Division of Medicinal Chemistry
Abstracts-235th ACS National Meeting
New Orleans, LA
April 6-10, 2008

Publication Date: February 27, 2008
http://www.acsmedchem.org/mediabstracts2008.pdf

MEDI 1

The history of integrase in HIV replication

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To replicate, HIV must integrate a DNA copy of its RNA genome in to a chromosome of the host cell. The development of inhibitors against HIV integrase, the enzyme responsible for the initial DNA breaking and joining reactions involved in integration, represents a major advance in drug development and HIV therapy. The lecture will trace the origins of concepts in this field from studies of related bacteriophage systems, through establishment of methods for assay of HIV integrase in vitro, to modern high throughput studies of inhibitors and genomic analysis of the integration step.

MEDI 2

The discovery of Isentress: From bench to the clinic

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Although integrase has long been considered promising target for the development of novel antiretroviral agents to treat HIV-1 infection, the complexities of the integration process and technical challenges of studying the enzyme itself proved problematic for early drug discovery efforts. After many years of effort, the viability of integrase as a therapeutic target for small molecules has now been validated in vitro as well as in experimental animal model systems of retroviral infection and clinical proof of concept has finally been achieved in HIV-1 infected patients. Understanding the basic biology of integration in HIV-1 infection and elucidating the mechanism of action of prototype inhibitors of integrase in vitro was instrumental in the evolution of compounds suitable for clinic testing and the development of Isentress. This presentation will review the role of integrase in HIV-1 infection, the mechanism of integrase inhibitors and key features shared by recently compounds from our lab and other groups as well as summarize the

results of clinical studies of Isentress including prospects and future drug discovery efforts in this class of agents.

MEDI 3

Tricyclic HIV-1 integrase inhibitors: SAR studies and preclinical evaluations

***Haolun Jin**, Matthew Wright, Sammy Matobo, Michael Mish, Salman Jabri, Rachael Lansdown, Maria Fardis, Ruby Cai, Peter Pyun, Richard Pastor, Laura Schacherer, Manuel Tsiang, Xiaowu Chen, James Chen, and Choung U. Kim, Gilead Sciences, Inc, 333 Lakeside Drive, Foster City, CA 94404, hjin@gilead.com*

The first HIV integrase inhibitor that demonstrated the efficacy in clinical trials, L-870810, and the first FDA approved integrase inhibitor, raltegravir, represent a major breakthrough in the battle against HIV infections for AIDS patients, in particular for those who are failing previously available therapies due to multi-drug resistance. In this presentation, we discuss progress in the research of a class of integrase inhibitors designed based on the conformationally constrained scaffold shown in Fig. 1. A number of highly potent inhibitors were identified. The studies of SAR and pharmacokinetic evaluation of lead compounds will be presented. Selected activity data on some of these compounds against a panel of HIV resistant mutants will also be presented.

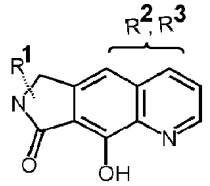

Fig. 1

MEDI 4

Naphthyridinone (NTD) integrase inhibitors: Discovery of the clinical candidate S/GSK364735

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The discovery of the diketoacid inhibitors of the HIV retroviral integration step nearly ten years ago was a seminal contribution that has served to foster the design and development of various heterocyclic scaffolds with increased drug-like properties. Among these second generation scaffolds is a novel series of orally bioavailable inhibitors of viral replication consisting of the naphthyridinone (NTD) core. The design, discovery and optimization of this series including SAR, DMPK properties, and protein binding will be the topics discussed. The above efforts culminated in the selection of S/GSK364735 for clinical evaluation which resulted in a greater than 2 log reduction in viral load in a Phase 2a study. The work presented herein including the

discovery of S/GSK364735 was a result of a joint research collaboration between GlaxoSmithKline and Shionogi & Co.

MEDI 5

A potential second generation HIV-1 integrase strand transfer inhibitor with a high genetic barrier to mutation

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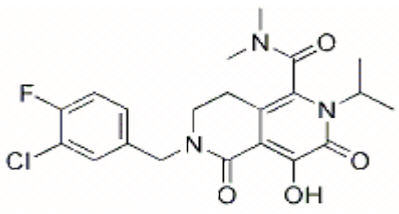
A series of novel bicyclic 4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide HIV-1 integrase inhibitors was designed and synthesized. Compounds in this series are selective inhibitors of HIV-1 integrase strand transfer. Compound A is a potent inhibitor of HIV-1 replication in cell culture (IC95 in 50% human serum = 38 ± 22 nM, n=77). It demonstrates excellent antiviral potency against a panel of mutant viruses selected *in vitro* using structurally diverse integrase strand transfer inhibitors and therefore may provide a high genetic barrier against the emergence of resistant mutants. Compound A maintains antiviral activities against mutants identified from clinical studies of Raltegravir and exhibits very good PK profiles in rat and dog.



Compound A

MEDI 6

Models of HIV-1 integrase/DNA complex

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We present an overview of the approximately ten different models published so far of HIV-1 integrase (IN) complexed with models of the viral DNA and, in some cases, additionally with models of the host DNA. We compare their overall geometries, and contrast them with

experimental evidence. We discuss their relevance for IN inhibitor design, in particular for the development of strand transfer inhibitors, and report on published applications of these models to computer-aided drug design projects.

MEDI 7

Design of a novel biphenyl class of CETP inhibitors

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Atherosclerosis and its clinical consequences, coronary heart disease (CHD), stroke and peripheral vascular disease, represent a truly enormous burden to the health care systems of the industrialized world. Metabolic control of lipoprotein levels is a complex and dynamic process involving many factors. One important metabolic control in man is the cholesteryl ester transfer protein (CETP), a plasma glycoprotein that catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL. It has been demonstrated that pharmacological inhibition of CETP in humans will result in increased levels of HDL-C and decreased concentration of LDL-C. The clinical benefit, if any, of such inhibition is still unknown.

A number of CETP inhibitor scaffolds have been reported, most notably the tetrahydroquinoline core of Pfizer's torcetrapib and the acylaminobenzenethiol core of the Roche / JTT inhibitor R1628 (JTT-705). This presentation will discuss the design, synthesis and biological evaluation of a novel biphenyl class of CETP inhibitor which shows potent in vitro activity and in vivo efficacy in a CETP transgenic mouse pharmacodynamic model.

MEDI 8

DNA Ligase inhibitors identified via computational and experimental methods

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DNA ligase functions in both DNA replication and repair by linking together DNA strands that have either single- or doubled-strand breaks. Inhibition of DNA ligase may, therefore, be of therapeutic utility for the treatment of cancer as an enhancer of radiation therapy. A molecular dynamics (MD) simulation was applied to generate multiple protein conformations of human DNA Ligase I (hLigI) to address the flexibility of the protein. Database screening of over 1 million

compounds was then performed targeting a putative binding site on the DNA binding domain using the MD-generated and crystal conformations of the protein. 192 hits selected according to a normalized docking score, chemical diversity and physical properties were experimentally tested by determining the inhibition of DNA ligation. 15 inhibitors have been identified which inhibit greater than 50% of hLigI activity at inhibitor concentration of 100 μM. Structure-activity relationship of the active compounds has subsequently been analyzed.

MEDI 9

Propylpiperidine-ketooxazole based inhibitors of Fatty Acid Amide Hyrolase

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Pharmacologically active preparations of *Cannabis sativa* have been recognized since ancient times as having potentially useful therapeutic effects, including analgesia. With the discovery and cloning of the cannabinoid receptors CB1 and CB2, and the subsequent discovery of anandamide, the first endogenous substance with agonist activity at both receptors, a rationale for the analgesic effects of cannabis was developed. It has been shown that the neuronal synthesis of anandamide, which itself has analgesic properties, is synthesized on demand in active neural pathways. Inhibitors of FAAH show amelioration of pain behaviors in rats without the motor impairment commonly seen with CB1 agonists. The present account describes the discovery of a new class of FAAH inhibitors and describes our work to characterize the SAR and pharmacological actions of these FAAH inhibitors.

MEDI 10

Antagonists of the calcium sensing receptor: Parathyroid hormone secretagogues

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The calcium sensing receptor, a family C G-protein coupled receptor, is the principle regulator of endogenous parathyroid hormone secretion. The CaR is negitively coupled to calcium ion concentrations in that a minute drop in the calium concentration elicits release of parathyroid hormone from the parathyroid gland. Antagonizing the CaR with a small molecule should mimic a state of hypocalciemia and promote release of endogenous parathyroid hormone. This release of PTH should ultimately lead to formation of new bone. In this presentaion we describe some recent advances in the synthesis, SAR and pharmacology of a series of calcium receptor antagonists.

MEDI 11

Calcitonin gene-related peptide (CGRP) receptor antagonists for the treatment of migraine: Development of orally bioavailable imidazoazepanes

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Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide that has been implicated in the pathogenesis of migraine. Since CGRP receptor antagonists promote normalization of dilated blood vessels through a non-vasoconstrictive mechanism, this class of compounds could prove effective in the relief of migraine without the adverse cardiovascular effects that are sometimes associated with existing therapies. Our research program targeted non-peptide, orally bioavailable CGRP receptor antagonists culminating in the discovery of caprolactam-azabenzimidazolone MK-0974, which has recently demonstrated efficacy in a Phase IIb clinical trial. Targeted areas for improvement in our backup program include aqueous solubility, in vivo potency, and rhesus pharmacokinetics. We have identified a series of imidazoazepanes which demonstrate improved potency and aqueous solubility. Concurrently, an investigation of replacements for the metabolically labile azabenzimidazolone of MK-0974 has produced a series of spiropiperidines with superior pharmacokinetic profiles. This strategy ultimately resulted in the identification of backup MK-2918.

MEDI 12

Novel series of CB2 selective agonists for the treatment of neuropathic pain

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Neuropathic pain, a debilitating condition characterized by severe, persistent pain that is refractory to traditional analgesia, results from heterogeneous conditions affecting the peripheral or central nervous system (CNS) and affects an estimated 8% of people worldwide. The cannabinoid receptor CB2, has emerged as a new target for the treatment of pain without the CB1 mediated psychotropic side effects. Two series of novel cannabinoid modulators based on two heterocyclic scaffolds, have been synthesized. Highly potent and selective CB2 agonists were identified in both series using in vitro binding and functional assays. Selected compounds were tested in vivo relevant models of neuropathic pain and were able to reverse allodynia and hyperalgesia, with no visible CNS side effects. In contrast, a CB1–CB2 agonist, Win 55,212, caused rigidity, spasm, and lethargy. Details of the synthesis, CB1 and CB2 receptors structure-activity relationships, in vitro, and in vivo data will be presented.

MEDI 13

Potent, brain-penetrant, hydroisoindoline-based human neurokinin-1 receptor antagonists

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Abstract: Substance P is the most abundant neurokinin in the mammalian central nervous system (CNS). The substance P-preferring neurokinin (NK1) receptor is highly expressed in brain regions that are critical for mediation of a variety of biological effects. The FDA has approved the NK1 antagonist aprepitant (EMEND®) for acute dosing in the prevention of chemotherapy-induced nausea and vomiting, and for prevention of postoperative nausea and vomiting. Aprepitant has also shown evidence of efficacy in a Phase IIa trial for overactive bladder syndrome.

We here describe a discovery process and preclinical results on a hydroisoindoline-based new generation NK1 antagonist which was chosen for further development studies. The presentation will also discuss synthesis of the enantiomerically pure NK1 antagonist which contains five stereocenters

MEDI 14

Radiolabeled multimeric chlorotoxin as a tumor–seeking radiodiagnostic agent

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Small peptide-based agents have attracted interest as cancer-targeting agents. Chlrotoxin (known as TM601), a 36-amino acid peptide, shows bind selectively to various malignant tumors. Radioiodinated chlorotoxin (I-131-TM601) is currently in Phase I/II clinical development. In this study, we explored the multimeric chlorotoxin labeled with Tc-99m as a SPECT imaging agent.Trimeric-TM601 was radiolabeled using Tc-99m-MAS3-NHS, in one step, with specific activity 3,133 Ci/mmol. Affinity and Bmax for various cancer cell lines were measured ranging from 3-8 nM and 14000-19000 binding sites per cell respectively. Biodistribution and clearance studies on tumor mice shows radiotracer cleared rapidly from the blood, with a beta phase half-

life of 52 min and the tumor uptake was significantly higher (1.8 ± 0.7%ID/g).We prepared radiochemically pure, Tc-99m-labeled chlorotoxin, multimerization of chlrotoxin resulted in enhanced affinity for cancer cell lines. The high uptake by tumor makes this trimeric chlorotoxin as the favorable ligand for tumor targeting in vivo.

MEDI 15

Multidentate small molecule inhibitors of VHR phosphatase: A new drug target for the treatment of cervical cancer

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VHR is a dual-specific phosphatase and a negative regulator of the Erk and Jnk mitogen-activated protein kinase pathways. Loss of VHR causes cell cycle arrest in HeLa cervix carcinoma cells, suggesting that VHR inhibition may be a useful approach to halt the growth of cancer cells. Moreover, VHR was found to be upregulated in several cervix cancer cell lines as well as in squamous intraepithelial lesions and squamous cell carcinomas of the uterine cervix. Here we report the development of novel multidentate small molecule inhibitors of VHR that inhibit its enzymatic activity at nanomolar concentrations in vitro and hold the growth of cancer cells at low micromolar concentrations. High throughput chemical library screening was used to identify hits, and structure-based methods were applied in the search for analogs with improved potency and selectivity, resulting in multidentate inhibitors. The binding mode of these novel compounds was confirmed by X-ray crystallography.

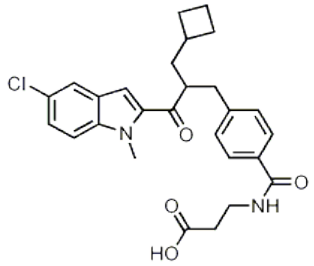
MEDI 16

Discovery of 2-acylindoles as potent, orally active human glucagon receptor antagonists

Christopher J. Sinz[1]*, Amy Bittner*[1]*, Ronald M. Kim*[1]*, Ed Brady*[2]*, Mari Rios Candelore*[3]*, Victor D-H. Ding*[3]*, Guoquiang Jiang*[3]*, Zhen Lin*[1]*, Ashley Rouse Lins*[1]*, Peggy McCann*[2]*, Corin Miller*[4]*, Kiyean Nam*[5]*, Sajjad A. Qureshi*[3]*, Gino Salituro*[1]*, Richard Saperstein*[2]*, Jackie Shang*[6]*, Deborah Szalkowski*[3]*, Laurie Tota*[3]*, Michael Wright*[3]*, Regina Wang*[6]*, Shiyao Xu*[6]*, Xiaodong Yang*[3]*, Bei Zhang*[3]*, Milton Hammond*[1]*, James Tata*[1]*, and Emma Parmee*[1]*. (1) Department of Medicinal Chemistry, Merck and Co., Inc, P.O. Box 2000, RY800-C303, Rahway, NJ 07065, Fax: 732-594-9473, christopher_sinz@merck.com, (2) Department of Pharmacology, Merck and Co., Inc, Rahway, NJ 07065, (3) Metabolic Disorders - Molecular Endocrinology, Merck & Company, Inc, Rahway, NJ 07065, (4) Research Imaging, Merck & Company, Inc, Rahway, NJ 07065, (5) Molecular Systems, Merck & Co., Inc, Rahway, NJ 07065, (6) Department of Drug Metabolism, Merck and Co., Inc, Rahway, NJ 07065*

Glucagon and insulin are the primary counter-regulatory hormones responsible for glucose homeostasis. Glucagon is secreted from pancreatic alpha-cells in response to falling plasma glucose levels. Activation of the glucagon receptor, a G-protein coupled receptor located

predominately in the liver, leads to increased hepatic glucose production via glycogenolysis and gluconeogenesis. In patients with type 2 diabetes, excessive hepatic glucose production is a key contributing factor to hyperglycemia. Thus, glucagon receptor antagonists have attracted significant interest as a novel treatment for type 2 diabetes. We found that N-alkyl-2-acylindoles such as compound 1 are potent glucagon receptor antagonists; however, these compounds show poor activity in vivo due to rapid metabolic turnover. Improved metabolic stability was realized by substitution of the indole nitrogen with an aryl group. Further optimization led to compound 2, a potent and selective human glucagon receptor antagonist that displays good efficacy in rodent diabetes models and favorable pharmacokinetic properties in preclinical species.



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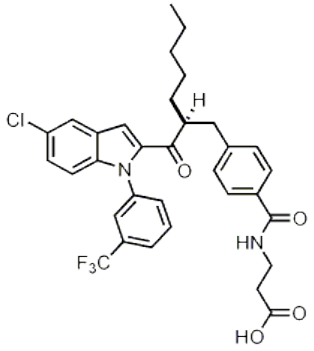

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MEDI 17

Synthesis and QSAR studies of CADA analogs wth CD4 down-modulating and anti-HIV activities

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HIV attachment via the CD4 receptor is an important target for developing novel approaches to HIV chemotherapy. Cyclotriazadisulfonamide (CADA) is a 1,5,9-triazacyclododecane that inhibits HIV at submicromolar levels by specifically down-modulating cell-surface and intracellular CD4. An effective 5-step synthesis of CADA has been modified to produce may analogs. Tail-group analogs have been made by removing the benzyl tail of CADA and replacing it with various alkyl, acyl, alkoxycarbonyl and aminocarbonyl substituents. A series of side-arm analogs has also been prepared by modifying the CADA synthesis, replacing the toluenesulfonyl side arms with other sulfonyl groups. Testing of these compounds in MT 4 cells shows a wide range of CD4 down-modulation potency, which correlates with ability to inhibit HIV-1. Three-dimensional quantitative structure-activity relationship (3D-QSAR) models were constructed , based on the X-ray crystal structures of four compounds, including CADA. Both models indicate that steric bulk of the tail group and, to a lesser extent, the side arms mainly determine CD4 down-modulation potency in this series of compounds.

MEDI 18

Discovery of MK-7009: A novel macrocyclic HCV NS3/4A protease inhibitor

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The hepatitis C virus (HCV) infects an estimated 200 million people worldwide including approximately 4 million people in the U.S. and is the leading cause for liver transplantation. The current standard of care for HCV infection is treatment with pegylated interferon alpha in combination with ribavirin, however, this regimen results in limited efficacy and significant side effects. Efforts toward improved HCV treatment include the development of direct antiviral agents which inhibit key steps in the viral replication process. One such target is the HCV NS3/4A protease.

Our interest has been in identifying novel HCV NS3/4A protease inhibitors with good enzyme potency, cellular activity and liver exposure. Toward this goal, initial targets were designed using molecular modeling. The development and optimization of lead compounds along with the profile of clinical candidate MK-7009 will be presented.

MEDI 19

Design, synthesis and biological profile of BMS-641988: A novel AR antagonist for the treatment of advanced prostate cancer

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Carcinoma of the prostate (CaP) is the 2nd leading cause of cancer related death in men in the United States. Androgen ablation via surgical or chemical castration or by treatment with an antiandrogens is currently the treatment of choice for advanced CaP. Although this therapy initially shows an 80-90% response rate, approximately 50% of patients progress to fatal androgen independent CaP (AI-CaP) after about 18 months of treatment. Recent advances in the field have shown that reactivation of the AR signaling pathway is the root cause for the development of AI-CaP. The identification of the role of the AR in AI-CaP suggests that new agents which act at the level of the AR may be effective in the treatment of this disease. Efforts in our lab have identified a novel and highly potent series of [2.2.1]-oxobicyclo-imide based AR antagonists. Optimization of this series by application of structural based drug design and medicinal chemistry approaches resulted in the identification of BMS-641988 as a development candidate for the treatment of advanced CaP.

MEDI 20

Discovery of APD791: A potent and selective 5HT2A inverse-agonist for the treatment of cardiovascular disorders

Bradley R. Teegarden*, Yifeng Xiong, Sonja Strah-Pleynet, Peter I. Dosa, Honnappa Jayakumar, Jin Sun Choi, Marc Decaire, Martin Casper, Lan Pham, Konrad Feichtinger, Brett Ullman, Katie Elwell, John Adams, Juan Ramirez, William Thomsen, Diane Yuskin, Michael Morgan, Abu Sadeque, Weichao Chen, Paul Maffuid, Hussien Al-Shamma, Graeme Semple, Robert R. Webb, and Daniel Connolly, Arena Pharmaceuticals, Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121*

The neurotransmitter, 5-Hydroxytryptamine (5-HT, serotonin), has been shown to have important effects in cardiovascular disease. 5-HT plays a key role in arterial thrombus formation by amplifying platelet aggregation in the presence of other agonists, such as collagen, ADP, epinephrine, and thrombin.

In this presentation we will describe the development of a new series of 5HT2A receptor inverse-agonists that inhibit the serotonin-induced amplification of platelet aggregation. An early lead provided in vivo proof of concept in a rat model of vascular injury, bleeding and ex vivo platelet aggregation. In this model, and in contrast to clopidogrel used as a control, we were able to demonstrate a favorable separation of anti-thrombotic activity from increased bleeding time. We will detail the complex, multivariate SAR of this series with respect to receptor activity and selectivity, as well as specific off target activities, resulting in the selection of APD791 for preclinical and clinical development.

MEDI 21

Discovery of a second generation FBPase inhibitor, MB07803, with reduced metabolism and improved oral bioavailability

Qun Dang[1], *Paul D. van Poelje*[2], *Robert H Lemus*[1], *Feng Tian*[1], *Haiqing Li*[1], *Scott C Potter*[2], *James Fujitaki*[2], *David Linemeyer*[2], *and Mark D. Erion*[3]. *(1) Department of Chemistry, Metabasis Therapeutics, Inc, 11119 North Torrey Pines Road, La Jolla, CA 92037, dang@mbasis.com, (2) Department of Biosciences, Metabasis Therapeutics, Inc, La Jolla, CA 92037, (3) Research & Development, Metabasis Therapeutics Inc, La Jolla, CA 92037*

MB06322 (CS-917, a prodrug of FBPase inhibitor MB05032) significantly lowered fasting plasma glucose levels in patients with type 2 diabetes (T2DM) during two phase 2a clinical trials. The second generation program sought to improve oral bioavailability and eliminate the formation of an N-acetyl metabolite of MB05032. Modification of the electronic character of the thiazole FBPase inhibitor series led to a potent human N-acetyltransferase-resistant lead, MB07729 (IC50 = 21 nM; 0% N-acetylation by NAT1 and NAT2). Prodrug optimization resulted in phosphonic diamide MB07803, which demonstrated good oral bioavailability in rats (30-40%) and monkeys (50-60%), and efficient conversion to MB07729. MB07803 elicited marked glucose-lowering effects in rodent models of T2DM (e.g. db/db mice and ZDF rats, MED of 10-30 mg/kg) and in normal fasted monkeys (MED = 3 mg/kg). In a phase 1 clinical trial, MB07803 was well tolerated and led to dose-linear exposure of MB07729, with minimal formation of the N-acetyl metabolite.

MEDI 22

From virtual screening to clinic: Discovery of Cevoglitazar

T. R. Vedananda[1], *Mike Sabio*[2], *James Stanton*[3], *Hollis Tomaselli*[2], *James Fraser*[4], *Goli Naderi*[2], *Jenny Tan*[2], *Travis Stams*[5], *Brian Boettcher*[3], *Barbara Fanelli*[2], *Jianping Gao*[6], *Richard Deacon*[3], *Shari Caplan*[3], *Ping Chen*[3], *Beatriz Dardik*[3], *and Ricardo Chatelain*[3]. *(1) Global Discovery Chemistry and Department of Diabetes and Metabolism, Novartis Institute for Biomedical Research Inc, Cambridge, MA 02139, (2) (3) Department of Diabetes and Metabolism, (4) Global Discovery Chemistry and Department of Diabetes and Metabolism, (5) Protein Stucture Biology, (6) School of Physics, Georgia Institute of Technology, Atlanta, GA 30332-0430*

Despite the availability of several classes of anti-diabetic agents, significant medical need remains due to limited impact of therapies on disease progression, restricted application of existing agents and a lack of pathophysiological impact. Peroxisome proliferators activated receptor (PPAR) alpha and gamma dual agonists are expected to improve glycemic control, insulin resistance and the metabolic syndrome as a consequence of their combined anti-diabetic and anti-dyslipidemic properties.

The discovery of Cevoglitazar as a potent PPAR alpha/gamma dual agonist was a combined effort of virtual screening of 3D databases and structure-based drug design. Computer aided molecular design was initiated by examining known ligand bound PPAR gamma X-ray structures. To develop a pharmacophore model for database searching, observed protein-ligand interactions were simplified to an essential set of three hydrogen bonds, identifying three

acceptor atoms as the core components of the pharmacophore model. Using Unity module of Sybyl, searches were performed on internal and external 3D databases covering nearly 1.3 million structures. All 4021 hits were visually inspected and those which could not be transformed into potential synthetic targets were eliminated. For the surviving hits, structural modifications were facilitated by docking calculations. Subsequent structure-based elaboration of most advanced leads led to the identification of Cevoglitazar as a potent PPAR alpha/gamma dual agonist.

Herein we wish to disclose for the first time, the discovery of Cevoglitazar, a potent PPAR alpha/gamma dual agonist advanced into clinical development.

MEDI 23

Design and synthesis of quinazoline derivatives as novel, potent multiacting HDAC and receptor tyrosine kinase inhibitors for the treatment of cancer

***Xiong Cai**, Hai-Xiao Zhai, Cheng-June Lai, Rudi Bao, and Changgeng Qian, Medicinal Chemistry, Curis Inc, 45 Moulton Street, Cambridge, MA 02138, xcai@curis.com*

HDACs and receptor tyrosine kinases (RTK) such as EGFR and Her2 are validated cancer targets. A multi-targeted HDAC and RTK inhibitor may offer more therapeutic benefits in cancer compared to single acting agents due to potential synergistic effects between HDAC and RTK inhibition. By incorporating HDAC inhibitory functionality into the RTK inhibitor pharmacophore, we designed and synthesized a novel quinazoline series of potent multi acting compounds. The synthesis and SAR surrounding this class of compounds will be discussed. CUDC-101 is one of the lead molecules in the series. In vitro, CUDC-101 displays potent inhibitory activity as well as anti-proliferation and apoptosis-inducing activities against a broad range of cancer cell types with equal or greater potency than SAHA (an HDAC inhibitor), erlotinib (an EGFR inhibitor) and lapatinib (an EGFR/Her2 kinase inhibitor) or combinations thereof. In vivo, CUDC-101 targets all three pathways and is effective against various cancer models. CUDC-101 also displays a favorable safety profile. These results suggest that CUDC-101 may represent a novel treatment option in cancer and a suitable candidate for clinical development.

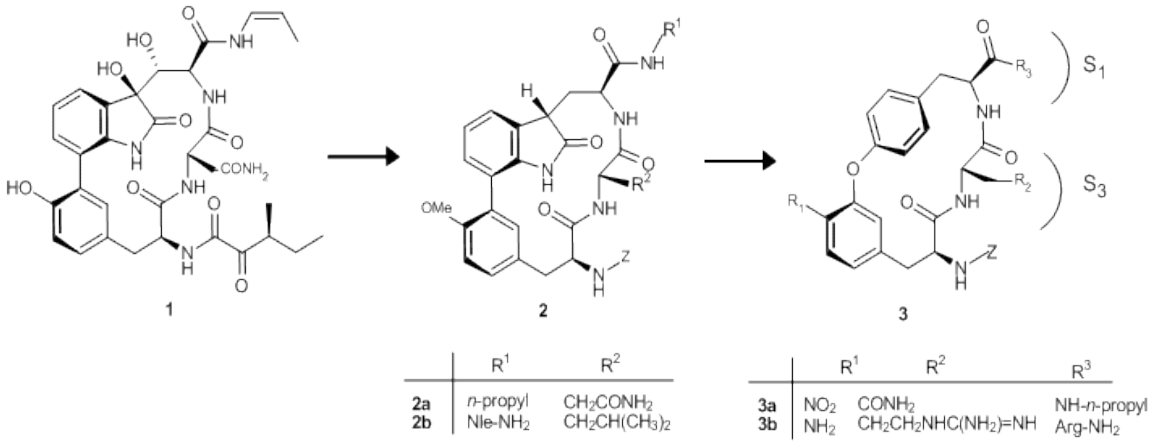
MEDI 24

Macrocyclic peptidyl biaryl-ether inhibitors provide evidence for the catalytic versatility of the 20S proteasome

***Marion G. Götz**[1], Michael Groll[2], Markus Kaiser[3], Elisabeth Weyher[3], and Luis Moroder[3]. (1) Department of Chemistry, Whitman College, 345 Boyer Ave, Walla Walla, WA 99362, gotzmg@whitman.edu, (2) Charité, Berlin, Germany, (3) Max-Planck-Institute for Biochemistry, Martinsried, Germany*

The 20S proteasome (core particle) forms together with the 19S regulatory cap the multicatalytic 26S proteasome. The core particle exhibits three different specific activities, a caspase-like, a trypsin-like and a chymotrypsin-like activity, which are controlled by the β1, β2, and β5 subsites. The potent natural product inhibitor TMC-95A (**1**) is a macrocyclic tripeptide derivative, which inhibits the active site by a non-covalent hydrogen bonding array. Previously, a simplified TMC-

95A analog **2a,b** with the essential functionalities sufficient for inhibition was derived. For further simplification the biaryl moiety was replaced with a nitro (**3a**) as well as an aniline (**3b**) biaryl ether macrocycle. Simultaneously we have optimised the amino acid sequence with the introduction of arginine residues targeting trypsin-like activity. X-ray crystallography as well as mass spectrometry gave evidence for the hydrolysis of this C-terminal amide.



	R^1	R^2
2a	*n*-propyl	CH_2CONH_2
2b	Nle-NH_2	$CH_2CH(CH_3)_2$

	R^1	R^2	R^3
3a	NO_2	$CONH_2$	NH-*n*-propyl
3b	NH_2	$CH_2CH_2NHC(NH_2)=NH$	Arg-NH_2

MEDI 25

Design and synthesis of polyketide-based affinity labels for acyl carrier protein domains

Erick K. Leggans *and Robert A. Fecik, Department of Medicinal Chemistry, University of Minnesota, 8-101 Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, MN 55455, legga001@umn.edu*

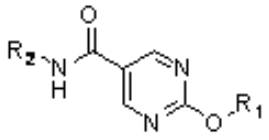
Polyketide synthases (PKSs) are a family of multienzyme complexes that biosynthesize natural products through the sequential condensation of simple two- or three-carbon building blocks. Polyketides have a wide range of biological and pharmacological activities and there has been much interest towards engineering PKSs systems for combinatorial biosynthesis in order to produce new drugs and novel molecules. However, an understanding of substrate stereospecificity and selectivity is unknown for nearly all of the PKS catalytic domains. The specific aim of this research is to design and synthesize polyketide-based affinity labels in order to understand this relationship. Here we present the design and synthesis of vinyl ketone affinity labels and their effective labeling of an acyl carrier protein which, with the aid of their crystal structures, will allow us to determine the stereochemical outcome of PKS activity.

MEDI 26

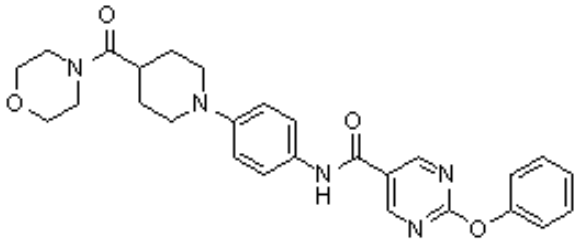
2-Phenoxypyrimidine-5-carboxamide derivatives as a novel Prostaglandin D synthase inhibitor

Keiko Yamane*, Yoshiki Tanaka, Kazuhiko Shigeno, Toshiyuki Hosoya, Shin-ichi Inoue, Makoto Kitade, Takafumi Harada, Hiroki Aoyagi, Nao Miyoshi, Toshiharu Mutoh, Michinori Togawa, Mamoru Kiniwa, and Yasundo Yamasaki, Advanced Research Lab, Taiho Pharmaceutical Co., Ltd, 1-27, Misugidai, Hanno-shi 357-8527, Japan, Fax: +81-42-972-0034*

Prostaglandin (PG) D_2 is an allergic and inflammatory mediator produced by mast cells and Th2 cells. Two distinct types of PGD synthase (PGDS) are known, lipocalin-type PGDS (L-PGDS) is localized in the central nervous system etc. and involved in the regulation of sleep and pain. The other hematopoietic PGDS (H-PGDS) is localized in mast cells, Th2 cells, microglia etc. and participates in allergic and inflammatory reactions. Therefore, selective H-PGDS inhibitors are expected for anti-allergic and anti-inflammatory drugs. We have found 2-phenoxypyrimidine-5-carboxamide (**1**) as a lead compound based on structure activities relationships. After the optimization of lead compound (**1**), we have developed orally available H-PGDS selective inhibitor **2**. IC_{50} value of **2** against H-PGDS is 0.28 mM, on the other hand, inhibitory activity of **2** against L-PGDS is 2% at 100 mM. The details of this work will be presented.



1: R_1 = Ph



2

MEDI 27

Cobalt(III) amine complexes as a potential antibacterial drugs

Christa Simmers[1]*, Eddie L. Chang*[2]*, and D. Andrew Knight*[1]*. (1) Department of Chemistry, Loyola University, 6363 St Charles Ave, New Orleans, LA 70118, csimmer@loyno.edu, (2) Center for Bio/Molecular Science and Engineering, Naval Research Laboratory, Washington, DC 20375-5438*

The antibacterial effects of cobalt hexammine were investigated using *E. coli* model as a model. The ability of the cobalt hexammine to stop bacterial growth was determined from the absorbance of a sample of the bacteria and the cobalt hexammine complex. A possible magnesium ion channel blocking mechanism of cobalt hexammine was tested through the use of a TolC mutant strain of *E. coli*.

MEDI 28

Acute osteomyelitis (OM): Nanometer-sized calcium phosphate (CP) particles as a carrier for bisphosphonate-ciprofloxacin (E41) antibiotic

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We synthesized E41, an antibiotic conjugated to a bisphosphonate, which binds CP, creating targeted drug delivery. E41 bound to bone-homeostatic CP and packed into traumatized bone, may prevent OM. We contrasted two CPs, µ-sized Skelite™ and nm-sized NanOss™. Adult rats received traumatic open tibial fracture with medullary contamination by Staphylococcus aureus (Sa), lavage, E41-CPs packed into the defect, and sacrificed at day 1. Tibial loads, expressed as log10 colony-forming units/gm, were: Infection controls, 4.40±0.9, E41-Skelite, 2.70±2.0, and E41-NanOss, 1.10±1.3 ($p \leq 0.01$). E41-NanOss produced significantly lower tibial loads vs. E41-Skelite ($p=0.001$). Sixteen of 16 Infection-control tibiae yielded bacteria, with high tibial loads, suggesting developing acute OM; E41-NanOss group, 16 of 19 tibiae sterile vs. 5 of 18 for E41-Skelite ($p=0.0005$). NanOss™ appears to be a better carrier for E41, than Skelite™, perhaps due to its higher particle surface area. E41-NanOss eradicated Sa infection in traumatized bone.

MEDI 29

First small molecule inhibitors of RecA in living bacteria

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Antibiotic resistance in bacteria is an escalating threat. RecA facilitates the development and transmission of antibiotic resistance genes, and promotes survival of bactericidal chemotherapy. We identified, synthesized, and tested several members of different classes of small molecules towards inhibition of the RecA protein. Initial leads came from high-throughput screening in collaboration with the BRITE Institute of North Carolina Central University. We report the first small molecules capable of inhibiting the bacterial SOS response in live bacteria resulting from exposure to Ciprofloxacin and appear to do so by inhibiting the RecA protein (IC50 < 10 µM).

MEDI 30

Methods for purifying and detoxifying sodium dodecyl sulfate-stabilized polyacrylate nanoparticles

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The tremendous impact that antibiotics have had on human health is well-appreciated. However, many microorganisms have rapidly acquired resistance for most of the currently available antimicrobials, displaying an amazing versatility to overcome the cidal or static effects of antibiotics on microbial growth and proliferation. The continuing rise in the numbers and prevalence of drug-resistant microbes that cause infections, most notably methicillin-resistant Staphylococcus aureus (MRSA), is further exasperated by the sheer difficulty and expense of developing new antimicrobially-active molecules. Moreover, many of the most promising drug candidates suffer from poor water solubility and systemic stability that limits their clinical development. Our laboratory has been working on ways to improve the performance of such antibiotic compounds, and for enhancing the activity of older classes of antibiotics, using polyacrylate nanoparticles. These nanoparticles can be easily prepared by emulsion

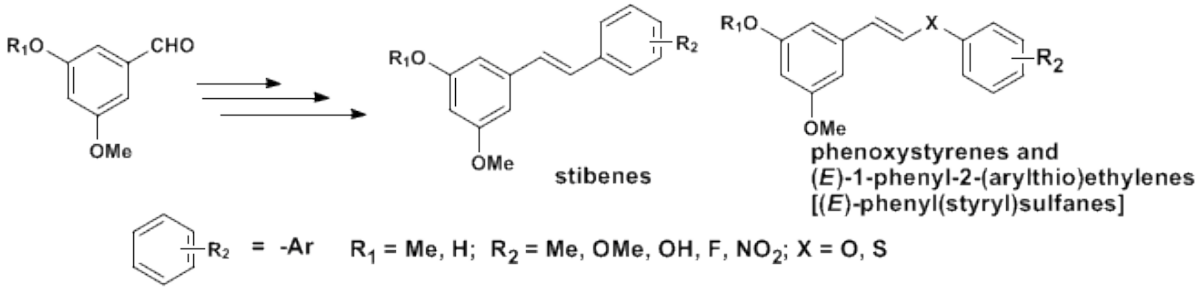
polymerization, as described, by pre-mixing the acrylated form of the antibiotic in a warm mixture of butyl acrylate-styrene, adding sodium dodecyl sulfate (SDS) in water, and inducing polymerization with a water-soluble radical initiator. Typically, the amount of surfactant and antibiotic used for the polymerization is each 3 weight %. We decided to focus our attention into investigate the role of the SDS as the major responsible for the toxicity of emulsions. This information is especially important, since high concentrations of SDS are going to be used during this study, in order to modify the size of the nanoparticle. This surfactant has excellent dispersion properties in the homogenization process , but at the same time, it has been widely reported in the literature that SDS, causes alterations of several toxic effects in studies done in keratonocytes and fibroblast cells mainly. Results we obtained using SDS during the preparation and biological screening would be presented in this poster.

MEDI 31

New classes of Gram-positive antibacterials: Inhibitors of MRSA and surrogates of the causative agents of anthrax and tuberculosis

M. Shahjahan Kabir[1]*, Kathleen Engelbrecht*[2]*, Aaron P. Monte*[3]*, Marc A Rott*[2]*, William R Schwan*[2]*, and James M. Cook*[1]*. (1) Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, 3210 N. Cramer St., Milwaukee, WI 53211, mkabir@uwm.edu, (2) Department of Microbiology, University of Wisconsin-La Crosse, La Crosse, WI 54601, (3) Department of Chemistry, University of Wisconsin-La Crosse, La Crosse, WI 54601*

The antimicrobial phenolic stilbene [(*E*)-3-hydroxy, 5-methoxystilbene] was isolated from the leaves of *Comptonia peregrina* (L) by Monte *et. al.*, and tested against a series of Gram-positive bacteria. This compound is inhibitory against drug-resistant Gram-positive bacteria including MRSA and surrogates of the causative agents of anthrax and tuberculosis (TB).These results prompted the design and synthesis of two new classes of compounds [functionalized phenoxystyrenes and (*E*)-1-phenyl-2-(arylthio)ethylenes {(*E*)-phenyl(styryl)sulfanes}] in addition to various functionalized stilbenes. These ligands were prepared through two new efficient coupling processes. Their inhibitory activities were evaluated on the same series of Gram-positive bacteria as the natural phenolic stilbenes. The structure-activity relationships indicated these two new classes of compounds and the phenolic stilbene analogues exhibit activity against several drug-resistant Gram-positive bacteria. The biological activity of these compounds appears very promising and comparable with natural phenolic stilbene against clinically significant drug-resistant Gram-positive bacteria.



