phase peptide synthesis (SPPS). This technology resolves problems such as intermolecular aggregation, beta-sheet formation and steric hindrance from amino acid protecting groups during peptide synthesis. Synthesis of longer and more challenging peptides such as human Nesfatin (82 amino acid residues) using microwave technique will be discussed.

**MEDI 414**

**Increased product purity with GraceResolv high resolution flash cartridges**

***Romulus Gaita***[1]*, romulus.gaita@grace.com, Scott Anderson*[2]*, and Paul Garms*[2]*, paul.garms@grace.com. (1) TCS, Grace Davison Discovery Sciences, 2051 waukegan rd, Deerfield, IL 60015, (2) Grace Davison Discovery Sciences, Deerfield, IL 60015*

To satisfy the need for flash cartridges with better resolution and higher loading capacity, GraceResolv™ high-resolution flash cartridges have been developed by Grace Davison Discovery Sciences. The silica packed in GraceResolv™ cartridges was specifically designed to increase cartridge efficiency (plates/meter) and reduce unwanted mixed-mode interactions thereby increasing resolution of closely eluting compounds. The increase in resolution also enables a significant increase in loading capacity, over two times greater in some cases, verses traditional flash cartridges. By

purifying greater amounts on a given cartridge size, users can reduce purification costs by 30% and increase productivity.

**MEDI 415**

**Amino column in purification of active pharmaceutical compounds**

***Shahnaz Ghassemi**, R&D, SynPure International, 801 West Main Street, Suite 207, Charlottesville, VA 22903*

Amino bonded media is a versatile chromatography reagent that can be used in a variety of chromatography mode such as normal phase, reverse phase and hydrophilic interaction chromatography (HILIC). This media also can be used in quick sample clean up in SPE format.

We have examined the application of this media for improving purification efficiency of quinolone carboxylic acids and short peptides which were prepared in rapid microwave assisted synthesis.

**MEDI 416**

**Synthesis of peptide nucleic acid-functionalized polydiacetylene liposomes: Potential novel colorimetric nucleic acid biosensors**

***Jennyfer Goujon** and Nicola M. Howarth, Chemistry, School of Engineering & Physical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom*

The ability to identify particular sequences of DNA, both quickly and precisely has become of increasing importance in recent years. Current DNA detection methods are limited by their need for the DNA in the sample to be chemically labelled before analysis. In this poster, the biosensor described does not. In fact, the detector is the DNA mimic, peptide nucleic acid (PNA) whilst the sensor is based on polydiacetylene (PDA) liposomes. It is envisaged that when the PNA detector binds to its target gene, the PDA sensor will be induced to change colour from blue to red. It is anticipated that this response will be detected visually and quantified through UV/Vis spectroscopy. In order to improve the hydrophilic character of the liposomes, a hydrophilic spacer has been included. Here, we report our progress to date on the preparation and evaluation of PNA-functionalised PDA liposomes as potential, novel colorimetric nucleic acid biosensors.

**MEDI 417**

**Total synthesis of hermitamides A and B, and their activity against human voltage-gated sodium channels**

***Kristin M. Graf**[1], kmg4u@virginia.edu, Mikell Paige[2], map65@georgetown.edu, Manoj Patel[3], and Milton L. Brown[2], mb544@georgetown.edu. (1) Department of Chemistry, University of Virginia, McCormick Rd, P.O. Box 400319, Charlottesville, VA 22904, (2) Drug Discovery Program, Georgetown University Medical Center, Washington, DC 20057, (3) Department of Anesthesiology, University of Virginia, Charlottesville, VA 22906*

The hermitamides are marine natural products isolated from the cyanobacterium Lyngbya majuscula collected in Papua, New Guinea. The compounds are lipopeptides that contain an S methoxy stereocenter at C7 of the aliphatic chain. We hypothesized that these ligands may also be a substrate for the sodium channel and can serve as templates for development of new therapeutic agents. Herein, we present the total syntheses of hermitamides A and B, and their precursor lyngbic acid. A BINOL-titanium complex was used to mediate asymmetric addition of allyltributylstannane into octanal to set the remote C7 stereocenter. The natural S stereoisomer, the corresponding R enantiomer, and the racemic mixture of each compound were prepared. The compounds were then tested for tritiated-BTX displacement at 10 micromolar, followed by whole-cell patch-clamping.

**MEDI 418**

**Stereoselectivity in nucleophilic addition to tropinone**

***Juliet M. Hahn**, Ruth Wamwati, and Nicole Morris, Department of Chemistry, Delaware State University, 1200 N. Dupont Hwy, Dover, DE 19901, Fax: 302-857-6539*

Tropanes are a class of natural products implicated in a number of potential pharmaceutical applications. Diastereoselectivity in reactions of tropinone has been investigated in this work. The effect of zwitterionic derivitization of the tropinone into N-methyl and N-oxide derivatives has been investigated and sodium borohydride reduction of both the parent tropinone and zwitterionic derivatives has been explored. The stereoisomeric ratios of all products has been fully characterized. Organometallic nucleophilic reactions of the tropinone has also been investigated. The zwitterionic effect and organometallic nucleophilic reactions of the tropinone in comparison to these effects in N-phenyltropinone will be discussed. A fundamental understanding of the stereoselectivity effect in these two molecules should result in synthetic methodology applicable to the synthesis of potential pharmaceuticals with applications in cocaine addiction, analgesics, and Alzheimer's.

**MEDI 419**

**Design and synthesis of cysteine based PNA monomers**

***Priyesh Jain**[1], pjain@mail.usf.edu, Sung Wook Yi[2], gowoogie@gmail.com, Sridhar Reddi Kaulagari[1], Mehul Ajmera[1], Laura Anderson[1], Mellisa Topper[1], and Mark L McLaughlin[1]. (1) Department of Chemistry, University of South Florida-Moffitt Cancer Center, 4202 East Fowler Avenue, Tampa, FL 33620, (2) Department of Chemistry, Drug Discovery Program, University of South Florida, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33620*

Many human diseases are caused by over-, under-, or misproduction of specific proteins. Defects in the gene cause production of m-RNA which codes for a non-functional protein. Gene expression can be regulated by binding of an oligonucleotide or oligonucleotide analogue to double stranded DNA or single stranded RNA. PNAs (Peptide Nucleic Acids) are excellent DNA mimics with neutral backbones. Several studies have indicated that poor cellular permeability and poor aqueous solubility of PNAs have limited its application as a potential candidate for gene-targeting drugs. Previously reported studies have shown that introduction of positively charged residues such as lysine and arginine into PNA molecules increase cellular uptake of PNAs. Herein we present the synthesis of Cysteine based Peptide nucleic acid (CPNA) monomers with various positively charged alkyl units in the side chain.

**MEDI 420**

**Synthesis of novel hemoglobin cross linkers based on 2,3-biphosphoglycerate**

***Tigist W. Kassa****, Jason S. Matthews, and Faith A. Brown, Department of Chemistry, Howard University, 525 College Street NW, Washington, DC 20059*

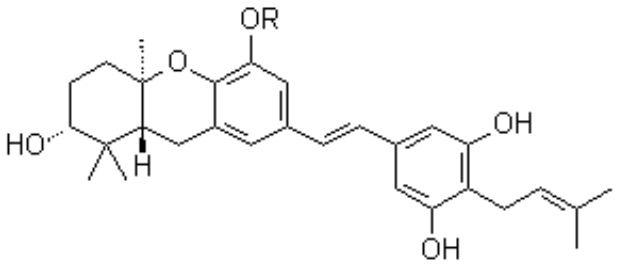
Hemoglobin (Hb), the natural oxygen carrier inside the red blood cell (RBC), has been the preferred choice for developing blood substitutes. However, there are two principal problems that must be overcome before hemoglobin can be utilized as a blood replacement. First, it suffers from short circulation times in the blood stream (1-4hrs) due mainly to its breakdown from a large tetrameric protein, ƒp1ƒp2ƒr1ƒr2, into two smaller dimeric units, ƒp1ƒr1 and ƒp2ƒr2, resulting in its rapid renal elimination causing considerable renal toxicity. Secondly, it has high oxygen affinity which does not allow it to release the bound oxygen. These drawbacks have been attributed to the loss of the natural allosteric effector of Hb, 2,3 bisphosphoglycerate (BPG), upon isolation of pure stroma-free Hb from RBC. We have designed compounds which we propose will mimic BPG outside RBC and can crosslink the Hb tetramer in the ƒr cleft. ƒp,ƒp-difluoro substituted phosphonates have been to explored as 2, 3-bisphosphoglycerate analogues and have been synthesized.

**MEDI 421**

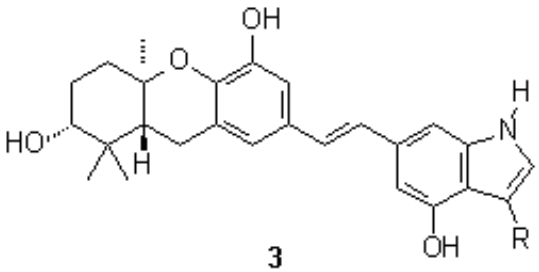
**Indole containing analogs of the natural schweinfurthins.**

***John G. Kodet****, Nolan R. Mente, Jeffrey D. Neighbors, and David F. Wiemer, Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294*

As part of an ongoing effort aimed at development of therapeutic agents based on the natural schweinfurthins F and G (1 and 2), a number of analogues have been synthesized. The prevalence of the indole moiety in therapeutically active compounds inspired preparation of indole-containing analogues of the schweinfurthins (e.g. 3) to probe the essential pharmacophore. The natural schweinfurthins contain a resorcinol moiety in the D-ring, and appear to be less stable than similar structures with a single D-ring phenol. The indole analogues can be viewed as replacing one of the phenolic oxygens on the natural D-ring with the indole nitrogen, and thus provide a more rigid and stable system for addition of further substituents. The strategies employed to synthesize these new indole-containing analogues will be presented, along with some preliminary studies of their activity.




**1** R = $CH_3$ Schweinfurthin F
**2** R = H Schweinfurthin G




**3**

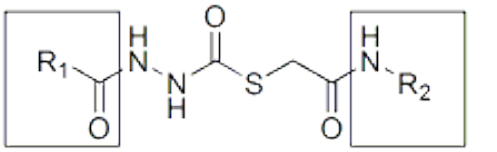
R = H,

**MEDI 422**

**Synthesis and biological characterization of a library of thiocarbazates**

***Zhuqing Liu***[1]*, zhuqliu@sas.upenn.edu, Michael C. Myers*[1]*, Parag P. Shah*[2]*, ppshah@seas.upenn.edu, Mary Pat Beavers*[2]*, Scott L. Diamond*[2]*, sld@seas.upenn.edu, Amos B. Smith III*[3]*, smithab@sas.upenn.edu, and Donna M. Huryn*[1]*, huryn@sas.upenn.edu. (1) Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, PA 19104, (2) Department of Chemical & Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104, (3) Department of Chemistry, Univerisity of Pennsylvania, Philadelphia, PA 19104*

Cathepsins comprise a family of enzymes within the papain superfamily of cysteine proteases that play important roles in physiological processes such as bone resorption, tumor metathesis, and rheumatoid arthritis. Recently we reported a series of novel compounds which exhibit potent inhibitory activity against cathepsin L. To explore further this novel class, we have constructed a library of thiocarbazates and tested them against a panel of serine and cysteine proteases. Preliminary studies reveal that some of these compounds are highly selective for cathepsin S over B and L, with nanomolar IC50 values. The results of these studies will be described.