MEDI 32

Synthesis of novel triazole-bearing nitroimidazoles with improved antimicrobial activity against the protozoan pathogen Giardia

Carlos A. Valdez[1]*, Jaroslaw Kalisiak*[1]*, Jonathan C. Tripp*[1]*, Barbara Davids*[2]*, Frances Gillin*[2]*, Valery V. Fokin*[1]*, K. Barry Sharpless*[1]*, and Lars Eckmann*[2]*. (1) Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Rd., La Jolla, CA 92037, (2) Department of Pathology and Medicine, University of California, San Diego, La Jolla, CA 92093*

The protozoan enteric parasite, Giardia lamblia, infects hundred of millions in the world and is a major cause of waterborne diarrheal disease. The infection is primarily treated with metronidazole (Mz), a compound belonging to a class known as the 5-nitroimidazole antibiotics. Standard treatment with Mz is safe and effective in 80-90% of cases, but treatment failure is common and Mz-resistant strains of the parasite have been reported. To overcome resistance, new and more potent antigiardial drugs are in needed. Herein, we describe the use of click chemistry, more specifically the copper(I)-catalyzed azide-alkyne cycloaddition reaction, to rapidly and efficiently generate a library of triazole-bearing 5-nitroimidazoles for use against the parasite and its resistant variants. The synthesis and biological evaluation of a number of novel 5-nitroimidazolides will be presented.

MEDI 33

Synthesis and biological activity of antagonists of AI-2-mediated bacterial quorum sensing in Vibrio harveyi

Yunfeng Cheng[1]*, Nanting Ni*[1]*, Minyong Li*[1]*, Han-Ting Chou*[2]*, Chung-dar Lu*[2]*, Phang C Tai*[2]*, and Binghe Wang*[1]*. (1) Department of Chemistry, Georgia State University, 50 Decatur Street, Atlanta, GA 30303, jerry_cyf@hotmail.com, (2) Biology Center for Biotechnology and Drug Design, Georgia State University, Atlanta, GA 30303*

Bacterial quorum sensing is a process of community-wide regulation of behaviors through the secretion and sensing of chemical autoinducers (AI). Because quorum sensing is implicated in pathologically relevant bacterial traits such as biofilm formation, conjugation, virulence factor production, and drug resistance, we are interested in developing quorum sensing inhibitors as potential therapeutic agents. In this effort, we conducted virtual screening against the audoinducer-2 (AI-2) receptor protein in Vibrio harveyi, LuxP. Among the 26 candidates selected for evaluation of their ability to inhibit AI-2 mediated quorum sensing, several showed good inhibitory activities in a bioluminescence assay (IC50: 40-50 micromolar). From these promising hits, 12 analogs were designed, synthesized, and evaluated. Several synthetic analogs showed improved activities. This presentation will discuss the design, synthesis, and structure-activity relationship studies of these AI-2 inhibitors.

MEDI 34

Pyrogallol and its analogs can antagonize bacterial quorum sensing in *Vibrio harveyi*

Nanting Ni[1]*, Gaurav Choudhary*[2]*, Minyong Li*[1]*, and Binghe Wang*[1]*. (1) Department of Chemistry, Georgia State University, 50 Decatur street, Atlanta, GA 30303, Fax: 404-413-5543, nni3@student.gsu.edu, (2) Department of Biology, Georgia State University, Atlanta, GA 30303*

Bacteria can coordinate community-wide behaviors through quorum sensing, i.e., the secretion and sensing of autoinducer (AI) molecules. Bacterial quorum sensing is implicated in the regulation of pathologically relevant events such as biofilm formation, bacterial virulence and drug resistance. Inhibitors of bacterial quorum sensing could therefore be useful therapeutics. We are interested in finding quorum sensing antagonists by using Vibrio harveyi a model organism. We have found several catechol compounds capable of antagonizing AI-2-mediated pathway in *V. harvey* with pyrogallol having the lowest IC_{50} at 2 μM. We postulate that the inhibitory effect of catechols was due to their ability to chelate boric acid the same way as DPD, the natural AI-2 molecule. It is interesting to note that these compounds also inhibit AI-1-mediated bacterial quorum sensing. Further studies are needed to fully understand their mechanisms of action.

MEDI 35

Synthesis of selectively functionalized steroid-2á, 3â-diol stereoisomer

Sunil K Upadhyay*, Department of Chemistry, University of New Orleans, LA-70148, 102-CSB, 2000-lakeshore drive, New Orleans, LA 70148, supadhya@uno.edu, and Branco S. Jursic, Department of Chemistry, University of New Orleans, New Orleans, LA 70148*

Natural sources for CAY-1 are laborious purification hampered further biological exploration of its antifungal activity and medical application. Hence there is demand for both structural simplification and preparation procedure for CAY-1 analogs as antifungal agents. Development of synthetic methodology for the preparation of mono OH-protected 2á, 3â-steroids, which are crucial building blocks for the preparation of potent antimicrobial therapeutic agents called saponins is of great importance. Previous studies shows that the 2á,3â-steroids part is essential part for good activity and the oligosaccharide part enhances solubility. We have developed highly efficient synthesis for mono protected-2á,3â-steroids isomer which in turn is very difficult as traditional methods will lead to the most favorable axial isomers due to steric reasons. Similar synthetic strategy was used for three different steroids from different sources to get the desired stereoisomer.

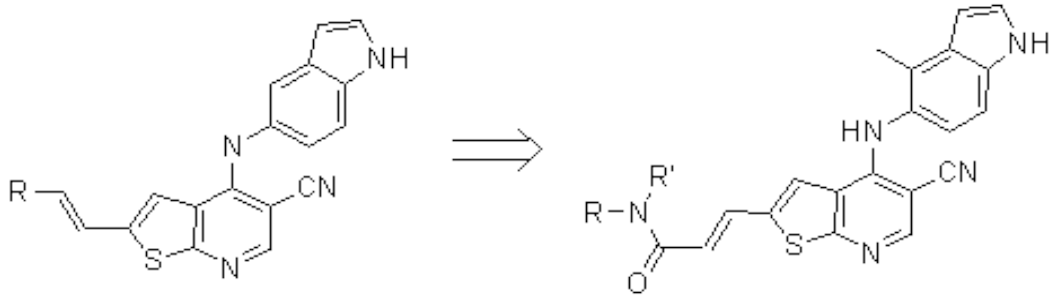
We have developed amino acid based functionalization of steroids with same isomers to improve water solubility. Various steroids from different sources have been used to make the similar isomers to explore their biological activity.

MEDI 36

2-Alkenyl thieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKCθ

L. Nathan Tumey[1]*, Diane H. Boschelli*[1]*, Divya Chaudhary*[2]*, and Julie Lee*[2]*. (1) Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, Fax: 845-602-5561, tumeyn@wyeth.com, (2) Inflammation, Wyeth Research, Cambridge, MA*

A series of 2-alkenyl thieno[2,3-b]pyridine inhibitors of PKCθ was synthesized as potential inflammatory modulators. This series led to the discovery of 2-alkenyl amides, which are exceptionally potent and selective inhibitors of PKCθ. The synthesis and SAR of this series will be presented in detail. In addition, kinase selectivity panel assays and pharmaceutical profiling data will be presented for selected compounds of interest.



MEDI 37

Synthesis and study of anti-inflammatory resolvins derived from docosahexaenoic acid

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

The beneficial health effects of docosahexaenoic acid (DHA) and other omega-3 fatty acids that occur in fish oils have been well documented. The detailed mechanisms of action of these lipids, however, have remained largely unknown until the recent discovery of several new lipid mediators derived from omega-3 fatty acids that were shown to exhibit potent anti-inflammatory properties, and to serve as promoters of the resolution of inflammation. These novel oxygenated polyunsaturated metabolites, termed resolvins, are formed in stereochemically defined form via enzymatic pathways, and behave as endogenous regulators of the inflammatory response. Herein, we report our studies on the chemical synthesis, stereochemical structure and biological actions of several members of D-series resolvins, which are derived from DHA.

MEDI 38

Synthesis and study of neuroprotectin D1, a potent antii-nflammatory lipid mediator

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It is now well recognized that inflammation plays a key role in a number of major neurodegenerative diseases, including Alzheimer's disease, stroke, and age-related macular degeneration. The recent discovery of a new metabolic pathway of docosahexaenoic acid (DHA) led to the identification of potent bioactive metabolites with cell protective functions. Herein, we present our investigations on the chemical synthesis, stereochemical structure and biological actions of neuroprotectin D1, a potent anti-inflammatory molecule derived from DHA via enzymatic biosynthesis which modulates cell survival in neural and retinal cells.

MEDI 39

Synthesis and study of polyisoprenyl phosphate analogs as regulators of acute inflammation

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Acute tissue injury elicits rapid recruitment of neutrophils, which play a central role in host defense and the early stages of the inflammatory response. Recent findings that certain polyisoprenyl phosphates, such as presqualene diphosphate, exist in cell membranes and act as endogenous downregulatory signals in neutrophils, have provided a novel mechanism for controlling these neutrophil actions, and for regulating the generation of reactive oxygen species. Herein, we present our studies on the synthesis of analogs of anti-inflammatory polyisoprenyl phosphates and their potential role in controlling acute inflammation.

MEDI 40

Preparation and lead optimization of potent neurokinin-2 receptor antagonists

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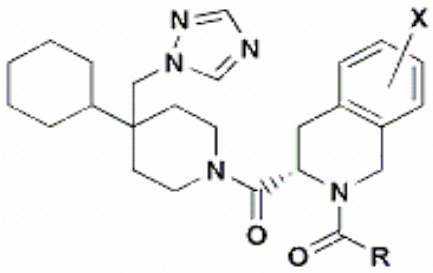
The Mammalian Tackykinins - or Neurokinins - including Neurokinin 2 (NK-2) are a family of small peptides widely distributed in the central and peripheral nervous system. The recently

established presence of NK-2 in the CNS suggests potential anxiolytic/antidepressant properties for NK-2 receptor antagonists. Therefore, the objective of this early phase research program was to develop a selective, potent and orally - active Neurokinin 2- receptor antagonist for the treatment of depression. The design, synthesis and evaluation of potent NK-2 receptor antagonists for the treatment of depression are described. Substituted piperidinyl 3,4-dihydroisoquinoline amides 1 were formally derived by a combination of classic SAR and solution phase library synthesis. Some members of this chemical series showed significant selectivity and binding affinity for the cloned human NK-2 receptor.



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MEDI 41

Novel 5-HT2A/D2/Sigma receptor ligands: Psychiatric disorder treatment agents

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Agents potently acting on the sigma receptors may be useful in the therapy of CNS diseases. Also, creating a specific drug for sigma receptor interaction and finding the novel pharmacological effect are important for developing new types of drugs. In our research strategy for new CNS drugs, we designed a novel ligand for sigma receptors and 5-HT2A/D2 receptors, conventional mechanism of atypical antipsychotics, which has potent affinity for triple mechanism. Potential applications of triple mechanism ligands are the treatment of depression, psychosis, and so on. Through our research strategy, we discovered that members of this class compounds demonstrate to be effective for schizophrenia and depression. This poster will highlight the SAR and biological data of these compounds.

MEDI 42

Synthesis and structure-activity relationship of a series of alpha-azole substituted phenyl alkyl amines as 5-HT2A/D2 receptor ligands: Potential psychosis treatment agents

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The discovery and development of MNRA (Mixed Neurotransmitter Receptor Antagonists) as potential anti-psychosis agents are an attractive approach since many antipsychotics are known as serotonin / dopamine antagonists. By applying our library, we have identified a series of alpha-azole substituted phenyl alkyl amines as a 5-HT2A/D2 ligands and psychosis disorder treatment agents. The synthesis and biological activity of these compounds will be presented.

MEDI 43

Structure activity relationship and pharmacological evaluation of carbamic acid benzoyl piperidine analog: YKP1358, novel atypical antipsychotics

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The development of atypical antipsychotics was an important milestone in the history of psychiatry, because it brought effective treatment options with reduced risks for adverse events. Unfortunately, current atypical antipsychotics did not clearly solve the side effect issues such as extrapyramidal syndrome, metabolic disorder. These side effects were due to low selectivity to side effect inducing receptor binding affinity / target receptor binding affinity. A clean ligand for target receptor is required for medical unmet need satisfaction. As a result of intensive and thorough research, we have found that a novel atypical antipsychotics, YKP1358, is more potent in efficacy and shows cleaner side effect profile than current atypicals. The SAR, antipsychotic efficacy and side effect profile of this novel compound will be presented along with a comparison with atypical antipsychotics.

MEDI 44

Synthesis and SAR of pyridinyl-pyrazole derivatives as selective $5HT_{2A}$ inverse-agonists for platelet aggregation

***Peter I. Dosa**, Bradley R. Teegarden, Jarrod Davidson, Martin Casper, John Adams, Juan Ramirez, William Thomsen, and Diane Yuskin, Arena Pharmaceuticals, Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121, pdosa@arenapharm.com*

Inverse-agonists of the 5-HT_{2A}-receptor subtype are known to alleviate negative symptoms in schizophrenia, influence sleep patterns, and reduce the aggregation of platelets. As part of our investigations on 5-HT_{2A} inverse-agonists, a series of pyridinyl-pyrazole derivatives was identified. Several compounds were determined to be potent in both a 5-HT_{2A} binding assay and a platelet aggregation assay and were inactive at both the 5-HT_{2B} and 5-HT_{2C} serotonin receptors. The synthesis and SAR of this series will be presented.

MEDI 45

Discovery and SAR of highly selective 5-HT_{2A} receptor subtype inverse-agonists for inhibition of platelet aggregation

***Yifeng Xiong**, Bradley R. Teegarden, Jin Sun Choi, Sonja Strah-Pleynet, Marc Decaire, Honnappa Jayakumar, Peter I. Dosa, Martin Casper, Lan Pham, Konrad Feichtinger, Brett Ullman, John Adams, Juan Ramirez, William Thomsen, Diane Yuskin, Michael Morgan, Abu Sadeque, Weichao Chen, Hussien Al-Shamma, Graeme Semple, Robert R. Webb, and Daniel Connolly, Arena Pharmaceuticals, Inc, 6166 Nancy Ridge Drive, San Diego, CA 92121, yxiong@arenapharm.com*

5-HT_{2A} receptor inverse-agonists have been proposed to be useful for the treatment of CNS disorders such as schizophrenia, depression, anxiety and insomnia. In addition, peripherally restricted 5-HT_{2A} inverse-agonists have potential for the treatment of arterial thrombotic disease by inhibiting platelet aggregation. We have identified a series of potent and highly selective pyrazole derivatives that have potent platelet inhibition properties. The design and SAR of these compounds will be discussed.

MEDI 46

Targeting serotonin transporter channel activity aids in the development of therapeutic drugs for clinical depression

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Clinical depression is a psychiatric disorder characterized by a decrease in serotonin levels. Current antidepressants, such as fluoxetin, act by blocking the serotonin transporter channel preventing the influx of serotonin into the post-synaptic neuron therefore increasing the level of serotonin in the synapse alleviating the symptoms of depression. This project focuses on the development of compounds that target the channel activity of serotonin transporter. This targeting mechanism increases the resting potential of pre-synaptic neuron enhancing the likelihood of action potential to release serotonin by the natural mechanism of vesicle diffusion.

MEDI 47

Tetrahydroindolizinone NK1 antagonists: SAR at 7-position

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A new class of potent NK1 receptor antagonists with a tetrahydroindolizinone core has been identified. This series of compounds demonstrated improved functional activity as compared to previous 5,5-fused pyrrolidine lead structures. SAR at the 7-position of the tetrahydroindolizinone core will be presented. A number of compounds displayed high NK1 receptor occupancy at both 1h and 24h in a gerbil foot tapping model. One of these compounds with high NK1 binding affinity, excellent selectivity for other NK receptors and promising in vivo properties will be discussed in detail.

MEDI 48

Tuning affinity on a tropane framework for dopamine D2/D3 receptor subtype ligands

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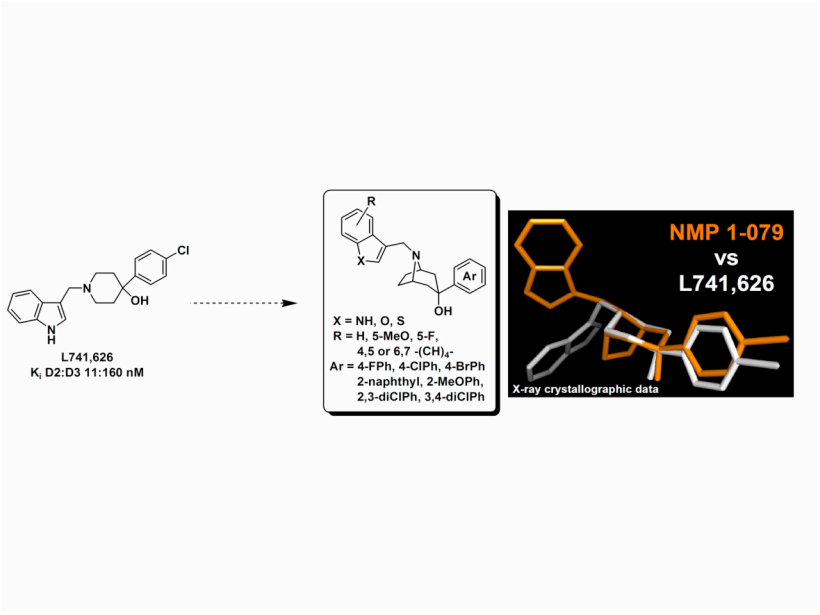
The dopamine D2-like receptor family is comprised of the D2, D3 and D4 subtypes and discovering subtype-selective ligands with which to differentiate the roles of these potentially drugable targets in neuropsychiatric disorders and drug addiction has been a focus of recent investigation. The D2-selective antagonist L741,626 provided a lead template for chemical modification, and a variety of analogues were synthesized wherein the central piperidine ring was replaced by a bicyclic tropane ring system. Overall, these bicyclic compounds displayed structure-activity relationships quite different from those derived in the analogous piperidine series. X-Ray crystallographic data revealed differences in the spatial arrangement of pharmacophoric elements in the piperidine v. tropane-ring analogues that resulted in compounds with subnanomolar affinities for the D2 and D3 receptor subtypes.



MEDI 49

Design, synthesis and evaluation of novel azole nucleoside analogs for their activity against hantaviruses

Sidath C. Kumarapperuma[1]*, Marjan Jeselnik*[1]*, Dong-Hoon Chung*[2]*, Yanjie Sun*[2]*, Qianjun Li*[2]*, Yong-Kyu Chu*[2]*, William B. Parker*[2]*, Colleen B. Jonsson*[2]*, and Jeffrey B. Arterburn*[1]*. (1) Department of Chemistry and Biochemistry MSC 3C, New Mexico State University, Las Cruces, NM 88003, Fax: 575-646-2649, sidath@nmsu.edu, (2) Department of Biochemistry and Molecular Biology, Southern Research Institute, Birmingham, AL 35205*

Hantaviruses are tri-segmented negative stranded RNA viruses that are distributed worldwide and cause two acute febrile diseases in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). The nucleoside analog, ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), shows promise in reducing the mortality rate when administered early following infection. We designed, modeled and synthesized a series of isosteres, homologated analogs, and substituted derivatives possessing altered steric and hydrogen-bonding profiles. Since the conversion of ribavirin to the monophosphate by adenosine kinase (ADK) is the rate-limiting step in the activation of this broad spectrum antiviral drug, we evaluated these compounds as substrates for ADK and their binding modes with human ADK using a computational docking study. The antiviral activity of these compounds was evaluated in vitro against Hantaan virus and Andes virus and in vivo against Hantaan virus. We have identified a promising new compound that exhibits potent hantaviral antiviral activity.

MEDI 50

Homology modeling and molecular dynamics simulation of Hepatitis B virus DNA polymerase: Validation using molecular docking

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Hepatitis B is among the top ten infectious diseases in the world. All nucleotide/nucleoside analogs approved for the treatment of HBV infections target HBV DNA polymerase (HDP). We built a three-dimensional comparative model of HDP based on an HIV-RT X-ray structure using multiple alignment followed by minimization, validation and molecular dynamics simulation. The resultant model demonstrates reasonable stereochemical properties. Further validation was carried out using docking of known inhibitors such as lamivudine into the active site.

MEDI 51

Design and synthesis of 3-deazaneplanocin A derivatives

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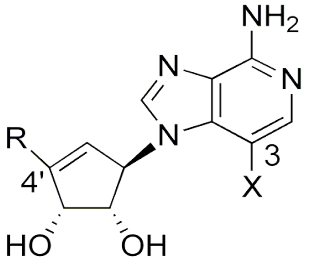
The significant antiviral properties of 3-deazaadenine nucleosides has been attributed to their potent inhibition of AdoHcy hydrolase. Within this category, the carbocyclic nucleoside 3-deazaneplanocin A (**1**) has shown particular promise and, consequently, provided a fruitful foundation for a wealth of structural units with potential antiviral properties. In the rational design of derivatives based on **1**, modifications at the C-3 and C-4' positions have been recognized by us and others as important means to promising new lead compounds. Derivatives of **1** possessing bromo (**2**) or methyl (**3**) groups at the C-3 position were sought as important targets. Precedent suggested compound **4**, which lacks the C-4' hydroxymethyl, would also be relevant to this study. A convergent synthesis of this series of compounds and their antiviral activities will be presented. This research was supported by funds from DHHS (AI 56540).



1, X=H, R=CH_2OH;
2, X=Br, R=CH_2OH;
3, X=Me, R=CH_2OH;
4, X=Br, R=H.

MEDI 52

Discovery of novel oxadiazolyl phenyl derivatives as herpes helicase-primase inhibitors with potent activity against HSV and VZV

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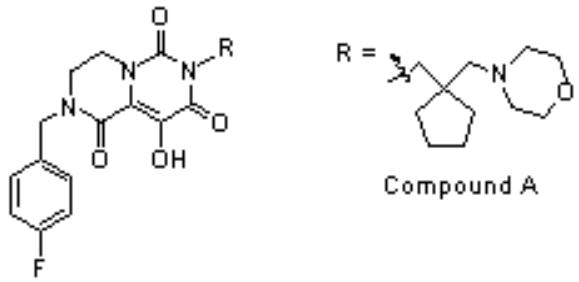
Herpes helicase-primase inhibitor is the potential therapeutic target for a novel antiherpesvirus agent, because it is essential for a viral DNA replication. Some helicase-primase inhibitors have been reported to possess antiviral activities against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). In our research for antiherpesvirus agent, a series of novel oxadiazolyl phenyl derivatives was identified as a helicase-primase inhibitor and demonstrated potent antiviral activities against varicella zoster virus (VZV) as well as HSV-1 and -2 in vitro. Some of these derivatives significantly inhibited the development of skin lesion in hairless mice cutaneously infected with HSV-1 at a dosage of 10 mg/kg by oral administration. These results suggest that these herpes helicase-primase inhibitors might be useful for the treatment of infectious diseases related to HSV-1, -2, and VZV such as herpes labialis, genitalis and zoster. The synthesis and structure-activity relationships of oxadiazolyl phenyl derivatives will be presented.

MEDI 53

Design and synthesis of a series of 7-substituted 2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,6,8(7H)-trione inhibitors of HIV-1 Integrase and viral replication in cells

*Mark W. Embrey[1], H. Marie Langford[1], **Theresa Booth**[2], Peter Williams[3], John Wai[1], Joseph Vacca[1], Daria J. Hazuda[4], Michael D. Miller[5], Peter J. Felock[6], Kara A. Stillmock[7], William A. Schleif[8], Lori J. Gabryelski[5], Lixia Jin[9], Joan D. Ellis[10], and Terry A. Lyle[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, Fax: 215-652-3971, mark_embrey@merck.com, (2) Department of Medicinal Chemistry, Merck & Co., Inc, Merck Research Laboratories, West Point, PA 19486, (3) Department of Medicinal Chemistry, Merck and Company, West Point, PA 19486, (4) MRL, West Point, PA, USA, Upper Gwynedd, PA 19454-2505, (5) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (6) Antiviral Research, Merck and Co. Inc, PO Box 4 West Point, PA 19486-0004, (7) MRL, West Point, PA, USA, West Point, PA 19486, (8) Vaccine and Biologics Research, Merck Research Laboratories West Point, West Point, PA 19486, (9) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (10) Drug Metabolism and Pharmaceutical Research, Merck Research Laboratories, West Point, PA 19486*

A series of novel bicyclic 2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrazino[1,2-c]pyrimidine-1,6,8(7H)-trione HIV-1 integrase inhibitors was designed and synthesized. These compounds selectively inhibit the stand transfer step of integration and are active against HIV-1 in cell culture. Further exploration in this series led to Compound A which exhibits moderate antiviral potency [IC50 250 nM (10% FBS), IC95 813 nM (50% NHS)] and good pharmacokinetics in rat.



Compound A

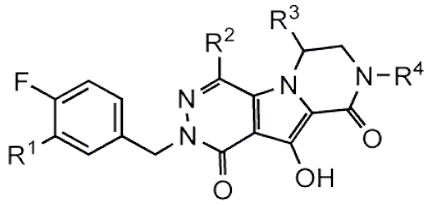
MEDI 54

Tricyclic 10-hydroxy-7, 8-dihydropyrazinopyrrolopyrazine-1, 9-diones as potent, orally bioavailable HIV-1 integrase strand transfer inhibitors

***Catherine M. Wiscount**[1], Lekhanh O. Tran[1], Mark W. Embrey[1], Thorsten E. Fisher[1], Vanessa Sherman[1], Donnette D. Staas[1], Peter Williams[1], John Wai[1], Terry A. Lyle[1], Joseph Vacca[1], Peter J. Felock[2], Marc V. Witmer[2], Lori Gabryelski[2], Michael D. Miller[2], Daria J. Hazuda[3], Linda Ecto[2], WA. Schleif[2], Christopher J. Kochansky[4], and M. Reza Anari[5]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3 Sumneytown Pike, PO Box 4, West Point, PA 19446, Fax: 215-652-3971, cathy_wiscount@merck.com, (2) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) MRL, West Point, PA, USA, Upper Gwynedd, PA 19454-2505, (4) Drug Metabolism, Merck Research*

Laboratories, West Point, PA 19486, (5) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486

A series of novel tricyclic 10-hydroxy-7, 8-dihydropyrazinopyrrolopyrazine-1, 9-dione HIV-1 integrase strand transfer inhibitors is described. Balancing overall lipophilicity with R group modifications was an important consideration in order to obtain high potency for inhibiting HIV-1 replication in cell culture in the presence of human serum. Excellent pharmacokinetic properties in rats was achieved with several analogs in which R^2 is hydrogen, and small alkyl substituents at R^3 and R^4 provided good activity against a panel of integrase mutants raised in the laboratory with different integrase inhibitors. Synthesis methods and structure-activity relationships for compounds in this structural series will be presented.

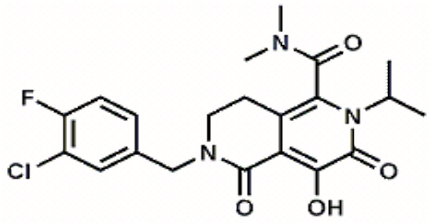


MEDI 55

Discovery and synthesis of a potent long-acting inhibitor of HIV integrase

Debra S. Perlow[1]*, Melissa Egbertson*[1]*, John Wai*[1]*, Linda S. Payne*[1]*, Wei Han*[1]*, Cuthbert D. Martyr*[2]*, Vanessa E. Obligado*[1]*, Kristi L. Hoffman*[1]*, Joseph Vacca*[1]*, Daria J. Hazuda*[3]*, Peter J. Felock*[4]*, Kara A. Stillmock*[4]*, William A. Schleif*[4]*, Lori Gabryelski*[4]*, M. Reza Anari*[5]*, Joan Ellis*[5]*, Marc V. Witmer*[4]*, Michael Miller*[4]*, Nancy N. Tsou*[6]*, Mirlinda Biba*[6]*, Christopher J. Welch*[6]*, and Terry A. Lyle*[1]*. (1) Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3, PO Box 4, West Point, PA 19486, Fax: 215-652-3971, debbie_perlow@merck.com, (2) Department of Chemistry, Purdue University, (3) Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, (4) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (5) Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, (6) Department of Process Research, Merck Research Laboratories, Rahway, NJ 07065-0900*

In the life-cycle of HIV, integration of viral DNA into the host genome is necessary for viral replication to occur. The HIV Integrase enzyme is required in the viral strand transfer step of the integration process (Hazuda et al, Science 2004, 305, 258). Inhibition of the HIV Integrase enzyme step has been shown to inhibit viral replication both in the laboratory and in HIV infected patients. We will describe the discovery and synthesis of Compound A, a potent, long-acting tetrahydronaphthyridine inhibitor of HIV Integrase.



Compound A

MEDI 56

Synthesis of 5,6-dihydropyran-2-ones as potential inhibitors of HIV-1 protease

Jesse L. Nye *and Levente Fabry-Asztalos, Department of Chemistry, Central Washington University, 400 East University Way, Ellensburg, WA 98926*

HIV/AIDS has affected about 40 million people. One type of drug that is used to treat HIV/AIDS is a protease inhibitor. HIV-1 protease eventually becomes resistant to the inhibitors; therefore, new drugs are needed. This research builds on a previous research effort, in which structures for HIV-1 protease inhibitors were designed using molecular modeling methods and a Quantitative Structure-Activity Relationship (QSAR) study was performed using a fuzzy neural network to predict their biological activities. We hope that these inhibitors will possess better inhibitory properties, have increased bioavailability, and possibly have less toxicity than the inhibitors currently in use. These novel structures are currently being synthesized using known methodologies. Once synthesized their inhibitory values will be determined and then compared to inhibitory values predicted by the neural networks. We hope that these compounds will become lead compounds for further drug discovery for HIV/AIDS.

MEDI 57

Synthesis and antiviral properties of 8-aza-7-deaza-Aristeromycin and Neplanocin

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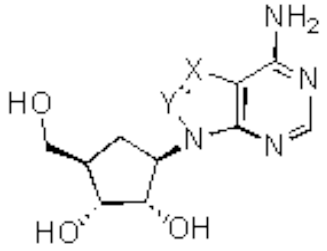
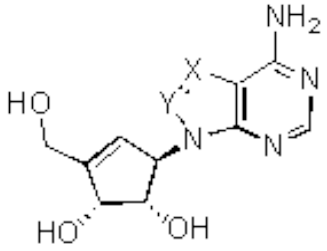
Our laboratory has an ongoing interest in the design and synthesis of adenine-derived carbocyclic nucleosides as a consequence of their anticipated antiviral properties arising from inhibition of viral mRNA processing. Prominent compounds in this series area are aristeromycin (1) and neplanocin (2). To vary these structural prototypes, the 8-aza-7-deaza analogues 3 and 4 became target compounds. The synthesis of 3 and 4 and their antiviral properties will be reported. This research was supported by funds from the Department of Health and Human Services (AI 56540).



1, X=N; Y=CH
3, X=CH;Y=N



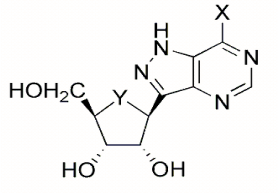
2, X=N; Y=CH
4, X=CH;Y=N

MEDI 58

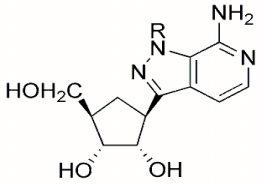
Preparation and antiviral activity of N-1 / N-2 methyl-4-deazacarbaformycin

***Yan Zhang**, Haisheng Wang, and Stewart W. Schneller, Department of Chemistry and Biochemistry, Auburn University, 179 chemistry building, Auburn, AL 36849, yzz0001@auburn.edu*

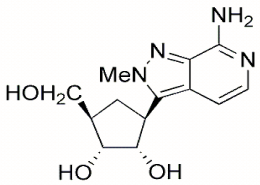
The medicinal potential of the naturally occurring C-nucleoside formycin (1) is limited by its metabolism by adenosine deaminase to formycin B (2). In our pursuit of the carbocyclic nucleoside congener of 1 (that is, 3) we sought the 4-deaza analog 4 with the possibility it would not be a substrate for the deaminase by analogy to 3-deazaadenosine. As part of that program, the N-1 and N-2 methyl derivatives of 4 (5 and 6) arose as relevant because of the established biological properties for the corresponding formycin methylated compounds. Our investigations of 5 and 6 will be presented. This research was supported by funds from the Department of Health and Human Services (AI 56540).



1, X=NH_2;Y=O
2, X=OH;Y=O
3, X=NH_2;Y=CH_2



4, R=H
5, R=Me



6

MEDI 59

Early screening for PXR- and CAR-mediated ADME-Tox liabilities: New fluorescence-based ligand binding and coregulator recruitment assays

***William J. Frazee**, Upinder Singh, Bryan D. Marks, Hildegard C. Eliason, Deborah K. Stafslien, Jill K. Wolken, and Kurt W. Vogel, Invitrogen Discovery Sciences, 501 Charmany Drive, Madison, WI 53719, Fax: 608-204-5200, jack.frazee@invitrogen.com*

Pregnane X receptor (PXR or SXR) and constitutive androstane receptor (CAR) are major regulators of drug metabolizing enzymes and transporters, playing key roles in the clinical efficacy and toxicity of drug candidates, including drug interactions. Like other nuclear receptors, the activities of PXR and CAR are modulated both by (endogenous or exogenous) ligands and by endogenous protein coregulators. We have developed a new competitive binding assay for PXR and a new coregulator recruitment assay for CAR. Ligand binding to PXR is detected by displacement of a fluorescent PXR ligand (tracer) from the receptor, resulting in loss of the FRET signal between the tracer and a terbium-labeled antibody to a GST tag on PXR. Modulation of coregulator peptide binding is detected by changes in the FRET signal between a terbium-labeled antibody to a GST tag on CAR and a fluorescein-labeled coregulator peptide. These assays enable the rapid evaluation of compounds for potential PXR- and CAR-mediated liabilities.

MEDI 60

Fluorescence detection of nucleic acids triggered by DNA-templated chemical reaction

Kazuhiro Furukawa[1]*, Hiroshi Abe*[2]*, Wang Jin*[2]*, Kazuma Oki*[1]*, Miwako Uda*[1]*, Satoshi Tsuneda*[3]*, and Yoshihiro Ito*[2]*. (1) Nano Medical Engineering Laboratory, RIKEN, Waseda University, 2-1, Hirosawa, Wako-Shi, Saitama 351-0198, Japan, k-furukawa@riken.jp, (2) RIKEN, (3) Waseda University*

Sequence specific detection of nucleic acids is crucial for genome study, for mRNA monitoring in living cells, and for disease diagnosis. Recently, DNA-templated chemical reactions, which produce a signal as ligation process through a quenching, FRET mechanism, catalytic hydrolysis, or catalytic transfer between two probes, are becoming general approaches for the detection of oligonucleotide sequences. However, it was difficult to eliminate the background fluorescence when the target DNA or RNA was absent.

Here, we developed a new nonenzymatic phosphorothioate–iodoacetyl ligation system combined with FRET system for fluorescence detection of nucleic acids. The new chemical system discriminated a single mismatch of DNAs. In addition, a novel fluorescence activation system, which minimized the background fluorescence in the absence of target DNA, was also developed.

MEDI 61

New fluorescence-based assays for identification and characterization of selective PPARα, $\delta(\beta)$, and γ ligands

Upinder Singh*, Bryan D. Marks, Hildegard C. Eliason, Deborah K. Stafslien, Jennifer M. Wilkinson, Therese De Rosier, Tina M. Hallis, Kurt W. Vogel, Guobin Miao, and William J. Frazee, Invitrogen Discovery Sciences, 501 Charmany Drive, Madison, WI 53719, Fax: 608-204-5200, upinder.singh@invitrogen.com*

The peroxisome proliferator-activated receptors (PPARs), important regulators of lipid metabolism, have three sub-types with different biological functions and tissue distributions: PPARα, $\delta(\beta)$, and γ. Like other nuclear receptors, the activities of the PPARs are regulated both by (endogenous or exogenous) ligands and by endogenous protein coregulators (coactivators or corepressors). We have developed new competitive binding and coregulator interaction assays for each PPAR sub-type using LanthaScreen™ TR-FRET technology and cellular b-lactamase reporter gene assays using GeneBLAzer® technology. Ligand binding to PPARs is detected by displacement of a fluorescent PPAR ligand (tracer) from the receptor, resulting in loss of the FRET signal between the tracer and a terbium-labeled antibody to the GST tag on PPAR. Modulation of coregulator peptide binding is detected by changes in the FRET signal between a terbium-labeled antibody and a fluorescein-labeled coregulator peptide. These assays enable the discovery and evaluation of compounds that bind to and modulate PPAR activity.

MEDI 62

Caco-2 cell based assay development for tight junction modulating peptides

Kelly M. Kitchens*, Shobha Gopalakrishnan, John Vere, Rosa Carrasco, Min Li, Ed Oliver, Mark Ginski, Niranjan Pandey, Blake Paterson, Sefik S. Alkan, and Amir P. Tamiz, Alba Therapeutics Corporation, 800 W. Baltimore Street, Suite 400, Baltimore, MD 21201*

Tight junctions maintain barrier integrity of the intestinal epithelium by regulating paracellular permeability. Epithelial barrier dysfunction is associated with a host of inflammatory and autoimmune diseases including celiac disease, irritable bowel disease, and type I diabetes. We developed in-vitro assays to study a series of paracellular permeability modulating peptides derived from zonula occludens toxin (ZOT), a protein secreted by Vibrio cholerae that transiently and reversibly opens epithelial tight junctions. The following techniques were applied using Caco-2 cells to screen various peptides for optimal compound selection: a) permeability and transepithelial electrical resistance (TEER) measurements in 24-well Transwell® format; b) cytotoxicity determination using CellTiter-Glo® cell viability assay; and c) tight junction protein reorganization using fluorescence microscopy. Our strategy has successfully identified non-toxic peptides that selectively modulate paracellular permeability for the potential treatment of autoimmune and inflammatory diseases.

MEDI 63

Identification and hit to head optimization of a series of pkc theta inhibitors for t cell mediated diseases

Magda Asselin*, Exploratory chemistry, Wyeth Research, 401 N Middletown Rd, Pearl River, NY 10965, Fax: 845-602-5561, asselim@wyeth.com*

1Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd. Pearl River, NY 10965. 2Inflammation and 3Chemical and Screening Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, 4Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426.

Protein Kinase C theta (PKCtheta) is a critical enzyme that regulates T cell function and is required for TCR signaling leading to IL-2 production and proliferation. T cells from mice deficient in PKC theta have severely impaired T cell responses and reduced IL-2 production. The Th2 cytokines IL-4, IL-5 and IL-13 drive the pathophysiology of asthma by contributing to airway inflammation and obstruction, and IgE production. Th2 cytokine production is also significantly reduced in PKC theta deficient Th2 cell responses in vitro and in vivo. In addition, PKC theta deficient mice mount a significantly reduced lung inflammation response to antigen challenge relative to normal wild type mice, and also exhibit reduced inflammation in rodent models of arthritis and autoimmune disease. Therefore inhibitors of PKC theta may have therapeutic potential in treatment of asthma and T cell mediated immune diseases.

A high-throughput screen was performed to identify PKCtheta inhibitors. The hits were characterized and prioritized based on enzyme and cell potency, evidence of binding to target, and selectivity against a panel of kinases. This poster will describe the characterization and initial hit-to-lead optimization of these novel and small molecule inhibitors of PKC theta.

MEDI 64

Indole-phenylacetic acid inhibitors of CRTH2

***Michael G. Johnson**, Jiwen Liu, An-Rong Li, Yingcai Wang, Wang Shen, Sarah Lively, Yongli Su, Bettina van Lengerich, Xuemei Wang, Sujen Lai, Matt Brown, Shauna Lawliss, Ying Sun, Qingge Xu, Tassie Collins, Jay Danao, Lisa Seitz, Mark Grillo, Jill Wait, and Julio Medina, Amgen Inc, 1120 Veterans Blvd, San Francisco, CA 94080, mgjohnso@amgen.com*

CRTH2 mediates inflammatory cell trafficking and has been identified as a target for the treatment of asthma. As part of our effort to develop CRTH2 antagonists we discovered a potent series of indole-phenylacetic acid derivatives that inhibit binding of 3H-PGD2 to CRTH2 receptors on 293 cells and have favorable pharmacokinetic profiles in the rat. However, the initial representative compounds of this class displayed CYP 3A4 time-dependent inhibition. Here we describe the optimization of this series of indole derivatives that led to the discovery of potent CRTH2 antagonists devoid of time-dependent 3A4 inhibition. These compounds and their analogs may be useful tools for the evaluation of CRTH2 activity in vivo.

MEDI 65

Synthesis and evaluation of a series of 7-substituted-8-azaquinazolinone CXCR3 antagonists

***Darin J. Gustin**[1], Phillipe Bergeron[1], Johann Chan[2], Xiaoqi Chen[1], Jeff Diegnan[1], Du Xiaohui[1], Jeff MIhalic[1], Theresa Carabeo[1], Collins Tassie[1], Lemon Brian[1], George Tonn[1], and Julio C. Medina[1]. (1) Amgen Inc, 1120 Veterans Blvd., South San Francisco, CA 94080, dgustin@amgen.com, (2) Amgen Inc, Thousand Oaks, CA 91320*

CXCR3 is a Gi coupled GPCR receptor that plays an important role in the recruitment of T-cells to sites of inflammation. Considerable evidence demonstrates that blocking T-cell infiltration has a benefit in the treatment of immune response mediated diseases. Thus, it is expected that the development of CXC3 antagonists may find use in the treatment of rheumatoid arthritis (RA) multiple sclerosis (MS) and cardiac transplant (allograph) rejection. We have previously described a series of 8-azaquinazolinone based CXCR3 antagonists. As part of our study of these inhibitors, a series of 7-substituted-8-azaquinazolinones were prepared and evaluated for CXCR3 binding affinity and for the inhibition of CXCR3 mediated cell migration of human PBMC cell induced by ITAC. It was found that certain C(7) substituents provided significant potency improvement in CXCR3 affinity while maintaining good in vivo PK parameters.

MEDI 66

Imidazoacridinones: Potent inhibitors of FLT3 for the treatment of autoimmune diseases

***Kenneth W. Duncan**, Xinqin Fang, Jennifer L. Christensen, MyDoanh Chau, Keith J. Goodman, Ann Locniskar, and Alfred M. Ajami, Xanthus Pharmaceuticals Inc, 300 Technology Square, Cambridge, MA 02139, kenneth.duncan@xanthus.com*

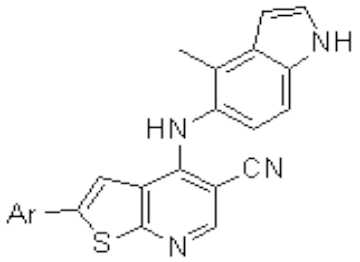
FMS-like tyrosine kinase 3 (FLT3) regulates the maturation of dendritic cells; a key pathway applicable to various autoimmune diseases. Symadex™ (C1311) is a member of a novel series of potent, imidazoacridinone based inhibitors of FLT3. In contrast to other FLT3 inhibitors currently under clinical investigation, the imidazoacridinone series do not inhibit c-KIT and PDGFR. In this presentation we will illustrate the development of novel imidazoacridinone core scaffolds suitable for targeted library synthesis and the SAR of non-cytotoxic Symadex™ analogues for the treatment of autoimmune diseases.

MEDI 67

Synthesis and evaluation of 2-aryl-thieno[2,3-b]pyridine-5-carbonitriles as PKCtheta inhibitors

Biqi Wu[1]*, Diane H. Boschelli*[1]*, Julie Lee*[2]*, Xiaoke Yang*[2]*, and Divya Chaudhary*[2]*. (1) Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, (2) Inflammation, Wyeth Research, Cambridge, MA*

PKCtheta is a serine/threonine kinase that plays an important role in T-cell activation. Therefore, small molecule inhibitors of PKCtheta may be useful for the treatment of autoimmune diseases. The thieno[2,3-b]pyridine-5-carbonitrile ring system is a useful template for inhibitors of this kinase. An indolylamino substituent at C-4 of the core provides potent inhibition of PKCtheta.We report here further optimization of this series, focusing on variation of the aromatic group at C-2. The synthetic routes used to prepare these analogs will be presented. Inhibition of PKCtheta activity by these compounds and their selectivity versus PKCdelta will also be reported.



MEDI 68

Synthesis and pharmacology of the novel HA-MTX conjugate (DK226) for osteoarthritis

Haruhiko Sato[1]*, Akira Okamachi*[1]*, Takashi Emura*[1]*, Akie Honma*[1]*, Takenori Ishizawa*[1]*, Tatsuya Kato*[1]*, Tetsu Matsuura*[1]*, Shigeo Sato*[1]*, Tatsuya Tamura*[1]*, Yoshinobu Higuchi*[1]*, Tomoyuki Watanabe*[1]*, Hidetomo Kitamura*[1]*, Kentaro Asanuma*[1]*, Tadao Yamazaki*[1]*, Masahisa Ikemi*[2]*, Hironoshin Kitagawa*[2]*, Tadashi Morikawa*[2]*, Kazuaki Maeda*[2]*, Koichi Takahashi*[2]*, Kenji Nohmi*[2]*, Noriyuki Izutani*[2]*, Makoto Kanda*[2]*, and Ryochi Suzuki*[2]*. (1) Research division, Chugai Pharmaceutical Co., Ltd, 1-135, Komakado, Gotemba, Shizuoka 412-8513, Japan, Fax: +81-550-87-5326, satohrh@chugai-pharm.co.jp, (2) Research Center, Denki Kagaku Kogyo K. K, Machida, Tokyo 194-8560, Japan*

DK226 is a conjugate of HA and methotrexate (MTX) designed to combine the advantages of the two agents and overcome their shortcomings. Since MTX has a potent anti-inflammatory effect, the binding ratio of MTX needed for DK226 to exert sufficient efficacy is as low as 3%, and that makes it possible for the conjugate to preserve properties of HA, such as high molecular weight and visco-elasticity.

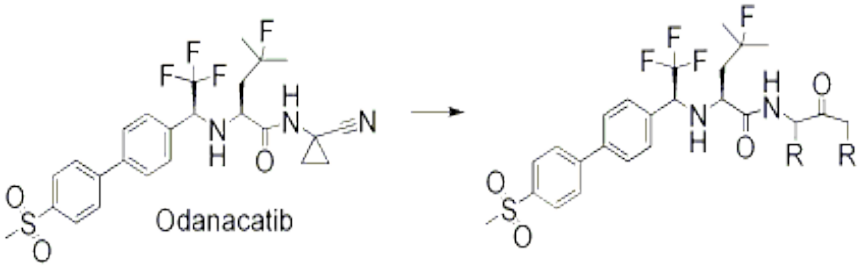
In rat arthritic models, it was demonstrated that DK226 has anti-inflammatory effects and a superior analgesic effect to conventional HA. No systemic and local toxicity have been observed in preliminary toxicity studies. DK226, therefore, could provide a safe and effective new therapy for the treatment of OA.

MEDI 69

Investigation of ketone warheads as alternatives to the nitrile for preparation of potent and selective cathepsin k inhibitors

Michael J. Boyd*, Sheldon N. Crane, Joel Robichaud, John Scheigetz, Cameron Black, Nathalie Chauret, Qingping Wang, Frédéric Massé, and Renata Oballa, Medicinal Chemistry, Merck Frosst, 16711 Trans Canada, Kirkland, QC H9H 3L1, Canada, Fax: 514-428-4900, michael_boyd@merck.com*

Osteoporosis is a condition where bone becomes thin, weak and brittle. Consequently, osteoporosis can significantly increase the risk of bone fractures. The condition is caused by an imbalance between bone formation and bone resorption and it is believed that the lysosomal cysteine protease cathepsin K (Cat K) plays a key role in the degradation of the bone matrix. More specifically, Cat K is involved in the degradation of type I collagen which is the major component of the organic bone matrix. It has been hypothesized that Cat K inhibitors could therefore be used in the treatment of osteoporosis, and there has been considerable effort directed towards the development of potent and selective Cat K inhibitors over the last decade. Most reported inhibitors of Cat K contain electrophilic “warheads” which covalently bind to the catalytic Cys 25 residue, such as nitriles and ketones. Recently, we have reported the development of odanacatib (MK-0822), a reversible, non-basic, potent and selective nitrile inhibitor of Cat K. Amino ketone warheads were explored as alternatives to the nitrile group of odanacatib. The ketones explored are potent and selective inhibitors of cathepsin K; however, they are generally less potent and selective than odanacatib. The SAR of the series of ketones will be discussed, as well as the effects of the nitrile replacement on metabolism and pharmacokinetics.



MEDI 70

Synthesis of bisphosphonates designed for selective attachment to proteins

Jivan Yewle[1]*, Yinan Wei*[1]*, David Puleo*[2]*, and Leonidas Bachas*[1]*. (1) Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055, (2) Center for Biomedical Engineering, University of Kentucky, Lexington, KY 40506-0070*

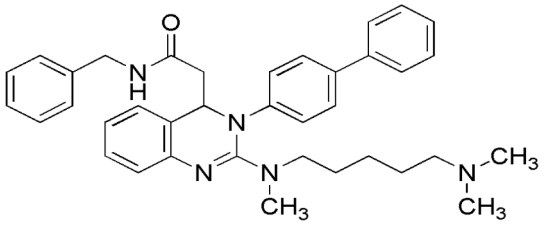
Bisphosphonates are organic molecules having a high affinity to hydroxyapatite, which leads to opportunities for targeting therapeutic agents to bone. Consequently, various analogues of bisphosphonates have been used as drugs for bone diseases. Pharmacological agents like radioisotopes, anti-inflammatory drugs, anti-neoplastic drugs, and proteins have been attached to bisphosphonates. Attachment of proteins at a specific position without disturbing their structure and function is important for their biological activity. In this presentation, we will discuss the synthesis of bisphosphonate molecules, which can be selectively attached to proteins through hydrazone linkage. We will also discuss the synthesis of bisphosphonates that have spacers of different length and polarity between the bisphosphonate and hydrazine groups. These specially-made bisphosphonates can be used to target different proteins to bone. Moreover, the synthesized bisphosphonates are novel and have similar structural characteristics to those of currently prescribed drugs for bone diseases, and as such may represent a new class of pharmaceuticals.

MEDI 71

Discovery of potent T-type calcium channel blocker

Han Na Seo[1]*, Ja Youn Choi*[1]*, Yun Jeong Choe*[1]*, Jungahn Kim*[2]*, Dong Joon Choo*[1]*, and Jae Yeol Lee*[1]*. (1) Department of Chemistry, Kyung Hee University, 1 Hoegi-dong, Dongdaemoon-gu, Seoul 130-701, South Korea, Fax: 82-2-966-3701, jellyppo21@hotmail.com, (2) Department of Chemistry, kyunghee university, seoul 130-701, South Korea*

For the development of potent T-type calcium channel blocker, the intensive SAR study of 3,4-dihydroquinazoline series leaded to the most potent compound **KYS05090** (IC_{50} = 41 ± 1 nM) against T-type calcium channel and its potency is nearly comparable to that of Kurtoxin. As a small organic molecule, this compound showed the highest blocking activity reported to date.



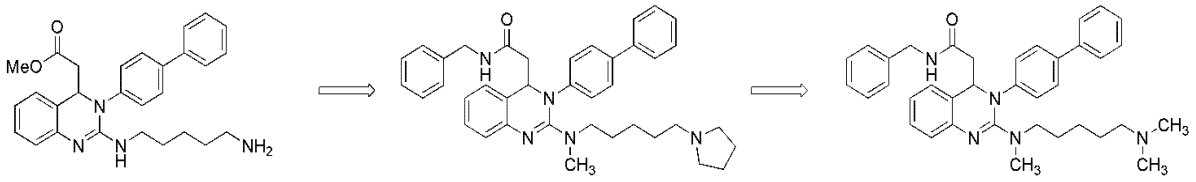
KYS05090 (IC_{50} = 41 ± 1 nM, SI = 119.5 for T/N-channel)

MEDI 72

Synthesis and SAR studies of a novel series of T-type calcium channel blockers

Yun Jeong Choe[1]*, Han Na Seo*[1]*, Ja Youn Choi*[1]*, Jungahn Kim*[2]*, Dong Joon Choo*[2]*, and Jae Yeol Lee*[2]*. (1) Department of Chemistry, Kyung Hee University, 1 Hoegi-dong, Dongdaemoon-gu, Seoul 130-701, South Korea, Fax: 82-2-966-3701, whitebear48@naver.com, (2) Department of Chemistry, Kyunghee University, Seoul 130-701, South Korea*

For the novel, potent, and selective T-type Ca^{2+} channel blockers, a series of 3, 4-dihydroquinazoline derivatives containing 1, 5-diaminopentane were prepared and evaluated for their blocking actions on T- and N-type Ca^{2+} channels. As a result of the structure-activity relationship study, **KYS05090** (IC_{50} = 41 ± 1 nM) was found to be as potent as Kurtoxin. Herein, we will discuss the detailed SAR result of this series of compounds.



KYS05044
IC_{50} = 0.56 ± 0.10 μM,
SI = >100 for T/N-channel

KYS05080
IC_{50} =0.26 ± 0.01 μM,
SI = 7.5 for T/N-channel

KYS05090
IC_{50} = 41 ± 1 nM,
SI = 119.5 for T/N-channel

MEDI 73

Thiols oxidation and covalent binding of BSA by cyclolignanic quinones are enhanced by the magnesium cation

Ajay Kumar[1]*, Antonio E. Alegria*[1]*, Pedro Sanchez-Cruz*[1]*, Carmelo García*[1]*, Fernando A. Gonzalez*[2]*, Aimee Orellano*[2]*, Beatriz Zayas*[3]*, and Marina Gordaliza*[4]*. (1) Department of Chemistry, University of Puerto Rico at Humacao, Humacao, PR 00791, Fax: 787-850-9422, a_kumar@uprh.edu, (2) Department of Chemistry, University of Puerto Rico - Rio Piedras, San Juan, PR 00931, (3) Department of Environmental Affairs, Universidad Metropolitana (UMET), San Juan, PR 00928-1150, (4) Departamento de Química Farmacéutica, Campus Miguel de Unamuno, Facultad de Farmacia, Salamanca 37007, Spain*

A novel cyclolignanic quinone, 7-acetyl-3,4-didemethoxy-3,4-dioxopodophyllotoxin (CLQ) inhibits topoisomerase II (TOPO II) activity. The extent of this inhibition was greater than that produced by the etoposide quinone (EQ) or etoposide. Glutathione (GSH) reduces EQ and CLQ to their corresponding semiquinones under anaerobic conditions. The later were detected by EPR spectroscopy in the presence of MgCl2 but not in its absence. Semiquinone EPR spectra change with quinone/GSH mol ratio suggesting covalent binding of GSH to the quinones. These orthoquinones react with nucleophilic groups from BSA to bind covalently BSA under anaerobic conditions. Thiol consumption and BSA binding are enhanced by MgCl2. Complex formation between the parent quinones and Mg+2 were also observed. Theoretical calculations predict the observed blue-shifts in the absorption spectra peaks when the quinones are complexed to Mg+2 and large increases in the partial positive charge of electrophilic carbons at the quinone

ring. These observations suggest a possible role of Mg+2 chelation by these quinones in increasing TOPO II thiol and/or amino/imino reactivity with these orthoquinones.

MEDI 74

Synthesis of 7-substituted benzyl-5-[(3,4,5-trimethoxyphenyl)ethyl]-4-methyl- 7*H*-pyrrolo[2, 3-*d*]pyrimidin-2-amines as microtubule inhibitors

*Aleem Gangjee[1], **Sonali Kurup**[1], and Charles D. Smith[2]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, SC 29425*

Microtubules are long protein polymers composed of α- and β-tubulin heterodimers. The crucial involvement of microtubules makes them a target for cancer chemotherapy. Antitumor agents that target microtubules are called antimitotic agents. However, several antimitotic agents have problems such as toxicity and drug resistance, hence there is a continuing effort to find novel, more effective microtubule inhibitors.

Gangjee *et al*. previously reported 7-benzyl-5-substituted phenylethyl-4-methyl-7*H*- pyrrolo[2,3-*d*]pyrimidin-2-amines as antimitotic agents. The compounds target tubulin and have a different binding site on tubulin from that of known inhibitors. In addition to their antitumor activity, some of the compounds also reversed tumor resistance to antimitotic agents via the PgP efflux pump. The 7-benzyl substitution in these compounds was suggested to be important for activity. Using the 7-benzyl-5-(3,4,5-trimethoxyphenyl)ethyl-4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine as the lead analog, we have explored varied substitutions on the 7-benzyl ring in order to optimize the inhibitory activity against tubulin. The design, synthesis and antimitotic activities of these compounds will be presented and discussed.

MEDI 75

Synthesis of analogs of trienomycin A, a potential inhibitor of Hsp90

***Geraldine Calvet**, Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, 4070 Malott Hall, Lawrence, KS 66045, gfcalvet@yahoo.fr, and Brian Blagg, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045-7583*

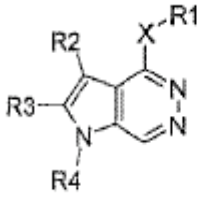
Trienomycin A is a member of the ansamycin family of antibiotics. Like geldanamycin, this molecule is a macrolactam containing an oxygenated aromatic ring. Both trienomycin A and geldanamycin have exceptional activity against several cancer cell lines. Considering the similarities between these two macrocycles, trienomycin A could be, like geldanamycin, an inhibitor of Hsp90 which is an emerging target in the treatment of cancers. The synthesis of analogs of trienomycin A will be described and the initial biological results presented.

MEDI 76

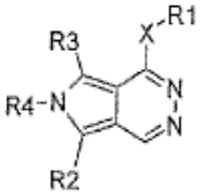
Synthesis and biological activities of pyrrolo-pyridazine derivatives

***TANG Peng Cho**, FENG Jun, ZHANG Lei, and **BIE Ping Yan**, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China, tangpc@shhrp.com, biepy@shhrp.com*

Receptor tyrosine kinases (RTKs) play a crucial role in signal transduction pathways that regulate cell differentiation, proliferation and angiogenesis. Inhibition of RTKs activation has become a compelling approach in the development of anticancer agents. The epidermal growth factor receptor (EGFR, ErbB1 or HER1) and the human epidermal growth factor receptor 2 (HER2, ErbB2) are members of the ErbB family of receptor tyrosine kinases and have been clinically validated as targets for cancer therapy. In the present study, a series of pyrrolo-pyridazine dericatives(I, II, III) were designed and synthesized for the evaluation as EGFR/Her-2 inhibitors in a cellular assay using A431 and SK-BR-3. The design, synthesis and inhibitory activities of these compounds will be discussed.



(I)



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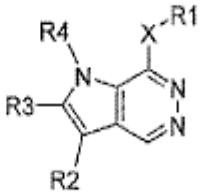


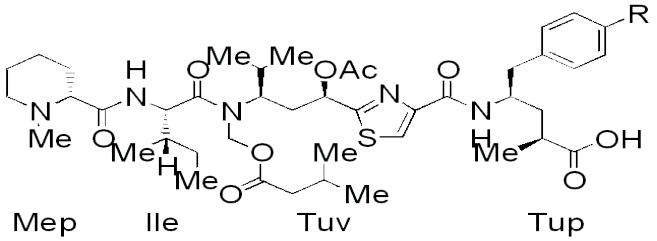
(III)

MEDI 77

Probing the structure-activity relationships of tubulysins

***Ranganathan Balasubramanian**, Bhooma Raghavan, and Robert A. Fecik, Department of Medicinal Chemistry, University of Minnesota, 8-120 WDH, 308 Harvard Street S.E, Minneapolis, MN 55455-0353, Fax: 612-624-0139, bala0072@umn.edu*

Tubulysins A and D (1 and 2) belong to a family of antimitotic peptides isolated from myxobacteria that have potent anticancer activity against multidrug-resistant cancer cell lines. Various studies suggest that the tubulysins bind to the peptide binding site located near the Vinca alkaloid binding site of â-tubulin. The structural features and their activity make tubulysins interesting leads for the development of new drugs for multidrug-resistant cancers. Our laboratory has developed an efficient route for the total synthesis of a series of simplified tubulysin analogs that were designed to define the minimum pharmacophore required for cytotoxicity. We sought to examine the effects of changes to the N-methylpipecolinic acid (Mep), tubuvaline (Tuv), tubuphenylalanine (Tup) fragments and hypothesized that the labile acetyl and N,O-acetal functionalities of tubuvaline were unnecessary for activity. Simplified tubulysin analogs retain significant cytotoxicity and reveal important structure-activity relationship data.



Tubulysin A (**1**), R = OH
Tubulysin D (**2**), R = H

MEDI 78

P2 site SAR development toward ABT-263, an orally bioavailable inhibitor of Bcl-2 family proteins

***Xiaohong Song**, Milan Bruncko, Hong Ding, Aaron R Kunzer, Christopher Lynch, Cheol-Min Park, Andrew M Petros, Xilu Wang, Michael D Wendt, Paul M Nimmer, Morey L. Smith, Stephen K Tahir, Haichao Zhang, Christin Tse, Andrew J Souers, Saul Rosenberg, and Steven W Elmore, Cancer Research, Global Pharmaceutical R&D, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064, Fax: 847-935-5165, xiaohong.song@abbott.com*

The Bcl-2 family proteins are key regulators of the intrinsic apoptotic pathway. Imbalances between pro- and anti-apoptotic Bcl-2 proteins are major cause of the increased cell survival. This involvement in cell function makes them an attractive target for cancer therapy. In this poster, we will present small molecule optimization efforts of our previously disclosed inhibitor of Bcl-2 family proteins, ABT-737. Specifically, by targeting site H2 on this molecule, the physicochemical properties were improved, culminating in the identification of ABT-263. This

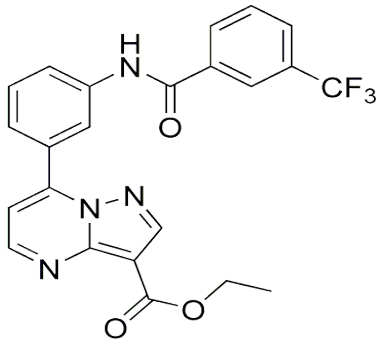
next-generation inhibitor binds with sub-nanomolar affinities to multiple anti-apoptotic Bcl-2 family proteins. ABT-263 is efficacious in several xenograft models, and is orally bioavailable.

MEDI 79

Identification of pyrazolo[1,5-a]pyrimidine-3-carboxylates as B-Raf kinase inhibitors: Part 1

Ariamala Gopalsamy[1], *Gregory M. Ciszewski*[1], *Yongbo Hu*[1], *Frederick Lee*[1], *Larry Feldberg*[2], *Eileen Frommer*[2], *Steven Kim*[2], *Karen Collins*[2], *Donald Wojciechowicz*[2], *and Robert Mallon*[2]. *(1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (2) Oncology Research, Wyeth Research, Pearl River, NY 10965*

Raf kinases play central role in cell growth and survival and are components of Raf-MEK-ERK signaling pathway. Of the three Raf isoforms, activating B-Raf mutations have been found in 66% of malignant melanomas and in a smaller fraction of other cancers including those of the colorectum. B-Raf mutations in these cancers were found in a systematic genome-wide screening effort to detect alterations in genes that control cell proliferation, differentiation, and death (Davies H, et al. 2002, Nature 417:906). Inhibitors of B-Raf could be used in the treatment of colorectal cancer, melanomas, and other Ras related human cancers. To identify B-Raf inhibitors we established an HTS assay to monitor the kinase activity of both wt and mutant (V600E) forms of this protein. From this effort pyrazolo[1,5-a]pyrimidine-3-carboxylate (1) was identified as a promising B-Raf kinase inhibitor. Expansion of this scaffold class to improve the potency and gather structure activity relationship will be discussed in detail.

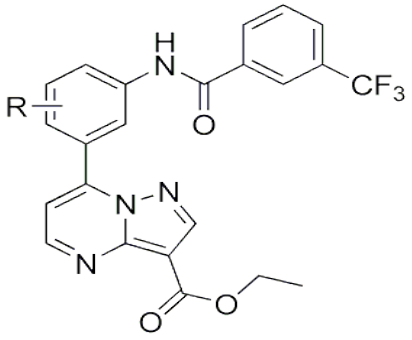


MEDI 80

Phenylpyrazolo[1,5-a]pyrimidines as B-Raf Inhibitors: Optimization of phenyl group: Part 2

Gregory M. Ciszewski[1], *Ariamala Gopalsamy*[1], *Jeremy I. Levin*[1], *Kyung-Hee Kim*[1], *Yongbo Hu*[1], *Frederick Lee*[1], *Larry Feldberg*[2], *Eileen Frommer*[2], *Steven Kim*[2], *Karen Collins*[2], *Donald Wojciechowicz*[2], *and Robert Mallon*[2]. *(1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, Fax: 845-602-3045, ciszewg@wyeth.com, (2) Oncology Research, Wyeth Research, Pearl River, NY 10965*

B-Raf kinase plays a critical role in the Raf-MEK-ERK signaling pathway and is a compelling target for cancer chemotherapeutics. From our high throughput screening effort, ethyl 7-(3-(3-(trifluoromethyl)benzamido)-phenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate was identified as a hit for inhibition of B-Raf kinase. While a number of regions of the molecule can be varied to explore the possibilities of improving the potency, the central phenyl group was chosen as a means to explore the electronic effects on the structure activity relationship still maintaining low molecular weight. Synthetic efforts to generate the analogs and the observed SAR will be discussed in detail.

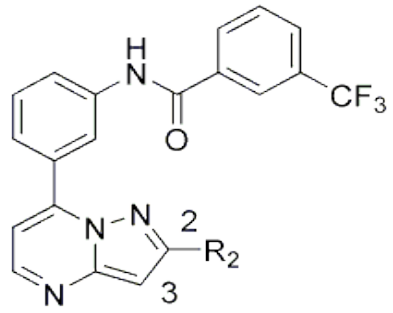


MEDI 81

Phenylpyrazolo[1,5-a]pyrimidines as B-Raf Inhibitors: Optimization of pyrazolopyrimidne ring substituents: Part 3

Mengxiao Shi[1]*, Ariamala Gopalsamy*[1]*, Dan M. Berger*[1]*, Minu Dutia*[1]*, Yongbo Hu*[1]*, Frederick Lee*[1]*, Larry Feldberg*[2]*, Eileen Frommer*[2]*, Steven Kim*[2]*, Karen Collins*[2]*, Donald Wojciechowicz*[2]*, and Robert Mallon*[2]*. (1) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, Fax: 845-602-3045, shim2@wyeth.com, (2) Oncology Research, Wyeth Research, Pearl River, NY 10965*

In continuation of our efforts to optimize the B-Raf kinase high throughput screen hit ethyl 7-(3-(3-(trifluoromethyl)benzamido)phenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate, we explored the importance and the position of the carboxylate moiety. Moving the carboxylate to the adjacent carbon at the 2-position decreased the activity significantly. However, our efforts to replace the labile ester in the 2-position with other ring systems including a number of heterocycles improved the potency significantly. The various analogs generated and the observed structure activity relationship for this region will be disclosed in detail.

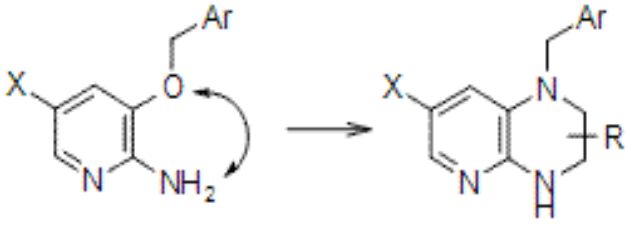


MEDI 82

Synthesis and SAR of 1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazines as c-Met and ALK inhibitors

Linda R. Weinberg[1], *Mark S. Albom*[2], *Thelma S. Angeles*[2], *Bruce D. Dorsey*[1], *Jean Husten*[2], *Karen L. Milkiewicz*[1], *Seetha Murthy*[2], *Douglas A. Pippin*[1], *Renee Roemmele*[3], *and Ted L. Underiner*[1]. *(1) Department of Medicinal Chemistry, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, lweinber@cephalon.com, (2) Department of Lead Discovery and Profiling, Cephalon, Inc, West Chester, PA 19380, (3) Department of Chemical Process Research and Development, Cephalon, Inc, Malvern, PA 19355*

Dysregulation of c-Met and ALK kinases are implicated in a variety of cancers. c-Met plays a key role in the proliferation, survival, motility, invasion and metastasis of cancer cells. Activation of c-Met is implicated in the genesis of papillary renal carcinomas, gastric CA and subsets of osteo-soft sarcomas. Chromosomal translocations generate multiple ALK oncogenic fusion proteins in tumors. The NPM-ALK and EML4-ALK proteins play a causative role in the pathogenesis of anaplastic large-cell lymphoma and non-small cell lung cancer, respectively. Starting from a Sugen/Pfizer c-Met/ALK dual inhibitor, chemistry was developed to rapidly elaborate the SAR around a pyridopyrazine scaffold. Analogs from this series were identified that inhibit c-Met and/or ALK enzyme with IC50 values less than 100 nM. The kinase inhibitory activity was dependent upon the nature of the X, R and Ar groups.



MEDI 83

Targeted binding of chitosan-based nanoparticles with galactose ligand to HepG2 cells

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Solid core-shell polymeric particles are attractive delivery vehicles, because they can efficiently encapsulate drugs of different physical and chemical characteristics. However, target-tracking particles for therapeutic purposes have been a somewhat elusive question. In this study we developed chitosan-based nanoparticles with galactose ligand which has special response activity with asialoglycoprotein (ASGPR) receptor in the surface carbohydrate of HepG2 cells. First the chitosan-200 (CS) was modified by lactose acid (LA) to synthesize galactose conjugated chitosan (Gal-CS) which was detected by FITR and 1H-NMR, the results showed that the degrees of substitution of LA coupled with chitosan-200 was about 17.6 mol%, then the

Gal-CS was used to prepare nanoparticles, TEM examination showed that the Gal-CS nanoparticles have uniform diameter of 130 nm and excellent dispersion. HepG2 cells and stem cells were co-cultured with the Gal-CS nanoparticles for 4days, and the results from staining experiment and SEM imaging showed that most of Gal-CS nanoparticles targeting adhered on the surface of HepG2 cells. This new kind of nanoparticles has potential application in the field of targeting drug delivery to cure liver cancer.

MEDI 84

Antibody conjugates for cancer therapy

Subhash C. Sinha *and Zhengzheng Huang, Department of Molecular Biology and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, Fax: 858-784-8732, subhash@scripps.edu*

Antibody conjugates have been developed using an aldolase monoclonal catalytic antibody and small molecule antagonists of integrin alpha(v)beta(3). These conjugates were shown to bind alpha(v)beta(3)-expressing human breast cancer cells efficiently. They did not bind cells that expressed alpha(v)beta(5), but lacked alpha(v)beta(3). Subsequently, we are developing second generation antibody conjugates in order to enhance the therapeutic efficiency. In this presentation, results of the in vitro and in vivo evaluations using animal models of human breast cancers will be presented.

MEDI 85

Studies of plant virus capsids as promising protein carriers for carbohydrate based anticancer vaccine development

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The conjugation of tumor-associated carbohydrate antigens to an immunogenic protein carrier is an attractive approach for anti-cancer vaccine development. The Tn antigen has been identified on numerous cancer cells surface and thus it became an excellent target for immunotherapy. Despite several designs using different protein carriers, to date inducing a high T-cell dependent immune response has been difficult. In this talk we will first outline the syntheses of Tn antigen analogs that can be conjugated to a protein carrier. Then the conjugation of Tn with two new carriers, Cow Pea Mosaic Virus (CPMV) capsid and Tobacco Mosaic Virus (TMV) capsid, will be described. Finally we will discuss the antibodies titers obtained. High antibodies titers and more importantly high IgG titers were induced when mice were inoculated with such conjugates. Based on those results we believe that virus capsids can be very promising carriers for carbohydrate based cancer vaccine studies.

MEDI 86

Targeting RING finger domain of HDM2 for cancer therapy

Zengjian Hu *and Lei Liu, Department of Computer-Aided Drug Discovery, Biogenova, Corp, 401 Rosemont Ave, 3rd Floor, Rosenstock Hall, Frederick, MD 21701*

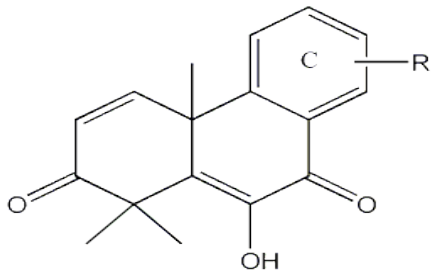
Human double minute 2 (HDM2) is by far the most studied and best understood p53-specific ubiquitin protein ligase. The C-terminal domain of HDM2, critical for its E3 ubiquitin ligase activity, was identified as the RING finger domain. Recently, a family of small molecules has been identified to inhibit HDM2's E3 activity which does not involve inhibition of the p53-HDM2 interaction. Therefore, HDM2 RING finger domain represents a new promising target for developing anticancer agents. In this study, we use structure-based virtual screening to identify novel small molecule inhibitors of HDM2 by using experimental structure of the HDM2 RING finger domain and our natural products library. The lead compounds from our studies are non-peptide, cell permeable small molecules that specifically bind to the RING finger domain of HDM2 and will inhibit HDM2's E3 activity. And this inhibition in turn will promote and/or induce apoptosis in human cancer cells.

MEDI 87

Total synthesis of new cytotoxic diterpenes

Daniel Rabouin, Lionel Dumas*, Eric Beaulieu, Kenza Daïri, Samuel Fortin, Eric Fournier, Gerson G. Gonzalez, Sasmita Tripathy, Sylvie Bailly, Gaetan Gagnon, Sandra Naranjo, Brigitte St-Denis, Nancy Steenaart, Jean-François Lavallee, Giorgio Attardo, Pierre Beauparlant, Xavier Billot, and Laurent Bélec, Gemin X Biotechnologies Inc, 3576 Avenue du Parc, suite 4310, Montréal, QC H2X 2H7, Canada, drabouin@geminx.com, ldumas@geminx.com*

We identified a diterpene of natural origin; (R)-10-hydroxy-6-methoxy-1,1,4a,7-tetramethylphenanthrene-2,9(1H,4aH)-dione , during a high throughput screening campaign. This compound induces the activation of caspase-3, an apoptotic effector. In an effort to generate derivatives of this compound we devised a synthetic methodology which allowed us to obtain a first series of analogs. In order to target some specifics analogues of general structure 1, a modified synthetic route was devised. A series of modifications on ring C was achieved by using a Wittig-Heck approach. We will describe the synthetic approaches used in this project along with examples of biologically active compounds.



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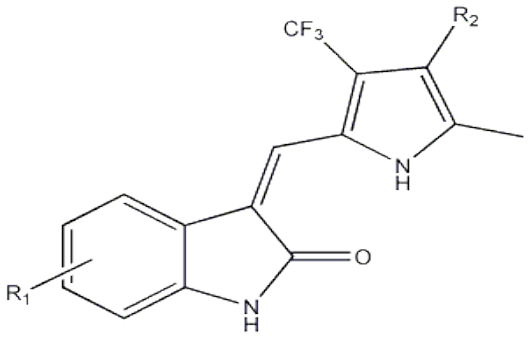
MEDI 88

Trifluoromethyl substituted pyrrole 2-indolinone derivatives as tyrosine kinase inhibitors

*TANG Peng Cho, **BIE Ping Yan**, LIU Wei Li, YANG Shi Bo, ZHANG Lei, and FENG Jun, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China, tangpc@shhrp.com, biepy@shhrp.com*

Receptor tyrosine kinases (RTKs) have been implicated as therapeutic targets for the treatment of human diseases including cancers, inflammatory diseases. A series of trifluoromethyl pyrrole substituted 2-indolinone derivatives of general formula (I) 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 89

Using novobiocin analogs to probe the C-terminus of Hsp90

***Alison C. Donnelly** and Brian S. J. Blagg, Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7583, adonnelly@ku.edu*

Hsp90 is a 90 kDa member of the heat shock family of proteins that act as molecular chaperones. These proteins are essential for folding nascent polypeptides and refolding denatured or misfolded proteins. Novobiocin, an antibiotic that inhibits DNA gyrase, is known to bind the C-terminus of Hsp90 with relatively poor affinity and induce degradation of Hsp90-dependent client proteins at ~700 μM in SKBr3 cells. Studies have been performed to improve the inhibitory activity of novobiocin analogues and convert a well-known DNA gyrase inhibitor into a selective inhibitor of Hsp90. Several analogues have been synthesized that probe the contribution of the benzamide, coumarin, and sugar moieties toward Hsp90 inhibitory activity. These compounds have been evaluated in vitro and structure-activity relationships for the C-terminus of Hsp90 have been revealed

MEDI 90

3-D-QSAR studies on benzothiadizapine hydroxamates as tumor necrosis factor-alpha converting enzyme inhibitors

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A set of twenty nine Benzothiadizepine hydroxamates having selective Tumor Necrosis factor-alpha converting enzyme inhibition activity were used to compare the quality and predictive power of 3D-QSAR, CoMFA and CoMSIA models for the atom based , centroid–atom based, data based and docked conformer based alignment. Removal of two outliers from the initial training set of 29 molecules improved the predictivity of the models. Among the 3D-QSAR models developed using the above four alignments, the database alignment provided the optimal predictive CoMFA model for the training set with cross-validated r2 = 0.510, non-cross validated r2 = 0.972, standard error of estimates (s) = 0.098 and F = 215.44 and the optimal CoMSIA model with cross-validated r2 = 0.556, non-cross validated r2 = 0.946, standard error of estimates (s) = 0.163 and F = 99.785. These models also showed the best test set prediction for the 6 compounds with predictive r2 values of 0.460 and 0.535, respectively. The contour maps obtained from 3D-QSAR studies were appraised for activity trends for the molecules analyzed. The CoMSIA models exhibited good external predictivity as compared to that of CoMFA models. The data generated from the present study helped us to further design and report some novel and potent TACE inhibitors.