**MEDI 423**

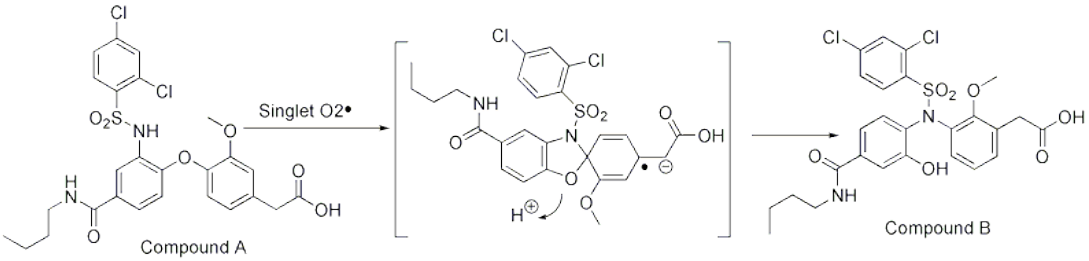
**Identification and characterization of a novel smiles type photo-rearrangement drug degradant**

***Stephen A. Osgood***[1]*, sosgood@amgen.com, Matthew Janson*[1]*, Randy Jensen*[2]*, Jack Hu*[1]*, Peter Zhou*[1]*, Nina Cauchon*[3]*, Anthony King*[2]*, Jackie Milne*[2]*, and Sophie Wang*[3]*, xuemeiw@amgen.com. (1) SMPD, Amgen Inc, One Amgen Center Drive, 21-1-C, Thousand Oaks, CA 91320-1799, (2) Amgen Inc, Thousand Oaks, CA 91320, (3) Small Molecule Analytical R&D, Amgen Inc, Thousand Oaks, CA 91320*

Evaluation of light sensitivity and photostability is an important part of developing new active substance to commercial drug products. During one of our investigations, a major degradation product of Compound A was observed and isolated from stressed samples under photo-oxidative conditions. This poster describes the preparation, isolation and characterization of this novel degradant (Compound B).

In this study, Compound A was exposed to light and a catalytic amount of a photo-sensitizer (Rose Bengal or Methylene Blue). The degradant has identical molecular weight and mass spectrometry fragments as the starting material. Further examination, indicated that an unusual Smiles-type rearrangement has occurred under the photolysis conditions. After purification by preparative RP-HPLC and lyopholization, the isolated Compound B was fully characterized using LC/MS/MS, 1D NMR and 2D NMR experiments. Effects of pH conditions, media and photosensitizers on the photostability of Compound A were also evaluated. The proposed reaction mechanism under the

photo-oxidative conditions helps to understand the photostability of this class of aryl ether compounds.

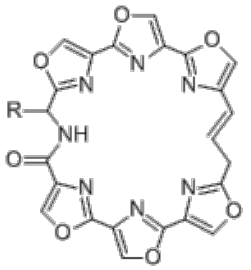



**MEDI 424**

**Ring-closing metathesis as an entry into cytotoxic macrocyclic polyoxazoles**

***Mavurapu Satyanarayana***[1]*, msatya@rci.rutgers.edu, Suzanne G. Rzuczek*[2]*, srzuczek@eden.rutgers.edu, Daniel S. Pilch*[3]*, pilchds@umdnj.edu, Angela Liu*[3]*, Leroy F Liu*[3]*, Edmond J. LaVoie*[1]*, elavoie@rci.rutgers.edu, and Joseph E. Rice*[2]*, jrice@rci.rutgers.edu. (1) Department of Pharmaceutical Chemistry, Rutgers University, 160 Frelinghuysen Road, Piscataway, NJ 08854, (2) Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020, (3) Department of Pharmacology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854*

The ring-closing metathesis reaction has become a standard synthetic tool for organic chemists. It has been employed to form rings comprised of 4 through 72-members. Most of the successful applications of this reaction involve substrates having a great deal of conformational flexibility. We report here the successful application of a ring-closing metathesis reaction to form a 24-membered ring comprised of six smaller oxazole rings and having few degrees of conformational freedom. The ring was formed in 32% yield for R = isopropyl. The resulting compound was evaluated for cytotoxic activity and G-quadruplex stabilizing ability. Several analogs were also synthesized for comparison of biophysical and biological activity.



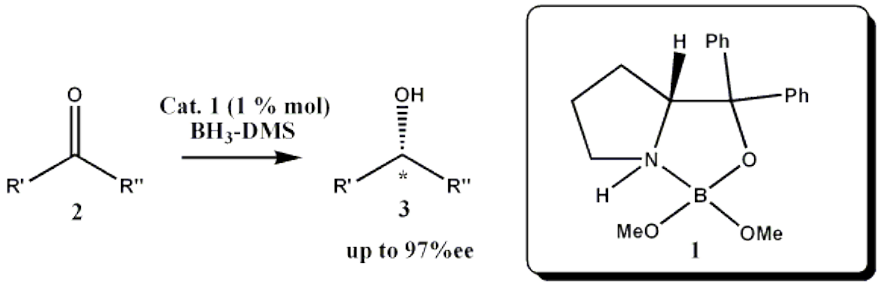
**MEDI 425**

**Highly enantioselective boron-mediated reduction of prochiral ketones with the aminoborate ester derived from (S)-diphenyl prolinole.**

***Viatcheslav Stepanenko***[1]*, the3spiritslava@hotmail.com, Margarita Ortiz-Marciales*[1]*, and Charles L. Barnes*[2]*. (1) Department of Chemistry, University of Puerto Rico at Humacao, CUH Station, 100 Rd*

*908, Humacao, PR 00791, Fax: 787-850-9422, (2) Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211*

Asymmetric reduction of prochiral ketones is one of most efficient method of the introduction of chirality in the synthesis of non-racemic biologically active compounds. Derived from chiral (S)-diphenyl prolinole the amino borate ester 1 has been prepared, fully characterized and used as highly effective catalyst for asymmetric reduction of ketons with borane. The optically pure alcohols 3 have been prepared using only 1mol % of catalyst 1 in enantioselectivity up to 97%.




**MEDI 426**

**Application of a one-pot Friedländer procedure toward the synthesis of IGR-1R inhibitors**

***Kathryn M. Stolz**, Heather R. Coate, Radoslaw Laufer, Andrew Kleinberg, An-Hu Li, Kam W. Siu, Arno G. Steinig, Yingchuan Sun, and Mark J. Mulvihill, Cancer Chemistry, OSI Pharmaceuticals, Inc, 1 Bioscience Park Drive, Farmingdale, NY 11735*

The quinoline moiety is present as a key pharmacophore in a broad range of both natural and unnatural biologically active compounds. Due to such biological importance, quinoline derivatives are becoming the synthetic targets of many organic and medicinal chemistry groups and new methods for constructing the quinoline ring appear regularly in the literature. Recently we reported the preliminary results of a one-pot Friedländer quinoline synthesis that involves reduction of *o*-nitroarylcarbaldehydes with iron in the presence of catalytic HCl (aq) and subsequent condensation with aldehydes or ketones *in situ*. Herein, we showcase its utility for the preparation of inhibitors of IGF-1R. Halogen-containing quinolines obtained by this method were converted into their respective boronic pinacol esters followed by Suzuki reaction with halo-imidazopyrazine building blocks. This sequence compares favorably with our previous linear route to such IGF-1R inhibitors and also with our earlier route to such quinoline boronates.

**MEDI 427**

**Design and synthesis of 1-aryl-3-(thiophen-2-yl)-1H-1, 2, 4-triazol-5(4H)-ones as detrusor muscle relaxants for the treatment of urinary incontinence**

***Li-Qiang Sun**, Dalton King, Kahnie Pham-Kaplita, Jie Chen, Piyasena Hewawasam, George Thalody, Harvey Weiner, Christopher G. Boissard, Robert A. Myers, Valentin K. Gribkoff, Nicholas Lodge, Steve Hansel, Lori Pajor, and John E. Starrett Jr., Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702*

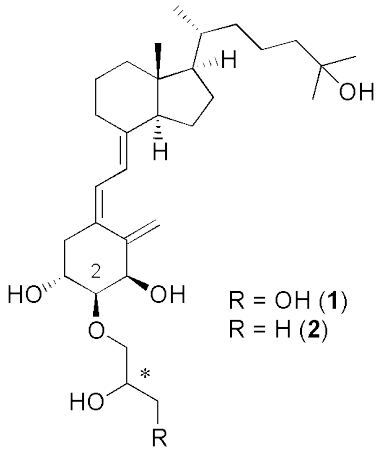
A novel series of 1-aryl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5(4H)-one derivatives was synthesized and evaluated as detrusor muscle relaxants for the treatment of urinary incontinence. The effects of these compounds on bladder contractile function were determined in vitro by using isolated rat bladder strips from male Sprague-Dawley rats that were pre-contracted with carbachol. The results of the SAR studies in this series led to the identification of several potent smooth muscle relaxants. The design, synthesis, and SAR of the series will be presented.

**MEDI 428**

**New vitamin $D_3$ analogs: 2alpha-(2,3-Dihydroxypropoxy)- and 2alpha-(2-hydroxypropoxy)-active vitamin $D_3$ with highly potent VDR agonism**

***Masashi Takano***[1]*, mtakano@pharm.teikyo-u.ac.jp, Daisuke Sawada*[1]*, Keiko Hayashi*[2]*, Shin-ichi Ikushiro*[2]*, Toshiyuki Sakaki*[2]*, Ken-ichiro Takagi*[3]*, Seiichi Ishizuka*[3]*, Midori Takimoto-Kamimura*[3]*, Maiko Gokoh*[1]*, Takayuki Sugiura*[1]*, and Atsushi Kittaka*[1]*, akittaka@pharm.teikyo-u.ac.jp. (1) Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Sagamihara, Kanagawa 229-0195, Japan, Fax: +81-42-685-3714, (2) Faculty of Engineering, Toyama Prefectural University, Toyama 939-0398, Japan, (3) Teijin Institute for Bio-Medical Research, Tokyo 191-8512, Japan*

Both diastereomers of 2alpha-(2,3-dihydroxypropoxy)-1alpha,25-dihydroxyvitamin $D_3$ (**1**) and 2alpha-(2-hydroxypropoxy)-1alpha,25-dihydroxyvitamin $D_3$ (**2**) were synthesized as novel vitamin $D_3$ derivatives with a chiral 2alpha-substituent. Stereoselective introduction of the chiral 2alpha-substituent into an A-ring fragment for synthesizing **1** or **2** was accomplished by our original method starting from D-glucose. Binding affinity for vitamin D receptor (VDR), HL-60 cell differentiation activity, and osteocalcin transcriptional activity on HOS cells were evaluated, and metabolism by hCYP24A1 was analyzed, and then compared with those of active vitamin $D_3$. We found that the stereochemistry of the stereogenic center on the 2alpha-substituent affected the biological activities of the ligands remarkably. The relative position of the hydroxyl group on the 2alpha-substituent against amino acid residues of the ligand binding pocket (LBP) around the A-ring part would be important for effective alternation with inherent water molecules existing in the LBP to form a water channel of the VDR.



**MEDI 429**

**Tagged approach toward synthesis of CAY-1 pentasaccharide moiety**

***Sunil Kumar Upadhyay*** *and Branko S. Jursic, Department of Chemistry, University of New Orleans, 2000 Lakeshore Dr, new orleans, LA 70148*

Synthesis of Oligosaccharides is a tedious process in terms of purification and handling of intermediates involved (most of them are sticky materials). Hence there is great need for development of a method to overcome such problem. The developed method will be used for synthesis of pentasaccharide moiety of CAY-1 which is an antifungal agent.Pentasaccharide will be joined to aglycone moiety via a glycosidic bond in the penultimate stage of total synthesis.

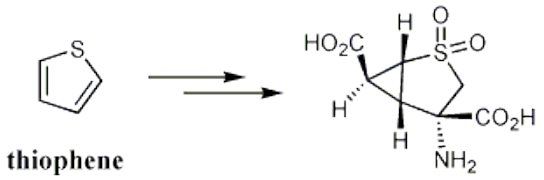
Our tagged based approach will introduce an aromatic part in the key intermediate which makes it insoluble in most of general organic solvents. Hence once reaction is done impurities can be removed by mere washing or recrystallization. Tagged molecule can be aromatic ring or ionic liquid based. This approach will provide away to construct oligosaccharides with greatly simplified purification requiring no chromatography. It offers the benefits of solution-phase synthesis ( homogeneous mass transportation and no temp. restriction may be suitable for large scale synthesis. The sugar-sugar coupling process and product structure can be easily monitored.