MEDI 91

A nonclassical NF- κB pathway in HUVEC cells revealed by small molecule probes

***Yidong Liu**[1], Gangli Gong[1], Yuli Xie[1], Alison Rinderspacher[1], Shi-Xian Deng[1], Donald W. Landry[1], Michael Wyler[2], Nathalie Aulner[2], Udo Toebben[2], Deborah H. Smith[2], Lars Branden[2], Caty Chung[3], Stephan Schürer[3], and Dušica Vidović[3]. (1) Department of Medicine, Columbia University, 650 W 168th St, BB 1029, New York, NY 10032, (2) Department of Physiology and Cellular Biophysics, Columbia University, New York, NY 10032, (3) Scientific Computing, The Scripps Research Institute, Jupiter, FL 33458*

The nuclear translocation of NF-κB is an early event in the NF-κB pathway. Using small molecule probes, we studied the translocation of P65 in human umbilical vein endothelial cells (HUVEC). The results showed that the translocation was inhibited by known NF-κB pathway inhibitors such as the proteasome inhibitor MG-132, the E3 ligase inhibitor Ro106-9920, non-specific IKK inhibitor Bay-11708. Intriguingly, the translocation was insensitive to a potent IKK2 inhibitor, suggesting that the classical IκB kinase type 2 is not involved in the pathway. To rule out the cell permeability played a role, a series of analogs with hydrophobic side chains were synthesized and all of them failed to inhibit the translocation. Another reported cell-permeable IKK inhibitor was also tested and unexpectedly showed activation effect, possibly due to its non-specific activities. In summary, our results indicated that a non-classical NF-κB pathway might involve in endothelial cells stimulation.

MEDI 92

Discovery of novel small molecule activators of NFkB pathway

Gangli Gong[1]*, Yuli Xie*[1]*, Yidong Liu*[1]*, Alison Rinderspacher*[1]*, Shi-Xian Deng*[1]*, Donald W. Landry*[1]*, Michael Wyler*[2]*, Nathalie Aulner*[2]*, Udo Toebben*[2]*, Deborah H. Smith*[2]*, Lars Branden*[2]*, Caty Chung*[3]*, Stephan Schürer*[3]*, and Dušica Vidović*[3]*. (1) Department of Medicine, Columbia University, 650 W 168th St, BB 1029, New York, NY 10032, gg2269@columbia.edu, (2) Department of Physiology and Cellular Biophysics, Columbia University, New York, NY 10032, (3) Scientific Computing, The Scripps Research Institute, Jupiter, FL 33458*

Nuclear factor-κB (NFκB) pathway has provided a focus for therapeutic targets. Small molecule regulation of NFκB transcription represents novel approaches to the treatment of diseases such as inflammation and cancer. In a cell based assay designed to identify inhibitors of TNFα-induced translocation of NFκB, we found that a known IKK2 inhibitor unexpectedly activated NFκB translocation in human umbilical vein endothelial cells (HUVEC). NFκB activators may have potential against certain type of cancers. A series of analogs of this activator have been synthesized and tested. Preliminary structure activity relationships have been established.

MEDI 93

GGTase I as an anticancer drug target: Development of GGPP analog SAR

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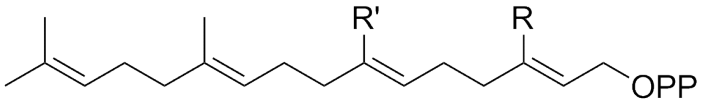
Protein prenyltransferases have been a focus of anti-cancer drug discovery due to their roles in posttranslational modification of Ras proteins and other key signaling proteins. We have recently reported that prodrug derivatives of certain farnesyl monophosphate analogs block protein prenylation in cells (J Med Chem 2007, 50, 3274). Our goal is to utilize our knowledge of FTase and FTIs to develop GGTIs and prodrugs targeting GGTase I. Currently, 3- and 7-substituted GGPP analogs are being synthesized for evaluation against GGTase I. This work has led to the discovery of both GGTase I inhibitors and alternative substrates that exhibit low nanomolar affinity for the enzyme. This group of compounds will enable us to further direct our GGTase I SAR, to develop more potent inhibitors of GGTase I.



GGPP R=Me, R'=Me
3-vGGPP R=vinyl, R'=Me
3-alGGPP R=allyl, R'=Me
7-vGGPP R=Me, R'=vinyl
7-alGGPP R=Me, R'=allyl

MEDI 94

Identification and optimization of N3, N6-diaryl-1H-pyrazolo[3,4-d]pyrimidine-3,6-diamines as a novel class of ACK1 inhibitors

Xiaolin Hao[1]*, David Kopecky*[2]*, XianYun Jiao*[1]*, Yi Chen*[1]*, Jiasheng Fu*[1]*, Juan Jaen*[3]*, Holger Wesche*[4]*, Josh Xiao*[5]*, Edward van der Horst*[5]*, Jinsong Liu*[5]*, Zhulun Wang*[6]*, Mario Cardozo*[6]*, Ji Ma*[7]*, Shichang Miao*[3]*, Liang Tang*[7]*, and Frank Kayser*[1]*. (1) Chemistry Research and Discovery, Amgen Inc, 1120 Veterans BLVD, South San Francisco, CA 94080, xhao@amgen.com, (2) Chemistry Research and Discovery, Amgen SF, South San Francisco, CA 94080, (3) Department of Chemistry Research and Discovery, ChemoCentryx, Inc, Mountain View, CA 94043, (4) Department of Oncology, Amgen Inc, South San Francisco, CA 94080, (5) Amgen Inc, South San Francisco, CA 94080, (6) Structural Biology, Amgen San Francisco, LLC, South San Francisco, CA 94080, (7) Department of PKDM, Amgen, Inc, South San Francisco, CA 94080*

Abstract -ACK1 (activated Cdc42Hs associated kinase 1) is a non-receptor tyrosine kinase, ubiquitously expressed, with highest expression levels in the brain. It has been shown to be over-expressed in a number of human tumor cell lines. The development of a potent and stable ACK1 inhibitor would allow the role of ACK1 in tumor progression to be probed via in vivo animal tumor models. Based on the structural information obtained from an earlier series of ACK1 inhibitors (I), potential new ligands were designed that retained key binding features but possessed alternative scaffolds. N3, N6-diaryl-1H-pyrazolo[3,4-d]pyrimidine-3,6-diamines (II) were identified as a novel series of inhibitors of ACK1.

MEDI 95

Signaling protein modulators as therapeutic agents based on tyrphostin dimer like structure

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A series of dimer like tyrphostin compounds have been designed, synthesized and primary screened against B-cell malignancies [multiple myeloma - MM-1] cell line. The lead compounds have nanomolar potency against a wide range of tumor types and inhibit against known kinase target. These new classes of compunds hold promise as a cancer therapeutic agent.

MEDI 96

Synthesis and antiproliferative evaluation of indeno[3,2-c]quinoline derivatives

Cherng-Chyi Tzeng*, Chih-Hua Tseng, and Yeh-Long Chen, Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan, Fax: 011886-7-3125339, tzengch@kmu.edu.tw*

Camptothecin and its derivatives such as topotecan (Hycamptin) and irinotecan (Camptosar) are prototypical topoisomerase I (top I) inhibitors which are currently used as anticancer drugs. However, several drawbacks such as easy opening of the lactone ring and the development of resistance to camptothecin has caused an urgent need in search of alternative top I inhibitors. We have prepared certain indeno[1,2-c]quinolin-11-one derivatives for antiproliferative evaluation on the ground these polycyclic heterocycles may intercalate into the DNA double helix resulting in the inhibition of DNA replication and transcription. The results indicated that 9-Methoxy-6-(piperazin-1-yl)-11H-indeno[1,2-c]quinolin-11-one O-3-aminopropyl oxime (1) exhibited GI50 values of 0.52 and 0.74 micro-M against the growth of HeLa and SKHep, respectively and was approximately 4-fold in potency compared to camptothecin against the growth of SAS, AGS, and A549 cells. Flow cytometric analysis indicated 1 can induce cell cycle arrest in S pahse, DNA polyploidy (> 4n) and followed by apoptosis.

MEDI 97

Bispurine polyamine analogs of spermine: Synthesis and growth inhibitory effects on human prostate cancer cells

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N-Alkylated analogues of the natural polyamines such as spermine H2N(CH2)3NH(CH2)4NH(CH2)3NH2, spermidine H2N(CH2)4NH(CH2)3NH2, and putrescine H2N(CH2)4NH2 exhibit strong cytotoxic activity against human tumor cell lines. We have been investigating the design and synthesis of purine and pyrimidine derived ‘N9-N9-bispurine polyamines' as analogues of ‘spermine' as potential antitumor agents. We have prepared series of purine and pyrimidine polyamine analogues keeping the key structural and pharmacologically important groups of ‘spermine' such as aliphatic polyamine chain linkers attached to two purine or pyrimidine bases. Thus, the N9-[3-chloropropane]purine was prepared by reacting an appropriate purine with the 1,3-dichloropropane in the presence of potassium carbonate in dimethylformamide. Two equivalent of N9-[3-chloropropane]purine was reacted with 1,4-diaminobutane in DMSO/CsCO3 to give the final N9,N9-bispurine polyamines. In this presentation, studies on the design, synthesis and anticancer activity of these ‘bispurine polyamines' in human prostate cancer cell lines will be presented.

MEDI 98

Design and synthesis of pyrazolone-based anaplastic lymphoma kinase (ALK) inhibitors

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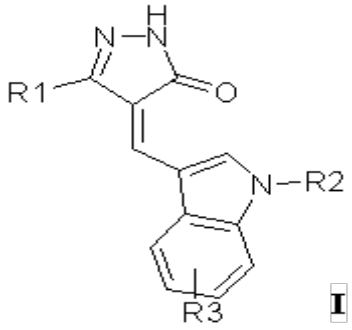
Anaplastic lymphoma kinase (ALK) is a transmembrane receptor tyrosine kinase implicated in the transformation of a non-Hodgkin lymphoma subtype known as anaplastic large-cell lymphoma (ALCL). A t(2;5) (p23;q35) chromosomal translocation results in the fusion of NPM (nucleophosmin) with ALK. Constitutive overexpression and activation of NPM-ALK system stimulates anti-apoptotic and mitogenic signaling pathways such as PI-3K/AKT, JAK/STAT, and PLCγ, which is associated with survival and proliferation of ALCLs. In a program to design ALK inhibitors as possible therapeutic intervention against such cancers, we have identified a class of highly potent and selective small-molecule based inhibitors of the said kinase derived from pyrazolones (I). Although pyrazolones are known for VEGFR-2 kinase inhibition, by appropriately modifying the specific sites on the core structure we have been able to design a range of ALK inhibitors. The kinase activities against the isolated enzyme and in cell, physiochemical properties and their mode of interactions with the protein will be presented.



I

MEDI 99

Development of novel anticancer agent via cell-cycle arrest

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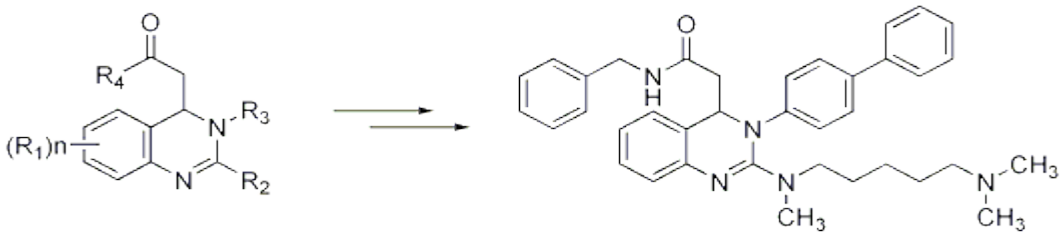
This work describes the preliminary biological results that novel T-type calcium channel blockers inhibit the growth of human cancer cells by blocking calcium influx into the cell, based on unknown mechanism on the cell cycle responsible for cellular proliferation. Among the selected compounds from compound library, KYS05090 was identified to be nearly similar to Doxorubicin against growth inhibition effect. Herein we wish to report the synthesis of KYS05090 and its biological activity.



KYS05090

MEDI 100

Discovery of 2-(3-pyridyl)-4-arylaminopyrimidines as a new series of apoptosis inducers using a cell- and caspase-based high throughput screening assay

***Nilantha Sirisoma**, Azra Pervin, Bao Nguyen, Candace Crogan-Grundy, John Drewe, Ben Tseng, Shailaja Kasibhatla, and Sui Xiong Cai, EpiCept Corporation, 6650 Nancy Ridge Drive, San Diego, CA 92121, nsirisoma@epicept.com*

It is known that many anti-cancer drugs kill cancer cells through the induction of apoptosis. We therefore have developed a cell- and caspase-based high throughput-screening assay termed Anti-cancer Screening Apoptosis Platform (ASAP) for the discovery of novel apoptosis inducers as potential anticancer agents. Applying this assay, we have discovered 4-anilino-2-(2-pyridyl)pyrimidines as a series of potent apoptosis inducers (Sirisoma S. et al. Bioorg. Med. Chem. 2006, 47, 7761). Additional SAR studies have identified several series of structurally related 2-aryl-4-arylaminopyrimidines as novel apoptosis inducers. Herein we will report the synthesis and SAR of 2-(3-pyridyl)-4-arylaminopyrimidines as a novel series of potent apoptosis inducers.

MEDI 101

Discovery of 2-chloro-N-(4-methoxyphenyl)-N-methylquinazolin-4-amine (EP128265, MPI-0441138) as a potent apoptosis inducer using anticancer screening apoptosis program (ASAP), a cell- and caspase-based platform

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Applying a cell- and caspase-based HTS (ASAP) assay, a novel series of 4-anilinoquinazolines has been discovered as potent inducers of apoptosis. 2-Chloro-N-(4-methoxyphenyl)-N-methylquinazolin-4-amine, compound 1 (EP128265, MPI-0441138) was identified as a highly active inducer of apoptosis (EC50 for caspase activation of 2 nM) and as a potent inhibitor of cell proliferation (GI50 of 1 nM). Compound 1 inhibits tubulin polymerization, is not a substrate for the ABC transporter Pgp-1 and is highly efficacious in MX-1 human breast and other cancer mouse models. SAR study of 1 showed that the 4-methoxy group in the phenyl ring is critical for its low nanomolar potency. In contrast to 4-anilinoquinazoline based kinase inhibitors, the methyl group in the nitrogen linker is essential for its apoptosis inducing activity and substitution in the 6- and 7-position of quinazoline decreased potency. We will report the SAR of 4-anilinoquinazolines and the discovery of 1 as a potent apoptosis inducer.

MEDI 102

Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based HTS assay: Modifications of the 2- and 3-positions

William Kemnitzer[1], *Songchun Jiang*[1], *Yan Wang*[1], *Shailaja Kasibhatla*[1], *Candace Crogan-Grundy*[1], *Monica Bubenik*[2], *Denis Labrecque*[2], *Real Denis*[2], *Serge Lamothe*[2], *Giorgio Attardo*[2], *Henriette Gourdeau*[2], *Ben Tseng*[1], *John Drewe*[1], *and* ***Sui Xiong Cai***[1]*. (1) EpiCept Corporation, 6650 Nancy Ridge Drive, San Diego, CA 92121, bkemnitzer@epicept.com, scai@epicept.com, (2) Shire BioChem Inc, Laval, QC H7V 4A7, Canada*

We have reported the discovery of 2-amino-3-cyano-4-aryl-4H-chromenes as a series of potent apoptosis inducers using our Anti-cancer Screening Apoptosis Program (ASAP), a cell- and caspase-based HTS assay. Several of these chromenes were found to have vascular disrupting activity and to be highly active in anti-cancer tumor models (Kasibhatla, S. et al. Mol. Cancer Ther. 2004, 3, 1365, and Gourdeau, H. et al. Mol. Cancer Ther. 2004, 3, 1375). A clinical candidate EPC2407 has been identified and is currently in phase I clinical studies. We have previously reported the SAR of the 4-position (Kemnitzer, W. et al. J. Med. Chem. 2004, 47, 6299) and the 7,8-positions of chromene (Kemnitzer, W. et al. Bioorg. Med. Chem. Lett. 2005, 15, 4745). More recently, we reported the SAR of fused rings at the 7,8-positions (Kemnitzer, W. et al. J. Med. Chem. 2007, 50, 2858). Herein we will report the chemistry and SAR of the 2,3-positions of chromene.

MEDI 103

Discovery of N-aryl-9-oxo-9H-fluorene-1-carboxamides as a new series of apoptosis inducers using a cell- and caspase-based HTS assay: SAR of the N-aryl group

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We wish to report the discovery of N-aryl-9-oxo-9H-fluorene-1-carboxamides as potent apoptosis inducers using our Anti-cancer Screening Apoptosis Platform (ASAP), a novel cell- and caspase-based HTS assay. Starting from the hit N-o-tolyl-9-oxo-9H-fluorene-1-carboxamide (1a), several potent compounds including N-(2-(1H-pyrazol-1-yl)phenyl)-9-oxo-9H-fluorene-1-carboxamide (1b) with improved solubility have been identified. These compounds were found to arrest cells at the G2/M stage followed by apoptosis as determined by the flow cytometry analysis assay. Selected compounds were also found to be highly active in the growth inhibition MTT assay. Herein we will report the chemistry and SAR of the N-aryl group.

MEDI 104

Virtual screening of natural compound library against N-Cadhein protein to identify new anticancer agents

*Li Bai and **Zengjian Hu**, Department of Computer-aided Drug Discovery, Taney Academy of Sciences, Gaithersburg, MD 20877, huzengjian@tasusa.org*

Tumor metastasis is a major problem in cancer therapy. Cell-cell adhesive interactions play important roles in this complex process. N-cadherin, one member of the classical cadherin family regulating cell adhesion, presents on certain tumor cells and established tumor blood vessels which makes it an important target for developing anti-cancer treatments. A simple cyclic peptide, ADH-1, as an N-cadherin antagonist, is currently in clinical development. Based on the structure of ADH-1, we have identified several non-peptide, cell permeable small molecules using pharmacophore-based virtual screening. In this study, we use structure-based virtual screening to identify novel small molecule inhibitors of N-cadherin by using experimental structure of the N-cadherin and our natural products library. The lead compounds from our studies are also non-peptide, cell permeable small molecules that specifically bind to the N-cadherin and inhibit its activity which might be developed as the therapeutic agents in the treatment of cancers.

MEDI 105

Lead optimization of 2-amino-3-benzyloxy-5-pyrazol-4-yl-pyridine for the discovery of clinical candidate PF-2341066 as potent and highly selective c-Met inhibitor

***Michelle Tran-Dube**, Hong Shen, Shinji Yamazaki, Helen Zou, James Christensen, Barbara Mroczkowski, and J. Jean Cui, Pfizer, Inc, 10646 Science Center Drive, San Diego, CA 92121, michelle.tran-dube@pfizer.com*

The c-Met-HGF signaling pathway is important in mediating a wide range of biological activities, e.g. embryological development, wound healing, tissue regeneration, and morphogenesis. HGF or c-Met are overexpressed in a large variety of solid tumors, and various c-Met mutations have been well described in many solid tumors and some hematological malignancies. Due to the role of aberrant HGF/c-Met signaling in human oncogenesis and invasion/metastasis, the inhibition of the c-Met-HGF signaling pathway has great potential in cancer therapy. 2-Amino-5-aryl-3-benzyloxypyridines have been discovered as a class of potent and selective c-Met inhibitors, as exemplified with PHA-806114. An extensive lead optimization was carried out for the further improvement of potency against c-Met and ADME properties. 2-Amino-3-benzyloxy-5-pyrazol-4-yl-pyridines demonstrated improved potency and pharmaceutical properties. Further optimization of the pyrazole substituents generated clinical candidate PF-2341066, which demonstrated potent in vitro and in vivo c-Met inhibition and tumor growth inhibition with good pharmaceutical properties.

MEDI 106

1,2-Dialkynylimidazoles: Anticancer aza-enediynes

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Enediynes and enyne allenes are known to undergo thermal rearrangements to reactive para-benzyne and α,3-didehydrotoluene diradical intermediates, respectively. Aza-variants of these rearrangements are of interest because the potential effect of nitrogen substitution on the nature and reactivity of the intermediates involved. A series of alkynyl- and propargyl-substituted heterocycles were designed to undergo aza-Bergman or Aza-Myers cyclization to reactive diradical intermediates. Here we report the cancer cell cytotoxicity of these heterocyclic aza-enediynes and skipped aza-enediynes, and compare these results to the DNA cleavage ability of these compounds. Although many heterocyclic skipped aza-enediynes cleave DNA and display cancer cell cytotoxicity, the 1,2-dialkynylimidazoles are as a class more cytotoxic to a wider range of human cancer cells.

MEDI 107

Synthesis and evaluation of potential antitumor antimitotics that also reverse tumor resistance

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Compounds that interfere with microtubules such as vinca alkaloids and taxanes are important antitumor agents. We have identified a novel series (Series I) of 7-benzyl-4-methyl-5-(2-substituted phenylethyl)-7*H*-pyrrolo [2,3-*d*]pyrimidin-2-amines, which demonstrate antimitotic and antitumor activities against antimitotic-sensitive as well as resistant tumor cells. The binding site of these agents is different from the colchicine, vinca alkaloid, and paclitaxel binding sites. In addition, some of these agents have the ability to reverse P-glycoprotein – mediated resistance to antimitotic agents like vinblastine. In an effort to explore the optimal structural requirements for antitumor activity, and the ability to reverse Pgp-mediated drug resistance, Series II was designed, with variations at the 5-phenylethyl portion of the molecules in Series I. Preliminary biological evaluation of Series II exhibited inhibition of both, antimitotic-sensitive and antimitotic-resistant tumor cells. In this report, the design, synthesis, and preliminary biological activities of compounds of Series II will be presented.

MEDI 108

Synthesis of substituted pyrrolo [2, 3-*d*] pyrimidines with N7 chain length difference as novel antitumor antimitotic agents that also reverse tumor resistance

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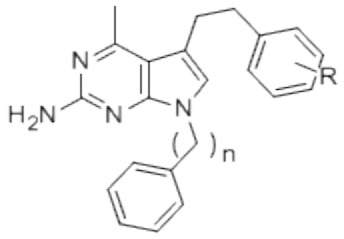
Gangjee *et al*. recently discovered a novel series of 2-amino-4-methyl-5-phenylethyl substituted-7-benzylpyrrolo[2,3-*d*]pyrimidines, some of which possess two digit nanomolar antitumor and antimitotic activity and are not subject to P-glycoprotein (Pgp) or Multidrug Resistance Protein 1 (MRP1) mediated tumor resistance (like the Vinca alkaloids and taxanes). In addition to their antitumor activity against antimitotic sensitive and resistant tumor cells in culture, some of these compounds also have the ability to reverse the Pgp-mediated resistance to antimitotic agents. From a structure activity relationship study we have determined that the pyrrole N7-substitution is essential to the antimitotic, antitumor and Pgp reversal properties of these agents. In an attempt to optimize the activities of the parent analog, in the present work, we varied the chain length of the N7-benzyl substitution. The general structure is shown is figure 1. The compounds are active against both resistant and nonresistant tumor cell lines. The design, synthesis and biological activities of these analogs will be presented.



n=0, 2,3
R=2-OMe
3,4,5-triOMe

MEDI 109

Synthesis of benzo[4,5]thieno[2,3-*d*]pyrimidine as potential dual TS and DHFR inhibitor

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The only *de novo* pathway for the synthesis of dTMP is catalyzed by thymidylate synthase (TS) via the reductive methylation of dUMP to dTMP. Inhibition of TS has long been considered as a useful mechanism for cancer chemotherapy, due to its crucial role in dTMP and DNA synthesis. We designed a benzo[4,5]thieno[2,3-*d*]pyrimidine classical compound as a TS inhibitor. Molecular modeling using human TS crystal structures suggested that the benzene ring in the molecule can have hydrophobic interaction with Trp109, which should afford potent inhibition of human TS. The synthesis and biological activities of the target compound will be reported and discussed.

MEDI 110

ABT-263, an orally bioavailable inhibitor of Bcl-2 family proteins

***Hong Ding**, Cheol-Min Park, Milan Bruncko, Christopher Lynch, Aaron R Kunzer, Andrew M Petros, Xiaohong Song, Xilu Wang, Michael D Wendt, Paul M Nimmer, Morey L. Smith, Stephen K Tahir, Haichao Zhang, Christin Tse, Andrew J Souers, Saul Rosenberg, and Steven W Elmore, Cancer Research, Global Pharmaceutical R&D, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064, Fax: 847-935-5165, hong.ding@abbott.com*

Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression and drug resistance, which make them compelling targets for anti-tumor therapy. ABT-737 is the first generation inhibitor of Bcl-2 family proteins. While this compound inhibits the anti-apoptotic proteins Bcl-2, Bcl-xL and Bcl-w with sub-nanomolar affinity, it lacks oral bioavailability. Further medicinal chemistry efforts have identified the nitro group as a cause for the low oral bioavailability, as several analogs with nitro replacements demonstrated enhanced oral exposure. Combination with structural modifications on additional sites led to the discovery of ABT-263, an orally active inhibitor with sub-nanomolar affinity for multiple anti-apoptotic Bcl-2 family proteins. This compound displays single-agent, mechanism-based cell killing in small cell lung cancer (SCLC) and lymphoma, and shows complete regression in SCLC tumor xenograft models upon oral dosing.

MEDI 111

Carbonyl reductase inhibition as a means to increase anthracycline efficacy

***Christopher K. Ewing** and Henry A. Charlier Jr., Department of Chemistry and Biochemistry, Boise State University, 925 W Sherwood Apt 102C, Boise, ID 83706, kif_ewing@yahoo.com*

Carbonyl reductase (CR) has been implicated in drug resistance and cardiotoxicity associated with anthracycline treatment. Inhibiting CR during anthracycline treatment may reduce the incidence of the associated drug resistance and cardiotoxicity. Several biphenyl CR inhibitors have been identified, one of which has a Kii of 220 nM, and represents one of the most potent inhibitors reported. Other structurally related biphenyl inhibitors were identified that have Kii values ranging from 10 - 21 μM. Treatment of cancer cell lines with biphenyl inhibitors during anthracycline cell killing studies were shown to reduce IC50 values by as much as four-fold. One particular biphenyl inhibitor also exhibited anti-cancer activity, thereby warranting further studies to address whether or not the combination of anthracyclines and inhibitor act additively or synergistically in cancer cell killing.

(NIH/P20RR016454)

MEDI 112

Comparisons between parthenolide and a new agent against acute myelogenous leukemia

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Parthenolide is a sesquiterpene lactone (SQL) and the primary anti-inflammatory agent in the herbal remedy feverfew (Tanacetum parthenium). Feverfew is well known in natural medicine, which has been used in the treatment of inflammatory conditions. Parthenolide has been shown to selectively target AML and CML, presumably through a mechanism involving IKK2 activation of NF-kappaB. We have identified both parthenolide and a new agent (MAC262) as specific inhibitors of the epigenetic suppressor histone deacetylase 1 (HDAC1), which plays an important role in many cancers, including AML. Both agents have similar chemical structures and may affect AML cells through the same functional group. We have also compared the effectiveness of both agents for suppressing the proliferation and viability of AML cells.

Keywords: Parthenolide, Histone Deacetylase, Acute Myelogenous Leukemia

MEDI 113

Design and synthesis of small-molecule inhibitors of the HIF-1 pathway

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Hypoxic conditions are commonly found in solid tumors. The activation of the transcription factor Hypoxia Inducible Factor-1 (HIF-1) is the major pathway through which hypoxic conditions in cancer induce gene expressions leading to increased malignancy, metastasis, angiogenesis and drug resistance. Therefore, inhibition of HIF-1 is a viable strategy for developing anti-tumor

therapeutics. Based on hits identified earlier through combinatorial library screening, we are interested in the structure optimization and eventual development of potent HIF-1 inhibitors as anticancer agents and research tools. About 20 compounds have been synthesized and evaluated. These compounds showed low micromolar inhibition activities in cell culture assays. This presentation will discuss the design and synthesis of new HIF inhibitors that have been successfully used for the identification of a novel biological target that interferes with the HIF-1 pathway and related structure-activity relationship studies.

MEDI 114

Discovery of a novel indenoheterocycle with potent apoptosis inducing properties through a systematic study of a multicomponent reaction involving indane-1,3- dione, adehydes and various amine-containing heterocyclic compounds

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A multicomponent reaction of indane-1,3-dione, an aldehyde and an amine-containing aromatic compound leading to the formation of indenopyridine-based heterocyclic medicinal scaffolds has been investigated. It was found that the yields significantly improve when oxygen gas is bubbled through the reaction mixture, facilitating the oxidation of the intermediate dihydropyridine-containing compounds to their aromatic counterparts. Investigation of the reaction scope revealed that formaldehyde as well as various aliphatic, aromatic and heteroaromatic aldehydes work well as the aldehyde component. In addition, substituted anilines and diverse aminoheterocycles can be utilized in this process as the amine-containing component. Preliminary biological evaluation of the synthesized library identified a pyrimidine-based polycycle, which rivals the anticancer drug etoposide in its toxicity and apoptosis inducing properties toward a human T-cell leukemia cell line.

MEDI 115

Effect of o-phenoxy caspase inhibitors on apoptosis

***Benjamin K Southerland**[1], William Grunwald Jr.[2], Kashmira Kulkarni-Datar[3], Chanel Hagler[4], Daniel M. Ketcha[1], Thomas L. Brown[3], and David R. Cool[2]. (1) Department of Chemistry, Wright State University, 3640 Colonel Glenn Highway, Fairborn, OH 45435, Southerland.2@wright.edu, (2) Department of Pharmacology and Toxicology, Wright State University, Dayton, OH 45435, (3) Department of Neuroscience, Wright State University, Dayton, OH 45435, (4) Department of Biology, Wright State University, Dayton, OH 45435*

Apoptosis is a process of cell death, in which a cell commits suicide. Apoptosis is essential for the maintenance of homeostasis and apoptotic dysregulation has been implicated numerous human diseases. Apoptotic events are mediated through a unique family of aspartyl proteases, caspases. Our study tested the effectiveness of nontoxic, O-phenoxy-conjugates caspase inhibitors to prevent cell death. Human leukemia cells were treated with Boc-D(OMe)-OPh, Cbz-D(OMe)-OPh, Q-D(OMe)-OPh, Boc-VD(OMe)-OPh, Cbz-VD(OMe)-OPh, Q-VD(OMe)-OPh, and Q-VE(OMe)-OPh. The cells were induced to undergo apoptosis and the inhibitory effectiveness of the compounds was evaluated. Our results indicate the drugs that contained the dipeptide VD were more effective at inhibiting cell death than those that contained aspartic acid (D) alone. Q-VE(OMe)-OPh had no apoptotic inhibitory activity and was identified as the first true O-phenoxy conjugate, negative control. Our data suggest that N-terminal protecting groups and amino acid composition significantly alter the effectiveness of peptide-based cell death inhibitors.

MEDI 116

Identification and synthesis of a metabolite of Symadex™, an inhibitor of FLT3 kinase

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Symadex™ (C-1311) is a potent, orally available, imidazoacridinone inhibitor of FMS-like tyrosine kinase 3 (FLT3) which has started development for oncology indications and is being investigated for autoimmune disease. The enzyme system implicated in formation of the primary circulating metabolite of Symadex™ was aldehyde oxidase, a molybdenum-containing enzyme present in the liver which is known to catalyze the oxidation of N-heterocyclic drugs such as famciclovir and zaleplon. We will we describe the in vitro and in vivo identification, synthesis and full characterization of an oxygenated metabolite of Symadex™.

MEDI 117

Multicomponent synthesis and anticancer evaluation of a library of novel indenopyridopyrimidines

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Based on our initial discovery of a novel 1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine, which exhibited potent apoptosis inducing properties in human cancer cells, we synthesized a library of forty analogues incorporating this structural scaffolds. The synthesis involved a

multicomponent reaction of indane-1,3-dione, 6-aminopyrimidine-2,4(1H,3H) dione and a variety of aldehydes. A number of analogues displayed low nanomolar cytotoxic potencies when tested in a number of human cancer cell lines, including HeLa and MCF-7 as models for cervical and breast adenocarcinoma respectively. In addition, these compounds rapidly intiated apoptosis and induced cell cycle arrest in leukemic Jurkat cells. The synthetic and biological aspects of this investigation as well as the discussion of the structure activity relationship in this library of analogues will be presented in this paper.

MEDI 118

New cathepsin D inhibitors: Synthesis and evaluation

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Cathepsin D has been suggested to play important roles in the metastatic potential of several types of cancer. Also, a high activated cathepsin D level in breast tumor tissue has been associated with an increased incidence of relapse and metastasis. High levels of active cathepsin D have also been found in lung cancer, colon cancer, prostate cancer, uterine cancer, and ovarian cancer. In fact cathepsin D levels have been used as markers to predict the prognosis of breast cancer and uterine cancer patients. The design and synthesis of new (hydroxyethyl)amine isosteres containing cyclized tertiary amines as inhibitors as cathepsin D is reported. These compounds utilize substituted N-phenyl piperazines as the hydroxyethyl tertiary amine. Ki values by fluorometric assay for inhibition of Cathepsin D hydrolysis of substrate: Ac-Glu-Glu(Edans)-Lys-Pro-Ile-Cys-Phe-Phe-Arg-Leu-Gly-Lys(Methyl Red)-Glu-NH2 is reported.

MEDI 119

Novel cannabinoids for the treatment of neuropathic pain obtained by Pd nanoparticle–catalyzed cyclization/cross-coupling tandem reaction

Philippe Diaz*, Jijun Xu, Fanny Astruc Diaz, Hao-Min Pan, and Mohamed Naguib, Anesthesiology and Pain Medicine - Research, The University of Texas M.D. Anderson Cancer Center, Unit 110, 1515 Holcombe Blvd, Houston, TX 77030, Fax: 713-794-4590, pdiaz@mdanderson.org*

Neuropathic pain, a debilitating condition characterized by severe, persistent pain that is refractory to traditional analgesia, results from heterogeneous conditions affecting the peripheral or central nervous system (CNS) and affects an estimated 8% of people worldwide. The cannabinoid receptor CB2, has emerged as a new target for the treatment of pain without the CB1 mediated psychotropic side effects. We synthesized novel cannabinoid modulators based on 2,3-dihydro-1-benzofuran ring using colloidal palladium nanoparticle–catalyzed tandem cyclization/cross-coupling reaction. Potent and selective CB2 agonists were identified using in vitro binding and functional assays. Selected compounds were tested in vivo relevant models of neuropathic pain and were able to reverse allodynia and hyperalgesia, with no visible CNS side effects. In contrast, a CB1–CB2 agonist, Win 55,212, caused rigidity, spasm, and lethargy. Details of the synthesis, CB1 and CB2 receptors structure-activity relationships, in vitro, and in vivo data will be presented.

MEDI 120

Novel purine based "atypical retinoids" as antitumor agents

***Shashikant Phadtare**, Tien Chung, Tien Banh, and Devangachinta Murthy, College of Pharmacy, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, LA 70125, Fax: 504-520-7930, sphadtar@xula.edu*

Among novel apoptosis based approaches, ‘atypical retinoids' such as 6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN) display significant potential as therapeutic agents in tumor treatment. We have been investigating the design and synthesis of purine and pyrimidine derived ‘atypical retinoids' as analogues of AHPN as potential antitumor agents. We have prepared series of purine retinoid analogues keeping the key structural and pharmacologically important groups of AHPN connected to different purine bases. Thus, the Friedel-Crafts reaction of 1-adamantanol with commercially available 4-hydroxy-benzyl bromide gave the alkylating agent 3-(1-adamantyl)-4-hydroxy benzylbromide. Several N9-[3-(1-adamantyl)-4-hydroxyphenyl]purines were prepared by reacting an appropriate purine base with the alkylating agent 3-(1-adamantyl)-4-hydroxy benzylbromide in the presence of potassium carbonate in dimethylformamide. In this presentation, studies on the design, synthesis and anticancer activity of these ‘atypical purine retinoids' at in cancer cell lines will be presented.

MEDI 121

Synthesis and structure-activity relationship of histone deacetylase (HDAC) inhibitors with triazole-linked cap group

*Po C Chen[1], Vishal Patil[1], **William R Guerrant**[1], Patience Green[1], and Adegboyega K Oyelere[2]. (1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 901 Atlantic Drive, Atlanta, GA 30332, gth799k@mail.gatech.edu, (2) Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332*

Histone deacetylase (HDAC) inhibition is a recent clinically validated therapeutic strategy for cancer treatment. Small molecule HDAC inhibitors identified so far fall in three distinct structural motifs: the zinc-binding group (ZBG), a hydrophobic linker, and a recognition cap group. Here we report the suitability of a 1, 2, 3-triazole ring as a surface recognition cap group linking-moiety in suberoylanilide hydroxamic Acid-like (SAHA-like) HDAC inhibitors. Using “click” chemistry (Huisgen cycloaddition reaction), several triazole-linked SAHA-like hydroxamates were synthesized. Structure-activity relationship reveal that the position of the triazole moiety as well as the identity of the cap group markedly affect the *in vitro* HDAC inhibition and cell growth inhibitory activities of this class of compounds.

MEDI 122

Cancer: Using tumor growth simulations to design treatment protocols

***Nemoy Rau** and Ileana Carpen, Chemical Engineering, Tennessee Technological University, Department of Chemical Engineering, P.O. Box 5013, Cookeville, TN 38505, Fax: 931-372-6352, nrau21@tntech.edu*

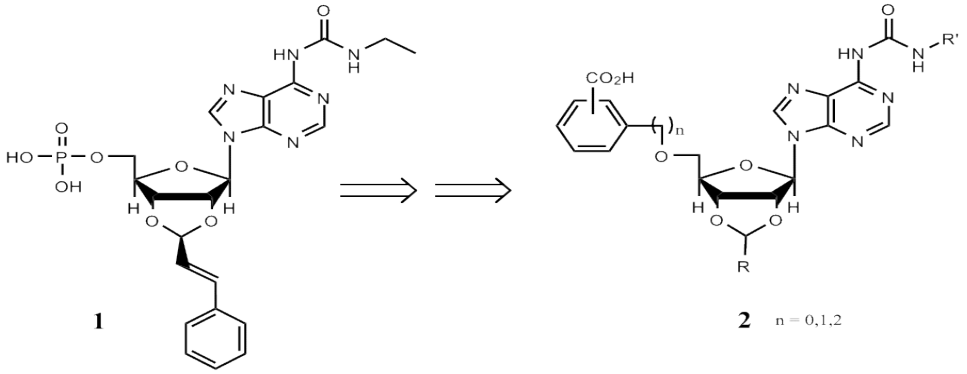
Cellular adaptation to changing environments is intricately coordinated through many molecular and mechanical responses. As cells evolve, abnormal growth patterns occur (that cannot be controlled by normal mechanisms) leading to cancer. With mathematical modeling we can integrate different characteristics of tumor growth for a non-experimental study of cancer. Through integration of some of the prior clinical, experimental, and mathematical studies, we utilize a cellular automaton model to take into account multiple factors affecting tumor growth in healthy tissue. This in silico simulation model of tumor growth is based upon molecular and life cycle features that effect the growth rates of cancer. The life cycle parameters used in this model include replication rate, nutrient and oxygen concentrations, and possible drug effects. The in silico model is used to study the effects of drugs upon the growth and development of the tumor and optimize a drug treatment protocol.

MEDI 123

Inhibition of platelet aggregation via $P2Y_{12}$ receptor antagonists: Synthesis, SAR, chemical stability data, and biological results

Paul S. Watson[1], Stephanie A. Anderson[2], James G. Douglass[1], José L. Boyer[3], Christopher S. Crean[2], Sanjoy Mahanty[3], Anna K. Morgan[3], Rozemarijn S. Verhoeven[2], and ***Carl A. Samuelson****[1]. (1) Department of Chemistry, Inspire Pharmaceuticals, Inc, 4222 Emperor Boulevard, Suite 200, Durham, NC 27703, Fax: 919-941-9177, asamuelson@inspirepharm.com, (2) Department of Drug Evaluation, Inspire Pharmaceuticals, Inc, (3) Department of Molecular Pharmacology, Inspire Pharmaceuticals, Inc*

Inhibition of platelet aggregation via antagonism of the platelet $P2Y_{12}$ receptor has been shown to be an effective clinical strategy for the management of the morbidity and mortality associated with thromboembolic events. Building on our previous findings that acetal and urea modifications to an adenosine monophosphate core (e.g. **1**) results in potent, selective, and reversible antagonists of platelet aggregation, we examined replacements for the 5' phosphate group, with the aim of rendering the chemotype orally bioavailable and stable. To this end, we have identified several benzoic acid modifications. The synthesis, SAR, chemical stability data, and biological results for these molecules will be presented.