**MEDI 430**

**Advances in the process development of a highly potent and selective agonist for mGlu2/3 receptors**

***Mario Waser***[1]*, mario.waser@dsm.com, Eric D. Moher*[2]*, MOHER_ERIC_D@LILLY.COM, Marcus Kordian*[1]*, Brigitte Herzog*[1]*, Tanja Leitner*[1]*, Martin Müllner*[1]*, Marvin M. Hansen*[2]*, David W. Hoard*[2]*, Michael E. LeTourneau*[2]*, Michael L. Phillips*[2]*, Kevin A. Sullivan*[2]*, Jeffrey A. Ward*[2]*, Chaoyu Xie*[2]*, xiech@lilly.com, Tricia E. Aust*[2]*, David Barlow*[2]*, Erica L. Buxton*[2]*, Guy J. Hansen*[2]*, Richard D. Miller*[2]*, Jacob R. Remacle*[2]*, Gary A. Rhodes*[2]*, Joshua M. Schenck*[2]*, Angela D. Thurnall*[2]*, David D. Anderson*[2]*, Brian P. Axe*[2]*, Cheryl A. Bye*[2]*, Mindy B. Forst*[2]*, Robert M. Montgomery*[2]*, and Timothy L. Shelbourn*[2]*. (1) Research and Development, DSM Pharma Chemicals, DSM Fine Chemicals Austria Nfg GmbH & Co KG, St. Peter Strasse 25, 4021 Linz, Austria, Fax: 0043732691663713, (2) Chemical Process Research and Development, Eli Lilly and Company, Indianapolis, IN 46285*

The conformationally restricted glutamic acid analog LY404039 (**1**) was recently found to be a selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors and has shown antipsychotic potential in animal studies. In order to fuel further development, a scalable and robust synthetic route for the 8-step synthesis of **1** from thiophene was developed and successfully implemented on 60-70 kg pilot-plant scale.




thiophene

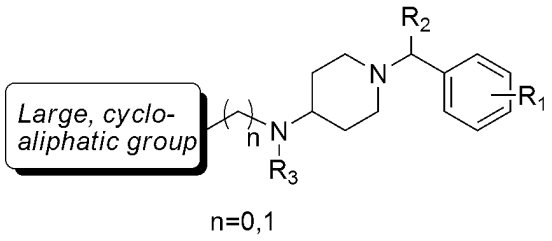
**1**

**MEDI 431**

## Novel CXCR3 antagonists: 4-Amino-piperidines flanked by lipophilic groups

***Maikel Wijtmans***, *Dennis Verzijl, Leontien Bosch, Rob Leurs, Martine J. Smit, and Iwan J. P. de Esch, Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, Netherlands, Fax: 31-020-5987610*

Small-molecule antagonists for the CXCR3 chemokine receptor are attracting much interest as a possible means to therapeutically combat inflammatory diseases and certain types of cancer. In an attempt to identify novel types of antagonist chemotypes, we applied a strategic merger of an existing class of patented, relative large antagonists with an in-house discovered adamantane-based small-molecule hit. This led to a novel class of amino-piperidine based compounds that were readily accessible by only a handful of synthetic transformations (2-4 steps). The synthetic convenience allowed a rapid exploration of the Structure-Activity Relationship at many positions of the structure. In general, a substituted benzyl group on the NH-terminus and a highly lipophilic, cycloaliphatic group (such as a bornyl or adamantyl group) on the $NH_2$-terminus seem preferred, leading to affinities around 130 nM. The full outcome of the synthetic and pharmacological studies on this series will be discussed.




**MEDI 432**

## AFP6 (TY-47) - synthesis optimization of a difficult peptide

***Lay Lay Wint***[1], *laylay.wint@amylin.com, Lala Mamedova*[2], *lala.mamedova@amylin.com, Fernando Ferrer*[3], *fernando.ferrer@amylin.com, Soumitra Ghosh*[4], *and Ved P Srivastava*[4]*. (1) Department of Chemistry, Amylin Pharmacetical, Inc, 9360 Towne Centre Dr, San Diego, CA 92121, Fax: 858-334-1162, (2) Department of Chemistry, Amylin Pharmaceuticals, Inc, San Diego, CA 92121, (3) Amylin Pharmaceutical, Inc, San Diego, CA 92121, (4) Amylin Pharmaceutical, Inc, CA 92121*

AFP-6 (TY-47) peptide consists of 47 amino acid residues and a disulfide bond between Cys10 and Cys15, forming a six amino acid-containing ring structure. A marked distinction of AFP-6 from h-CT and h-Amylin is its extension of sequence on the N-terminal side of its disulfide bridge. AFP-6 peptide is a member of the CGRP/Amylin peptide family that expresses primarily in the pituitary and GI tract and is capable of signaling through the CRLR/RAMP receptor complex. AFP-6 (TY-47) displayed a potent anorectic effect in an acute food intake assay. AFP-6 peptide is synthetically challenging and fairly stable peptide. We developed a new synthesis methodology that improves yield, purity and efficiency of desired peptide.

**MEDI 433**

**Identification, synthesis and structural elucidation of the sulfate and glucuronidate conjugates of ARQ 501 (ß-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b] pyran-5,6-dione)**

***Rui-Yang Yang**, Darin Kizer, Erika Volckova, Xiusheng Miao, Syed Ali, Ron Savage, Thomas C. K Chan, and Mark A. Ashwell, ArQule, Inc, 19 Presidential way, Woburn, MA 01801*

ARQ 501 is a fully synthetic version of ß-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b] pyran-5,6-dione) and has shown promising anticancer activity in multiple Phase II clinical trials. Recently, we disclosed the identification and characterization of the phase I metabolites of ARQ 501 from human blood. In continuation of our studies on the metabolism of ARQ 501, we studied the phase II metabolites in vivo. The sulfate and glucuronidate conjugates were identified as the two major metabolites formed in vivo. In this presentation, we will discuss the synthesis and structural elucidation of these sulfate and glucuronidate conjugates of ARQ 501.

**MEDI 434**

**Isoform-selective inhibition of the human UDP-glucuronosyltransferases 2B7 and 2B17**

*Ingo Bichlmaier[1], Moshe Finel[2], Tobias Rüffer[3], Heinrich Lang[3], heinrich.lang@chemie.tu-chemnitz.de, and **Jari Yli-Kauhaluoma**[1], jari.yli-kauhaluoma@helsinki.fi. (1) Division of Pharmaceutical Chemistry, University of Helsinki, Faculty of Pharmacy, P. O. Box 56 (Viikinkaari 5 E), FI-00014 Helsinki, Finland, Fax: 358-9-19159556, (2) Drug Discovery and Technology Center, University of Helsinki, Faculty of Pharmacy, FI-00014 Helsinki, Finland, (3) Lehrstuhl für Anorganische Chemie, Technische Universität Chemnitz, D-09111 Chemnitz, Germany*

A set of 104 bicyclic and tricyclic stereoisomers with various functional groups was synthesized. The stereoisomers were assessed for their ability to inhibit the human UDP-glucuronosyltransferases (UGTs) 2B7 and 2B17. The best inhibitor was a phenyl-substituted longifolol derivative, which displayed a competitive inhibition constant (Kic) of 0.91 nM towards UGT2B7. Inhibition assays employing 14 other UGT enzymes indicated that the inhibitor was highly isoform-selective for UGT2B7 (true selectivity approx. 20000).

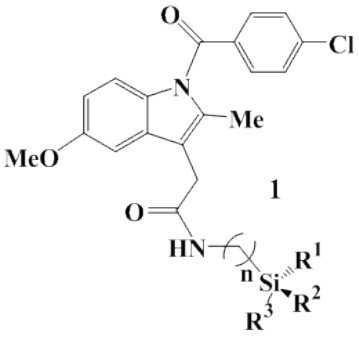
**MEDI 435**

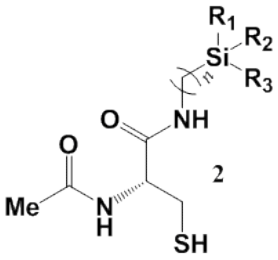
**Organosilicon chemistry as a new source in drug design**

***Uzma I Zakai**[1], zakaiu@chem.wisc.edu, Galina A. Bikzhanova[2], galina@chem.wisc.edu, Stephen Gately[3], sgately@silamed.com, and Robert West[2], west@chem.wisc.edu. (1) Chemistry, Organosilicon Research Center, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706, Fax: 608-262-6143, (2) Organosilicon Research Center, Department of Chemistry, University of Wisconsin - Madison, Madison, WI 53706, (3) Silamed, Inc, Scottsdale, AZ 85258*

Drug repurposing offers a rich alternative to diversifying the chemical scaffolds available to target cancer. An advantage of this approach is that the parent chemical agents that are derivatized are carefully selected from a library of compounds that have already been assessed for safety. Further

introduction of silicon into these derivatives offers a new facet to drug repurposing that exploits the differences in atomic size, electronegativity, and lipophilicity between carbon and silicon to produce more efficient and selective analogs. Such advantages have been used to produce improved sila-indomethacin amide derivatives of type 1 that display increased carcinostatic selectivity and decreased toxicity. These results have been exploited to tune lipophilicity in these sila-indomethacin compounds. In addition, we have synthesized sila-amide derivatives of N-acetyl L-cysteine (NAC) of type 2. These NAC sila compounds are anticipated to be of use in cancer treatment and in alleviating the adverse cognitive impact of chemotherapy.




**MEDI 436**

**Molecular modeling studies on selective inhibitors of trypanosomatids glyceraldehyde-3-phosphate dehydrogenase**

***Rafael V. C. Guido**, Glaucius Oliva, and Adriano D. Andricopulo, Institute of Physics of Sao Carlos, University of Sao Paulo, Av. Trabalhador Saocarlense, 400, Sao Carlos 13560-970, Brazil, Fax: +55-11-33939881*

Human parasitic diseases are the foremost threat to human health and welfare around the world. Leishmaniasis and trypanosomiasis are very serious infectious diseases against which the currently available drugs are limited and not effective. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is as an attractive target for the development of novel antitrypanosomatid agents. In the present work, comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) were conducted on a large series of inhibitors of Leishmania mexicana GAPDH. Four statistically significant models were obtained ($r2 > 0.90$ and $q2 > 0.70$), indicating their predictive ability for untested compounds. The models were then used to predict the potency of an external test set, and the predicted values were in good agreement with the experimental results. Molecular modeling studies provided further insight into the structural basis for selective inhibition of trypanosomatid GAPDH.

**MEDI 437**

**Rational design of peptidomimetics for class B GPCRs using α-helix mimetics**

***Jung-Mo Ahn**, Department of Chemistry, University of Texas at Dallas, 800 W. Campbell Rd., Richardson, TX 75080, Fax: 972-883-2925*

Class B G-protein coupled receptors (GPCRs) is characterized to interact with large peptide hormones. Playing critical roles in human physiology, they have been considered as attractive targets to treat diseases, however their large peptides suffer from serious limitations like rapid enzymatic degradation and poor bioavailability. Thus, small molecules which modulate these receptors will be highly valuable tools, but achieving such compounds has been extremely challenging.

A peptide hormone, GLP-1 belongs to this family, and plays a critical role in glucose homeostasis. As other class B peptides, it adopts α-helical structures which we have designed α-helix mimetics to represent. Using a rigid tris-benzamide scaffold, a number of α-helix mimetics were synthesized based on the sequence of GLP-1 and led to develop potent GLP-1 peptidomimetics. These are the first precedent of rationally designed GLP-1 mimetics and of great interest in treating diabetes. Supported by Welch Foundation, Texas ARP, and American Diabetes Association.

**MEDI 438**

**Probabilistic prediction of the human CYP3A4 and CYP2D6 metabolism sites in a molecule**

*Justas Dapkunas, justas@pharma-algorithms.com, Faculty of Natural Sciences, Vilnius University, M.K.Ciurlionio g. 21/27, LT-03101 Vilnius, Lithuania, Andrius Sazonovas, andrius@pharma-algorithms.com, Faculty of Chemistry, Vilnius University, LT-03225 Vilnius, Lithuania, and **Pranas Japertas**, pranas@pharma-algorithms.com, Pharma Algorithms, Inc, A.Mickeviciaus g. 29, LT-08117 Vilnius, Lithuania*

Here we present a considerably renewed model for prediction of the most probable human CYP3A4 metabolism sites in molecule and a completely new analogous model for the CYP2D6 isoform. Following critical evaluation of the latest publications, the CYP3A4 model is now based on experimental indications of >600 sites of reactions involving CYP3A4. The CYP2D6 model uses a dataset of >200 sites of metabolic reactions known to be mediated by CYP2D6. Both models utilize atom-centered fragments in binomial PLS and share the benefits of the ‘Trainable Model' methodology implementation. I.e., the predicted probabilities of any atom in a molecule being the target of CYP3A4 or CYP2D6 activity are accompanied with the estimations of their Reliability Indices (RI) and the Applicability Domain of the models can be easily expanded to cover specific compound classes of user interest with the help of ‘in-house' databases containing experimental metabolism data.

**MEDI 439**

**Trainable model of hERG channel inhibition prediction**

*Liutauras Juska[1], liutauras@pharma-algorithms.com, Remigijus Didziapetris[2], remis@pharma-algorithms.com, and **Pranas Japertas**[2], pranas@pharma-algorithms.com. (1) Faculty of Chemistry, Vilnius University, Naugarduko g. 24, LT-03225 Vilnius, Lithuania, (2) Pharma Algorithms, Inc, A.Mickeviciaus g. 29, LT-08117 Vilnius, Lithuania*

Cardiotoxicity of drug-like compounds associated with human ether-a-go-go (hERG) channel inhibition is a common cause of drug candidates' attrition. Therefore, early computational prediction of hERG channel affinity of drug candidates is becoming increasingly important in the drug discovery process. Binary QSAR model with threshold values at IC(50)=10 uM was generated using binomial regression with 2-D fragmental descriptors. Model was trained on more than 600 binary data points

mainly derived from the published hERG inhibition studies by patch-clamp method. For the full dataset, the accuracy of classification of hERG inhibitors was >85%, which meets prior classification models. Predictions of hERG inhibition probability are supported with estimations of Reliability Index. The novel similarity based methodology implemented in the model can be used to add new ‘in-house' data on hERG inhibition to the existing training set, allowing for the straightforward expansion of the Model Applicability Domain to the specific classes of industrial compounds.

**MEDI 440**

**CoMFA, CoMSIA and docking studies of N3-substituted coformycin aglycon analogs as potent adenosine 5'-monophosphate deaminase (AMPDA) inhibitors**

***Shridhar Kulkarni**, kshridhar_3@yahoo.co.in, Department of Pharmaceutical Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, and Tanaji T Talele, talelet@stjohns.edu, Department of Pharmaceutical Sciences, College of Pharmacy & Allied Health Professions, St. John's University, Jamaica, NY 11439*

Adenosine 5'-monophosphate deaminase (AMPDA) is the enzyme responsible for the regulation of adenosine levels, a role having physiological importance for the treatment of ischemia. In the present study, a group of 132 AMPDA inhibitors with varying potencies and known structure-activity relationships were used to carry out comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA), and docking studies. The 3D QSAR models were derived using 90 training set of molecules and validated with a robust 42 test set. The r2cv and r2ncv derived from the CoMFA model were 0.673 and 0.877, respectively, and those from the CoMSIA model were 0.803 and 0.907, respectively. An external model validation performed using a set of 42 test compounds yielded significant statistical predictions, with r2pred of 0.741 and 0.807, respectively, for the CoMFA and CoMSIA models. The 3D contour maps in relation to the binding site of co-crystal structure of AMPDA will be discussed in the poster.

**MEDI 441**

**In silico ADME modeling: Predictive QSAR models for human intestinal absorption and oral bioavailability**

***Tiago L. Moda** and Adriano D. Andricopulo, Medicinal and Computational Chemistry Laboratory, Center for Structural Molecular Biotechnology, University of São Paulo, Institute of Physics, PO Box 369, Av. Trabalhador Sao Carlense, 400, São Carlos-SP 13566-970, Brazil, Fax: 55-16-3373-9881*

The high number of compounds emerging from combinatorial chemistry and high throughput medicinal chemistry programs is increasing the demand for new compounds that need to be screened in a wide range of biological assays. New chemical entities expected to advance into clinical trials should have an ideal balance of pharmacodynamic and pharmacokinetic properties. Problems with absorption, distribution, metabolism, and excretion (ADME) have been identified as a major cause of drug candidate failure in late stages of the pharmaceutical R&D process. The early evaluation of ADME properties in drug research has driven the need for large-scale screening methods. Computational methods have emerged during the past decade as a powerful strategy for the prediction of human pharmacokinetics. In the present work, we have organized large data sets of structurally diverse molecules with known human intestinal absorption and human oral bioavailability, and used the data to create predictive QSAR models, employing the hologram QSAR (HQSAR)

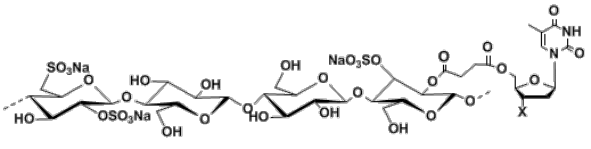
method. Significant HQSAR models were obtained, and the predictive ability of the model was evaluated by robust external test sets containing several molecules not included in the training sets. The final predictive QSAR models should be useful for the design of new drug candidates having increased intestinal absorption and bioavailability. The results of modeling these data sets will be presented.

**MEDI 442**

**Synthesis of cellulose sulfate-nucleoside conjugates as bifunctional anti-HIV agents**

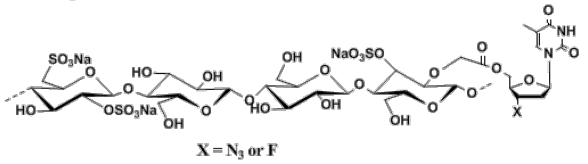
***Hitesh Kumar Agarwal***[1]*, hkag@rediffmail.com, Anil Kumar*[1]*, kanilkadian@mail.uri.edu, Gustavo F. Doncel*[2]*, doncelgf@evms.edu, and Keykavous Parang*[1]*, kparang@uri.edu. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, 41 Lower College Road, Kingston,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

Sodium cellulose sulfate has been introduced as an inhibitor of HIV entry and sperm-function. Bifunctional conjugates containing sodium cellulose sulfate and anti-HIV nucleoside reverse transcriptase inhibitors (AZT, FLT, and 3TC) were synthesized using different linkers to obtain synergistic activity. Three linkers, succinate, acetyl, and glutamate, were used to conjugate the nucleosides with the polymer. Nucleosides (AZT and FLT) were reacted with succinic anhydride to make nucleoside succinate building blocks. Nucleoside succinates were then reacted with the polymer in presence of DIC as a coupling reagent to give KPH-4ASC and KPH-4FSC. When acetyl group was used as a linker, sodium cellulose sulfate was first reacted with 2-bromoacetic acid to make modified cellulose sulfate that was reacted with AZT, FLT, and 3TC to give KPH-4ACA, KPH-4FCA, and KPH-43CA, respectively. Finally, FLT was reacted with Fmoc-Glu-O *t*Bu. Deprotection of *t*-butyl followed by the reaction with sodium cellulose sulfate in the presence of DIC afforded KPH-43GC.



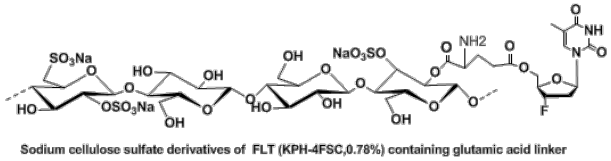
X = $N_3$ or F

Sodium cellulose sulfate derivatives of AZT ( KPH-4ASC, 17.23%)] and FLT (KPH-4FSC, 7.78%) containing succinate linker



X = $N_3$ or F

Sodium cellulose sulfate derivatives of AZT (KPH-4ACA, 1.73%) and FLT (KPH-4FCA, 1.25%) containing acetate linker



Sodium cellulose sulfate derivatives of FLT (KPH-4FSC,0.78%) containing glutamic acid linker

"Support for this subproject (MSA-03-367) was provided by CONRAD, Eastern Virginia Medical School under a Cooperative Agreement (HRN-A-00-98-00020-00) with the United States Agency for International Development (USAID). The views expressed by the authors do not necessarily reflect the views of USAID or CONRAD."

**MEDI 443**

**Structure similarity-based profiling of combinatorial libraries**

***Joseph Rios**, Marc Giulianotti, and Jose L. Medina-Franco, Torrey Pines Institute for Molecular Studies, 5775 Old Dixie Highway, Fort Pierce, FL 34946, Fax: 772-462-0886*

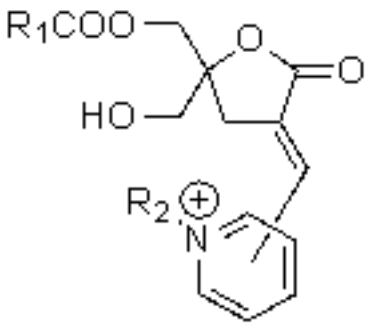
The chemical structure of several combinatorial libraries was compared with a set of molecules known to interact with the KAPPA receptor. The similarity was determined using 2D fingerprints, including the MACCS keys. Results obtained in-silico enables selecting molecules from the combinatorial libraries ranging from the very similar to the very dissimilar to the set of known active compounds. Further experimental evaluation of the activity of selected compounds will help to determine the accuracy of the fingerprints in correctly predicting activity.

**MEDI 444**

**DAG-lactones containing 4-alkylpyridinium cations in the alpha-arylidene position: Evaluation of their interaction with protein kinase C (PKC) and membranes**

***Saïd El Kazzouli**[1], elkazzoulis@ncifcrf.gov, Nancy E. Lewin[2], Peter M. Blumberg[2], Raz Janilek[3], and Vicror E. Marquez[1]. (1) Laboratory of Medicinal Chemistry, National Institutes of Healt, Center for Cancer Research, National Cancer Institute-Frederick, Frederick, MD 21702, Fax: 301-846-6033, (2) Laboratory of Cancer Biology and Genetics, National Institutes of Health, Bethesda, MD 20892, (3) Ben-Gurion University of the Negev, Beersheva 84105, Israel*

The diacylglycerol (DAG) binding site is a complex between the C1 domain of the target protein (PKCs and other C1-domain containing proteins) and the lipid bilayer. The C1 domain is only a half-site and the specific cellular localization of the activated protein is determined in part by the different lipid composition of the membranes. Because membranes are rich in negatively charged phospholipids located at the inner leaflet of the bilayer, we have modified our potent DAG-lactone template to incorporate 4-alkylpyridinium cations of different lengths at the alpha-arylidene position (R2), which will direct the positive charge to the C1 domain/lipid interface. This poster will present physicochemical analysis of the interactions of these compounds with both PKCs and RasGRPs, as well as with artificial membranes. Our results indicate that the DAG lactones are predominantly localized at the membrane interface.

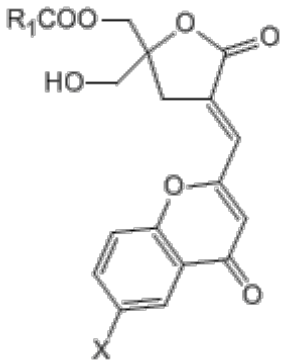


**MEDI 445**

**DAG-lactones containing 6-substituted chromen-4-ones as alpha-arylidene groups expand the repertoire of diacylglycerol (DAG) lactones that bind specifically to protein kinase C (PKC) and other DAG-responsive proteins**

***Saïd El Kazzouli***[1]*, elkazzoulis@ncifcrf.gov, Nancy E. Lewin*[2]*, Peter M. Blumberg*[2]*, and Vicror E. Marquez*[1]*. (1) Laboratory of Medicinal Chemistry, National Institutes of Healt, Center for Cancer Research, National Cancer Institute-Frederick, Frederick, MD 21702, Fax: 301-846-6033, (2) Laboratory of Cancer Biology and Genetics, National Institutes of Health, Bethesda, MD 20892*

The major recognition motif for DAG in PKC and other DAG-responsive proteins is a zinc finger structure called a C1 domain. These highly conserved structures of ca. 50 amino acids bind to DAG and phorbol esters. We have developed a conformationally rigid DAG scaffold in the form of a DAG-lactone, which when substituted with an array of side chains to achieve an appropriate hydrophobic/hydrophilic balance provides ligands with strong and diverse binding affinities toward different C1 domain-containing proteins. To expand our strategy in search for novel DAG-lactones capable of binding selectively to additional C1 domains, we have expanded this strategy to include DAG- lactones containing a diverse family of 6-substituted chromen-4-ones attached as alpha-arylidene moieties. These ligands were designed to explore additional interactions between the ligand and the surrounding area of the C1 domain, including ligand-lipid and ligand-protein interactions.