MEDI 124

Efficient removal of ruthenium-based catalysts using Silia*Bond*® metal scavengers

***Geneviève Gingras**, Annie Michaud, Lynda Tremblay, Steeves Potvin, and François Béland, SiliCycle Inc, 114-1200, St-Jean-Baptiste Avenue, Quebec City, QC G2E 5E8, Canada, Fax: 418-874-0355, genevievegingras@silicycle.com*

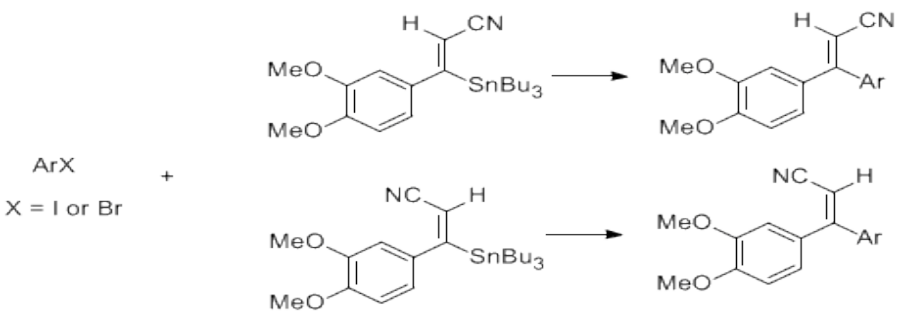
Ruthenium-based catalysts are very useful in organic synthesis, mainly in olefin metathesis reaction (ROM(P) and RCM). Grubbs and Hoveyda-Grubbs catalysts are certainly the most popular ruthenium-based complexes in that field of applications. Complete ruthenium removal can be difficult using conventional methods. SiliCycle® has developed innovative functionalized silica- based products that allow to reduce the residual ruthenium concentration: the **Silia*Bond*® Metal Scavengers**. The silica matrix offers many advantages: no swelling, mechanical and thermal stabilities, scalable and ease of use (SPE, flash cartridges and, bulk formats). Results of ruthenium scavenging efficiency using different **Silia*Bond*®** functionalized silicas will be presented in this poster for a variety of ruthenium-based catalysts used under several experimental conditions.

MEDI 125

3,3-Diarylacrylonitriles as tubulin polymerization inhibitors for cancer chemotherapy

***Zhenglai Fang**, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, Heine Pharmacy Building, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, fang@purdue.edu, Mark Cushman, Department of Medicinal Chemistry and Molecular Pharmacology and The Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, Ernest Hamel, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD 21702, and Gregory E. Agoston, EntreMed, Inc, Rockville, MD 20850*

3,3-Diarylacrylonitriles were synthesized stereoselectively using Stille coupling reaction from aromatic or heteroaromatic halide and vinylstannane intermediates. This divergent approach allows rapid syntheses of both E/Z isomers of many 3,3-diarylacrylonitriles with diversified substitutents. These compounds were tested against tubulin polymerization inhibition in an enzymatic assay and their cell growth inhibitory properties against human breast adenocarcinoma cell line (MDA-MB-231), renal epithelial cell line (LLC), and human umbilical vein endothelial cells (HUVEC). The biological results indicate these compounds are effective tubulin polymerization inhibitors for possible cancer chemotherapy.



MEDI 126

Molecular basis of the selectivity of fluorinated neurotransmitters for adrenergic receptors

Chaya Pooput[1], *Erica Rosemond*[1], *Stefano Costanzi*[2], *Francesca Deflorian*[3], *Kenneth L. Kirk*[1], *and Jürgen Wess*[1]. *(1) Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, 8 Center Drive, Bldg 8, Rm B1A06, Bethesda, MD 20892, Fax: 301-402-4182, pooputc@niddk.nih.gov, (2) Laboratory of Biological Modeling, NIDDK, National Institutes of Health, Bethesda, MD 20892-5646, (3) Computational Chemistry Core Laboratory, NIDDK, National Institutes of Health, Bethesda, MD 20892-5646*

Norepineprhine (NE) and epinephrine (EPI) play key roles in neurotransmission, metabolism and in the control of many physiological processes such as heart rate and blood pressure. Several years ago, our group discovered that site-specific fluorine substitution on the aromatic ring of norepinephrine and epinephrine dramatically influences the selectivity of these agonists for alpha- and beta-adrenergic receptors. Specifically, the 2-fluoro analogs selectively bind to beta-receptors, whereas the 6-fluoro analogs selectively bind to alpha-receptors. To understand the molecular basis of these fluorine-induced selectivities, molecular models of the alpha and beta adrenergic receptors were constructed with their natural ligands docked into the orthosteric binding site of the receptor. These models predicted slight differences between the two ligand binding pockets which may be responsible for the selectivity of the fluorinated compounds. Based on these models, site-directed mutagenesis and radioligand binding assays were used to probe the binding sites of the receptors. The identification of the molecular basis for selectivity of these fluorinated compounds for the individual subtypes of the adrenergic receptorsgave an insight into the structure of the orthosteric binding pocket and these results will provide a basis for further development of fluorinated compounds with increased selectivity and activity for the adrenergic receptors.

MEDI 127

Synthesis and SAR of a partial mGluR5 antagonist lead: Unexpected modulation of pharmacology with slight structural modifications to a 5-(phenylethynyl)pyrimidine scaffold

Sameer Sharma[1], *Richard Williams*[2], *Alice L Rodriguez*[3], *Colleen M Niswender*[3], *Charles D. Weaver*[4], *P. Jeffrey Conn*[3], *and Craig W Lindsley*[3]. *(1) Chemical and Physical Biology Program, Vanderbilt University, 2222 Pierce Avenue, RRB 804, Nashville, TN 37232, sameer.sharma@vanderbilt.edu, (2) Department of Pharmacology, Vanderbilt Program in Drug Discovery, Nashville, TN 37232-6532, (3) Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, (4) Department of Pharmacology, Vanderbilt University, Nashville, TN 37232*

Modulation of the mGluR5 subtype of metabotropic glutamate receptors has been demonstrated to offer a therapeutic benefit for a number of disorders of the central nervous system (CNS) including Parkinson's disease, pain, anxiety, depression, addiction, schizophrenia, and fragile X syndrome. Selectivity for the mGluR5 subtype can be achieved by targeting allosteric binding sites. High throughput screening was conducted with Ca2+ fluorescence used as a measure of receptor activation. We describe the synthesis and SAR, developed through an iterative analog

library approach using technology-enabled parallel organic synthesis, of an mGluR5 partial antagonist lead based on a 5-(phenethynyl)pyrimidine scaffold, EC50 = 62 nM, 17.9% antagonism. With slight structural modifications to the distal phenyl ring, analogues demonstrated a range of pharmacology from mGluR5 partial antagonism to full antagonism (inverse agonism) to positive allosteric modulation.

MEDI 128

Practical application of quantum mechanics to drug design: A tour of hydrogen bond donors and acceptors of perennial interest to the medicinal chemist

***Daniel L. Cheney**, Department of Macromolecular Structure, Bristol Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, Fax: 609-818-3545, cheneyd@bms.com, and Dale Braden, Schrodinger, Inc, Portland, OR 97201*

Hydrogen bonding is central to molecular recognition. Yet categorizing common organic functionalities according to weak or strong donors or acceptors is difficult and at times controversial given the scarcity of experimental data. Herein we describe a relatively fast and accurate protocol for estimating gas phase hydrogen bonding strengths of common organic functional groups of interest to drug discovery scientists. The method appears to be robust in that high level quantum mechanical (CCSD(T)) benchmarks spanning a wide range of chemistry and energy (-1.5 kcal to -30 kcal) are generally reproduced within 6% error. Relative hydrogen bonding strengths are calculated and given for a wide range of functional groups and heterocycles.

MEDI 129

Raising HDL levels by a small molecule LCAT activator

*Frank Kayser[1], **Jian Zhang**[1], Marc Labelle[1], Preston Ford[2], Sindhu Padmanabhan[2], and Mingyue Zhou[2]. (1) Department of Chemistry, Amgen Inc, 1120 Veterans Boulevard, South San Francisco, CA 94080, Fax: 650-244-2015, fkayser@amgen.com, jian@amgen.com, (2) Department of Metabolic Disorders, Amgen Inc, South San Francisco, CA 94080*

Abstract:

Lecithin cholesterol acyltransferase (LCAT) is an enzyme which is secreted from the liver and released into plasma. LCAT is well known to be involved in the esterification of free cholesterol present in circulating plasma lipoproteins to form cholesteryl ester and lysophosphatidylcholine, and therefore has been regarded as a major determinant of plasma HDL concentrations. Recent studies have established that transgenic rabbits overexpressing human LCAT have 6-7 fold higher plasma HDL levels than control animals. In addition, LCAT transgenic rabbits have reduced plasma concentrations of the atherogenic LDL and apoB-containing lipoproteins. In hamsters, LCAT overexpression has been proveen to help increase cholesterol excretion.

LCAT is considered as an attractive target for drug discovery for treating coronary heart disease and atherosclerosis. This poster presentation will report our efforts to identify a series of

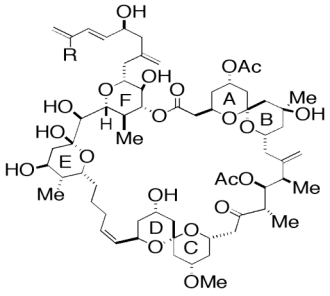
pyrazine analogs as LCAT activators including SAR and in vivo prove of concept studies using the tool compounds developed during the research.

MEDI 130

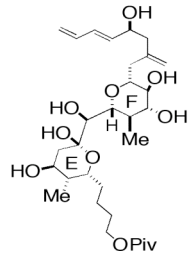
Synthesis and biological evaluation of analogs of Altohyrtin C (Spongistatin 2)

***Carl Edward Wagner**, Integrated Natural Sciences, Arizona State University at the West Campus, 4701 West Thunderbird Road, Glendale, AZ 85306, Fax: 602-543-6073, Carl.Wagner@asu.edu, Qiang Wang, Chemocentryx, Inc, Mountainview, CA 94043, and Clayton H. Heathcock, Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720*

Several structural analogs that contain only part of the altohyrtin structure have been prepared and compared with synthetic altohyrtin C (**2**) for *in vitro* cytotoxicity against human colon (HCT116) and ovarian (A2780) cell lines. Whereas altohyrtin C was found to be exceedingly potent against these lines (IC50 = 0.0003 mM), analogs **3-5** were >27,000-fold less potent (IC50 >8 mM). Analogs **6** and **7** also demonstrated weak cytotoxicity with IC50 values for the HCT116 and A2780 cells of 4.8 mM and 2.4 mM, respectively for **6**.



1: R = Cl (altohyrtin A; spongistatin 1)
2: R = H (altohyrtin C; spongistatin 2)



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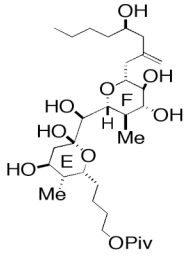

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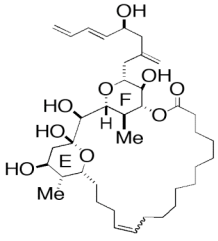
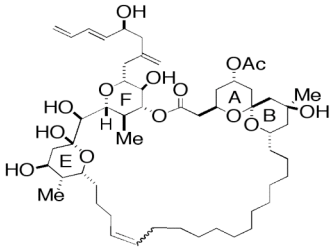
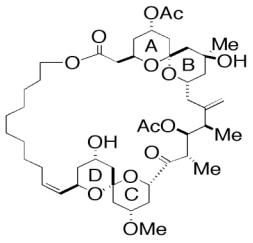


5a *cis* double bond
5b *trans* double bond



6 (inseparable mixture of *cis* and *trans* isomers)



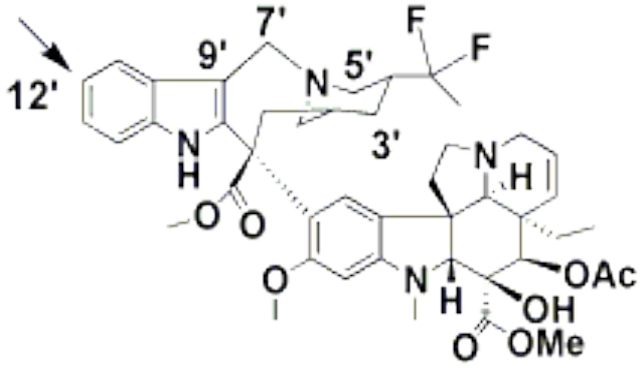
7

MEDI 131

Synthesis and biological evaluation of c-12' substituted vinflunine derivatives

*LEI Xin Sheng, TANG Peng Cho, YU Xiang Da, LIU Zhen Hong, LV He Jun, YIN Long, and **YANG Fang Long**, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China, tangpc@shhrp.com, yangfl@shhrp.com*

A series of novel C-12' substituted vinfunine derivatives has been synthesized. Several compounds in this series possess comparable potency in vitro cytotoxicity against A549 cell lines. The preparation and biological evaluation of these compounds will be presented.



MEDI 132

Investigation of glyburide and its metabolites in urine and plasma of pregnant patients under treatment for gestational diabetes

Selvan Ravindran[1]*, Olga Zharikova*[1]*, Tatiana Nanovskaya*[1]*, Ronald Hill*[2]*, Donald Mattison*[3]*, Gary Hankins*[1]*, and Mahmoud Ahmed*[1]*. (1) Department of Obstetrics and Gynecology, Univeristy of Texas Medical Branch, 301, University Blvd, Galveston, TX 77550, seravind@utmb.edu, (2) Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA, (3) Center for Research for Mother and Children NICHD, Obstetric-Fetal Pharmacology Research Units (OPRU) Network, Bethseda, MD*

Glyburide is metabolized by human hepatic and placental microsomes to seven metabolites. The aim of this investigation is to determine the concentration of these metabolites in urine and plasma of gestational diabetics under treatment with glyburide. Human plasma and urine were obtained from patients according to an approved protocol. Glyburide and its metabolites were identified by their retention times and selected ion monitoring at m/z 510 and m/z 494, respectively. Analysis of urine samples revealed the presence of M1, 4-trans-hydroxycyclohexyl glyburide; M2a, 4-cis-hydroxycyclohexyl glyburide; and M2b, 3-cis-hydroxycyclohexyl glyburide along with glyburide. Few more metabolites are observed in low quantities. Preliminary data for plasma revealed the metabolites observed in Urine. The ratio of the amount of each metabolite to the total varied between individuals. For each patient, the concentrations of metabolites in urine were higher than in plasma. The pharmacological effects of these metabolites, if any, are currently unclear. Supported by the OPRU of NICHD.

MEDI 133

Synthesis and structure-activity relationship of pyridyl sulfonamide 11-β-HSD1 inhibitors

David S. Yoon[1]*, Shung C. Wu*[1]*, James Li*[1]*, Haixia Wang*[1]*, Ligaya M. Simpkins*[1]*, Zheming Ruan*[2]*, Christopher B. Cooper*[2]*, Katy Van Kirk*[2]*, Zhengping Ma*[3]*, Ramakrishna Seethala*[3]*, Rajasree Golla*[3]*, Akbar Nayeem*[4]*, Stanley R. Krystek Jr.*[4]*, David A. Gordon*[3]*, Jeffrey A. Robl*[1]*, and Lawrence G. Hamann*[1]*. (1) Discovery Chemistry, Bristol-Myers Squibb Company, P.O. Box 5400, Princeton, NJ 08543-5400, david.yoon@bms.com, (2) Early Discovery Chemistry, Bristol-Myers Squibb Company, Princeton, NJ 08543, (3) Discovery Biology, Bristol-Myers Squibb Company, Princeton, NJ 08543-4000, (4) Computer-Assisted Drug Design, Bristol-Myers Squibb Company, Princeton, NJ 08543-5400*

The intracellular enzyme 11-β-hydroxysteroid dehydrogenase type I ("11-β-HSD1") catalyzes the transformation of cortisone to cortisol. Over expression of 11-β-HSD1 in the liver and adipose has been shown to increase the level of tissue cortisol. Moreover, excess tissue cortisol has been linked to various metabolic disorders such as type 2 diabetes, obesity and metabolic syndrome. Numerous animal models and preclinical studies strongly support the hypothesis that inhibition of 11-β-HSD1 will therefore be an efficacious treatment for severe metabolic disorders. Reported herein is a series of novel pyridyl sulfonamide 11-β-HSD1 inhibitors. Several molecules were discovered that had improved characteristics compared to the lead compound. Key structural modifications enhanced *in vitro* potency, aqueous solubility and liver microsomal stability and addressed off-target liabilities such as hERG and CYP inhibition.

MEDI 134

Multiple chemical ligation under thermal cycle

Yuko Kondo[1]*, Hiroshi Abe*[1]*, Hiroshi Jinmei*[1]*, Naoko Abe*[1]*, Kyoko Aikawa*[2]*, Isamu Matsumoto*[2]*, and Yoshihiro Ito*[1]*. (1) Nano Medical Engineering Laboratory, RIKEN, 2-1, Hirosawa, Wako-Shi, Saitama 351-0198, Japan, Fax: +81-(0)48-467-9300, yukok@riken.jp, (2) Department of Chemistry, Ochanomizu University, Tokyo 112-8610, Japan*

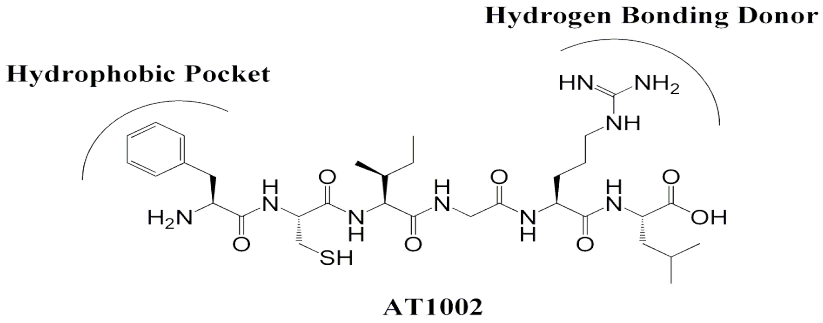
Enzymatic ligation methods have been used for the diagnostic detection of DNA sequences. Here, we investigated a nonenzymatic phosphorothioate–iodoacetyl DNA chemical ligation as a method for detection and identification of RNA and DNA. The specificity of chemical ligation on the DNA target was shown to allow the discrimination of a single point mutation, that is, ligation yield on complementary DNA was 16.1-fold higher than that on the template containing one nucleotide mismatch. Although the activity of usual enzymatic ligation was very low for RNA targets, the newly developed chemical reaction was very efficient for RNA targets. The yield of chemical ligation with an RNA target was 70% during 5 seconds. The reaction also exhibited 60-fold signal amplification by catalytic reaction on RNA template under thermal cycling in periods as short as 90 min.

MEDI 135

Identification of AT-1002 as a mucosal permeability modulator

*Min Li, **Ed Oliver**, John Vere, Kelly M. Kitchens, Mark Ginski, Shobha Gopalakrishnan, Niranjan Pandey, Sefik S. Alkan, Blake Paterson, and **Amir P. Tamiz**, Alba Therapeutics Corporation, 800 W. Baltimore Street, Suite 400, Baltimore, MD 21201, atamiz@albatherapeutics.com*

Zonula occludens toxins (ZOT), a 44.8 kDa protein has proven to be a tight junction modulator and promising candidate in drug delivery. Previously, we had identified ΔG, a 12 kDa peptide as the permeability inducing fragment of ZOT. The goal of this study was to probe the minimal structural requirement for permeability modulation. Herein, we describe structure activity relationship (SAR) of AT-1002, a six amino acid peptide and its permeability modulating activity in vitro. Initial SAR study has been conducted by employing the following strategies: 1) Alanine scan; 2) truncation, and 3) Retro-Inverso studies to identify the key amino acid(s) contributing to AT-1002 activity. Our studies have identified two pharmacophores that are crucial for potent permeability modulation.



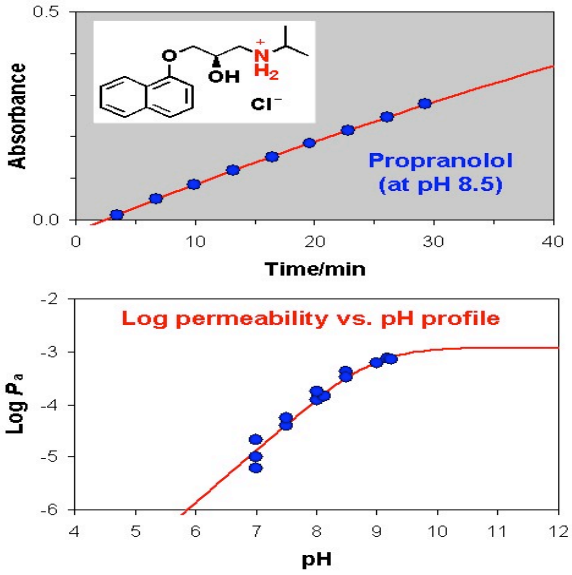
AT1002

MEDI 136

Semi-automatic permeability vs. pH profile assay for pharmaceutical drugs using a diffusion cell and a PC-controlled UV spectrophotometer

***Arno Kraft**, Nicola M. Howarth, Joanne C. Morris, and Claire Knox, Chemistry, School of Engineering & Physical Sciences, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, United Kingdom, Fax: 44-131-4513180, a.kraft@hw.ac.uk*

Permeability assays are increasingly used by the pharmaceutical industry and academic labs alike to predict the oral absorption of potential drug candidates early in the development of a new drug. In this poster, we present a semi-automated procedure for determining the permeability of selected drugs (e.g. ibuprofen, diclofenac, propranolol, chlorpromazine) across a nitrocellulose membrane coated with a 2% solution of phosphatidyl choline in hexadecane and placed between two chambers of a diffusion cell. Drug permeability was measured by following changes in drug concentration with time spectrophotometrically in a flow-through UV cell. A macro allowed UV data to be acquired every 3 – 5 minutes and then stored in a spreadsheet, while the pH was changed manually every 30 minutes. Data analysis made use of spreadsheets, and permeability coefficients obtained by curve-fitting were subsequently plotted as a function of pH to provide a permeability vs. pH profile for the drug.



MEDI 137

Spectroscopic study of cyclodextrin inclusion complexes with A-007 prodrugs

***Sarada Sagiraju**, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEWORLEANS, 102 CHEMICAL SC BLDG, 2000 LAKESHORE DR, Neworleans, LA 70148, ssagira1@uno.edu, and Branko S. Jursic, Department of Chemistry, Room # 102, University of New Orleans, New Orleans, LA 70148*

Spectroscopic evidence was used to demonstrate formation of cyclodextrin inclusion complexes with several A-007 prodrugs. These inclusion complexes are loosely formed by complexation of phenol moiety of the A-007 prodrug and β-cyclodextrin. The α-cyclodextrin seems not to have substantial effect on A-007 prodrugs due to the small size. On the other hand γ-cyclodextrin (γ-CD) with larger cavity is capable to form ternary cyclodextrin complexes (two A-007 molecules with one γ-CD). The formation of these complexes has been established by NMR, mass and NOESY NMR spectroscopy. It has been realized that complexation with CD helps not only with the modification of solubility of prodrug, but also with half life time of prodrug in vivo. The stability of these complexes is found to be concentration dependent. This fact has important implications with respect to establishing the shelf life of A-007 prodrugs.

MEDI 138

Synthesis and biological evaluation of isophosphoramide mustard(IPM)prodrugs

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Ifosfamide is an antitumor prodrug with broad spectrum clinical activity. It is biotransformed in vivo by P-450 mixed-function oxidases to an unstable intermediate, 4-hydroxyifosfamide, which breaks down to form IPM, the presumed active metabolite. Unfortunately, the clinical utility of ifosfamide is limited by the formation of acrolein and chloroacetaldehyde, oxidative by-products that cause serious organ toxicities. To overcome this problem we have synthesized a number of prodrugs of IPM that do not require oxidative bioactivation. Instead, the prodrugs are converted to IPM by the action of carboxylate esterases, enzymes that are ubiquitous in mammalian tissue. The prodrugs are more effective than IPM at inhibiting the growth of tumor cells in culture and several are as active as the clinical agent, ifosfamide, at prolonging the life-span of mice bearing intraperitoneally-implanted L1210 Leukemia.

MEDI 139

Preparation of polymeric spheres encapsulating photosensitizers for the treatment of leishmaniasis

***Swathi Gannavaram**, David L. Cedeño, and Marjorie A. Jones, Department of Chemistry, Illinois State University, Campus Box 4160, Normal, IL 61790-4160, sgannav@ilstu.edu*

Leishmaniasis is a parasitic disease affecting millions of people around the world. Our group is evaluating novel porphyrin photosensitizers as potential therapeutic drugs against this disease. Effective treatment may require a proper delivery system to enhance selectivity and reduce their toxicity to the host. We are exploring the encapsulation of photosensitizers in biodegradable polymers as a useful method of drug delivery. Polymeric spheres (50:50 PLGA (poly(D,L-lactide-co-glycolide)) containing photosensitizers (meso-tetra phenyl porphyrin, TPP or aluminum phthalocyanine chloride, AlPCCl) have been prepared using an emulsification-diffusion method. The preparation yields particles with size in a 200-400 nm range. The polymer-porphyrin preparations have been evaluated for their physicochemical properties and

their effectiveness against the growth of Leishmania tarentolae promastigotes using the MTT assay. In addition, since the photosensitizing properties of TPP and AlPCCl can be utilized to enhance their pharmacological activity, time dependent exposure of the parasites cultures to visible light was studied.

MEDI 140

Preparation and evaluation of novel porphyrins incorporated in liposomes to treat leishmaniasis

***Shruti Padhee**, David L. Cedeño, and Marjorie A. Jones, Department of Chemistry, Illinois State University, Campus Box 4160, Normal, IL 61790-4160, spadhee@ilstu.edu*

Leishmaniasis is a parasitic disease that affects 12 million people around 88 countries in the world. Leishmania parasites are aerobic and depend on oxidative phosphorylation for survival. However, they cannot produce heme so they depend on their host to obtain it. We have incorporated three novel acenaphthoporphyrins into small liposomes as a potential drug delivery system to treat leishmaniasis. The liposomes are made up of phosphatidylcholine, cholesterol and phosphatidylglycerol (10:5:4 mol ratio). Porphyrin to lipid molar ratios in the range 1:10 to 1:1000 were evaluated. These porphyrins are good photosensitizers and induce the production of reactive oxygen species when exposed to visible light. Reactive oxygen species generated via a photodynamic mechanism induces cellular death. The efficacy of the liposome preparations and the viability of Leishmania tarentolae promastigotes have been determined using the MTT assay method. In addition, confocal microscopy is being used to track the porphyrins inside the Leishmania parasite.

MEDI 141

Ligands assisted protein structure (LAPS) of the endocannabinoid targets

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

The endocannabinoid system encompasses two GPCRs (CB1 and CB2), enzymes involved in the biosynthesis and biotransformation of their endogenous cannabinoid ligands (endocannabinoids), and a partially-characterized transport system. The function of these proteins can be modulated by selective ligands which may serve as potential drug-discovery leads. Structural information on the endocannabinoid-system proteins allows us to optimize our ligand design and lead optimization efforts. We have developed a method for obtaining direct information on the binding motifs of ligands with the CB1 and CB2 receptors and the enzymes associated with the endocannabinoid system by using high affinity covalent ligands. To indentify the site(s) of attachment of individual ligands we use a combination of chemical and biochemical methods, including suitable receptor mutants, receptor expression and purification followed by analysis of the digests by LC/MS methods. The experimental information is used to develop computational models for ligand-receptor interactions.

Supported by R37-DA03801 and P01-DA09158.

MEDI 142

Molecular basis for irreversible inhibition of EGFR kinase and beta-lactamases

***Tarek S. Mansour**, Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5580, mansout@wyeth.com*

Protein kinases regulate all cellular signaling pathways and many have emerged as druggable targets by small molecule inhibitors. In eukaryotic cells, the primary mechanism for regulating protein functions is associated with a phosphorylation reaction of either a serine, threonine or tyrosine residue. Most kinase inhibitors that advanced in preclinical and clinical studies target the conserved adenosine triphosphate (ATP) binding site which renders molecular target selectivity a formidable challenge. However, recent studies highlighted the roles of reactive cysteine residues that form a covalent bond with the inhibitor and gatekeeper residues, which allow access to a hydrophobic site, both as important determinants of kinase inhibition specificity. Irreversible inhibitors of the epidermal growth factor receptor (EGFR) and ErbB receptors such as EKI-785, EKB-569, and HKI-272 are effective against several cancers. The molecular basis for the activity of HKI-272, currently in advanced Phase II studies, in terms of structural information with the gatekeeper threonine 790 to methionine substitution and the potential implication to drug design will be discussed.

Serine and metallo beta-lactamases catalyze the hydrolysis of beta-lactam rings in all classes of beta-lactam antibiotics which is a major cause of bacterial resistance to beta-lactam antibiotics. Reports from our laboratories on 6-methylidene penems as mechanism-based inhibitors of serine-reactive class A and C beta-lactamases disclosed extensive structure activity relationships with penems containing monocyclic, bicyclic, and tricyclic heterocycles that adopt the Z configuration at the C6 position.

The mode of action of penem inhibitors involves acylation by the catalytic serine residue followed by beta-lactam ring opening and a sequence of transformations amounting to a remarkable 7-endo trig rearrangement reaction. On the basis of computational and structural information, further insights concerning the mechanism of inactivation and the stereochemical question of the C7 absolute configuration in the rearranged product 1,4-dihyrdothiazepine will be discussed.

MEDI 143

Challenge of CNS drug discovery

***Peter R. Bernstein**, LO Chemistry, CNS Discovery, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, Fax: 302-886-4989, peter.bernstein@astrazeneca.com*

The serotonin 5-hydroxytryptamine 1B receptor (5-HT_{1B}) has been found to play a crucial role in the modulation of synaptic release of serotonin. Since clinically effective antidepressants enhance serotonergic neurotransmission it has been hypothesized that 5-HT_{1B} antagonists are potential agents for the treatment of anxiety and depression.

AstraZeneca's continuing research in this area will be described, with a focus on our providing compounds that will effectively test this hypothesis by: the discovery of multiple clinical candidates, the development of the first 5-HT_{1B} PET ligand, and the synergies achieved in CNS drug discovery by the combination of these work streams.

MEDI 144

Emerging therapeutic opportunities for the treatment of Alzheimer's Disease

***Ronald L Magolda**, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, magoldr@wyeth.com*

Alzheimer's disease (AD) is the most common form of progressive dementia and afflicts millions of people. Current therapies afford only modest relief and can neither permanently arrest nor reverse symptoms. At present, there are no disease-modifying therapies available. AD research is focused on a few major strategies. One direction involves developing agents that enhance cognition by manipulating neurochemistry. Modulation of serotonin receptors (5HT6 or 5HT1a) offers attractive options. A second direction focuses on identifying disease-modifying agents that lower the level of putative pathogens such as Ab40 or Ab42 derived from the proteolytic processing of amyloid processing protein (APP). Inhibiting proteinases involved in processing APP (b-secretase (BACE), g-secretase (GS)) could diminish brain pathology and improve cognitive capability. This presentation will describe our multi-target strategy dedicated to the design, synthesis and biological characterization of small molecules that may offer physicians several new therapeutic options to treat AD patients.

MEDI 145

Discovery of innovative small molecule therapeutics

***Magid Abou-Gharbia**, Chemical and Screening Sciences, Wyeth Research, Princeton, 500 Arcola Road, Collegeville, PA 19426, abougam@wyeth.com*

Transition of early leads into developmental drug candidates is the cornerstone of drug discovery and development. Several medicinal chemistry approaches have been utilized successfully to optimize initial leads identified via screening of natural products, compound libraries, rational and/or structure-based drug design. Advances in technology have enabled natural products-based drug discovery to operate on a more rational basis, and this spurred renewed interest in natural products as platforms for drug discovery. Targeted modification of complex natural products is now feasible, using precise synthetic methods and high-resolution analytical tools. Genetic engineering of biosynthetic pathways of proven natural product scaffolds can provide new starting points for optimization of these privileged structures. Multi-dimensional lead optimization is an essential component of many strategies since the critical path activities have become broader and requirements for compound advancement more rigorous Sequential improvement of individual characteristics of compounds or series is no longer a viable avenue for successful lead optimization. The presentation will highlight contrasting tactics leading to the discovery of a number of small molecule drug candidates and highlighting the unique attributes of Wyeth's recently marketed products.

MEDI 146

Effect of fluorine on substrate and inhibitor activity toward GABA aminotransferase

***Richard B. Silverman**, Department of Chemistry and Center for Drug Discovery and Chemical Biology, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208-3113, Fax: 847-491-7713, Agman@chem.northwestern.edu*

This will be a two-part lecture related to the interaction of molecules containing fluorine with the pyridoxal 5'-phosphate dependent enzyme, gamma-aminobutyric acid aminotransferase (GABA-AT). The first part will describe studies of the reaction catalyzed by GABA-AT on (R)- and (S)-4-amino-3-fluorobutanoic acid (3-F-GABA) as a way of using the fluorine atom to provide insight into the binding conformation of the substrate. Using a combination of computer modeling and the knowledge that vicinal C-F and C-NH_3^+ bonds have a strong preference to align gauche rather than anti to each other, the dynamic binding process and the bioactive conformation of GABA bound to GABA-AT can be inferred based on the different biological behavior of the two enantiomers of 3-F-GABA when they bind to the enzyme.

The second part of the lecture will describe the incorporation of fluorine into an inactivator of GABA-AT to enhance its potency, the evaluation of the compound as an inactivator, and some animal studies that show its effectiveness in a rat model for drug addiction.

MEDI 147

Importance of fluorine in the design of non-ATP competitive MEK inhibitors

***Haile Tecle**, Pfizer Research Technology Center, 620 Memorial Drive, Cambridge, MA 02139, haile.tecle@pfizer.com*

N-Aryl anthranilic acids with micromolar potency against MEK were first identified from HTS screening. Since, at the time, the crystal structure of MEK was not known, conventional medicinal chemistry was employed to optimize the SAR to improve potency. The role fluorine played in transforming the micromolar inhibitors into clinical candidates CI-1040 and PD-0325901 with sub-nanomolar potency for MEK will be described. The role these potent inhibitors played in solving the MEK structure will, also, be discussed.

MEDI 148

HTS to MK-0731: The role of fluorine in optimization of Kinesin Spindle Protein (KSP) inhibitors for the treatment of cancer

***Christopher D. Cox**[1], Paul J. Coleman[1], Mark E. Fraley[1], Robert M. Garbaccio[1], Michael J. Breslin[1], David B. Whitman[1], John D. Schreier[1], Maricel Torrent[1], Rob Lobell[2], Carolyn Buser[2], Wiekang Tao[2], Keith Rickert[2], Hans Huber[2], Nancy E. Kohl[2], Thomayant Prueksaritanont[3], Chunzi Li[3], Donald E. Slaughter[3], Youwei Yan[4], Lawrence C. Kuo[5], and George D. Hartman[1]. (1) Department of Medicinal Chemistry, Merck & Co., Inc, 770 Sumneytown Pike, P O Box 4, WP14-2, West Point, PA 19486, Fax: 215-652-7310, chris_cox@merck.com, (2) Department of*

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Kinesin spindle protein (KSP) is a molecular motor essential for proper separation of the spindle poles during mitosis. Disruption of KSP function results in mitotic arrest due to collapse of the bipolar spindle, triggering the apoptotic pathway in tumor cells. KSP inhibitors therefore have potential as antiproliferative agents useful for the treatment of cancer, and may be devoid of mechanism-based side effects common to agents that directly target microtubules. This talk will describe the optimization of KSP inhibitors beginning with an HTS-derived lead and culminating in the identification of MK-0731, a molecule that recently entered clinical trials for the treatment of taxane-refractory cancer. The presentation will highlight how fluorine was used to control physicochemical properties of leading compounds in order to minimize P-glycoprotein efflux and ion channel activities.

MEDI 149

Beneficial effects of fluorine substitution in inhibitors of cholesteryl ester transfer protein

***Roger B. Ruggeri**, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340*

Inhibition of cholesteryl ester transfer protein (CETP) is an intriguing target for the elevation of HDL cholesterol and the treatment of cardiovascular diseases. Inhibitor series of this highly lipophilic protein target have displayed a variety of instances where fluorine substitution provides beneficial effects on inhibitory activity as well as plasma clearance in vivo.

MEDI 150

The use of fluorine in the design of new beta-secretase inhibitors

***James C. Barrow**, Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 4, West Point, PA 19486, james_barrow@merck.com*

Inhibition of the aspartyl protease beta-Secretase (BACE-1, beta amyloid precursor protein cleaving enzyme) is considered to be a promising approach for the treatment of Alzheimer's disease. The large, hydrophilic active site provides challenges for medicinal chemists in the search for brain penetrant, small molecule inhibitors with drug-like properties. Truncation of traditional aspartyl protease transition state isosteres has led to several series of lower molecular weight beta-secretase inhibitors, and judicious placement of fluorine atoms can be used to modulate cellular activity and brain penetration. In addition, fluorine has been used in the process of optimizing the potency of a completely novel structural template of beta-secretase inhibitors. This new class uses a piperidine core that interacts with the catalytic aspartates, and incorporation of fluorine into the initial compounds was critical in obtaining the requisite properties for x-ray structure determination of these compounds in the enzyme active site.

MEDI 151

Overview of newer approaches to treating depression

***Nicholas J. Lodge**, Neuroscience Biology Department, Bristol-Myers Squibb Co, 5 Research Parkway, Wallingford, CT 06492-7660, nicholas.lodge@bms.com*

Depression is a debilitating psychiatric illness that affects millions of people world-wide. Currently available pharmacological therapies for depression are based the serendipitous discoveries of the tricyclic agents and monoamine oxidase inhibitors more than 50 years ago and act either through the prevention of monoamine metabolism or inhibition of monoamine reuptake. The current monoamine-based antidepressants typically require several weeks for onset of effect, only achieve remission rates of approximately 35% and exhibit a number of tolerability issues. Thus, there continues to be a significant unmet medical need for antidepressants with improved efficacy, more rapid rate of response, and reduced side effects. Fortunately, a broad array of novel mechanisms, including agents that act on the stress axis, glutamate targets and two-pore potassium ion channels, are currently being explored as potential antidepressants with the promise of providing improved therapies. Additionally, systematic improvements in monoamine therapies also have the potential to deliver improved efficacy and reduced side effects.

MEDI 152

1H-Pyrazolo[3,4-g]hexahydro-isoquinolines as selective glucocorticoid receptor antagonists with high functional activity

***Karen Williams**, Argenta Discovery, 8/9 Spire Green Centre, Flex Meadow, Harlow, Essex, CM19 5TR, United Kingdom, Karen.Williams@argentadiscovery.com*

Psychotic major depression (PMD) is associated with central hypercortisolemia and has been effectively treated with the glucocorticoid receptor (GR) antagonist mifepristone in mid-stage clinical trials. However, the abortifacient activity of mifepristone, which results from progesterone receptor antagonism, will limit its clinical utility. We will describe the discovery of selective, high-affinity GR antagonists as potential second-generation drugs for PMD. These GR antagonists are based on N-arylsulfonyl pyrazolo-fused azadecalins. SAR of substitution on peripheral sites of the scaffold (X,Y,Z) will be covered.