**MEDI 446**

**Phenyl substituted cyclopropylamides as potent and selective progesterone receptor agonists**

***David T. Fosbenner***[1]*, David.T.Fosbenner@gsk.com, Todd L Graybill*[1]*, Terence J Kiesow*[1]*, Yonghui Wang*[1]*, Kevin Madauss*[2]*, Chaya Duraiswami*[3]*, Chaya.2.Duraiswami@gsk.com, Su-Jun Deng*[4]*, Jeffrey D. Bray*[5]*, jeffrey.d.bray@gsk.com, Eugene T Grygielko*[5]*, Scott K. Thompson*[6]*, and Marlys Hammond*[6]*. (1) Discovery Medicinal Chemistry, GlaxoSmithKline, 1250 South Collegeville Rd, Collegeville, PA 19426, Fax: 610-917-7391, (2) GlaxoSmithKline, Research Triangle Park, NC 27709, (3) Computational and Structural Sciences, GlaxoSmithKline Pharmaceuticals, Collegeville, PA 19426, (4) Gene Expression and Protein Biology, GlaxoSmithKline, Research Triangle Park, NC 27709, (5) Urogenital Biology/Cardiovascular and Urogenital Center for Excellence in Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, PA 19406, (6) GlaxoSmithKline, King of Prussia, PA 19406*

Progesterone affects menstruation and gestation through the Progesterone Receptor (PR). Recently, the idea of Selective Progesterone Receptor Modulators (SPRM's) has been suggested as a way to

treat gynecological disorders with reduced side effect profiles. A Phenyl substituted cyclopropylamide series was identified through high-throughput screening as a selective PR agonist. The modifications of screening hit, aided by molecular modeling and analysis of its crystal structure, which led to potent agonists of the Progesterone Receptor, will be described.

**MEDI 447**

**Research toward the next generation of novel therapeutic delivery systems.**

***Muriel Funck**, Neil D. Bowley, Gareth W. V. Cave, Stéphanie E. B. McArdle, and Robert C. Rees, School of Science and Technology, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, United Kingdom*

Supramolecular nanometre-sized host capsules, constructed from six pyrogallol[4]arene macrocyclic cavitands, self assemble *via* 72 hydrogen bonding interactions into globular capsules, with an internal volume of *ca*. 1300 $Å^3$, have been realised. There are 24 readily available potential binding sites forming the exterior of these capsules, however until now, they have not found application. Our research aims towards the synthesis and the characterisation of a library of biologically active therapeutics derived from the *C*-butan-4-ol-pyrogalloll[4]arene macrocycles, functionalised externally with a myriad of bioactive groups. Preliminary results focus on the selective functionalisation of the hydroxyl groups, both phenolic and primary alcohols. The subsequent addition of groups facilitating *in vitro* and *in vivo* imaging, hydrophilicity and bioactivity is described. Due to the potential applications of these materials, we continue to assess their cytotoxicity and bioactivity. Ultimately, we demonstrate that these nanometre-scale architectures offer huge potential as a seeded scaffold for grafting bioactive substrates, for therapeutic delivery.

**MEDI 448**

**Predicting the acid dissociation constants for drug-like molecules**

***Shuming Zhang**, Jon Baker, and Peter Pulay, Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR 72701, Fax: 479-575-4049*

The pKa value is one of the most important properties of an effective drug molecule and plays a significant role in many aspects of drug absorption, distribution, metabolism, and excretion (ADME). The accurate prediction of pKa values directly from the molecular structure is very desirable in evaluating drug candidates at an early stage. A major difficulty in precise prediction is that most drugs have more than one ionizable group, and thus multiple pKa values. Using our previously derived protocol (OLYP/6-311+G(d,p)//OLYP/3-21G(d) with the COSMO solvation model) and fitting equations ($pKa = \alpha\Delta E + \beta$, where $\alpha$ and $\beta$ are constants), we have successfully predicted the pKa values of over 300 drug-like molecules and clinical drugs with a mean absolute deviation (MAD) of less than 0.65 pKa units. These compounds affect the central nervous, hormonal, cardiovascular, and immune systems, and act as diuretics, hypnotics, stimulants, antibiotics, anti-inflammatory, and chemotherapeutic agents.

**MEDI 449**

## Design and synthesis of indenopyrrolocarbazole tetrahydropyrans and 1,3-dioxanes as potent inhibitors of VEGF-R2

***Reddeppareddy Dandu***[1], *dreddy@cephalon.com, Diane E. Gingrich*[1], *dgingric@cephalon.com, Edward Bacon*[1], *Shi Yang*[2], *Mark S. Albom*[3], *Thelma S. Angeles*[3], *and Robert L. Hudkins*[1]. *(1) Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: NA, (2) Department of Biochemistry, Cephalon, Inc, West Chester, PA 19380, (3) Department of Lead Discovery and Profiling, Cephalon, Inc, West Chester, PA 19380*

Angiogenesis is a dynamic and very complex process that involves the formation of new blood vessels from the existing vasculature but also critical processes during early embryonic development as well as in a number of processes including cancer, rheumatoid arthritis and psoriasis. Normal vasculature development is believed to be dependent on vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase, mainly VEGF-R2. Thus, disruption of VEGF-R2 signaling is an attractive target to prevent tumor angiogenesis, which can then lead to the inhibition of tumor growth and metastasis. We have identified indenopyrrolocarbazole tetrahydropyrans and 1,3-dioxanes as low nanomolar potent dual VEGF-R2 receptor tyrosine kinase inhibitors. Presented will be VEGF-R2 structure-activity relationships (SAR) for indenopyrrolocarbazole tetrahydropyrans and 1,3-dioxanes.

**MEDI 450**

## Development of peptoid antibody surrogates that antagonize VEGF receptor activity

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We report a two-color, cell-based screen to identify specific receptor-binding compounds in a large combinatorial library of peptoids displayed on beads. We applied this strategy to isolate peptoids that bind specifically to Vascular Endothelial Growth Factor Receptor 2 (VEGFR2). A dimeric derivative of a lead compound (GU40C4) displayed low nanomolar binding and was shown to be a potent antagonist of VEGFR2 activity in vitro and in vivo via a more complicated un-competitive mechanism of action. We subsequently identified the important residues of the peptoid that determine binding and resynthesize about a 150 compound parallel library to obtain further improved compounds for potential development as novel anti-angiogenic therapies. This methodology provides a potentially general route to synthetic molecules that bind integral membrane receptors with affinities similar to those of antibodies, but which are far smaller and easier to make and manipulate.

**MEDI 451**

## Structure activity relationship studies toward the understanding of active site in nerve agent catalyzing enzyme paraoxonase 1: Interplay of experimental and computational studies

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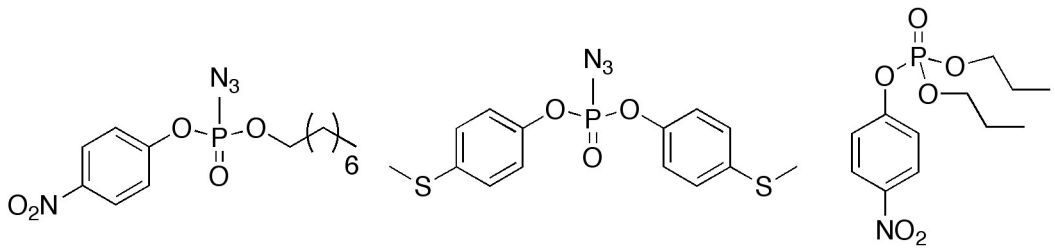
Paraoxonase-1 (PON1) is a human enzyme capable of hydrolyzing organophophorous (OP) nerve agents with moderate activity. In order develop a more viable prophylactic bio-scavenger, it is desirable to develop mutants of PON-1 with several fold improvement in activity. However, the mechanism of hydrolysis of PON1 is poorly understood and no crystal structure with substrate or inhibitor bound is available. In order to identify the key residues involved in the binding of the substrates to PON1, we employed both experimental and computational structure activity relationship studies. We designed and synthesized a library of 35 OP compounds and identified 8 inhibitors and 10 substrates. A few representative structures are shown in Figure 1. We performed extensive molecular dynamics simulations on the chimeric PON1 and docked a library of 120 substrates to the MD relaxed protein and identified the key residues to which the OPs bind. Relevant experimental and computational data will be presented.




**Substrates** **Inhibitor**

**Figure 1**

**MEDI 452**

## $O^2$-Glycosylated diazeniumdiolates: Targeting nitric oxide to macrophages for antileishmanial activity

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*21702, (5) Naval Research Laboratory, Washington, DC 20375, (6) Universitatsklinikum Erlangen, Erlangen D-91054, Germany*

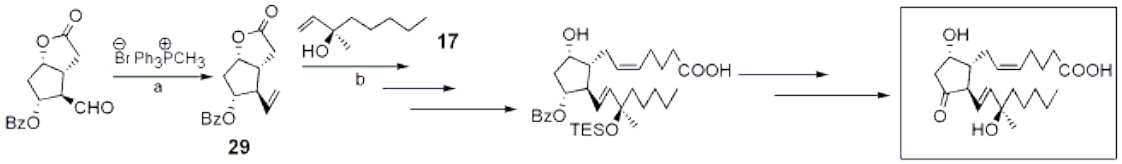
Glycosylated diazeniumdiolates of structure $R_2NN(O)=NOR'$ (R' = a saccharide residue) are potential prodrugs of the nitric oxide (NO)-releasing but acid-sensitive $R_2NN(O)=NO^-$ ion. Moreover, cleaving the acid-stable glycosides under alkaline conditions provides a convenient protecting group strategy for diazeniumdiolate ions during synthetic manipulations. Here we report comparative hydrolysis rate data for five representative glycosylated diazeniumdiolates at pHs 14, 7.4, and 3.8 – 4.6 as background for further developing both the protecting group application and the ability to target NO pharmacologically to macrophages harboring intracellular pathogens. Confirming the potential in the latter application, adding $R_2NN(O)=NO$-GlcNAc (where $R_2N$ = diethylamino or pyrrolidin-1-yl and GlcNAc = N-acetylglucosamin-1-yl) to cultures of infected mouse macrophages deficient in inducible NO synthase caused rapid death of the intracellular protozoan parasite *Leishmania major* at concentrations that were not toxic to the host cells.

**MEDI 453**

**15(R)-Me-$PGD_2$, a potent $DP_2$-receptor agonist: total synthesis**

***Pranav Patel***[1]*, patelp@fit.edu, Gue-Jae Lee*[1]*, Seongjin Kim*[1]*, Gail E Grant*[2]*, William S Powell*[2]*, and Joshua Rokach*[1]*. (1) Claude Pepper Institute , Department of Chemistry, Florida Institute of Technology, 150 W University Blvd, Melbourne, FL 32901, Fax: 321-674-7743, (2) Meakins-Christie Laboratories, Department of Medicine, McGill University, Montreal, Canada*

Recently we have discovered a new $PGD_2$ receptor. We have termed this receptor $DP_2$. We have found that 15(R)-Me-$PGD_2$ **3** is a potent and selective agonist for the $DP_2$ receptor, being about 5 times more potent than $PGD_2$.We are reporting now on the first total synthesis of this synthetic agonist. The synthetic design for the synthesis of **3** relies on the enantioselective and stereospecific syntheses of synthon **17** and its attachment to the 5-membered ring synthon **29** by a Grubbs' reaction.




15(R)-Me-$PGD_2$ 3

**MEDI 454**

**Introduction to case histories of array-driven lead optimization**

***Martin J Slater****, Infectious Diseases Chemistry Stevenage, GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom, Fax: 44-1438-768232*

The use of parallel synthesis approaches (arrays or focussed libraries) in the lead identification field is widespread with many examples published in the chemistry literature and presented at conferences. In contrast, there are significantly fewer examples in the public arena from lead optimisation programmes. We believe this reflects the ongoing debate within in the pharmaceutical industry

around the utility of such approaches in medicinal chemistry lead optimisation programmes. In this symposium session we will share some recent impactful examples of parallel synthesis in designing drug candidates, and aim to discuss the pros and cons of parallel synthesis approaches vs traditional bespoke synthesis of individual target molecules. In addition to outlining the objectives and scope of the symposium, we will present some metrics from the Respiratory CEDD within GSK and define some of the terms used in the forthcoming presentations.

**MEDI 455**

**Oral small molecule anticancer lead optimization: Lessons in campaign design, synthesis and testing**

***David M Andrews**, CIRA Chemistry, AstraZeneca R&D, Mereside, Alderley Park, Macclesfield SK10 4TG, United Kingdom*

A case history describing the campaign optimisation of pyridine and piperidine-based Histone Deacetylase (HDAC) anticancer agents will be presented, leading to the discovery of an orally-active small molecule development candidate. All aspects of the design-make-test-analyse cycle will be explored, with particular emphasis on data analysis

**MEDI 456**

**Lead optimization libraries: Challenges and potential**

***Christoph M. Huwe**, Medicinal Chemistry, Bayer Schering Pharma AG, Global Drug Discovery, Muellerstrasse 178, 13353 Berlin, Germany*

In the presentation, the different requirements for lead optimization libraries, which can be considered more challenging to automated medicinal chemistry and building block management groups compared to hit-to-lead and lead generation libraries, will be outlined. In this context, aspects including number of analogs, cycle time, complexity of chemistry, degree of automation, and building block logistics will be discussed. In order to address these challenges, a workflow based on a balanced mixture between flexibility and standardization, which is achieved by utilizing complementary automated synthesizer systems in order to be able to provide a large diversity of chemotypes and HPLC-MS systems that can adapt to a variety of purification problems, will be outlined. Real-life examples from lead optimization projects will be used throughout the presentation to illustrate the concepts discussed.

**MEDI 457**

**Free-Wilson additivity: Applications in library design**

***J. Guy Breitenbucher**, Michael Hack, and McClure Kelly, Johnson & Johnson PRD, 3210 Merryfield Row, San Dlego, CA 92121*

The combination of matrix library data and additivity analysis informs on the limitations of certain QSAR analysis, and aids in prospective library design. The use of additivity theory as applied to library design will be discussed in the context of specific medicinal chemistry examples.

**MEDI 458**

**Rapid generation of structure activity data using a dedicated parallel synthesis team**

***Cullen Cavallaro**, BMS, Princeton, NJ 08540*

Parallel synthesis has become an increasingly important tool for the optimization of medicinal chemistry leads. We have established a centralized parallel synthesis/purification team that collaborates with medicinal chemistry program groups for this purpose. The goal is to quickly provide substantial SAR to these teams in order to enable rapid decision making and iterative exploration of interesting chemotypes. Lean manufacturing concepts have been employed to optimize our processes and increase efficiency. We will describe the evolution of our process and lessons learned over the past two years.

**MEDI 459**

**Lessons in array driven lead optimization with an example from the discovery of orally bioavailable glucocorticoid agonists**

***Simon JF Macdonald**, GlaxoSmithKline, Respiratory CEDD, Stevenage SG1 2NY, England*

Across the industry and within GSK itself, medicinal chemists differ in the value they place on preparing arrays of analogs in the lead optimisation (LO) process. Within the Respiratory CEDD at GSK we have a dedicated arrays team and this presentation will (i) relate the pros and cons that we have learnt in the application of arrays for LO programmes and (ii) illustrate an array driven LO process that resulted in the discovery of orally bioavailable glucocorticoid receptor agonists.

**MEDI 460**

**Inhibition of human glutaminyl cyclase: A potential new treatment for AD**

***Ulrich Heiser**, Department of Chemistry, probiodrug AG, Weinbergweg 22, Halle (Saale) 06120, Germany, Fax: +49 345 5559901*

Amyloid Precursor Protein (APP) derived amyloid peptide (Abeta) depositions in brains of Alzheimer's syndrome (AD) -patients preferentially consist of N-terminal modified pyroglutamyl (pGlu) Abeta in

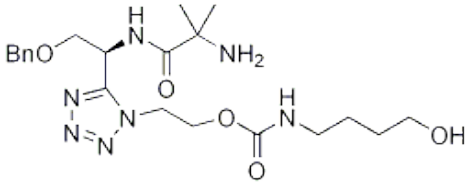
contrast to Abeta-compositions found in non-demented, aged people. We have discovered that such pGlu-containing Abpeptides are originated by N-terminal glutamate cyclization facilitated by human Glutaminyl Cyclase (hQC, EC 2.3.2.5). This N-terminal modification leads to an increase of hydrophobicity, stability and proteolytic resistance of the pGlu-Abspecies, resulting therefore in a enhanced tendency to form aggregates and fibrils. Moreover, recent data suggest that those truncated Abeta-species have an impact on learning and memory and can cause neuronal apoptosis. Hence, the qualification of hQC as a potential target for the treatment of AD has led to the development of enzyme inhibitors as new potential drugs for AD-treatment and is pioneered by Probiodrug AG, Germany. We present here the progress made during development of new inhibitors of hQC as well as results of animal experiments which demonstrate the efficacy of QC inhibition preventing the pGlu-Abformation in vivo and the consequences of such treatment for animal behavior.

**MEDI 461**

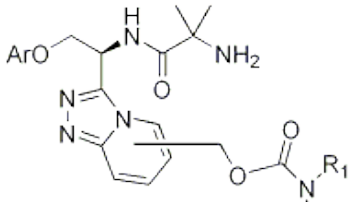
**Discovery of a novel, potent growth hormone secretagogue receptor agonist BMS-604992**

*Jun Li[1], jun.li@bms.com, Stephanie Y. Chen[1], Guixue Yu[1], Amarendra B. Mikklineni[1], Ximao Wu[1], Richard B. Sulsky[1], Andrés S. Hernández[1], James J. Li[1], Yeheng Zhu[1], Haixia Wang[1], Shiwei Tao[1], Jung-Hui Sun[1], Leslie Leith[1], Arvind Mathur[1], Bang-Chi Chen[1], Dorothy Slusarchyk[2], Ramakrishna Seethala[2], Mujing Yan[2], Neil Flynn[2], Brian J. Murphy[2], Paul Sleph[2], Donald Egan[2], Aberra Fura[3], Viral Vyas[3], Kamelia Behnia[3], James Smalley[3], Danshi Li[3], Mary Lee Conder[3], Huabin Sun[3], Lucy Sun[3], Paul Levesque[3], Yi-Xin Li[3], Mary Ellen Salyan[3], Ronald West[4], Mandar Dali[5], Michael A. Blanar[2], Robert Zahler[1], Elizabeth Govek[6], Ken Longo[6], Peter S. DiStefano[6], Brad J. Geddes[6], William R. Ewing[1], David A. Gordon[2], and **Joseph A. Tino**[7], Joseph.Tino@bms.com. (1) Discovery Chemistry, Bristol-Myers Squibb, P. O. Box 5400, Bldg 13, Princeton, NJ 08543-5400, (2) Discovery Biology, Bristol-Myers Squibb, Princeton NJ 08543, (3) PCO/Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton, NJ 08543-5400, (4) Toxicology, Bristol-Myers Squibb, New Brunswick, NJ, (5) Pharmaceutics, Bristol-Myers Squibb, New Brunswick, NJ, (6) Elixir Pharmaceuticals, Inc, Cambridge, MA 02139, (7) Discovery Chemistry, Bristol-Myers Squibb, P. O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-3993*

The growth hormone secretagogue receptor (GHSR) is a GPCR whose natural ligand is the 28 amino acid peptide ghrelin. Ghrelin agonism of the GHSR in the CNS leads to growth hormone (GH) secretion and increased IGF-1 production in the liver. Ghrelin administration increases feeding acutely through activation of GHSR in the CNS. GH secretagogues (GHSs) are being developed as clinical agents for the treatment of age-related frailty, cachexia and gastrointestinal hypomotility. We have previously reported a tetrazole based GHS 1 (BMS-317180) as our first generation GHSR agonist. Herein, we disclose for the first time BMS-604992, currently in clinical development as EX-1314 at Elixir Pharmaceuticals. A systematic SAR study around the triazolopyridine skeleton 2 was explored in order to modulate GHSR functional activity and pharmacodynamic properties. Side chains based on the natural ligand ghrelin led to increased potency and decreased cardiac channel activities. The in vitro and in vivo profiles of BMS-604992 (EX-1314) will be presented.




**1** (BMS-317180)




**2** (triazolopyridine core)

**MEDI 462**

## Balancing cardiac liabilities and PK properties: Discovery of triazolopyridine based growth hormone secretagogues

***Jun Li***[1]*, jun.li@bms.com, Stephanie Y. Chen*[1]*, Guixue Yu*[1]*, Amarendra B. Mikklineni*[1]*, Ximao Wu*[1]*, Yeheng Zhu*[1]*, James J. Li*[1]*, Haixia Wang*[1]*, Richard B Sulsky*[1]*, Shiwei Tao*[1]*, Andrés S. Hernández*[1]*, Dorothy Slusarchyk*[2]*, Ramakrishna Seethala*[3]*, Mujing Yan*[4]*, Neil Flynn*[4]*, Brian J Murphy*[4]*, Paul Sleph*[4]*, Donald Egan*[4]*, Aberra Fura*[5]*, Viral Vyas*[5]*, Kamelia Behnia*[5]*, James Smalley*[5]*, Danshi Li*[5]*, Mary Lee Conder*[5]*, Huabin Sun*[5]*, Lucy Sun*[5]*, Paul C Levesque*[5]*, Mary Ellen Salyan*[5]*, Michael A Blanar*[4]*, Robert Zahler*[1]*, William R Ewing*[1]*, David Gordon*[3]*, and Joseph A. Tino*[1]*, Joseph.Tino@bms.com. (1) Discovery Chemistry, Bristol-Myers Squibb, P. O. Box 5400, Bldg 13, Princeton, NJ 08543-5400, (2) Discovery Biology, Bristol-Myers Squibb, Princeton NJ 08543, (3) Metabolic Disease Research, Bristol-Myers Squibb Co, Princeton NJ 08543, (4) Metabolic Disease Research, Bristol-Myers Squibb, Princeton NJ 08543, (5) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton NJ 08543*

Orally active growth hormone secretagogues (GHSs) have a potential application for treating frailty in the elderly, osteoporosis, perisurgical or parenteral nutrition. More recent studies have additionally indicated that GHSs may be beneficial in the treatment of cancer cachexia, HIV wasting syndrome, as well as other catabolic diseases. These discoveries have renewed interest in agonists of the GHS receptor.

Although the area of growth hormone secretagogue research has been explored for years, only a few compounds were successfully advanced into clinical evaluation. Most of these failed at different stages due to reasons such as potential CV liabilities, poor PK properties or lack of efficacy. Discovery of potent and efficacious GHS receptor agonists with acceptable PK properties that are devoid of CV liabilities has been a great challenge for medicinal chemists.

Herein, we wish to disclose for the first time our triazolopyridine based chemotype, leading to the discovery of BMS-606056, a potent GHSR agonist with an EC50 of 0.2 nM. BMS-606056 exhibits a much improved CV liability profile and has promising pharmacokinetics in preclinical animal models, with oral bioavailabilities of 11%, 67%, and 21% in rat, dog, and cynomolgus monkeys, respectively. To the best of our knowledge, BMS-606056 represented the first reported compound with acceptable bioavailability in monkeys, a predictive animal PK model for humans for this class of agents. The compound also has an excellent profile in preclinical in vitro liability and toxicology panels as well as other pre-clinical toxicity evaluations.

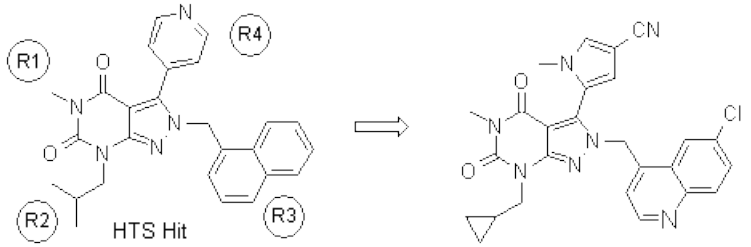
In pre-clinical in vivo efficacy studies, BMS-606056 demonstrated excellent potency and efficacy in animal models, robustly increasing endogenous growth hormone secretion in both the rat and dog. Based on its excellent potency, efficacy, PK and pharmaceutical properties, as well as safety profile, BMS-606056 is suitable for further developmental evaluation.