MEDI 153

Derivatives of 7H-imidazo[1,2-a]imidazoles are corticotropin releasing factor receptor type 1 (CRF1R) antagonists: Lead discovery ad optimization

***Dmitry Zuev**, Department of Neuroscience, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702, dmitry.zuev@bms.com*

6 - Chloro - 2 - trifluoromethyl - 7 - aryl - 7H - imidazo [1,2-a] imidazol - 3 -ylmethylamines represent a novel series of high-affinity corticotropin-releasing factor type 1 receptor (CRF1R) antagonists. The studied analogs 2 were conveniently prepared in a parallel fashion with high yields from common chloromethyl intermediate 1 by selective monoamination. The discovery of the lead compound and the optimization of its binding potency is discussed herein.

MEDI 154

Potent and selective 5-HT1B/D antagonists/inverse agonists with reduced hERG affinity for the treatment of depression

***Christopher J Helal**, Neuroscience Medicinal Chemistry, Pfizer Global Rersearch and Development, MS 8118W-314, Groton, CT 06340, chris.j.helal@pfizer.com*

5-HT1B/D antagonists have potential to be novel, efficacious, rapid-onset antidepressants. Medicinal chemistry efforts to optimize a series of aryl piperazines to yield potent and selective 5-HT1B/D antagonists with reduced affinity for the hERG channel will be discussed. Optimization of CNS penetration utilizing in vitro systems and the biological profiles of key compounds will also be presented.

MEDI 155

The design and development of triple uptake inhibitors as a novel treatment of depression

***Zhengming Chen**, DOV Pharmaceuticals, 150 Pierce Street, Somerset, NJ 08873-4185, zchen@dovpharm.com*

The evolution of antidepressants over the past four decades has involved the replacement of drugs with a multiplicity of effects (e.g., TCAs) by those with selective actions (i.e., SSRIs). This strategy was employed to reduce the adverse effects of TCAs, largely by eliminating interactions with certain neurotransmitters or receptors. Although these more selective compounds may be better tolerated by patients, selective drugs, specifically SSRIs, are not superior to older drugs in treating depressed patients as measured by response and remission rates. It may be an advantage to increase synaptic levels of both serotonin and norepinephrine, as in the case of dual uptake inhibitors like duloxetine and venlafaxine. An important recent development has been the emergence of the triple uptake inhibitors (TUIs/SNDRIs), which inhibit the uptake of the three neurotransmitters most closely linked to depression: serotonin, norepinephrine, and dopamine. Preclinical studies and clinical trials indicate that a drug inhibiting the reuptake of all three of these neurotransmitters may produce more rapid onset of action and greater efficacy than traditional antidepressants. This presentation will detail the medicinal chemistry involved in the design, synthesis and discovery of DOV's triple uptake inhibitors.

MEDI 156

Defining structure-activity relationships for substrates of drug efflux transporters

***Thomas J. Raub**, Drug Disposition, Eli Lilly and Company, Lilly Research Labs, Indianapolis, IN 46285, raubtj@lilly.com*

It is recognized that efflux transporters like P-glycoprotein (P-gp; ABCB1) and breast cancer resistance protein (BCRP, ABCG2) can affect absorption, distribution, metabolism, excretion and toxicology of compounds in development. Investing in screening structure-activity relationships is warranted in early discovery when exposure and/or target activity in an in vivo efficacy model is not achieved and transport is identified as a rate-limiting factor. Designing a chemistry strategy for circumventing a limiting transporter interaction can be daunting. Retaining biological potency and metabolic stability restricts what can be done, and the factors for transporter recognition of substrates are complicated and poorly understood. Often, no single functional group is the cause, but one group can accentuate the recognition points existing within a scaffold. We will examine practical examples defining our understanding of how efflux transporters recognize compounds as substrates and what structural changes can be made in a chemotype to influence transporter effects.

MEDI 157

Mechanism of action of the multidrug resistance-linked P-glycoprotein (ABCB1)

***Suresh V Ambudkar**, In-Wha Kim, Luciann L Cuenca, Krishnamachary Nandigama, and Zuben E Sauna, Laboratory of Cell Biology, National Cancer Institute, NIH, 37 Convent Drive MSC4256, Building 37, Room 2120, Bethesda, MD 20892-4256, Fax: 301-435-8188, ambudkar@mail.nih.gov*

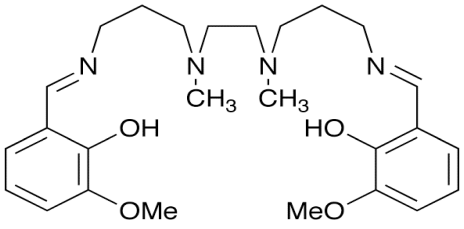
The ATP-binding cassette (ABC) drug transporters play a major role in the development of multidrug resistance in cancer cells. One of the many unresolved issues of transport cycle of P-glycoprotein (Pgp) is whether it is the nucleotide binding alone or nucleotide hydrolysis that provides the “power-stroke” for the transport of drug-substrate. We used the Walker B double mutant of Pgp (E556Q/E1201Q), where ATP hydrolysis is severely impaired resulting in the occlusion of nucleotide in a non-exchangeable form. This reaction intermediate in wild-type Pgp can be generated by using non-hydrolyzable ATP analog ATP-g-S. Our studies suggest that although two ATP molecules may initially bind to the two NBDs of Pgp, only one is driven to a pre-hydrolysis reaction intermediate E·S state of the ATPase reaction and occlusion of nucleotide at this step provides the “power-stroke” for the movement of drug-substrate from a high-affinity to a low-affinity site in the transmembrane domains.

MEDI 158

Gallium radiopharmaceuticals for imaging MDR1-Pgp transport function with PET: Effects of chelate stereochemistry on tracer fate in vivo

***Mark A. Green**, Carla J. Mathias, and Yui-May Hsiao, Department of Industrial & Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, Fax: 765-496-3367, magreen@pharmacy.purdue.edu*

Lipophilic monocationic Ga(III) complexes of linear hexadentate salicylaldimine ligands, such as H_2[(3-MeOsal)$_2$DMBAPEN], have potential utility in imaging with positron emission tomography (PET) to non-invasively assess tumor MDR1 Pgp transport function when radiolabeled with generator-produced ^{68}Ga ($T_{1/2}$ = 68 minutes). Chelates of this type, in which the oxygen donor atoms occupy trans-coordination sites, exhibit chirality due to the clockwise, or anticlockwise, arrangement of the ligand about the octahedral metal center. Baseline resolution of racemic [^{67}Ga][Ga(3-MeOsal)$_2$DMBAPEN]$^{1+}$ into its (+)- and (–)-stereoisomers was achieved by chiral HPLC, with the resolved ^{67}Ga-chelate stereoisomers showing no HPLC evidence of racemization over 8-days. The effects of chelate stereochemistry on compound biodistribution and pharmacokinetics have been investigated using Mdr1a/b knock-out (KO) mice and FVB wild-type controls. The biodistribution and pharmacokinetics of the [^{67}Ga][Ga(3-MeOsal)$_2$DMBAPEN]$^{1+}$ chelate are found to be significantly influenced by Pgp expression, as well as by stereochemistry about the metal center.



H_2[(3-MeOsal)$_2$DMBAPEN]

MEDI 159

Signals that modulate p-glycoprotein at the blood-brain barrier: Potential therapeutic targets

***David S. Miller**, Laboratory of Pharmacology and Chemistry, NIH/NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709, Fax: 919-541-5737, miller@niehs.nih.gov, Anika MS. Hartz, Biochemistry and Molecular Biology, University of Minnesota Medical School, Duluth, Duluth, MN 55812, and Björn Bauer, University of Minnesota College of Pharmacy, Duluth, MN 55812*

The blood-brain barrier that resides within the brain capillary endothelium limits pharmacotherapy of CNS disorders, e.g., neurodegenerative diseases, epilepsy, brain cancer, and neuro-AIDS. High level of expression, luminal membrane location, multispecificity and high transport potency make P-glycoprotein a gate-keeper of the blood-brain barrier and thus a primary obstacle to drug delivery into the brain. Using intact brain capillaries from rats and mice, we have identified multiple extracellular and intracellular signals that regulate P-glycoprotein; several extended signaling pathways have been mapped. Three pathways are triggered by elements of the brain's innate immune response, one by glutamate and one by xenobiotic-nuclear receptor (PXR) interactions. Signaling is complex, with several pathways having common signaling elements (TNF-R1, ETB receptor, PKC, NOS), suggesting a regulatory network. Finally, several steps in signaling are potential therapeutic targets that could be used to modulate P-glycoprotein activity in the clinic.

MEDI 160

Bivalent inhibitors of P-glycoprotein

***Jean A. Chmielewski**, Marcos Pires, Dana Emmert, and Christine A. Hrycyna, Department of Chemistry, Purdue University, West Lafayette, IN 47906, chml@purdue.edu*

P-glycoprotein (P-gp) is an ATP-dependent pump that reduces accumulation of drugs within cells and is a member of the large ATP-binding cassette (ABC) superfamily of membrane transporters. P-gp is over-expressed on the surface of cancer cells and HIV-infected macrophages, and, as such, plays a major role in multi-drug resistance in cancer and HIV. P-gp is also present on apical side of the luminal membrane of brain capillary endothelial cells (the blood brain barrier), and precludes access of a number of anti-cancer, anti-HIV, anti-Alzheimer's and other therapies to the brain. By taking advantage of the multiple substrate binding sites within the transporter domain of P-gp, we have developed novel dimeric prodrug inhibitors of P-gp based on the therapeutic agents themselves. Inhibition of P-gp transport with these agents will be discussed.

MEDI 161

Pharmacoinformatic approaches to Target P-glycoprotein: From inhibitor design to substrate prediction

***Gerhard F Ecker**[1], Rita Schwaha[1], Michael Demel[1], and Peter Chiba[2]. (1) Department of Medicinal Chemistry, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria, Fax: 431-4277-9551, gerhard.f.ecker@univie.ac.at, (2) Institute of Medical Chemistry, Medical University of Vienna, Vienna A-1090, Austria*

The polyspecific ligand recognition pattern of P-glycoprotein (ABCB1) and other ABC-transporter requires more sophisticated algorithms than those routinely used in computational drug design. Especially non-linear methods such as artificial neural networks and similarity-based approaches showed excellent performance in in silico screening runs both for identification of new P-glycoprotein inhibitors and in lead optimisation cycles. Furthermore, combined pharmacophor modelling/QSAR-studies gave first insights into strategies for designing compounds with selectivity for either of the two polyspecific transporters ABCB1 and ABCG2.

With the increasing knowledge on the physiological role of P-glycoprotein for bioavailability and brain uptake also the prediction of substrate properties becomes increasingly important. . Computational models rely on support vector machines, decision tree analysis or filter rules. We used a set of VSA-descriptors in combination with counterpropagation artificial neural networks to establish a classification model for P-glycoprotein substrates and non-substrates. Due to the high speed of VSA-descriptor calculation, this is a versatile model for high throughput in silico filtering of large compound libraries.

Financial support provided by the Austrian Science fund (#L344-N17) and the Austrian Research Promotion Agency (#B1-812074)

MEDI 162

Chemical strategies to alter P-glycoprotein efflux of drug molecules

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Medicinal chemists engaged in the discovery of therapeutic agents whose target is located within cancer cells or the CNS are often plagued by efflux due to transporters such as P-glycoprotein (P-gp). Though P-gp evolved with a great deal of substrate promiscuity to help protect the body from various xenobiotic threats, small chemical changes to key regions of a drug molecule can result in a dramatic change in its ability to be effluxed. This talk will present two case studies where judicious incorporation of fluorine modulates the physicochemical properties of leading compounds in such a way as to maintain on-target potency while eliminating P-gp efflux liabilities. Conversely, an example will be presented where P-gp susceptibility was engineered into a leading compound to restrict its access to the CNS. Lessons learned from these case studies should encourage and inform medicinal chemists struggling to alter the efflux profiles of leading compounds.

MEDI 163

CCR2/CCR5 Antagonists: A new approach for the treatment of autoimmune diseases

***Wolfgang Miltz**[1], Pius Loetscher[2], Philipp Janser[2], Rene Hersperger[2], Peter Hiestand[2], and Josef Meingassner[2]. (1) Global Discovery Chemistry, Novartis Institutes for BioMedical Research, CH-4001 Basel, Switzerland, wolfgang.miltz@novartis.com, (2) Novartis Institutes for BioMedical Research, CH-4001 Basel, Switzerland*

Literature data from transgenic and knockout animals underline the importance of chemokine receptor signaling in various diseases and several inhibitors are in development by different companies. For inflammatory diseases, CCR2 and to some extent CCR5 play a crucial role since they are expressed on most inflammatory cells, in particular monocytes.

In this presentation, we would like to show the in vitro and in vivo results obtained with our dual CCR2/CCR5 antagonists. They potently inhibit the binding of human CCR2/MCP-1 and CCR5/MIP-1alpha in the nanomolar range and they are cross-reactive with rodent and monkey receptors. In functional assays, calcium-flux and chemotaxis are inhibited, both in transfected and in primary cells. The effects in a mechanistic model of monocyte migration will be discussed and activities in animal models of autoimmune diseases will be presented.

MEDI 164

Molecular basis for efficacy of ligands and receptors: Balancing between agonism and inverse agonism/antagonism

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It is known among medicinal chemists that small chemical modifications occasionally can turn antagonists into agonists, and vice versa. We have studied this phenomenon in a systematic manner using multiple terminally-modified wFw tripeptides, in combination with a large library of mutants of the constitutively active ghrelin receptor. Efficacy –switch epitopes were identified in the ligand, where certain types of chemical changes swapped the ligand between high potency agonism and equally high potency inverse agonism. The wFw-containing peptides – agonists as well as inverse agonists – are affected by receptor mutations covering the whole main ligand-binding pocket with key interaction sites being an aromatic cluster in TM-VI and VII and residues on the opposing face of TM-III. Importantly, gain-of-function in respect of either increased agonist or increased inverse agonist potency or in respect of swap (up and down) between high potency versions of these properties, was obtained at a number of key positions. In particular, space generating substitutions at position III:04 shifted the efficacy of this chemotype ligands from inverse agonism toward agonism, whereas similar substitutions at position III:08 shifted the efficacy from agonism toward inverse agonism. It is suggested that the relative position of the ligand in the binding pocket between this “efficacy shift region” on TM-III and the opposing aromatic cluster in TM-VI and TM-VII leads either to agonism – via superficial binding – or it leads to inverse agonism – via more profound binding (Annu.Rev.Pharmacol. Toxicol. (2006) 46: 481-519). In the chemokine receptors most non-peptide compounds have a key anchor-point – GluVII:06 - in the same interface between TM-III and VIII and can in a similar fashion swap between antagonism and agonism. Thus, it is clear that efficacy can be structurally “uncoupled” from affinity / potency which can form the basis for knowledge-based design of ligands with the desired pharmacological profiles.

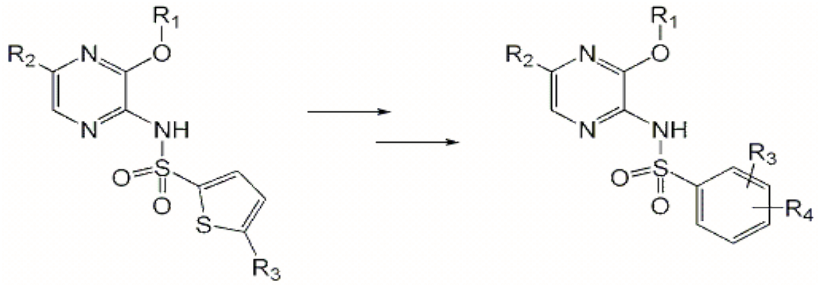
MEDI 165

Discovery and optimization of a series of CCR4 antagonists from Hit to CD

***Antonio Mete**[1], Glen Andrews[2], Andrew Baxter[1], David Cheshire[1], Lorna Ewart[2], Steve Harper[2], Kevin Hickling[3], Nicholas Kindon[1], Dermot McGinnity[4], Claire Murray[2], Michael Stocks[1], Nicholas Tomkinson[1], Keith Wregget[2], and Simon Young[2]. (1) Department of Medicinal Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH, United Kingdom, Fax: +44 (0)1509 645571, Antonio.Mete@Astrazeneca.com, (2) Department of Discovery Bioscience, AstraZeneca R&D Charnwood, Leicestershire LE11 5RH, United Kingdom, (3) Department of Safety Assessment, AstraZeneca R&D Charnwood, Leicestershire LE11 5RH, United Kingdom, (4) Department of DMPK, AstraZeneca R&D Charnwood, Leicestershire LE11 5RH, United Kingdom*

Several series of CCR4 antagonists were discovered by screening a sub-set of our corporate compound collection, consisting of compounds structurally related to known chemokine antagonists. Use was made of in vitro and in vivo DMPK data to select one of the series, (N-pyrazin-2-yl-arylsulphonamides), for rapid optimisation. The lead optimisation (LO) phase of the

project was able to identify the first candidate drug (CD) in 12 months. A number of toxicological issues were encountered during the early safety evaluation of the CD, which were associated with an unexpected metabolite. A strategy was put in place to front-load some safety evaluation, which guided medicinal chemistry in the design of a second CD, which was devoid of such issues. The compounds demonstrated excellent DMPK in a number of pre-clinical species and good activity in relevant animal models, which support the utility of CCR4 antagonists in asthma.



MEDI 166

Binding site expansion and induced fit docking for GPCR ligand binding mode prediction: Application to the chemokine family of receptors

Andrew Tebben[1]*, S. Roy Kimura*[2]*, Stanley Krystek*[3]*, George V. De Lucca*[4]*, Qihong Zhao*[5]*, Jian Pang*[5]*, Mary Ellen Cvijic*[6]*, Jing Chen*[6]*, and Percy H Carter*[4]*. (1) Computer-Assisted Drug Design, Bristol Myers Squibb Company, Research & Development, P. O. Box 4000, Princeton, NJ 08543-4000, andrew.tebben@bms.com, (2) Department of Computer-Assisted Drug Design, Bristol-Myers Squibb Company, Wallingford, CT 06492, (3) Computer-Assisted Drug Design, Bristol-Myers Squibb Company, Pennington, NJ 08534, (4) Discovery Chemistry, Bristol-Myers Squibb Company, Princeton, NJ 08543, (5) Immunology Biology, Bristol-Myers Squibb Company, Princeton, NJ 08543-4000, (6) Lead Evaluation, Bristol-Myers Squibb Company, Princeton, NJ 08543-4000*

Crystal structures of Rhodopsin and, more recently, the beta-2 adrenergic receptor have become useful templates for the modeling of class-A G protein-coupled receptors as they likely represent the overall topology of this family of proteins. However, because of low sequence homology and the inherent mobility of integral membrane proteins, it is unlikely that a single model accurately reflects the ensemble of conformations accessed by the receptor. We have devised a procedure using induced fit modeling coupled with binding site expansion that enables an ensemble approach to binding mode prediction. Utilizing these methods, models of several chemokine receptors complexed with antagonists have been produced and validated against mutagenesis and structure activity data. Comparison of these models provides insight into receptor specific interactions and the basis for selectivity.

MEDI 167

Discovery of the highly potent, selective and orally bioavailable CCR9 antagonist CCX282-B

Solomon B. Ungashe[1]*, Zheng Wei*[1]*, Werner Rubas*[1]*, Nu Lien Lai*[1]*, Linda Ertl*[1]*, Trageen Baumgart*[1]*, Helen Wang*[1]*, Zhenhua Miao*[1]*, Sok-Ying Hor*[2]*, Brett Premack*[1]*, Jimmie Moore*[1]*, Edward Sullivan*[1]*, Andrew Pennell*[1]*, Satish Keshav*[2]*, Martin Sanders*[1]*, Maureen Howard*[1]*, J. J. Kim Wright*[1]*, Pirow Bekker*[1]*, and Thomas J. Schall*[1]*. (1) ChemoCentryx, 850 Maude Ave, Mountain View, CA 94043, Fax: 650-625-8940, sungashe@chemocentryx.com, (2) Centre for Gastroenterology, Royal Free Hospital, London, United Kingdom*

The CC chemokine receptor 9 (CCR9) mediates migration of gut-homing T cells to the intestine, where its ligand TECK (CCL25) is highly expressed. Although the exact cause of Crohn's disease remains unknown, the hallmark of the disease is infiltration of inflammatory T cells to the intestinal mucosa. Blockade of the interaction between CCR9 and its ligand TECK with a small molecule antagonist thus represents a novel approach to the treatment of Crohn's disease. We have discovered a series of highly potent, selective, safe, and orally bioavailable CCR9 antagonists. Here we will summarize medicinal chemistry work that led to the discovery of CCX282-B and present a brief summary of Phase 1 and Phase 2 clinical studies with the compound.

MEDI 168

Introductory Remarks

Patrick M. Woster*, Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, Fax: 313-577-2033, pwoster@wayne.edu*

An introduction to the lysine-specific demethylase as a target for antitumor therapy symposium will be presented

MEDI 169

Pharmacologic manipulation of the components of aberrant gene silencing in cancer

Stephen B. Baylin*, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins University School of Medicine, 1650 Orleans Street, Baltimore, MD 21231, Fax: 410-614-9884, sbaylin@jhmi.edu*

Aberrant gene function and altered patterns of gene expression are key features of cancer. Growing evidence shows that acquired epigenetic abnormalities participate with genetic alterations to cause epigenetic dysregulation. Much is now known about the importance of promoter cytosine methylation in CpG islands and gene silencing, and it has been established beyond doubt that such methylation is intimately involved in cancer development. Many hundreds of genes may be inactivated in a single cancer by promoter methylation. Recently, the enzyme lysine-specific demethylase 1 (LSD1) was identified and found to play a significant role in the control of gene expression. The methylation of specific lysine residues, once thought to

be a stable modification, has now been shown to be a reversible process, and serves as an additional control site for gene expression. The fact that epigenetic changes are so prevalent in cancers and play a causative role in their biologies has led to the development of an entirely new therapeutic approach in which the goal is to reverse gene silencing. In this presentation, an overview of the role of gene silencing in human cancer will be presented, and epigenetic control points that can serve as sites for pharmacologic intervention will be described

MEDI 170

Histone demethylases: From enzyme discovery to biological impact

***Johnathan R. Whetstine**, Harvard Medical School and Massachusetts General Hospital Cancer Center, Building 149, 13th Street , Room 7-213, Charlestown, MA 02129, jwhetstine@hms.harvard.edu*

Events within the nucleus are governed by a number of processes, but an ever increasing amount of information is emphasizing the relationship between post translational modifications (PTMs) on the histones within the chromatin and proper developmental patterning and pathologies like cancer. The N-terminal tails of histones are subject to a plethora of PTMs including phosphorylation, ubiquitination, acetylation, and methylation. Each modification can affect chromatin architecture, but the total sum of these modifications may be the ultimate determinant of the chromatin state and biological outcome. Multiple lysine (K) residues on the tails of histone H3 and H4 have been shown to be sites for methylation. The site and degree of methylation (mono-, di-, or tri-) are linked to both transcriptional activation and repression, as well as DNA damage response. Many biological processes like heterochromatin formation and X-inactivation are regulated by histone methylation, therefore, aberrant methylation can result in human diseases such as cancer. For this reason, organisms have developed enzymes that are responsible for both adding and removing the methyl mark. However, only recently enzymatic demethylation was discovered. This discovery has lead to the development of entirely new area of chromatin biology that needs to be understood at both the enzymatic and biological levels. We are currently using genomic, molecular and cytological approaches on human tissue culture cells and model organisms like C. elegans to reveal their role in cell fate and differentiation as well as genomic integrity. Our findings will provide connection between methylation dynamics and the regulation of gene expression, cell fate and genomic integrity, which has direct implications in both stem cell biology and cancer pathophysiology.

MEDI 171

Crystal structure and mechanism of human lysine-specific demethylase 1

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The reversible methylation of specific lysine residues in histone tails plays a crucial role in epigenetic gene regulation. LSD1, the first known lysine-specific demethylase, selectively removes monomethyl and dimethyl, but not trimethyl modifications of lysine 4 or 9 of histone 3 (H3-K4/9). Here, we present the crystal structure of LSD1 at 2.9 Å resolution. LSD1 forms a

highly asymmetric, closely packed domain structure from which a long helical tower domain protrudes. The active site cavity is spacious enough to accommodate several residues of the histone tail substrate, but does not appear capable of recognizing the different methylation states of the substrate lysine. This supports the hypothesis that trimethylated lysine is chemically rather than sterically discriminated. We present a biochemical analysis of LSD1 mutants that identifies critical residues in the active site cavity, and illustrates the importance of the SWIRM and tower domains for catalysis.

MEDI 172

Re-expression of aberrantly silenced genes resulting from inhibition of lysine-specific demethylase 1 (LSD1) by polyamine analogs in human colon cancer cells

*Yi Huang[1], Eriko Greene[1], Tracy Murray Stewart[1], Andrew C. Goodwin[1], Stephen B. Baylin[1], Patrick M. Woster[2], and **Robert A. Casero Jr.**[1]. (1) Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins University School of Medicine, 1650 Orleans Street, Baltimore, MD 21231, Fax: 410-614-9884, yhuang19@jhmi.edu, rcasero@jhmi.edu, (2) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202*

Modification of histone tails, including methylation, plays a role in regulation of gene expression. Such modifications in concert with an aberrant promoter CpG DNA methylation have been associated with the epigenetic silencing of tumor suppressor genes. Identification of Lysine Specific Demethylase (LSD1) demonstrates that histone methylation is a dynamic process. LSD1, a homologue of FAD-dependent polyamine oxidases, oxidatively demethylates mono- or dimethyl-Lys4 of histone H3 (H3K4). We now report that novel polyamine analogues potently inhibit LSD1 resulting in increased global H3K4me2 in human colon carcinoma cells and re-expression of aberrantly silenced genes important in the development of colon cancer, including members of the secreted frizzle-related proteins (SFRPs) and the GATA family of transcription factors. Chromatin immunoprecipitation analysis revealed that reactivation of genes is concurrent with increased H3K4me2 and acetyl-H3K9 marks, decreased H3K9me1 and H3K9me2 repressive marks at their promoters. We thus define new agents that reverse aberrant gene silencing in cancer cells.

MEDI 173

Synthesis and evaluation of trans-2- arylcyclopropylamine-based inhibiltors of lysine-specific demethylase 1

***Dewey G. McCafferty**, Department of Chemistry, Duke University, B120 Levine Sciences Research Center, Durham, NC 27708, dewey@duke.edu*

Demethylation of histone H3 lysine 4 is carried out by LSD1, a flavoenzyme oxidase whose catalytic domain shares close homology to flavin-dependent polyamine (PAO) and monoamine oxidases (MAO). Monoamine oxidase A or B are frequent targets of selective and nonselective small molecular inhibitors used for treatment of depression. Here we will discuss the chemical mechanism of LSD1 and report advances in the inhibition of LSD1 by small molecules in vivo and in vitro. Towards this end, a facile synthetic route to substituted trans-2-arylcyclopropylamines has been recently developed to provide mechanism-based inhibitors of

LSD1. These results will provide a foundation for the design of cyclopropylamine-based inhibitors that are selective for LSD1 to probe its role in vivo.

MEDI 174

Discovery of MK-4965: A potent, orally bioavailable HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI) with improved potency against key mutant viruses I

Thomas J Tucker[1], *Sandeep Saggar*[1], *John T Sisko*[1], *Robert M Tynebor*[1], *Peter J. Felock*[2], *Jessica A Flynn*[3], *Ming-Tain Lai*[2], *Yuexia Liang*[4], *Meiquing Liu*[2], *Georgia McGaughey*[1], *Michael D. Miller*[2], *Gregory Moyer*[3], *Vandna Munshi*[2], *Rebecca A. Poehnelt*[1], *Sridhar Prasad*[1], *Rosa I. Sanchez*[4], *Maricel Torrent*[1], *Joseph P Vacca*[1], *Theresa M. Williams*[1], *Bang-Lin Wan*[1], *and Youwei Yan*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 4/WP14-3, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-7310, tom_tucker@merck.com, (2) Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, (3) Vaccines and Biologics Research, Merck Research Laboratories, West Point, PA 19486, (4) Drug Metabolism Department, Merck Research Laboratories, West Point, PA 19486*

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been shown to be a key component of highly active anti-retroviral therapy(HAART). The use of NNRTI's such as efavirenz and nevirapine has become part of standard combination antiviral therapies producing clinical outcomes with efficacy comparable to other antiviral regimens. There is however a critical issue with the emergence of clinical resistance, and a need has arisen for novel NNRTIs with a broad spectrum of activity against key HIV-1 RT mutations. The NNRTI program at Merck has been directed towards finding novel NNRTIs that possess high levels of antiviral potency against key clinically observed mutant viruses. Using a combination of traditional Medicinal Chemistry/SAR analysis, crystallography, and molecular modeling, we have designed and synthesized a series of novel, highly potent NNRTIs that possess broad spectrum antiviral activity and good pharmacokinetic profiles. Further refinement of key compounds in this series to optimize physical properties and pharmacokinetics has resulted in the identification of MK-4965, which has high levels of potency against wild-type and key mutant viruses, excellent oral bioavailability and overall pharmacokinetics, and a clean ancillary profile. Based on its overall profile, MK-4965 has progressed to Phase I clinical evaluation for the treatment of HIV infection. The presentation will highlight the progression from early lead structures to the clinical compound, and will provide details of the in vitro and in vivo profiles of the compound. Details of the synthetic chemistry developed to prepare the compounds will also be presented.

MEDI 175

Discovery of MK-4965: A potent, orally bioavailable HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI) with improved potency against key mutant viruses II

Thomas J Tucker[1], *Sandeep Saggar*[1], *John T Sisko*[1], *Robert M Tynebor*[1], *Peter J. Felock*[2], *Jessica A Flynn*[3], *Ming-Tain Lai*[2], *Yuexia Liang*[4], *Meiquing Liu*[2], *Georgia McGaughey*[5], *Michael D. Miller*[2], *Gregory Moyer*[3], *Vandna Munshi*[6], *Rebecca A. Poehnelt*[1], *Sridhar Prasad*[1], *Rosa Sanchez*[4], *Maricel Torrent*[1], *Joseph P Vacca*[1], *Theresa M. Williams*[1], *Bang-LIn Wan*[1], *and Youwei Yan*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box*

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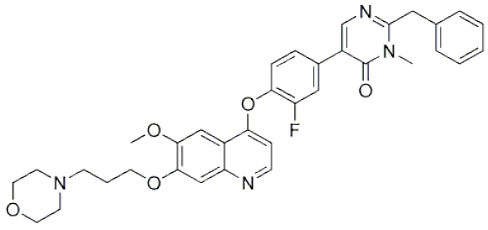
The description of discovery of MK-4965 will be continued in this second half of the presentation.

MEDI 176

Design, synthesis, and biological evaluation of potent c-met inhibitors

Noel D. D'Angelo[1]*, Steve Bellon*[2]*, Shon K. Booker*[1]*, Teresa L. Burgess*[3]*, Celia Dominguez*[4]*, Isabelle Dussault*[3]*, Ingrid Fellows*[5]*, Randall W. Hungate*[6]*, Matthew Lee*[7]*, Longbin Liu*[1]*, Elizabeth Rainbeau*[8]*, Paul J. Reider*[9]*, Aaron Siegmund*[1]*, Andrew Tasker*[1]*, Ning Xi*[1]*, Shimin Xu*[1]*, and Tae-Seong Kim*[1]*. (1) Medicinal Chemistry, Amgen, Inc, One Amgen Center Drive, Mail Stop 29-2-C, Thousand Oaks, CA 91320-1799, dangelo@amgen.com, (2) Department of Molecular Structure, Amgen, Cambridge, MA 02139, (3) Oncology Research, Amgen, Inc, Thousand Oaks, CA 91320, (4) MRSSI/CHDI, Inc, CA, (5) Department of Chemistry, California State University Fresno, Fresno, CA 93740, (6) Department of Chemistry Research & Discovery, Amgen, Inc, Thousand Oaks, CA 91320, (7) Molecular Structure, Amgen, Inc, Thousand Oaks, CA 91320, (8) Chemistry R&D Outsourcing, Amgen, Inc, Thousand Oaks, CA 91320, (9) Department of Chemistry Research & Discovery, Amgen Inc, Thousand Oaks, CA 91320*

c-Met is a receptor tyrosine kinase that has been found to play a key role in several cellular processes such as motility and proliferation. In particular, overexpression and mutation of this kinase has been implicated in different types of cancers. Consequently, the targeting of c-Met by small molecules has seen significant research as a means for chemotherapy. This paper outlines the development of a series of pyrimidone compounds for this purpose. This work initially led to the identification of compound 20 as a potential lead, a compound which exhibited in vitro and in vivo efficacy as well as a desirable pharmacokinetic profile. However, an X-ray crystal structure of a closely-related structure bound to c-Met revealed an unexpected binding mode. This lead to the design and synthesis of 63, which exhibited greater potency in vitro and in vivo than 20.



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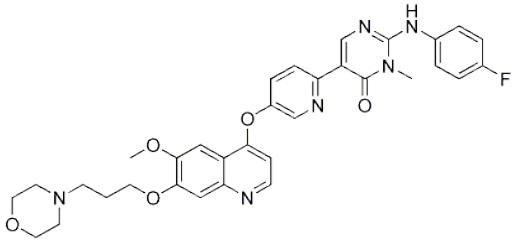

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MEDI 177

Structure based drug design for the discovery of clinical candidate PF-2341066 as potent and highly selective c-Met inhibitor

***J. Jean Cui**, Iriny Botrous, Hong Shen, Michelle Tran-Dube, Mitchell Nambu, Pei Pei Kung, Lee Funk, Lei Jia, Jerry Meng, Mason Pairish, Michele McTigue, Neil Grodsky, Kevin Ryan, Gordon Alton, Shinji Yamazaki, Helen Zou, James Christensen, and Barbara Mroczkowski, Pfizer, Inc, 10646 Science Center Drive, San Diego, CA 92121, jean.cui@pfizer.com*

c-Met receptor tyrosine kinase is an attractive oncology target due to the critical role of aberrant HGF/c-Met signaling in human oncogenesis and tumor invasion/metastasis. PHA-665752, 5-(2,6-dichloro-phenylmethanesulfonyl)-3-[1-[3,5-dimethyl-4-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-1H-pyrrol-2-yl]-meth-(Z)-ylidene]-1,3-dihydro-indol-2-one, was the first reported potent and selective c-Met inhibitor. The co-crystal structure of PHA-665752 revealed a unique binding environment of c-Met kinase domain, which was used to design the second generation of c-Met inhibitor with better drug-like properties. 2-Amino-5-aryl-3-benzyloxypyridine series was designed as a mimic of PHA-665752 with 2-aminopyridine replacing oxindole as a hinge binder. The 3-benzyloxy group was designed to reach the same hydrophobic pocket occupied by 2,6-dichlorophenyl group in PHA-665752, however, from a more direct angle which permitted less molecular weight and conformational constrain. Lead optimization of 2-amino-5-aryl-3-benzyloxypyridine series generated clinic candidate PF-2341066, which demonstrated potent in vitro and in vivo c-Met inhibition, effective tumor growth inhibition, and good pharmaceutical properties.

MEDI 178

Design, synthesis and optimization of several novel NNRTI series

***Lyn H. Jones**, Sandwich Chemistry, Pfizer, IPC 388, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom, Fax: +44 1304 651821, lyn.jones@pfizer.com*

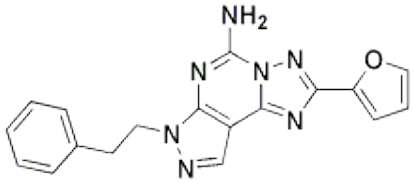
A major problem associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of HIV is their lack of resilience to mutations in the reverse transcriptase (RT) enzyme. This talk will describe the design and synthesis of a number of novel NNRTI series which possess excellent potency against both wild-type and the clinically relevant mutations of the enzyme/virus. Key features of this work include the use of co-crystal structures to enable the creation of new series using molecular hybridization and structure-based drug design to help guide series optimization. The correlation of structure with function, (potency, metabolism and toxicity), will be presented. The effect of synthetic complexity on medicinal chemistry design is also an important aspect of this work.

MEDI 179

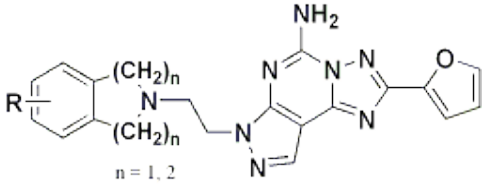
Design, synthesis, and evaluation of fused heterocyclic analogs as adenosine A_{2A} receptor antagonists

Unmesh Shah[1], *Craig D. Boyle*[1], *Samuel Chackalamannil*[1], *William J. Greenlee*[1], *Claire Lankin*[1], *Bernard Neustadt*[1], *Mary Cohen-Williams*[2], *Ahmad Fawzi*[2], *Guy Higgins*[2], *Jean Lachowicz*[2], *Kwokei Ng*[3], *Geoffrey Varty*[2], *and Hongtao Zhang*[2]. *(1) Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, unmesh.shah@spcorp.com, (2) CV/CNS Biology, Schering-Plough Research Institute, Kenilworth, NJ 07033, (3) Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, Kenilworth, NJ 07033*

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors classified as A_1, A_{2A}, A_{2B}, and A_3. The adenosine A_{2A} receptor, a member of the G-protein-coupled receptor family, is found in large amounts in brain striatum. Adenosine A_{2A} receptors coexist with dopamine D_2 receptors and stimulation of A_{2A} receptors causes a decrease in D_2 receptor-mediated neurotransmission. It has been discovered that dopamine deficiency in the brain leads to Parkinson's disease. Thus, adenosine A_{2A} receptor antagonists could be of value as anti-Parkinson's drugs. SCH 58261 has previously been identified as a high-affinity A_{2A} receptor antagonist, which shows potent *in vivo* activity in animal models of PD. However, SCH 58261 is only moderately selective for A_{2A} receptors over A_1 receptors and possesses very poor solubility. Our plan was to use the tricyclic core of SCH 58261 and incorporate polar groups on the left-side of the molecule. Toward this goal, we wish to report the discovery of highly potent and selective A_{2A} antagonists exhibiting improved solubility and promising *in vivo* and pharmacokinetic properties.



SCH 58261



MEDI 180

Small molecule antagonists of the Histamine receptor type3 (H3) as a novel treatment for cognitive dysfunction

Ji-In Kim[1], *Magid Abou-Gharbia*[1], *Suzan Aschmies*[2], *Nicholas Brandon*[2], *Thomas Comery*[2], *Mark Day*[2], *Jonathan Gross*[1], *Warren D. Hirst*[2], *Cody Kelley*[2], *Katie Kubek*[2], *Ronald L Magolda*[1], *Menelas Pangalos*[2], *William R. Solvibile*[1], *Gregory J. Tawa*[1], *and Albert Robichaud*[1]. *(1) Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, kimj1@wyeth.com, (2) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543*

The discovery of novel biaryl amines as small molecule antagonists of the Histamine Receptor Type 3 (H3) will be reported. Analogs discovered are potent and selective for the human H3 receptor, and demonstrate in vivo efficacy in a rodent behavioral model of cognition. The

design, synthesis, SAR and pharmacological profile of these new analogs as potential treatments for cognitive dysfunction will be described.

MEDI 181

Indoleazepines as a new class of nonsteroidal agonists of the farnesoid X receptor: Identification of WAY-362450 (FXR-450) as a clinical candidate for the treatment of dyslipidemia

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The nuclear hormone receptor farnesoid X receptor (FXR) plays a critical role in the regulation of bile acid synthesis and triglyceride and cholesterol homeostasis. Synthetic agonists of FXR that are potent in vitro, including GW4064, fexaramine, and 6-ethyl chenodeoxycholic acids (6-ECDCAs) have been previously described; however, they have limited clinical utility due to poor physiochemical, pharmacokinetic, and/or toxicological profiles. Here we report the identification of a new structural scaffold of FXR agonists, namely the indoleazepines which were identified as weak, partial agonists via high-throughput screening. SAR investigations led to the identification of two important interactions within the ligand-binding domain, a lipophilic interaction made with a geminal dimethyl group, and a hydrogen-bonding interaction formed with a carbonyl group on a pendant amide. These interactions were confirmed using X-ray structural information. Based on these observations, a highly potent FXR agonist, WAY-362450 was identified having an EC50 value of 5 nM in a co-transfection functional assay with 149% efficacy when compared to the endogenous ligand, CDCA. In addition, WAY-362450 had an EC50 value of 16 nM in an alternate functional assay using the FXR-LBD with a Gal4-DBD in HEK293 cells, exhibiting 179% efficacy versus GW4064. WAY-392450 also activated known FXR target genes following treatment of primary human hepatocytes. In LDLRKO mice consuming a western diet or in KKAy mice predisposed to dyslipidemia, WAY-362450 decreased serum triglyceride levels comparable to the PPARalpha ligand, fenofibrate. Gene expression analysis clearly demonstrated that WAY-362450 modulates genes distinct from fenofibrate involved in both triglyceride clearance and triglyceride synthesis; however, unlike fenofibrate, WAY-362450 also decreased total cholesterol levels in both models. Taken together, these and other data, support the clinical evaluation of WAY-362450 as a treatment for dyslipidemia.

MEDI 182

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

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Alzheimer's Disease (AD) is a progressive, degenerative disease of the brain and most common form of dementia. One primary theory on the etiology of AD is that in AD patients, amyloid precursor protein (APP) is processed in the brain and converted to beta amyloid protein, a precursor to amyloid plaques. β-Secretase (β-site APP cleavage enzyme or BACE1) and γ-secretase are two important enzymes involved in the amyloid synthetic cascade. Inhibition of secretases responsible for Aβ formation may stop or slow AD progression by preventing its production. The design and synthesis of highly potent, selective and orally active inhibitors of β-secretase (BACE1) was based on the HTS hit 2-amino-3-methyl-5,5-diphenyl-3,5-dihydro-4H-imidazol-4-one (IC_{50} = 3 μM). Our SAR design strategy was supported by X-ray structures of BACE1 co-crystallized with various ligands, and molecular modeling studies. These studies led to the design and synthesis of pyrrole substituted 2-amino-3,5-dihydro-4H-imidazol-4-ones that are extremely potent (IC_{50} <10 nM) and selective (>1000x vs Cathepsin D) inhibitors of BACE-1. Key differences noted in the S2' sub-site of BACE-1 to that of BACE-2 allowed us to attenuate the selectivity of these molecules to create molecules with varying BACE-1/BACE-2 selectivity (2-125 fold). Several compounds have demonstrated high potency in cell-based assays (5-40 nM) and been shown to be efficacious in vivo, near normalizing plasma Aβ levels and significantly reducing Aβ levels in the brain. These potent and selective BACE1 inhibitors will contribute toward the understanding of APP processing, as well as the development of disease-modifying AD therapeutics.

MEDI 183

Synthesis and transport studies on serine side-chain-linked peptidomimetic prodrugs of cyclic cidofovir

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Cidofovir (**1**) and its equivalently potent cyclic form (**2**) are possible therapies for orthopox virus infections, but are limited in this role by low oral bioavailability. We compare prodrugs of **2** in which the phosphonic acid group of **2** is esterified by a hydrophobic amino acid (aa_1) – ethylene glycol moiety (aa_1-$CO_2CH_2CH_2OH$) (**3**), or else by an aa_1-Ser-CO_2R dipeptide through the free serine side-chain hydroxyl group (**4**). Both conjugates **3** and **4** are activated in cellular and

tissue homogenates to release the parent drug. However, only **4** exhibits enhanced transport properties in a single pass perfusion assay. Analogues of **4** in which the amino acid stereochemistry or the peptide carboxyl R group are modified show significant differences in transport and activation properties, providing insight into prodrug design. The potential of **4** as the basis for an effective oral form of **2** will be discussed.

MEDI 184

Multiple parallel approaches to steroid hormone receptor lead identification

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The early stages of target-based medicinal chemistry often follow a hits-to-leads paradigm. In this approach, target-specific 'hit' templates, e.g. from a chemically-diverse high-throughput screen, are progressed to 'leads.' The definition of a lead can vary, but typically includes some criteria for target-specific potency, selectivity over related targets, and predictive SAR. Recently at GSK, the PR and ER beta nuclear receptor programs took advantage of multiple, parallel hit ID & progression approaches to complement, or even function in the absence of, high-throughput screens.

MEDI 185

A novel inhibitor of thyroid hormone receptor function

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The thyroid hormone receptors (TR) responds directly to circulating thyroid hormones to maintain homeostatic balance, particularly for energy metabolism, temperature regulation, and lipid metabolism. The signaling pathways regulated by the TR are very complex and the selective pharmacological regulation of those pathways is difficult to achieve. In an effort to better understand the events underlying regulation of signaling and provide for more closely tuned pharmacological approaches we have developed a set of tools for studying and regulating TR signaling. High throughput screening afforded several novel chemotypes that inhibited the interaction of liganded TR with its requisite cofactors. Careful lead optimization has allowed conversion of one of these hits into a validated leads useful in cellular studies and potentially in animal models.

MEDI 186

Discovery and optimization of acyl guanidines as novel BACE-1 inhibitors

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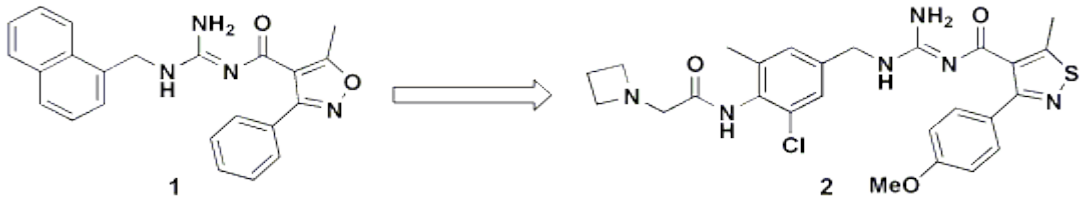
Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by dementia, amyloid plaques, and neurofibrillary tangles in the brain. One promising therapeutic target for AD is BACE-1, an aspartyl protease which cleaves amyloid precursor protein to form the N-terminus of Abeta, the major constituent of amyloid plaques. Knockout of the gene encoding BACE-1 reduces brain Abeta levels in animal models, but small molecule inhibitors with in vivo activity remain elusive. Screening the BMS deck provided 1 as a micromolar BACE-1 inhibitor containing an acyl guanidine as a novel aspartyl protease chemotype. This presentation will describe the optimization of 1 to 2, a selective BACE-1 inhibitor with single digit nanomolar activity in both binding and cell-based assays.



MEDI 187

Discovery and development of allosteric modulators of Class A and Class C GPCRs

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Current drug therapies for Alzheimer's disease (AD) lack satisfactory symptom relief, fail to modify disease progression and carry severe side effects. Likewise, in Schizophrenia, most antipsychotic drugs suffer from unacceptable side effects and incomprehensive alleviation of symptoms. The M1 and M4 subtypes of the muscarinic acetylcholine receptor (mAChR) represent more attractive therapeutic targets for these pathologies in light of their localization in the CNS and their respective roles in cognition and neurotransmission. Furthermore, absence of truly selective muscarinic agents has hindered basic research aimed at elucidating the detailed physiological roles of the M1 and M4 receptors. We report the discovery and preliminary characterization of novel muscarinic agonists and potentiators that modulate either the M1 or M4 receptor in an allosteric manner with high subtype-selectivity. This work provides novel subtype-selective muscarinic agents that with high utility for both basic and translational neuropharmacology with particular relevance to AD and Schizophrenia.

MEDI 188

Hsp90 inhibitors: The journey from a designed lead to a clinical candidate

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Heat shock protein 90 (Hsp90), an important target in cancer and other diseases, has became recently the focus of several drug discovery and development efforts. The initially identified natural product inhibitors of Hsp90, such as geldanamycin, played a major role in elucidating its biological functions and in determining its clinical relevance. Upcoming synthetic inhibitors, such as the purine-scaffold class, furthered our understanding on Hsp90 in cancer and neurodegenerative diseases, and delivered, what are promised to be, clinical candidates with favorable pharmacological profiles. This talk will inform the audience on the discovery and design of purine-scaffold Hsp90 inhibitors, the strategies used for their development, and finally, will present strategies for their translation in the treatment of cancers and neurodegenerative diseases.

MEDI 189

Natural products and natural product models in drug discovery

***Sheo B. Singh**, Natural Products Chemistry, Merck Research Laboratories, 126 E. Lincoln Avenue, RY80Y-350, Rahway, NJ 07065, Fax: 7325946880, sheo_singh@merck.com*

Natural products continue to play significant role in delivery of life saving drugs, lead for drugs, model for drug leads, tools for identification of targets and target validations. These compounds use a cascade of signal transduction pathways for their biological and therapeutic effects. Examples of natural product discoveries from Merck illuminating these categories will be discussed.

MEDI 190

Synthesis and biological evaluation of marine natural products that modulate PI3kinase signaling

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The PI(3)K pathway has been implicated in cancer ever since its discovery some 20 years ago and recent estimates suggest that mutation in one or another PI(3)K pathway component accounts for up to 30% of all human cancers. PI(3)K signaling also plays a central role in the inflammatory responses of mast cells and macrophages. Therefore, potent and selective inhibitors of PI(3)K signaling represent interesting lead compounds for the development of new anticancer and antiinflammatory drugs. We have screened a library of crude extracts of marine invertebrates for the presence of isoform-selective PI(3)K inhibitors and activators of the lipid

phosphatase SHIP. Bioassay guided fractionation of two marine sponge extracts led to the identification of liphagal, a selective and potent inhibitor if PI(3)K alpha, and pelorol, a selective activator of SHIP. We have completed total syntheses of both these novel meroterpenoid natural products in order to provide material for biological evaluation and made numerous analogs in order to explore the SAR for these new pharmacophores. The lecture will describe the discovery of liphagal and pelorol, their total syntheses, and the analog synthesis program based on the pelorol lead structure that has identified the SHIP activator MN100, a promising clinical trials candidate for multiple myeloma. Evidence will be presented that shows MN100 is an allosteric activator of SHIP. Using an activator of a phosphatase to inhibit a kinase signaling pathway is a largely unexploited approach to drug development. The in vitro and in vivo biological activities of the SHIP activator MN100 that will be presented provide strong preclinical proof of principle validation for this approach to treating hematopoietic cancers and inflammation.

MEDI 191

Novel natural product immunophilin ligands are potent leads for the treatment of neurodegenerative diseases and provide insights into mechanisms of neuroprotection

***Edmund I. Graziani**, Chemical & Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, graziaei@wyeth.com*

Immunophilin ligands have been shown to have neuroprotective activities and FK506-binding proteins (FKBPs) were proposed as likely targets for mediating this activity. A structure-based drug design approach identified ILS-920, a semi-synthetic analog of rapamycin, and 3-normeridamycin (3-Nor) as candidates for in vivo and mechanism of action studies. ILS-920 and 3-Nor significantly enhanced neuronal survival and promoted neurite outgrowth in cultured cortical neurons. ILS-920 was shown to bind selectively to the immunophilin FKBP52 and to the â1 subunit of L-type voltage-gated calcium channels (VGCC). An investigation of the mechanistic basis of its action revealed novel interaction partners resulting in the modulation of intracellular Ca2+ homeostasis. ILS-920 dramatically improved neurological deficits following rodent permanent middle cerebral artery occlusion (MCAO) model of stroke, even when administered 24 hours post occlusion. When evaluated in the mouse MPTP model of Parkinson's disease (PD), 3-Nor was found to partially attenuate MPTP-induced depletion of TH immunoreactivity in the striatum. This work provides the beginnings of an increased understanding of the multiple functionalities that are essential for immunophilin ligands to retain neuroprotective activity, as well as outlining an approach for developing novel natural products for unmet medical needs in neuroscience.

MEDI 192

Genomics of secondary metabolite biosynthesis provide a new efficient route to novel natural products

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Advances in genomics have found applications in the identification of novel targets for drug intervention and for the development of screening assays. Less exploited has been the application to the discovery of novel secondary metabolites. This is surprizing, given the tremendous advances that have occurred in the last 20 years in the understanding of their biosynthesis at the gene level. The typical actinomycete contains between 10 and 30 gene clusters encoding the biosynthetic enzymes for a wide variety of natural products. Today the total genome of a bacterium can be read in a day or two and analysed and annotated, in silico, overnight. The natural product scientist can know much of the secondary metabolic potential of an organism before embarking on any classical extraction experiments. This provides a completley new paradigm for natural product discovery and an order of magnitude increase in the efficiency of NCE discovery. Several examples of this approach will be outlined.

MEDI 193

Combining bioprospecting, biodiversity conservation, and economic development: A new paradigm for natural products based drug discovery

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Natural products originally identified from plants, animals and microorganisms are the basis for approximately 28% of the new chemical entities approved as drugs over the past 25 years, and for 42% of anticancer drugs. Ironically the realization of the importance of natural products to the drug discovery process comes at a time when as much as three quarters of the world's plants and half of the marine invertebrates are threatened with extinction. The solution to this problem requires not only increased efforts at biodiversity conservation, but also attention to the economic factors which often drive people to eco-destructive practices for their very survival. The talk will describe an approach to bioprospecting which combines it with conservation and development activities, and will be illustrated with examples of recent work in Madagascar. The talk will also discuss a novel series of lead compounds from Suriname.

MEDI 194

Natural products as research probes: Impact on pharmacology, physiology and drug development

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Natural products have been a major source of many medicinal agents, including antibiotics, anticancer agents, antimalarials and analgetics. In addition, natural products as resarch probes have had a major impact on progress in pharmacology and physiology. Such natural products include reserpine and yohimbine for biogenic amines, ouabain for Na/K-ATPase, ryanodine for certain calcium-release channels, thapsigargin for a calcium-ATPase, caffeine for phosphodiesterases and adenosine receptors, and forskolin for adenylyl cyclase. The study of ion channels has prospered because of batrachotoxin for sodium channels, and most recently of

epibatidine for nicotinic channels. Such natural products have come from plant, marine, and amphibian sources.

MEDI 195

Overview of solubility in drug discovery: Impact, measurement, and structure design

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Physicochemical and metabolic properties of compounds play a crucial role in the selection and optimization of leads by discovery teams to achieve quality clinical candidates. ADME/Tox properties are measured in a parallel workflow with biological assays for effective decision-making that integrates multiple-SARs/SPRs.

Solubility is a crucial physicochemical property, which has long been studied for its impact on intestinal absorption. More recently, the impact of solubility biological assays, property measurement, and discovery dosing form selection has been more fully exploited. Strategies for incorporating solubility insights into various aspects of discovery will be overviewed.

It is important to recognize that solubility is highly dependent on the solution conditions and experimental protocol. Thus, different types of solubility assays will be discussed for accurate prediction or diagnosis in different stages and aspects of drug discovery. With this data in hand, medicinal chemists have several strategies available for structural modification of a lead series to improve solubility, including adding an ionizable group, reducing Log P, adding hydrogen bonds, adding a polar group, reducing molecular weight, an out of plane substitution, and constructing a prodrug.

MEDI 196

Highly soluble prodrugs of the oxazolidinone antibacterial agents eperezolid and linezolid (Zyvox™)

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The oxazolidinone antibiotics, exemplified by linezolid (Zyvox™), are a new class of antibacterial agents with activity against multi-drug resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus species (VRE). During Pharmacia & Upjohn's early development stages of our first two Phase I clinical candidates linezolid and eperezolid, we examined various approaches to improving the aqueous solubility of these oxazolidinones. Two highly successful prodrug approaches will be described: 1) use of ester prodrugs attached to the hydroxyacetyl piperazine group in eperezolid, and 2)

formation of N-oxides. The morpholinyl N-oxide of linezolid, having very high solubility, demonstrated excellent oral bioavailability, and was rapidly converted back to linezolid in the rat. A number of ester prodrugs of eperezolid similarly demonstrated high solubility and excellent in vivo efficacy. Ultimately, the inherent solubility of linezolid was deemed to be sufficient to allow development of a marketable i.v. forumulation, and tablets and suspension for oral therapy. Nonetheless, the SAR of the prodrugs to be described in the talk may have utility in other compound series, as very significant increases in aqueous solubility were observed. In a number of cases, this improvement in solubility was approximately a factor of 100 over the parent drug.

MEDI 197

A computational approach to modeling solubility that includes crystal packing, ionization, and intrinsic solubility for use in iterative design

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The optimization of aqueous solubility is often a challenging component in the discovery and development of a new drug. We will discuss the development, validation, and use of a computational model for aiding in the design of drug candidates. The model is comprised of three primary components: a QSAR model for the prediction of the intrinsic solubility of the neutral solute, an estimated pKa for use in the Henderson-Hasselbach equation for ionization effects, and a series of short molecular dynamics simulations to estimate crystal packing effects on solubility. Along with a point estimate of the solubility at a given pH, a confidence interval is generated using a Monte Carlo error function to convey the sensitivity of the prediction to the variability in the underlying mathematical terms. We will also discuss a more intuitive approach to presenting the model to the end user than has typically been utilized.

MEDI 198

Readily activated and highly soluble pyrazoloquinazoline phosphate derivatives with potent and durable antitumor activity

***Kevin M. Foote**, Department of Medicinal Chemistry, AstraZeneca R&D Mereside, Alderley Park, Macclesfield SK10 4TG, United Kingdom, kevin.foote@astrazeneca.com*

The Aurora kinases have been shown to play critical roles in coordinating cell progression through mitosis by controlling chromosome segregation and cytokinesis. The irregular expression of Aurora A and B kinases have been implicated in tumour progression; therefore inhibitors of these proteins may have utility in the treatment of cancer.

Several Aurora kinase inhibitors have shown potent anti-tumour activity in pre-clinical models and entered clinical evaluation. AZD1152 is a novel pyrazoloquinazoline-dihydrogen phosphate

derivative with striking solubility (up to 25 mg/mL) in simple pH-adjusted aqueous vehicles making it suitable for parenteral administration. AZD1152 is readily converted to the active species (AZD1152HQPA), which is a highly selective inhibitor of Aurora B kinase.

In human cancer xenograft models AZD1152 causes pharmacodynamic changes that result in durable anti-tumour growth inhibition at well-tolerated doses. AZD1152 has the potential for activity in a wide range of human tumours and is currently in Phase I/II clinical trials.

MEDI 199

Alkaloid biosynthesis in periwinkle

***Sarah E. O'Connor**, Department of Chemistry, MIT, 18-592, 77 Massachusetts Ave., Cambridge, MA 02139, soc@mit.edu*

Madagascar periwinkle (Catharanthus roseus) produces more than 100 alkaloids from the terpene indole alkaloid family. We study the mechanism, substrate specificity and redesign of the central enzyme of the terpene indole alkaloid biosynthetic pathway and explore the capacity of this pathway for production of novel alkaloid structures.

MEDI 200

Modified microtubule stabilizing agents: Candidates for the treatment of neurodegenerative tauopathies

***Donna Huryn**[1], Carlo Ballatore[1], Kurt Brunden[2], Edward Hyde[2], Robert F. Deiches[2], Virginia MY. Lee[2], John Trojanowski[2], Justin Potuzak[1], and Amos B. Smith III[1]. (1) Department of Chemistry, University of Pennsylvania, 231 S. 34th St., Philadelphia, PA 19104, huryn@sas.upenn.edu, (2) Center for Neurodegenerative Disease Research, Institute on Aging, University of Pennsylvania, Philadelphia, PA 19104*

Recent studies have demonstrated the potential of Microtubule (MT) stabilizing agents for the treatment of Alzheimer's Disease (AD) and related neurodegenerative diseases, known as tauopathies. In these conditions, the MT-associated protein, tau, becomes hyperphosphorylated, then sequestered into paired helical filaments (PHF's) that aggregate into neurofibrillary tangles (NFT's), a hallmark of AD and related tauopathies. As tau plays an essential role in MT stabilization, its sequestration, and therefore the loss of its function, results in neurotoxicity via disruption of axonal transport in neurons. A number of natural products, such as Taxanes, discodermolides and epothilones stabilize MT's, however their evaluation has primarily centered on their anti-proliferative properties. We recently initiated a program on the synthesis and characterization of members of different classes of MT-stabilizing natural products with the overall goal of identifying agents that could gain access to the central nervous system, and compensate for the loss of tau function in tau biological systems at non-toxic doses. Our progress towards these goals will be described.

MEDI 201

Production of novel acidic lipopeptide antibiotics by genetic engineering in Streptomyces roseosporus

***Richard H. Baltz**, K. Nguyen, M-F. Coëffet-Le Gal, V. Miao, and P. Brian, Cubist Pharmaceuticals, Inc, 65 Hayden Avenue, Lexington, MA 02421, Richard.Baltz@Cubist.com*

Streptomyces roseosporus produces A21978C, a family of acidic cyclic lipodepsipeptide antibiotics. The three major A21978C factors have different branched-chain fatty acids. Daptomycin is a related molecule which has an n-decanoic acid side chain. The genes encoding the biosynthetic enzymes for daptomycin and the related lipopeptides, A54145 and CDA, have been cloned and sequenced. Methods to express the individual nonribosomal peptide synthetase (NRPS) subunits in ectopic locations in the S. roseosporus chromosome have been developed. Individual NRPS genes or the complete daptomycin gene cluster can be engineered in Escherichia coli using the l-Red recombination system, introduced into S. roseosporus by conjugation and site specific insertion into bacteriophage fC31 or insertion sequence IS117 attachment sites, and expressed from the strong constitutively-expressed ermEp* promoter. Using this system, we were able to generate many derivatives of daptomycin by combinations of complete NRPS gene exchanges, NRPS module exchanges, and gene deletion coupled with multiple lipidations. A number of the products of recombinants were produced in good yields, and some had antibiotic activities similar to daptomycin in in vitro tests.

MEDI 202

Generation and analysis of new phoslactomycins and prodiginines

***Kevin Reynolds**, Chemistry - Liberal Arts & Sciences, Portland State University, PO Box 751, Portland, OR 97207*

Phoslactomycin (Plm) and fostriecin are members of a group of potent and selective inhibitors of serine-threonine phosphatase 2A (PP2A) with potential biological applications as antifungal and anticancer agents. We report a genetic and biochemical analysis of the Plm and fostriecin biosynthetic pathways and the generation of Plm intermediates through use of blocked mutants. Enzyme-catalyzed esterification, directed-biosynthesis, and combinatorial biosynthesis with the Plm and fostriecin biosynthetic genes have provided an additional array of new Plms. Compounds with relatively unchanged PP2A inhibition activity but altered (increased and decreased) antifungal activities are observed. Compounds with both increased and decreased PP2A inhibition activity are also observed.

Prodiginines are a family of linear and cyclic oligopyrrole red-pigmented antibiotics with broad antifungal, antibacterial, antimalarial and anticancer activities. We have analyzed the role of 23-gene products responsible for biosynthesis of undecylprodiginine and streptorubin B in Strepomyces coelicolor. New prodiginines have been generated by creation of hybrid pathways, directed-biosynthesis, use of blocked mutants and chemical synthesis. Preliminary analyses of these have shown which structural features are required for potent activity (2-20 nm range) against the malaria parasite Plasmodial falciparum in the erythrocytic stage.

MEDI 203

Core-modified mannopeptimycins

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The mannopeptimycins are a novel class of glycopeptide antibiotics that contain a cyclic hexapeptide core decorated with three α-linked mannose residues. We have previously disclosed that certain naturally-occuring and semisynthetic lipophilic derivatives of the parent system, mannopeptimycin-α, possess potent activity against susceptible and resistant strains of gram-positive microorganisms. This talk will focus on the generation and derivatization of various core-modified mannopeptimycins obtained through synthetic and biosynthetic means, and will highlight the roles played by Wyeth's Medicinal Chemistry, Microbiology, Natural Products, and Bioprocess Development groups in delineating the structure-activity relationships and defining the mechanism of action of these glycopeptides.

MEDI 204

Synthetic biology approaches to natural product lead optimization

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Natural product (NP) leads are usually more potent than those identified from synthetic libraries and can possess valuable characteristics in structural diversity and in modulating difficult targets e.g. protein-protein interactions. However their complex structures can limit the scope of optimization by total or semi synthesis. Moreover semi-synthetic approaches often lead to further increase in molecular size, resulting in decrease of ligand efficiency.

Synthetic biology approaches can be used to optimize complex NP leads without losing ligand efficiency. This is particularly evident in the field of polyketide lead optimization. A toolbox of genetic materials is available for preparing SAR-directed analogues by engineered biosynthesis. These include sets of loading modules with different and broad ‘starter acid' recognition; genes encoding acyltransferases with different extender specificity; and various auxiliary genes encoding post-PKS enzymes responsible for oxidation, alkylation, glycosylation, etc. These coupled with mutasynthesis by suppressing natural starter biosynthesis provide a wide scope of analogue preparation.

MEDI 205

Discovery of 2-aminobenzoxazole carboxamides as 5-HT3 receptor antagonists

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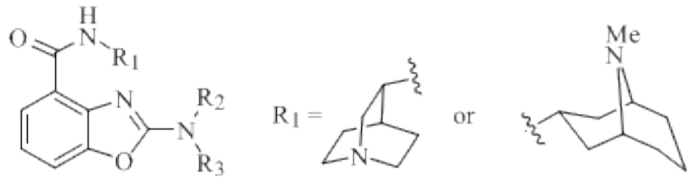
The serotonin type-3 receptor is a ligand-gated ion channel which mediates fast synaptic neurotransmission in the CNS and periphery. 5-HT_3 antagonists have become successful and important therapeutics for the treatment of chemotherapy-induced nausea and vomiting (CINV) and more recently for diarrhea-predominant irritable bowel syndrome (IBS-d). These achievements as well as the rich pharmacology associated with the 5-HT_3 receptor have led to further clinical investigations of this drug class. Findings now suggest that 5-HT_3 antagonists may be valuable for treating additional chronic diseases like fibromyalgia and cognitive deficits in schizophrenia patients. The opportunity to add treatment options for chronic maladies prompted us to search for new 5-HT_3 receptor antagonists. AMRI's research program has now identified 2-aminobenzoxazole carboxamides as potent, orally active 5-HT_3 receptor antagonists with good metabolic stability. Early structure-activity relationships and efficacy assessment will be described.



MEDI 206

Thermo- and pH-responsive hydrogel-coated gold nanoparticles prepared from rationally designed surface-confined initiators

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Gold core nanoparticles (~40 nm in diameter) were encapsulated by hydrogel shells generated by the free radical polymerization of *N*-isopropyl acryl amide-co-acrylic acid (NIPAm-AAc) on the surface of gold nanoparticles functionalized by a specifically designed radical initiator. The amount of the initiator was varied to control the thickness of the hydrogel shells. The size and morphology of the shell/core nanoparticles were characterized by field emission scanning electron microscopy (FE-SEM) and transmission electron microscopy (TEM). In addition, the optical properties of the nanoparticles were characterized by UV-visible spectroscopy, and the particle size was evaluated as a function of temperature and pH using dynamic light scattering (DLS). The shell/core hydrogel nanoparticles undergo reversible volume changes in water at a lower critical solution temperature (LCST) of ~34 °C as well as at pH values between 3 and 4. Furthermore, the hydrogel shells can be thermally collapsed by activation of the plasmon resonance on the gold nanoparticles upon exposure to visible light. The unique properties of the shell/core hydrogel nanoparticles make them attractive for use as nanoscale drug-delivery vehicles.

Keywords: Gold nanoparticles, Hydrogel coating, Photothermal modulation, Drug delivery

MEDI 207

Enhancing the kinetic profile and bioavailability of ophthalmic drugs

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The unique anatomy of the eye limits topically applied drug delivery by rapid clearance and limited absorption across the various tissues. Retaining the drug on the eye for extended release using a proprietary chitosan matrix allows for a sustained elution of topical formulations. Use of this chitosan matrix allows us to significantly lower drug concentrations while achieving similar and/or higher intraocular concentrations. This promising technology shows robustness by allowing its application to non-steroidal and steroidal anti-inflammatory drugs and prostaglandins.

MEDI 208

Introduction of a new strategy to drug discovery: Systems-based drug discovery

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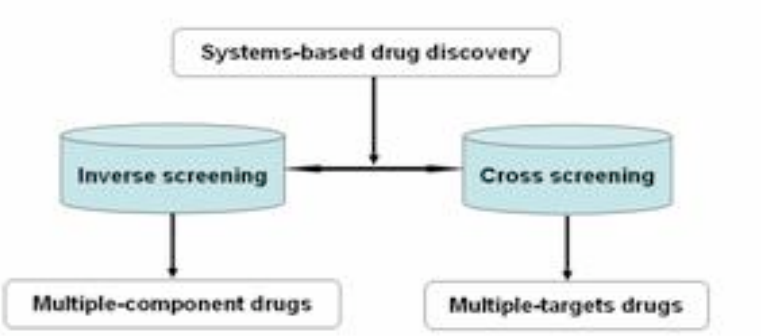
Modern drug discovery has been driven by the search for new molecular targeted therapeutics. Despite all recent technical innovations and advancement, the number of drugs produced by pharmaceutical companies remains at disappointingly low level. Recently, we have proposed a new drug discovery approach - systems-based drug discovery (SBDD), which is complementary to the target-based approach, to accelerate the identification of new leads with improved efficiency and reduced adverse effects. Systems-based drug discovery is a powerful drug discovery strategy that is based on the complexities of biological systems, using effective screening methods and software tools to discover systems-oriented drugs that take into account the robustness of biological systems to achieve the desired therapeutic goals. This new approach offers the prospect of a more efficient strategy to drug discovery, resulting in the generation of high-quality drugs with a better chance of success in clinical development.



MEDI 209

Mechanistic study of the thiol mediated biotransformation of organic nitrates

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The vasodilator action of organic nitrates has been known for over a century. Most recently it has been established that organic nitrates have significant neuroprotective effects. The promising diverse therapeutic application of organic nitrates emphasizes the need to understand the molecular mechanism of nitrate biotransformation. In this study we have tried to explore the mechanism of the thiol-mediated biotransformation of nitrates in the anaerobic reaction of organic nitrates (GTN, ISDN) with different thiols (C, NAC, AET) in phosphate buffer. NO chemiluminescence and Greiss assay were used to simultaneously monitor the release of NO and nitrite.We have also studied the effects of different micellar surface charge on the rates of nitrite release. Our study indicates: (1) a common intermediate is involved in the release of NO and nitrite from the reaction of nitrates with thiol (2) the nature of the intermediate is independent of the nitrate used and depends solely on the nature of the thiol. The observations provide further evidence of the involvement of thionitrate intermediate in the thiol mediated biotransformation of organic nitrates.

MEDI 210

Synthesis of new carbon-11 labeled carboxamides as PET radioligands for imaging of dopamine D_3 receptor

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The dopamine D_3 receptor is implicated in various physiological and pathophysiological processes and recognized as potential therapeutic target for the treatment of various neurological and psychiatric disorders such as Parkinson's disease, schizophrenia and substance abuse. A series of carboxamides have been developed as partial D_3 agonists by Hacking et al. New carbon-11 labeled carboxamides were designed and synthesized as PET radioligands for imaging of D_3 receptor. The lead compound BP897 and unlabeled carboxamides were synthesized from 1-(2-methoxyphenyl)piperazine and *N*-(4-bromobutyl)phthalimide in 3 steps with moderate to excellent yields. The hydroxyl precursors were synthesized from 1-(2-hydroxyphenyl)piperazine and 3-cyanopropyl bromide in 3 steps with moderate to excellent yields. The target tracers *N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)naphthyl-2-carboxamide ([^{11}C]BP897), *N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)biphenyl-4-carboxamide, (*E*)-4-fluoro-*N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)cinnamoylamide, (*E*)-4-chloro-*N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)cinnamoylamide, (*E*)-4-bromo-*N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)cinnamoylamide and (*E*)-4-methoxy-*N*-(4-(4-(2-[^{11}C]methoxyphenyl)piperazin-1-yl)butyl)cinnamoylamide were prepared from their corresponding precursors *N*-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)naphthyl-2-carboxamide, *N*-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)biphenyl-4-carboxamide, (*E*)-4-fluoro-*N*-(4-(4-(2-

hydroxyphenyl)piperazin-1-yl)butyl)cinnamoylamide, (*E*)-4-chloro-*N*-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)cinnamoylamide, (*E*)-4-bromo-*N*-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)cinnamoylamide and (*E*)-4-methoxy-*N*-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)cinnamoylamide with [^{11}C]CH_3OTf under basic condition (NaOH) through *O*-[^{11}C]methylation and isolated by the solid-phase extraction (SPE) method in 40-55% radiochemical yields.

MEDI 211

Synthesis and evaluation of a series of new 7-methyl-2-(pyridinyl)pyridin-3-yl)-7-azabicyclo[2.2.1]heptane derivatives as potential radioligands for imaging of the nicotinic acetylcholine receptors (nAChRs) by positron-emission tomography

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Nicotinic acetylcholine receptors (nAChRs) are associated with various neurophysiological processes including Alzheimer's, Parkinson's diseases, Tourette's syndrome, epilepsy, schizophrenia, depression and tobacco smoking. The ability to image CNS nAChRs with positron mission tomography (PET) may aid in the diagnosis and monitoring response to therapy in neurological degenerative diseases and other psychiatric disorders. A series of new racemic 7-methyl-2-(pyridinylpyridin-3-yl)-7-azabicyclo[2.2.1]heptane derivatives with picomolar in vitro binding affinity at nAChRs were synthesized and their enantiomers were resolved by semipreparative chiral HPLC. The (-)-enantiomers showed substantially greater in vitro inhibition binding affinity than the corresponding (+)-enantiomers. The (-)-enantiomers have been radiolabeled with positron emitting isotope 18F-Fluoride and exhibited remarkable binding potentials, high brain uptake, rapid brain kinetics and good safety profile as practical PET radioligands for imaging of extra-thalamic nAChR in baboon brain and hold promise for further investigation for human studies.

MEDI 212

Synthesis of new carbon-11 labeled naphthalene-sulfonamides as potential PET agents for imaging of human CCR8

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Human CC-chemokine receptor 8 (CCR8) regulates development, activation, and recruitment of leukocytes through binding and activation of seven transmembrane G-protein-coupled receptors and plays an important role in diseases such as asthma, multiple sclerosis and cancer. A novel series of naphthalene-sulfonamides have been developed as human CCR8 antagonists by Jenkins et al. New carbon-11 labeled naphthalene-sulfonamides were designed and synthesized as potential radiotracers for biomedical imaging technique positron emission tomography (PET) to image human CCR8. Unlabeled naphthalene-sulfonamides were

synthesized from 4-amino-naphthalene-1-sulfonic acid in multiple steps with moderate to excellent yields. The target tracers *N*-[4-[[(4-[^{11}C]methoxyphenyl)amino]sulfonyl]-1-naphthalenyl]-benzamide, *N*-[4-[[(4-[^{11}C]methoxyphenyl)amino]sulfonyl]-1-naphthalenyl]-2-methyl-benzamide, *N*-[4-[[(4-[^{11}C]methoxyphenyl)amino]sulfonyl]-1-naphthalenyl]-3-methyl-benzamide, *N*-[^{11}C]methyl-*N*-methyl-4-[[[(4-benzoylamino)-1-naphthalenyl]sulfonyl]amino]-1-piperdinecarboxamide and *N*-[^{11}C]methyl-*N*-methyl-4-[[[4-[(2-methylbenzoyl)amino]-1-naphthalenyl]sulfonyl]amino]-1-piperdinecarboxamide were prepared from their corresponding precursors *N*-[4-[[(4-hydroxyphenyl)amino]sulfonyl]-1-naphthalenyl]-benzamide, *N*-[4-[[(4-hydroxyphenyl)amino]sulfonyl]-1-naphthalenyl]-2-methyl-benzamide, *N*-[4-[[(4-hydroxyphenyl)amino]sulfonyl]-1-naphthalenyl]-3-methyl-benzamide, *N*-methyl-4-[[[(4-benzoylamino)-1-naphthalenyl]sulfonyl]amino]-1-piperdinecarboxamide and *N*-methyl-4-[[[4-[(2-methylbenzoyl)amino]-1-naphthalenyl]sulfonyl]amino]-1-piperdinecarboxamide with [^{11}C]CH_3OTf under basic condition (NaH) through either *O*-[^{11}C]methylation or *N*-[^{11}C]methylation and isolated by HPLC method in 30-50% radiochemical yields.

MEDI 213

Synthesis of [^{11}C]DAA1106, a PET radioligand for peripheral benzodiazepine receptors

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The peripheral benzodiazepine receptor (PBR) has become a clinical biomarker of neuroinflammation and tumor progression. It also provides an attractive target for the development of receptor-based PET (positron emission tomography) radioligands to study brain and cancer diseases. [^{11}C]DAA1106 (*N*-(2-[^{11}C]methoxy-5-methoxy-benzyl)-*N*-(5-fluoro-2-phenoxyphenyl)-acetamide) has been developed as a clinically useful PET tracer for characterizing PBR. Although a few papers dealing with the synthesis of [^{11}C]DAA1106 have appeared, there are gaps in synthetic detail among them, and certain key steps gave poor yields or were difficult to repeat in our hands. Consequently, we investigated an improved synthesis of [^{11}C]DAA1106. The precursor DAA1123 was synthesized from 1,4-difluoro-2-nitrobenzene and phenol in 4 steps with moderate to excellent yields. The direct methylation of DAA1123 with methyl iodide provided authentic standard DAA1106 in 70% yield. The target tracer [^{11}C]DAA1106 was prepared by *O*-[^{11}C]methylation of DAA1123 with [^{11}C]CH_3OTf and isolated by HPLC method in 60-70% radiochemical yields.

MEDI 214

Semisynthetic modifications and SAR studies of manzamine A analogs

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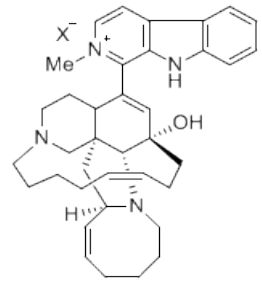
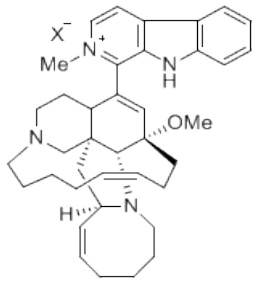
Malaria is a serious health problem worldwide causing deaths to a large number of populations each year, especially due an increasing volume of international tourism to infected areas, and

migration of people from these areas to other parts of the world. Despite its potent activity as an antimalarial agent the toxicity of manzamine A hampers its development as a drug candidate. Our current aim is to generate manzamine A analogs that decrease in vivo toxicity, and improve the therapeutic window for malaria by continuing other studies of the structure-activity relationship. The rational modification of the ß-carboline moiety through methylation of the pyridine nitrogen to form quaternary ammonium salt was based on previous work[1] wherein several synthesized ß-carboline analogs showed reduced toxicity and increased antimalarial activity by the formation of quaternary ammonium salts utilizing either alkyl tosylates or alkyl halides as a correlation to the π-delocalization of the cationic species. Methylation of manzamine A was carried out in the presence of methyl trifluoromethanesulfonate in two different molar ratios to yield a monomethylated product **1** and dimethylated product **2**. The structures of **1** and **2** were confirmed using high resolution ESI-MS, as well as ^{1}H-NMR, ^{13}C-NMR and HMBC, HMQC. Bioactivity data of these manzamine A analogs against *Plasmodium falciparum* will be presented.