**MEDI 463**

## Design, synthesis, and SAR of pyrazolo[3,4-d]pyrimidinediones as highly potent and selective inhibitors of *Helicobacter pylori* glutamate racemase (MurI)

***Madhusudhan Gowravaram**, Gregory Basarab, Charles Eyermann, Oluyinka Green, Pamela Hill, Lawrence MacPherson, Marshall Morningstar, Ekundayo Osimboni, Abdullah Rastagar, and Alok Singh, Infection Discovery, Cancer and Infection Research Area, AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, MA 02451*

*Helicobacter pylori* colonizes the gastric mucosa, causing a chronic infection that has been linked to peptic ulceration and gastric cancer. A drug discovery program was initiated to find selective inhibitors of *H. pylori* glutamate racemase (MurI) for use as a novel monotherapy. MurI catalyzes the transformation of L-glutamate into D-glutamate, a reaction essential for cell-wall biosynthesis. High-throughput screening of the AstraZeneca compound collection identified a class of Pyrazolo[3,4-d]pyrimidinediones as low uM inhibitors of *H. pylori* glutamate racemase. Moreover, this chemical series was shown to be highly specific for *H. pylori*. We developed several parallel synthesis methodologies to diversify all four positions on the scaffold to rapidly generate analogs to establish the SAR. A systematic medicinal chemistry study incorporating structure-based design led to the identification of compounds with low nanomolar potency and good microbiological activity. The detailed SAR results and DMPK properties of these compounds will be presented.




*H. pylori* MurI $IC_{50}$ = 1440 nM
*H. pylori* MIC = 8 μg/ml

*H. pylori* MurI $IC_{50}$ = 26 nM
*H. pylori* MIC = 0.25 μg/ml

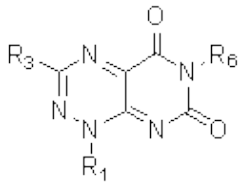
**MEDI 464**

## New antagonists of the ß-catenin/tcf complex

***Anjanette J. Turbiak**[1], koritnik@umich.edu, Guido T. Bommer[2], gbommer@umich.edu, Eric R. Fearon[2], fearon@umich.edu, and H. D. Hollis Showalter[1], showalh@umich.edu. (1) Department of Medicinal Chemistry, University of Michigan, Ann Arbor, MI 48109, Fax: 734-647-8430, (2) Department of Internal Medicine- Molecular Medicine and Genetics, University of Michigan, Ann Arbor, MI 48109*

Colorectal cancer is a major cause of cancer-related morbidity and deaths with over 150,000 new cases diagnosed each year in the United States alone. Nonetheless, the mutations that drive colorectal cancer are among the best characterized of any human tumor, proffering immense potential for therapeutic targets. In particular, the high prevalence of APC tumor suppressor gene mutations in colorectal tumors leads to increased nuclear levels of ß-catenin and dysregulation of the Tcf (T cell factor)/ß-catenin-dependent transcription. As such, disruption of the Tcf/ß-catenin interaction might have therapeutic effects. With the goal of targeting the ß-catenin/Tcf complex, a series of pyrimidotriazinediones with the general structure below were synthesized. Testing of

analogues was carried out in several complementary assays, including a functional in vitro assay that uses rat epithelial (IEC18) cells transfected with the TOPFLASH luciferase reporter gene. Overall, among the synthesized analogues, their inhibitory effects show promise towards future series development. Both the synthesis and assay results for this series of analogues will be presented.

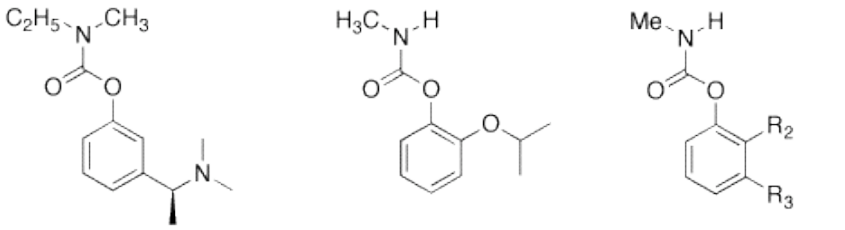


**MEDI 465**

**Highly species-selective acetylcholinesterase inhibitors for control of Anopheles gambiae, the mosquito vector of malaria**

*Paul R. Carlier[1], pcarlier@vt.edu, **Joshua Hartsel**[1], jhartsel@vt.edu, Ming Ma[1], mma@vt.edu, Dawn Wong[1], Jeffrey R. Bloomquist[2], jbquist@vt.edu, Troy D. Anderson[3], anderst@vt.edu, Sally Paulson[2], Ania Wysinski[3], Eric Wong[4], ewong@vt.edu, and Ranginee Choudhury[4], ranginee@vt.edu. (1) Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, Fax: 425-984-8099, (2) Department of Entomology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, (3) Department of Entomology, Virginia Tech, Blacksburg, VA 24061, (4) Department of Animal and Poultry Sciences, Virginia Tech, Blacksburg, VA 24061*

Acetylcholinesterase (AChE) inhibition can present therapeutic or toxic effects, depending on the degree of inhibition. Thousands of structurally diverse aryl carbamate-based AChE inhibitors have been evaluated for use as treatments for Alzheimer's disease (AD) memory loss (e.g Rivastigmine) and as insecticides (e.g. Propoxur). To combat emerging pyrethroid-resistant strains of Anopheles gambiae in sub-Saharan Africa, it would be useful to develop insecticide treated nets impregnated with carbamates. However, currently available insecticidal carbamates offer little selectivity for inhibition of Anopheles gambiae AChE (AgAChE) over human AChE (hAChE). Since AgAChE has only 49% sequence identity to hAChE, we thus undertook selectivity-based optimization of the aryl carbamate pharmacophore, determining inhibition potencies at both AgAChE and hAChE. Contact toxicity to live Anopheles gambiae was confirmed using the WHO protocol. These studies have culminated in the discovery of aryl carbamates possessing >1,000-fold selectivity for inhibition of AgAChE over hAChE.

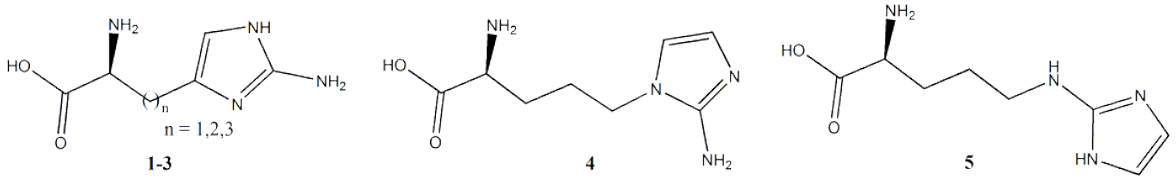


**MEDI 466**

## 2-Aminoimidazoles derivatives as new arginase inhibitors

***Monica Ilies***[1]*, milies@sas.upenn.edu, Luigi Di Costanzo*[2]*, luigidi@sas.upenn.edu, and David W. Christianson*[2]*, chris@sas.upenn.edu. (1) Roy & Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231S 34th Street, Philadelphia, PA 19104, Fax: 215-573-2201, (2) Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104*

Arginase is a key metalloenzyme of the urea cycle that converts L-arginine into L-ornithine and urea. Through ornithine arginase promotes cellular proliferation and collagen biosynthesis; by depleting the substrate pool of L-arginine arginase also acts as an endogenous inhibitor of NO-synthase. Therefore, this enzyme is a pharmaceutical target for the management of asthma, cardiovascular diseases, and erectile dysfunction. Two structural elements are important for generating powerful arginase inhibitors: the Mn-cluster and the aminoacid-binding residues at the active site entrance. Aiming at novel arginase inhibitors with improved potency and bioavailability we coupled the aminoacid motif with an aminoimidazole ring (as a guanidine-mimetic) through different linkers, at various positions of the heterocycle. Aminoimidazole-functionalized aminoacids (1-5) were synthesized and assayed as human arginase I inhibitors. The synthetic strategies, biological data, and the X-ray crystal structures of representative members of the series are presented in a structure-activity relationship study.




**MEDI 467**

## Identification and synthesis of 2,7-diamino-thiazolo[5,4-d]pyrimidine derivatives as TRPV1 antagonists

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The transient receptor potential vanilloid 1 (TRPV1 or VR1) is a ligand-gated, non-selective cation channel that is primarily expressed in nociceptive fibers. The TRPV1 receptor is activated by a wide range of stimuli including heat, low pH, vanilloid ligands such as capsaicin and resiniferatoxin (RTX), and a wide range of endogenous mediators such as bradykinin and anandamide. As an integrator and mediator of nociceptive and/ or inflammatory stimuli, TRPV1 is an attractive therapeutic target for the treatment of various neuro-inflammatory disorders. This presentation will discuss the design,

synthesis, structure-activity relationship, and in vivo efficacy of 2,7-diamino-thiazolo[5,4-d]pyrimidine derivatives as novel TRPV1 antagonists.

**MEDI 468**

**Synthesis and SAR optimization of diaryl ether second generation HIV-1 nonnucleoside reverse transcriptase inhibitors**

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Non-Nucleoside reverse transcriptase inhibitors (NNRTIs) are a standard component of highly active anti-retroviral therapy(HAART). Current NNRTIs are prone to decreased efficacy with chronic therapy due to development of NNRTI resistant viral mutations. Our medicinal chemistry efforts have focused on producing novel NNRTIs with an improved potency profile against key clinically observed mutant viruses. We have developed a novel diaryl ether NNRTI series that possesses potent activity against wild type and clinically relevant mutations while displaying a favorable pharmacokinetic profile. This presentation will highlight the design and optimization of the SAR in this series of compounds and will describe the progression of these compounds from early lead structures to mature second generation NNRTIs.

**MEDI 469**

**Divergent enantioselective pathways for the cycloaddition of hydrazones and dienes**

***Uttam K. Tambar*** *and James L. Leighton, Department of Chemistry, Columbia University, 3000 Broadway, MC 3116, New York, NY 10027, Fax: 212-932-1289*

In light of recent mechanistic data on the cycloaddition chemistry of acyl hydrazones, we have developed a series of enantioselective transformations between hydrazones and dienes. Unlike most imine equivalents, acyl hydrazones have the potential to react as 3-atom or 2-atom coupling partners in cycloaddition reactions. We have exploited this dual reactivity of hydrazones by coupling them with various dienes. As a result, we have developed silicon-mediated enantioselective [3+2] and [4+2] cycloadditions. For the first time, the scope of dienes in the enantioselective aza-Diels Alder reaction has been extended to include acyclic dienes that are traditionally unreactive in concerted [4+2] processes.

**MEDI 470**

**New methods for the efficient synthesis of centrally modified farnesyl pyrophosphate analogs**

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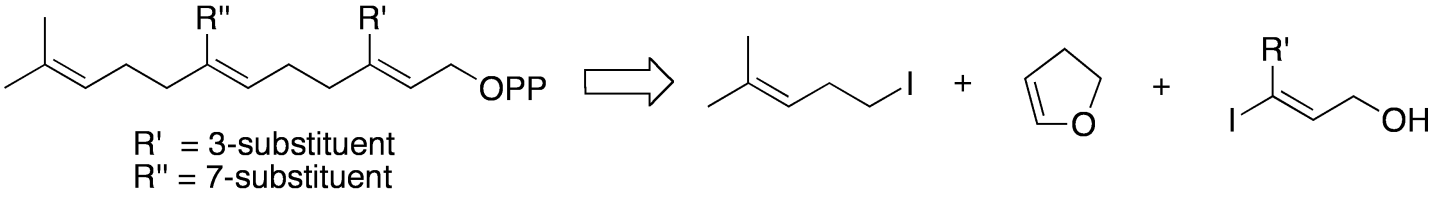
The ability to differentiate the biological impact of one farnesylated protein over another may lead to the development of more powerful anti-cancer therapeutics. Currently our lab is developing farnesyl-pyrophosphate (FPP) analogs that selectively farnesylate molecular targets. Previously, we synthesized and evaluated a library of 7-substituted FPP analogs. Several of these compounds selectively modified certain CAAX box-containing peptides but not others. In order to diversify the 7-substituted FPP analog library, we reduced the number of steps required to synthesize 7-substituted FPP compounds. Using a 1,2-metallate rearrangement, followed by a Negishi cross-coupling reaction, we developed methodology leading to the synthesis of 7-substituted FPP compounds in only 5 steps. The new synthetic route is also applicable to the synthesis of 3,7-disubstituted FPP and central isoprene-modified FPP compounds. We believe the new synthetic approach will result in the discovery of unique and biologically selective chemical tools.




R' = 3-substituent
R'' = 7-substituent

**MEDI 471**

**New strategy to fight tuberculosis: The discovery of thioamide drugs boosters**

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Tuberculosis remains a major cause of mortality and morbidity killing each year more than two million people. The emergence of multidrug-resistant strains of Mycobacterium tuberculosis, stresses the need for alternative therapies. Ethionamide (ETH), a second-line antibiotic, is used to treat multidrug-resistant tuberculosis. ETH is a prodrug and needs to be activated by the mycobacterial enzyme EthA in order to inhibit InhA, the enoyl-acyl ACP reductase involved in mycolic acid biosynthesis. We demonstrated that the limited effectiveness of ethionamide is due to the transcriptionnal repression of ethA by the bacterial regulator EthR.

Using SPR screening, crystallography, click-chemistry in situ and rational design, we have identified EthR drug-like inhibitors that increase the efficacy of ethionamide by at least 25-fold in vitro and 3-fold

in vivo. Efforts are now continued to develop a clinical candidate. This work is to our knowledge the first strategy to fight tuberculosis by boosting existing drugs.

**MEDI 472**

**Computer-aided drug discovery: Virtual screening and free energy calculations applied to the search for MIF inhibitors**

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Macrophage migration inhibitory factor (MIF), a proinflammatory cytokine, is overexpressed in multiple cancer types and has been recently defined as a pro-oncogenic factor. Deactivation of MIF by antibodies or inhibition of MIF binding its receptor, CD74, has been shown to reduce cellular proliferation and to attenuate tumor growth and angiogenesis. The wealth of MIF crystal structures render it suitable for a structure-based, or 'rational', drug design approach, which is presented in this talk. Virtual screening was performed on over 2.1 million compounds from the Maybridge and ZINC databases with the Glide software (Schrödinger, LLC). Our screening protocol began by docking the compounds with the Glide SP scoring function in the MIF active site. The best 40,000 SP-ranked structures were then re-docked and scored in Glide with the extra-precision (XP) scoring function. After close inspection of the top 1000 ligands in the MIF binding pocket, 26 possible inhibitors were selected, purchased, and assayed. The *in vitro* binding assay for MIF interaction with its receptor, CD74 showed six compounds with inhibitory activity in the μM regime, which to our knowledge, are the most potent MIF antagonists yet discovered. Further optimization of the active compounds is being guided by state-of-the-art FEP calculations that yield relative free energies of binding.

**MEDI 473**

**Predicting drug-receptor binding affinity: Additivity vs. non-additivity of free energies of weak interactions**

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Accurately predicting the binding affinity of ligands to their receptors by computational methods is one of the major challenges in structure-based-drug design. One of the potential sources of error is the assumption of thermodynamic additivity between non-covalent interactions such as hydrophobic interactions, hydrogen bonding, salt bridge interactions, etc. Herein we present data obtained from two separate series of systematically modified thrombin inhibitors containing hydrophobic side chains of varied size and with or without an adjacent side chain that engages in hydrogen bonding. The data

demonstrates additivity of the binding free energy contribution for these two side chains interactions with thrombin in one series of inhibitors, but non-additivity in the other. The underlying cause and the implications of this observation will be discussed in detail.

**MEDI 474**

**DeNovo design as a tool for medicinal chemists: Minimal requirements for a renewed consideration**

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Due to the amount of techniques/programs used, there is a growing need in the medicinal chemistry community to define and deliver validation studies aimed at benchmarking the current "state of art". A noticeable amount of work has been recently published in the field of virtual screening for what concerns, for instance, flexible docking techniques and similarity search methods. For some techniques, like structure-based de novo design, comprehensive retrospective validation work has still to be published. This particular design technique is emerging as a viable source of computer-aided designed molecules. However, it has not yet delivered a large and comprehensive evidences of its generality and efficacy. Here we would like to propose a standard approach for the validation of this particular technique. We propose a standardization of retrospective validation studies. In doing so, we show how FlexNovo, a recently introduced program, behaved. We define requirements for strict validation cases and propose suggestions for real-life cases, where it is difficult to judge the quality of the molecules obtained. First, the software should be capable to reproduce known ligands in, second, the same binding mode as presented by experimental structural data taken as reference. This latter requirement should be preferentially accomplished by ranking the candidate within the first five or ten entries of the final list. High ranking is more a preference than a strict requirement as it is usually strictly dependent on the reliability of scoring function in measuring binding energy contributions. Beside this, we also identified a third requirement for those cases where successfull prospective studies are presented. A denovo design software should be able to propose candidate molecules, which can be actually made and be stable enough to be chemical-physically characterized and tested. We presented here the results of a retrospective validation study which follows the above mentioned requirements

**MEDI 475**

**Discovery of orally active met kinase inhibitors**

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Met, a receptor tyrosine kinase has a high binding affinity for hepatocyte growth factor (HGF). Met activation is implicated in a variety of human cancers and can occur via ligand binding, met overexpression and activating mutation. Upon activation, Met mediates various cellular responses that can lead to tumor metastasis and progression. We recently identified a series of potent inhibitors of Met kinase activity derived from pyrrolopyridine kinase inhibitor scaffold. Analysis of x-ray co-crystal structures of several analogs bound to the Met kinase domain resulted in the understanding of key interactions engaged between inhibitor and protein, which facilitated the design of new series of analogs. The SAR studies led to the discovery of novel inhibitors with single digit nanomolar IC50

values in the Met kinase assay and enhanced potency in a met-driven tumor cell anti-proliferation assay. In addition, several analogs demonstrated significant antitumor activity in a GTL-16 human gastric carcinoma xenograft model.

**MEDI 476**

**Mitotic kinesin inhibitors as novel anticancer agents: Inhibition of KSP by three different biochemical mechanisms**

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Kinesins that play essential roles in the mechanics of mitosis are attractive targets for novel antimitotic cancer therapies. We report the mechanism of actions of representative compounds from three different KSP inhibitor classes: (1). Ispinesib (SB-715992) is a potent, highly specific small-molecule inhibitor of KSP being tested in multiple phase II clinical trials. Ispinesib binds to a binding pocket within the loop L5 region and inhibits KSP by preventing the release of ADP; (2) GSK-1 is an ATP-competitive inhibitor of KSP that is ATP-competitive yet bind to a site distinct from the nucleotide-binding site; (3) KSPA-1, which is a basal KSP ATPase activator that activates KSP catalyzed ATP hydrolysis in the absence of microtubules, yet inhibits microtubule-stimulated ATP hydrolysis by KSP. Taken together, these examples demonstrate the diversity of novel mechanisms by which conformationally dynamic enzymes, such as KSP, can be targeted by small molecule effectors of catalytic function.

**MEDI 477**

**Synthesis and SAR of novel 11'-vinorelbine, 12'-vinblastine, and 12'-vincristine alkaloid analogs**

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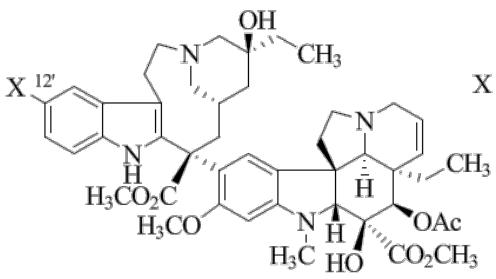
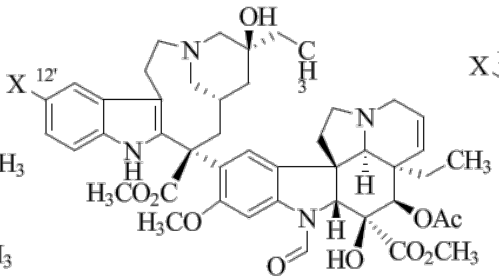
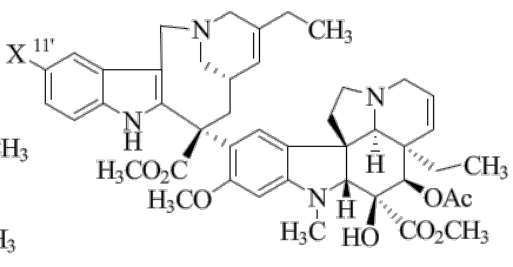
The utility of 12'-halovinblastine, 12'-halovincristine and 11'-halovinorelbine as substrates for recently developed transition metal based methodology was recognized and led to the preparation of novel analogues of the vinca alkaloids. The synthesis of key iodo intermediates and their transformation into final products along with the SAR based upon Hela and MCF-7 cell toxicity assays will be presented.




Vinblastine




Vincristine




Vinorelbine

**MEDI 478**

## Novel potent cyclic-imide peptidomimetics as anticancer agents metalloproteases inhibitors

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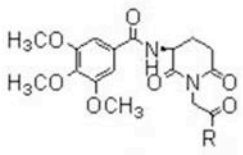
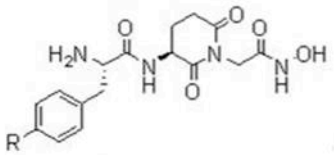
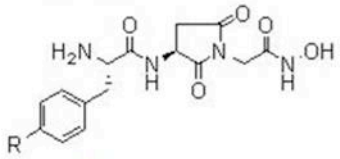
Abstract: Both of Aminopeptidase N (APN) and matrix metalloproteinase (MMP) are essential metallopeptidases in extracellular matrix (ECM) degradation and play critical role in the development of tumor invasion and angiogenesis. A novel class of very potent inhibitors of metallopeptidases is described utilizing mechanism-based and structure-based drug design strategies comprehensively. In this paper a serues of cyclic-imide scaffold peptidomimetics were designed and synthesized. The preliminary biological test revealed that most of compounds displayed high inhibitory activity against MMP that is a ‘two-zinc' enzyme. Two of the gallolyl compounds, 7l and a hydroxamate acid 9a appeared to be very potent inhibitor of APN with the IC50 value of 5.2μM and 3.1μM, respectively, which exhibit similar potency to Bestatin (IC50=2.4μM). Another series of cyclic-imide peptidomimetics with free amino group, 24f and 34f displayed higher affinity toward APN than bestatin with the IC50 value of 1.8μM and 1.0μM.the potent compounds (9a, 24f, 24i, 34f, 34i) both in enzymes assay and cells assay displayed potent inhibition of metastasis of tumor cells in H22-bearing mice model. The inhibitory rate of all inhibitors tested was more than 50%, among which 9a and 24f displayed high inhibitory rate of 81% and 72%, respectively, and are promising for further study in preclinical research.



7l: R= His-OMe
9a: R= -NHOH



24f: R= H
24i: R= -OH



34f: R= H
34i: R= -OH

**MEDI 479**

## Discovery and SAR of highly potent, orally efficacious inhibitor of poly(ADP-ribose) polymerase (PARP) for the treatment of cancer

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Poly(ADP-ribose) polymerases (PARPs) are a family of abundant nuclear enzymes that play a critical role in DNA repair mechanism triggered by DNA damaging agents or radiation. Inhibition of PARPs that often over-express in a variety of tumors, would retard this intracellular DNA repair and maximize the antitumor effects of radiation or cytotoxic agents. We have developed ABT-888, an orally efficacious PARP inhibitor currently being evaluated in several human phase I clinical trials. Herein, we disclose our discovery of another series of highly potent and orally efficacious PARP inhibitors. The SAR, structural characterization, and in vivo evaluation of this series of PARP inhibitors in a number of rodent tumor models in combination with temozolomide (TMZ) will be presented.