2-methyl-manzamine A salt **1**
$X^- = CF_3SO_2O^-$



2,12-Dimethyl-manzamine A salt **2**
$X^- = CF_3SO_2O^-$

1-Kiyosei Takasu, bioorganic & medicinal chemistry Letters 14 (2004)1689-1692

MEDI 215

Lead optimization of next generation quinoline methanols

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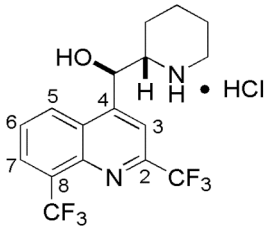
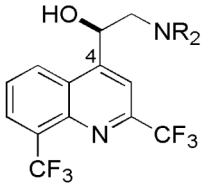
Current research focuses on a convergent synthesis that is amendable and will provide a plethora of mefloquine analogs at the 4-position. The aim is to identify a next generation quinoline methanol which is more potent and less neurotoxic than mefloquine 1, subsequently functioning as a replacement for existing clinical indications such as treatment and prophylaxis. The non-piperidine scaffolds, 2 and 3, are based on earlier work with N-alkylaminoquinolinyl methanols (AAQMs), which exhibited greater antimalarial potency and reduced direct neurocytotoxicity. With a synthetic blueprint in place, paradigms of analogs are currently being generated. These synthetic explorations are increasing the U.S. Army's understanding of the corresponding structure activity relationship (SAR) and determining whether alterations at the 4-

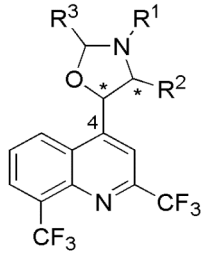
position will prevent central nervous system (CNS) accumulation through the elimination of the physiochemical properties associated with passive penetration of the blood brain barrier.



mefloquine **1**



2



3

MEDI 216

Saturation transfer difference NMR studies on the binding of the antitubercular agent pyrazinamide to *Mycobacterium tuberculosis* fatty acid synthase I

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We have previously shown that an analog of pyrazinamide (PZA), 5-chloropyrazinamide (5-Cl-PZA) inhibits fatty acid synthase I (FASI) in *Mycobacterium tuberculosis (Mtb)*. FASI has been purified from *Mtb* mc^2 2700, a recombinant strain where the native *fas1* gene has been deleted and replaced with *Mtb fas1* gene. Following purification, FASI enzymatic activity was measured using a spectrometric assay which monitors NADPH oxidation. Both 5-Cl-PZA and PZA showed concentration and substrate dependence consistent with competitive inhibition of FASI.

To further prove that 5-Cl-PZA and PZA bind to FASI, we used saturation transfer difference (STD) NMR experiment. The binding of the ligand (PZA or 5-Cl-PZA) to the target (FASI) is measured by the degree of ligand NMR signal saturation. We also report competitive binding of NADPH to FASI.

5-Cl-PZA binds to FASI with dissociation binding constant K_D of 90 µM which is significantly lower than the PZA constant $K_I$of 250 µM

MEDI 217

Design and synthesis of aza-peptide epoxide and Michael acceptor inhibitors targeting the legumain of the flatworm pathogen, Schistosoma mansoni

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Schistosomiasis is, after malaria, the second most important parasitic disease in tropical areas. The parasite feeds on blood and digests host hemoglobin which is essential for its growth, development, and reproduction. Cysteine and aspartic proteases are involved in proteolytic degradation of hemoglobin by schistosomes. Among these is a clan CD, family C13 legumain that requires an asparagine (Asn) residue at the P1 position for peptide bond hydrolysis. Accordingly, aza-peptides with an aza-Asn residue at P1 were designed and synthesized as specific inhibitors of the legumain from Schistosoma mansoni. Aza-peptides are ideal inhibitors because they are resistant to cleavage by proteases in vivo and can incorporate a reactive warhead. Michael acceptor and epoxide warheads were used in the inhibitor design since they belong to classes of irreversible inhibitors that are specific for clan CD proteases. Kinetic studies showed that most potent inhibitors have IC50 values in the range of 35-100 nM.

MEDI 218

Design and synthesis of potent peptidyl vinyl sulfones and allyl sulfones for inhibition of parasitic cysteine proteases

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Parasitic cysteine proteases are essential for the life cycles or pathogenicity of parasites. Cruzain is essential for the development of T. cruzi, which cause Chagas' disease while rhodesain and TbCatB are vital in the developments of T. bruei that causes African sleeping sickness. Although human homologues exist, parasite cysteine proteases have distinctive structural and biological properties including pH optima and stability, diverse substrate specificity and cellular location. Many parasite proteases, therefore, are targets for the development of chemotherapeutic agents. Peptidyl vinyl sulfones and allyl sulfones were developed as potent inhibitors of parasitic cysteine proteases such as cruzain, rhodasain and TbCatB. The vinyl sulfones and allyl sulfones are irreversible inhibitors. The most potent inhibitor has an IC50 value in the low nM concentration range

MEDI 219

Design and synthesis of novel and potent broad spectrum caspase inhibitors

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Caspases are a family of cysteine proteases with specificity for aspartic acid at the S1

subsite of the enzyme. Most caspases are involved in apoptosis while caspase-1 is involved in inflammation. Caspases are associated with several diseases including cardiac disease, stroke, traumatic brain injury, Alzheimer's and Parkinson's disease. Previous research has focused on

increasing the specificity of inhibitors for specific caspeses. However, in some diseases it is less clear which caspase must be inhibited in order to reduce cell damage since there are fourteen different human caspases. In order to tackle this shortcoming we designed a series of novel and potent broad spectrum peptidomimetic caspase inhibitors. These inhibitors showed potent inhibitory activity towards a broad range of caspases.

MEDI 220

Design of bioavailable InhA inhibitors with activity against drug-resistant strains of Mycobacterium tuberculosis

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Every year Tuberculosis claims approximately 1.7 million lives, and the treatment for drug resistant tuberculosis can be made much more time and cost efficient. We can do this by targeting the current drug target of the front line drug Isoniazid (INH), InhA, which is an enzyme in the fatty acid synthesis (FAS-II) cycle that synthesizes the precursor to mycolic acids, a vital component of the cell wall of M. tuberculosis. INH is a prodrug that needs to be activated within the mycobacteria by a catalase-peroixdase enzyme called KatG before it can inhibit InhA. About 80% of INH resistance is caused by mutations in the KatG enzyme. To bypass this undesirable activation step, we have synthesized compounds which are direct picomolar inhibitors of InhA, as our lead compound has a Ki of 5 pM with a Mic90 value of 1.56 + 0.0 µg/ml These compounds are derivatives of triclosan which has a Ki of 2.2 µM + 0.02 and a Mic99 value of 12.5 + 0.0 µg/ml for the enoyl reductase (InhA) enzyme. Despite these novel derivatives having excellent inhibition properties in vitro, in animal models they showed low bioavailability. Therefore, current work focuses on increasing solubility of the inhibitor in order to help the drug reach a stage of preclinical trials for the treatment of patients infected with drug resistant tuberculosis. This research is supported by the grant NIH 1057765-1-407000, and AI 070J8J, and the Beckman Foundation.

MEDI 221

Synthesis and biological evaluation of novel sulfonyl-naphthalene-1,4-diols as FabH inhibitors

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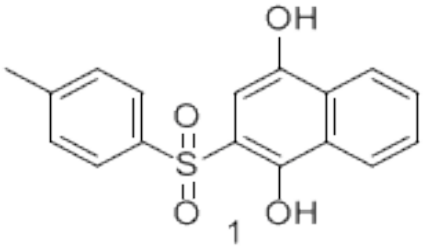
b-Ketoacyl-ACP-synthase III (FabH) has proven to be a potential target for antibacterial, antiparasitic, and antimycobacterial agents. We have identified a series of novel sulfonyl-naphthalene-1,4-diols (1) that are potent and reversible inhibitors of E. coli, M. tuberculosis and P. falciparum FabH enzymes. Preliminary SAR studies focused primarily on modifying the toluene or naphthalene parts of the molecule or changing the oxidation state of the sulfur and 1,4-diol. These studies resulted in the synthesis of a series of analogues that followed a consistent activity profile against the three FabH enzymes. The in vitro activity of the analogues against E. coli FabH parallel the in vivo activity against TolC E. coli strain. Replacement of the toluene part of the molecule with a methyl group greatly improved the activity against P. falciparum FabH. Many of the compounds were also shown to have antimalarial activity against the erythrocytic stage of (D6) P. falciparum.



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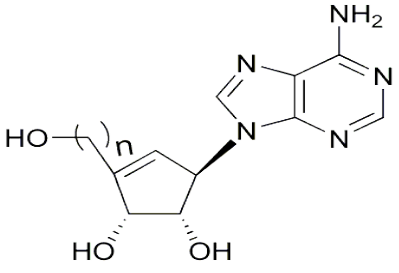
MEDI 222

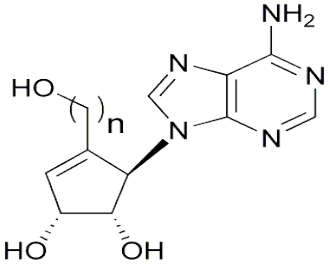
Synthesis and biological properties of 6′-*iso* analogs of neplanocin A and 5′-homoneplanocin A

Wei Ye *and Stewart W. Schneller, Department of Chemistry and Biochemistry, Auburn University, Auburn University, AL 36849, yewei01@auburn.edu*

The antiviral potential of neplanocin A (**1**) is limited by its toxicity as a result of metabolism to its 5′-nucleotide derivatives. In seeking ways to limit these undesirable transformations, 5′-homoneplanocin A (**2**) was synthesized and found to have significant antiviral activity against HBV and HCV without associated toxicity. From those investigations the 6′-*iso* analogues **3** and **4** emerged in our lab as interesting targets, which could retain the significant antiviral activity of **1** while reducing toxicity. The synthesis and antiviral properties of compound **3** and **4** will be reported. This research is supported by funds from the Department of Health and Human Services (AI56540).



1 n=1
2 n=2



3 n=1
4 n=2

MEDI 223

Synthesis of picomolar inhibitors of InhA, the enoyl reductase in Mycobacterium tuberculosis

Christopher am Ende[1]*, Todd J. Sullivan*[1]*, Nina Liu*[2]*, Hua Xu*[1]*, Sylvia Luckner*[3]*, Francis Johnson*[4]*, Richard A. Slayden*[5]*, and Peter J. Tonge*[1]*. (1) Department of Chemistry, Stony Brook University, Stony Brook, NY 11794, amendecw@yahoo.com, (2) Department of Chemistry, SUNY Stony Brook, NY, (3) Institute for Structural Biology, University of Wurzburg, Wurzburg, Germany, (4) Department of Pharmacological Sciences, State University of New York, Stony Brook, NY 11794, (5) Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins 80523-1682*

Mycobacterium tuberculosis (MTB) is responsible for 1.7 million deaths annually. The current treatment for MTB relies on the front line pro-drug isoniazid (INH) which targets InhA the enoyl reductase in the fatty acid biosynthesis pathway (FASII). Mutations in KatG, the activating enzyme for INH are responsible for much of the multi-drug resistant strains of MTB. A series of alkyl diphenyl ethers have been developed that circumvent this activation step and target InhA directly. The most potent compound has a Ki of 5 pM with MIC99 value of 1.5 μg/mL. Furthermore, these compounds are active against drug-resistant strains of MTB.

MEDI 224

Synthesis of pyrimido[4,5-*b*]indoles as selective inhibitors of *Toxoplasma gondii* dihydrofolate reductase

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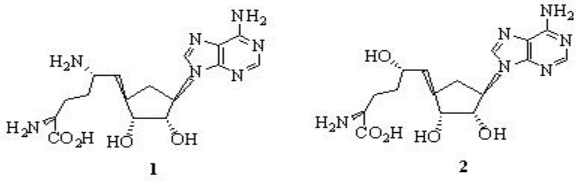
Patients with acquired immune deficiency syndrome (AIDS) suffer from and succumb to opportunistic infections caused by *Pneumocystis carinii* (*P. carinii*) and *Toxoplasma gondii* (*T. gondii*). Dihydrofolate reductase (DHFR) inhibitors are currently used drugs. Combinations of current DHFR inhibitors with other agents such as sulfa drugs are often required for synergistic effects or to prevent host toxicity, which leads to high costs. As part of a continuing effort in our laboratory to develop single agents which not only display high potency but are also selective against DHFR from *T. gondii* over mammalian DHFR, a series of pyrimido[4,5-*b*]indoles were designed and synthesized. The synthesis and selective *T. gondii* DHFR inhibitory activity of these compounds will be presented.

MEDI 225

Synthesis of the analog of carbocyclic sinefungin

Guoxia Zhao[1]*, Xueqiang Yin*[1]*, and Stewart W. Schneller*[2]*. (1) Auburn University, Department of Chemistry and Biochemistry, Auburn, AL 36849, (2) Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849*

To build upon our recent disclosure of carbocyclic sinefungin (1, Tetrahedron Lett. 2007, 48, 4809.), the corresponding hydroxy analog 2 became a target compound. Commencing with D-ribose, the synthesis of 2 has been achieved in 18 steps that include the Schöllkopf chiral auxiliary. This sequence will be presented along with the accumulated antiviral data. This research was supported by funds from the Department of Health and Human Services (AI 56540).



1 2

MEDI 226

Synthesis toward novel 1,3-azaborine heterocycles as potential dual-mode HIV-1 protease inhibitors

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Drug discovery has resulted in many life-saving therapies, making a great impact on modern medicine and the human condition. Even though new therapies are available many drugs are highly susceptible to resistance development, have poor bioavailability, and some of them are toxic. HIV-1 protease inhibitors presently on the market show high specificity but have low bioavailability and high toxicity. Furthermore, the available drugs have a very low affinity for mutant forms of HIV-1 protease. Recent studies have shown that boronated HIV-1 protease inhibitors, which demonstrate both competitive and associative inhibition, have a higher affinity for HIV-1 protease at lower concentrations than their corresponding carbon analogs and also

inhibit a mutant form of HIV-1 protease. In this study three novel 1,3-azaborine type of heterocycles are being synthesized. Their biological characteristics will be analyzed and compared with other inhibitors to determine their effectiveness as novel anti-HIV drugs.

MEDI 227

Tetrahydro-beta carbolines as a novel antituberculosis agent

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In search for more efficacious anti-tuberculosis agents, our groups have identified a class of compounds, possessing tetrahydro-beta-carboline framework, which exhibits promising anti-tubercular activity. Several closely-related analogues were synthesized and evaluated for their biological activities. Structure-activity relationships are also discussed.

MEDI 228

To a synthesis of substituted 4-quinolones

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The 4-quinolone scaffold plays an extremely important role in medicinal chemistry. New findings reveal a need to increase the diversity of substituents around this framework. Thermolysis of substituted 1-aryl-pyrrole-2,3-diones provides a convenient method of synthesis of 3-acyl-4-quinolones with several points of diversity, that later can be easily modified by the means of reactions with nucleophiles. We are using this methodology for construction of a library of new compounds containing 4-quinolone fragment. Diacylation of aminovinyl ketones with oxalyl chloride affords 1H-pyrrole-2,3-diones. The decarbonylation of the latter by elevated temperatures (165-190°C) in inert solvents leads to the generation of acyl(imidoyl)ketenes, that undergo intramolecular cyclization to substituted 3-acyl-4-quinolones. Unexpected results were obtained in some cases when starting aminovinyl ketones have fluorinated aliphatic substituents. Different compounds containing 4-quinolone fragment, including b-annelated, are synthesized. Results of synthesis and biological test data, including anti-tuberculosis activity, are reported.

MEDI 229

Structure-based virtual screening to discover small molecular inhibitors of ubiquitin-activating enzyme (E1)

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Inflammatory diseases such as rheumatoid arthritis, asthma, and multiple sclerosis are among the most common threats to human health. Transcription factor NF-kappaB plays a critical role in the initiation and development of these diseases. Ubiquitination is essential for the activation of NF-kappaB during inflammation and is a new promising target for their treatment. In this study, we use structure-based virtual screening methods to identify inhibitors of ubiquitin-activating enzyme (E1), the protein that initiates the ubiquitination process, in our natural products library. The lead compounds from our studies are cell permeable small molecules that specifically inhibit ubiquitin E1 and block the activation of NF-kappaB. Their anti-inflammation activities will be evaluated in cells and animal models.

MEDI 230

Discovery of a novel class of CB2 agonists

Renee Zindell[1]*, Doris Riether*[1]*, Lifen Wu*[1]*, Angela Berry*[1]*, Todd Bosanac*[1]*, Mark Gemkow*[2]*, Andreas F. Kahrs*[2]*, Andreas Ebneth*[2]*, Diane Thome*[3]*, Kathy O'Shea*[3]*, Roger Dinallo*[4]*, Ernest Raymond*[3]*, Daw-Tsun Shih*[3]*, and David Thomson*[1]*. (1) Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368, Fax: 203-791-6072, renee.zindell@boehringer-ingelheim.com, (2) Evotec AG, Hamburg, Germany, (3) Department of Immunology, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT 06877-0368, (4) Department of Drug Discovery Support, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT 06877-0368*

Cannabinoid receptors CB2 and CB1 are G-protein coupled receptors which may be useful in the treatment of inflammatory diseases and chronic pain. The use of ligands which modulate the cannabinoid receptor have been hampered by the psychotropic effects resulting from CB1 activity in the CNS. Several CB2 selective agonists have been reported which should lack the undesired CB1 side effects. These include PRS-211375, GW 405833 and GW 842166. Our goal is the identification of CB2 selective agonists and the evaluation and optimization of their pharmacological properties.

MEDI 231

Study on inhaling asarone for an interference function of the cell medium of the chronic obstructive pulmonary disease

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Objective: To discuss effect and possible mechanism of asarone on inflammatory cells that has significant influences upon the exacerbating of chronic obstructive pulmonary disease. **Method:** Determine the contents of tumor necrosis factor α(TNF-α)in phlegm of patients who suffered acute paroxysm of chronic obstructive pulmonary disease, transforming growth factor β1(TGF-β1)being synthesized by activation of the nuclear factor and interleukin-8 (IL-8). After inhaling asarone for periods of treatment, determine the contents of the cell medium mentioned above again (Besides treated group, a control group was also designed). **Result:** After being treated, each content of tumor necrosis factor α(TNF-α), transforming growth factor β1(TGF-β1)being synthesized by activation of the nuclear factor and interleukin-8 (IL-8) is lower. **Conclusion:** Asarone has an evident inhibiting effect on inflammatory cells that have significant influences upon the exacerbating of chronic obstructive pulmonary disease.

MEDI 232

Development of a Src/VEGFr2 inhibitor for the potential treatment of age-related macular degeneration

***Moorthy S. S. Palanki**, Jianguo Cao, Zoe Chen, Chun P. Chow, Luis Dellamary, John Doukas, John Hood, Dan Lohse, Sankaranarayana Mahesh, Chi Ching Mak, Michael Martin, Andrew McPherson, Glenn Noronha, Ved P. Pathak, Joel Renick, Richard Soll, and Binqi Zeng, TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830, palanki@targegen.com*

Age-related macular degeneration (AMD) is one of the leading causes of loss of vision in the industrialized world. A large body of evidence suggests that inhibitors targeting the VEGFr2 pathway are effective for the treatment of AMD. Recent studies using Src knockout mice suggest that along with VEGF, Src plays a crucial role in vascular leak and might be useful in treating edema associated with AMD. Internal drug discovery efforts lead to the identification of dual inhibitors targeting Src/VEGFr2 as potential treatment for AMD. We have developed **TG100801**, a topically administered prodrug delivered as an eye-drop, for age-related macular degeneration. Here we present an overview of the pre-clinical efforts that lead to the nomination of **TG100801** as a clinical candidate for the potential treatment of AMD.

MEDI 233

Strategies for the synthesis of the phase II clinical candidate TG100801

***Andrew McPherson**, Geoffrey E Barker, Jianguo Cao, Chun P. Chow, Raylyn DeGuzman, Luis Dellamary, David E. McClure, Chi Ching Mak, Glenn Noronha, Moorthy S. S. Palanki, Ved P. Pathak, Joel Renick, Richard Soll, and Binqi Zeng, TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830*

The leading causes of vision loss in many industrialized countries are diabetic retinopathy and age-related macular degeneration (AMD). A large body of evidence suggests that inhibitors targeting both VEGF and Src pathways have potential utility in the treatment of AMD. **TG100572** was identified as a potent inhibitor of VEGFr2 and Src. **TG100801**, a prodrug of **TG100572**, is currently in a phase II clinical trial for the treatment of AMD. We present here various synthetic strategies that were used in the structure activity relationship studies and further improvements used in making **TG100801** to support clinical trials.

MEDI 234

TG100801: A prodrug for the potential treatment of age-related macular degeneration (AMD)

***Chi Ching Mak**, Jolene Brown, Jianguo Cao, Zoe Chen, Chun P. Chow, Luis Dellamary, John Doukas, John Hood, Ahmed Kousba, Dan Lohse, Sankaranarayana Mahesh, Michael Martin, Andrew McPherson, Glenn Noronha, Traci Olafson, Moorthy S. S. Palanki, Ved P. Pathak, Adrienne Racanelli-Layton, Joel Renick, Richard Soll, and Binqi Zeng, TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830, cmak@targegen.com*

Age-related macular degeneration (AMD) is the leading cause of non-preventable blindness in the industrialized world. Lucentis, an intravitreally injected agent, is the standard of care for AMD. Recent studies using Src knockout mice suggest that targeting both VEGFr2 and Src have potential utility in the treatment of AMD. In order to develop a dual VEGFr2/Src inhibitor delivered by a less invasive route, TargeGen has developed TG100801, a topically administered small molecule prodrug that is readily converted to the active compound TG100572 in the eye. TG100801 is currently in a clinical trial as a first in class, topically applied compound for the treatment of AMD. The details of the rationale for the use of the prodrug approach to improve ocular pharmacokinetics and prodrug optimization strategy will be described. We will also present the efficacy of TG100801 in a pre-clinical model.

MEDI 235

Discovery of TG100572, a dual VEGFr2/Src inhibitor, for the potential treatment of AMD

***Jianguo Cao**[1], Chun P. Chow[1], Luis Dellamary[1], John Doukas[1], Richard Fine[2], John Hood[1], Xinshan Kang[2], Boris Klebansky[2], Dan Lohse[1], Chi Ching Mak[1], Michael Martin[1], Andrew McPherson[1], Glenn Noronha[1], Moorthy S. S. Palanki[1], Ved P. Pathak[1], Joel Renick[1], Richard Soll[1], and Binqi Zeng[1]. (1) TargeGen, Inc, 9380 Judicial Drive, San Diego, CA 92121-3830, Fax: 858-678-0029, jcao@targegen.com, (2) BioPredict, Inc, Oradell, NJ 07649-1525*

TG100801 — a prodrug of TG100572 is currently in a Phase II clinical trail for topical treatment of age-related macular degeneration (AMD). Current therapy requires repeated intraocular injections with VEGF-targeting macromolecules. Recent studies using Src knockout mice suggest that along with VEGFr2, Src plays a crucial role in vascular leak and might be useful in treating edema associated with AMD. TargeGen has developed a series of dual VEGFr2/Src inhibitors. Here we present our molecular modeling guided SAR efforts in optimizing compounds in our benzotriazine series for their biochemical potency against VEGFr2 and Src as well as the identification of TG100572 as a potent dual inhibitor.

MEDI 236

A novel lead-like library aims kinase target

Q. John Yu *and F. Nancy Wei, CGeneTech, Inc, 7128 Zionsville Road, Indianapolis, IN 46268, Fax: 317-295-1926, jyu@cgenetech.com*

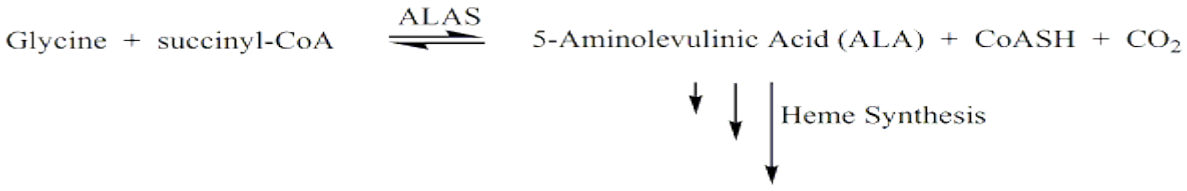
Based on computer-aided design, a group of unique molecules have been synthesized. These fragments obeyed “Rule of 3” theory for lead-like molecules. Synthetic method and biological data will be explored.

MEDI 237

Screening of libraries for inhibitors or activators of the enzyme 5-aminolevulinate synthase

Richard M. Cross[1]*, Roman Manetsch*[1]*, Gloria Ferreira*[2]*, and Gregory A. Hunter*[2]*. (1) Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620, rmcross@mail.usf.edu, (2) Department of Molecular Medicine MDC 7, University of South Florida, Tampa, FL 33612*

5-Aminolevulinate synthase (ALAS, EC 2.3.1.37), a pyridoxal 5'-phosphate-dependent enzyme, catalyzes the first, and regulatory step of the heme biosynthetic pathway in humans, animals, other nonplant eukaryotes and some bacteria. ALAS catalyzes the synthesis of 5-aminolevulinic acid (ALA) from glycine and succinyl-coenzyme A. Commonly, ALAS activity is monitored spectrophotometrically by a coupled enzyme assay, which is not practical for the screening of large libraries of molecules. Herein, we report the use of mass spectrometry with electrospray ionization (ESI-MS) to screen small molecule libraries for potent inhibitors or activators of the enzyme ALAS. The developed assay has been adapted to a 96-well-pate format and it takes advantage of the excellent ESI-MS sensitivity to detect small amounts of ALA generated in the microliter incubation assays. A known ALAS inhibitor, L-serine (IC50 = 200 μM), is used as a control in our screening attempts.



MEDI 238

Repurposing compound collections for new drug discovery paradigms

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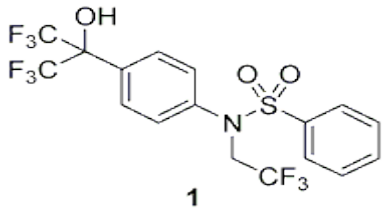
In the past, large collections of compounds were compiled and synthesized for both high throughput screening and parallel synthesis. As new rules and methods for drug discovery have emerged, most compound collections need to be revised, with different collections required for the different discovery methods. We examined several commercial compound collections with a variety of the newer approaches in mind (lead-like, fragment screening, drugs in other drugs, drug repurposing). Compounds were also screened to fall within biologically relevant space, pass physiochemical requirements, and avoid known bad moieties (Rishton filters, frequent hitters, aggregators). From this study, we determined useful methods to allow quick parsing of large collections when looking for specific libraries of interest. We then generated unique compound subsets that are more applicable to specific types of screening methods. Our results also assisted in determining what compounds to synthesize in the future to fill gaps in the current collections.

MEDI 239

Structure-guided design of pan-LXR antagonists

*Frank Kayser[1], Anne Chai[2], Peter Coward[3], Martin Harrison[2], Juan Jaen[2], **XianYun Jiao**[1], Stuart Jones[2], David Kopecky[1], Derek Piper[4], and Andy Shiau[2]. (1) Chemistry Research and Discovery, Amgen SF, 1120 Veterans Blvd, South San Francisco, CA 94080, Fax: 650-244-2015, fkayser@amgen.com, xjiao@amgen.com, (2) (3) Metabolic Disorders Research and Discovery, Amgen SF, (4) Structural Biology, Amgen SF*

The liver X receptors (LXR's) play an important role in cholesterol homeostasis and lipid biosynthetic pathways. LXRa and LXRb have been identified. While LXRa is mainly expressed in the liver, the kidneys, and the intestine, LXRb is more ubiquitously expressed. Several structurally distinct classes of LXR ligands have been described, which include the synthetic ligand T1317 (1). We have shown that LXR agonists increase the expression of SREBP-1c and fatty acid biosynthetic enzymes in mouse liver and human hepatocytes. Mice treated with LXR agonists have increased levels of VLDL triglycerides, while LXRa/b k.o. mice have reduced VLDL levels. At the same time, intestinal expression of ABCA1 is elevated and absorption of cholesterol is unaffected in LXRa/b k.o. mice. We therefore believe that a LXR antagonist will lower triglyceride levels without affecting HDL. Herein we describe the synthesis and the SAR of several potent pan-LXR antagonists obtained from a structure-based design approach in which the agonist compound binding mode of T1317 was used to design antagonists.



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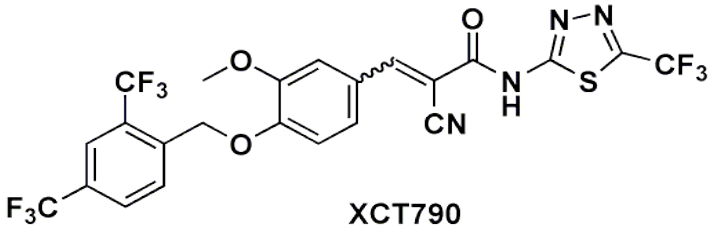
MEDI 240

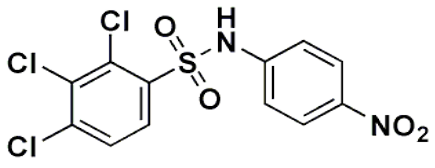
Estrogen related receptor α (ERRα) agonists: HTS hit evaluation

Kaapjoo Park[1], *Ariamala Gopalsamy*[1], *John C McKew*[1], *Yongbo Hu*[2], *Franklin Moy*[1], *James LaRocque*[1], *Ruth Gimeno*[3], *Dongmei Li*[3], *Christian Johnson*[3], *Yan-Ling Zhang*[3], *Zheni Gjoka*[3], *and Vipin Suri*[3]. *(1) Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-3045, ParkK3@wyeth.com, (2) Department of Structural Biology & Computational Chemistry, Wyeth Research, Pearl River, NY 10965, (3) Cardiovascular and Metabolic Disease, Wyeth Research, Cambridge, MA*

ERRα (Estrogen Related Receptor α) is an orphan nuclear hormone receptor most closely related to ERRβ/γ (~60% identity, ligand binding domain (LBD)) and estrogen receptors (~30% identity, LBD). ERRα does not bind estrogen or estrogen derivatives and has no known endogenous ligands. ERRα is master regulator of oxidative phosphorylation gene expression and agonists of ERRα are thought to be beneficial for the treatment of type 2 diabetes. We performed a high-throughput screen for compounds that increase coactivator peptide binding to the ERRα LBD using an AlphaScreen assay. 1416 confirmed hits were characterized further using a FRET assay, various biophysical binding assays, as well as cell-based reporter assays. All assays were validated using the ERRα inverse agonist, XCT-790. One compound, benzensulfonamide A, showed moderate ERRα agonist activity in the AlphaScreen assay and displayed binding to ERRα LBD. ROCS search, virtual screening and library synthesis around this hit were performed.



XCT790



A

MEDI 241

Identification of small molecular inhibitors of lymphocyte specific protein tyrosine phosphatase

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LYP, encoded by the PTPN22 gene, plays an important role in T cell signaling. A single-nucleotide polymorphism in PTPN22 causes many autoimmune disorders such as type 1 diabetes,rheumatoid arthritis, systemic lupus erythematosus and Grave's disease. The autoimmunity-predisposing allele has bee proven to be a gain-of-function mutation and its deleterious effect could be suppressed by specific inhibitors, and therefore provides a novel

approach to the treatment of autoimmune diseases. To identify its small molecule inhibitors, a high throughput screening assay was established. An active thiazolidine cluster was found in the screening of a 100k small molecule library. Subsequent modification led to the discovery of several potent inhibitors of LYP with sub-micromolar IC50s.

MEDI 242

Discovery of oxazolo[4,5-b]pyridines and related heterocyclic analogs as novel SIRT1 activators

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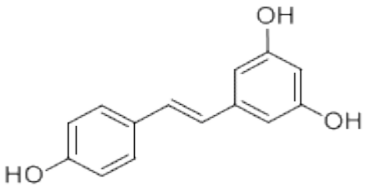
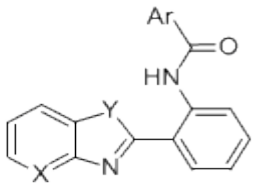
SIRT1, an NAD+-dependent protein deacetylase, has been implicated as a key modulator in pathways downstream of calorie restriction that produce beneficial effects on metabolic parameters such as glucose and insulin homeostasis. Activation of SIRT1 by resveratrol (1) has been shown to modulate insulin resistance, increase mitochondrial content and prolong survival in lower organisms and in mice on a high fat diet. We have identified novel small molecule activators of SIRT1 that are structurally unrelated to and more potent than resveratrol. Here we present the initial SAR of oxazolo[4,5-b]pyridines (2) and related analogs as activators of SIRT1.



(1) resveratrol



(2) X = N, Y = O

MEDI 243

Differentiation of binding and geometric decoys generated from molecular docking using cheminformatics approaches

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Protein structure based scoring functions frequently fail to prioritize true binders and correctly predict bound ligand poses. We have employed cheminformatics approaches to address these challenges in structure based drug design. In the first study, k- Nearest Neighbor (kNN) classification QSAR approach was applied to the AmpC beta-lactamase 'binding decoy' dataset to differentiate inhibitors and non-binders; the correct classification rates for both training and test sets exceeded 0.90. In the second study, the ENTess chemical geometrical descriptors of protein-ligand interface (J. Med. Chem. 2006, 49, 2713-2724) were applied to 264 protein-ligand complexes to generate Quantitative Structure Binding Affinity Relationship (QSBAR) classification models for four 'geometric decoy' datasets. The classification accuracy for discriminating native-like poses from decoys ranged from 0.50 to 0.96. We suggest that cheminformatics approaches that are typically used in ligand-based approaches can be successfully extended towards innovative applications in structure-based drug discovery.

MEDI 244

Modeling blood-brain barrier permeability by passive diffusion

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This study presents a mechanistic QSAR analysis of blood-brain barrier permeability of drugs and drug-like compounds in rats. The experimental data were expressed as LogPS (logarithm of permeability-surface area product) constants which account for the rate of passive diffusion across blood-brain barrier. A data set of 178 LogPS values was compiled from original literature sources. Dependence of LogPS values on ionization, lipophilicity, hydrogen bonding potency and molecule size was considered. A single predictive model for neutral, acidic and basic compounds was built using non-linear fitting method. The residual mean square error of LogPS prediction was 0.5 units. No model was produced for zwitterionic drugs due to the lack of high-quality experimental data as most zwitterions enter the brain via carrier-mediated processes.

MEDI 245

Modeling permeability across caco-2 monolayers

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This study presents a mechanistic QSAR analysis of Caco-2 permeability of drugs and drug-like compounds. Experimental data were represented by more than 600 logPe (logarithm of permeability coefficient) values obtained at various pH and stirring rates. Caco-2 permeability was split into the paracellular and transcellular routes which were considered separately. A theoretical model of molecular size-restricted diffusion through aqueous pores was used to estimate the paracellular permeability, while characteristic functions relating permeability to ionization, lipophilicity and hydrogen bond donor capacity were built to account for the transcellular route. The effects of unstirred water layer resistance were also considered. Statistical modeling was performed by non-linear fitting to a set of experimentally determined

logPe values. The residual mean square error of prediction of Caco-2 permeability was 0.54 units.

MEDI 246

Probabilistic prediction of the human CYP3A4 metabolism sites in a molecule

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In this work we present an attempt of in-silico prediction of the most probable human CYP3A4 metabolism sites in a molecule. Critically evaluated experimental data for nearly 500 compounds (representing more than 500 sites known to participate in hydroxylation or N and O-dealkylation reactions mediated by CYP3A4) collected from public sources was used as an input in binomial PLS model using atom-centered fragments followed by an application of a novel ‘Trainable Model' methodology. The resulting predictive algorithm provides probabilities of being a target of CYP3A4 activity for any atom in a molecule and allows forecasting the most probable phase I metabolites. As a result of ‘Trainable Model' concept application each prediction is provided with an estimation of its quality in the form of calculated Reliability Index (RI). Further we illustrate that the Applicability Domain of the model can be expanded utilizing user-defined experimental metabolism data.

MEDI 247

Similarity based correction for the predictions of compounds physicochemical properties

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Here we present a novel similarity based methodology that provides a possibility for a user to expand the Applicability Domain of the existing Pharma Algorithms models with the help of a custom database of experimental values for the property of interest. A Reliability Index (RI) is also calculated as a measure of the quality of the particular prediction. The use of the method is illustrated with examples of its application in predicting logP, logD and solubility of the compounds. It is shown that a relatively small amount (5 to 10) of similar compounds has to be added to substantially improve the prediction for a group of problematic compounds that is not represented in the original training set. The Reliability Index is shown to be closely related to the overall quality of any given prediction that is represented by a clear correlation of the RI and RMSE values.

MEDI 248

Modeling of HIV integrase-DNA active site with two magnesium ions

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Even though human immunodeficiency virus type 1 (HIV-1) integrase (IN) has been recognized as an important target for developing anti-AIDS drugs, it has proven so difficult in over fifteen years of worldwide development efforts that the very first drug based on IN inhibition went to market only very recently. One of the biggest obstacles has been that there is no detailed experimental information about how the many known inhibitors interact with the protein and its substrate, viral DNA. Tn5 transposase and rous sarcoma virus IN, together with HIV-1 IN, belong to the superfamily of polynucleotidyl transferases. The catalytic sites of the former, resolved by X-ray diffraction (PDB structure 1MUS), include the protein, two metal ions and substrate DNA. Combining these structures with the X-ray structure (1BL3) of the IN core domain, we have developed active site models with two magnesium ions. A 20 bp viral DNA was placed in the active site, making sure that it has the same orientation as in 1MUS. We built two models in which either the 3'-OH or 5'-OH chelate the two magnesium ions. We report on subsequent docking studies utilizing these models.

MEDI 249

Synthesis and biological evaluation of 3-aryl-3-arylmethoxytropane derivatives at monoamine transporters

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A series of 3-aryl-3-arylmethoxytropane derivatives has been synthesized and evaluated for potency and selectivity at dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters in rat brain tissue preparations. Lead compounds in the series have been found to exhibit subnanomolar affinity and high selectivity for the SERT. The synthesis, monoamine transporter affinity and structure-activity relationships of these novel compounds will be presented.

MEDI 250

Oligochitosan-TPP nanoparticles: Preparation and optimization

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Oligo-chitosan (OCS) which is a kind of non-toxic, biodegradable polycationic polymer with low immunogenicity can self-assemble with sodium tripolyphosphate (TPP). Oligo-chitosan based nanopariticles have attracted great attention in pharmaceutical applications including colon targeted drug delivery, mucosal delivery, cancer therapy, vaccine delivery, gene delivery. The size, stability, and uniformity of nanoparticles are important properties in determining loading factors. In this research we prepared the oligochitosan-TPP (OCS-TPP) nanoparticles from OCS and TPP, OCS of various molecular weights was used, weight ratio of OCS to TPP and the pH value of solutions were examined systematically for their effects on nanoparticle size, uniformity and the stability. By means of grain-size analyzer, transmission electron microscopy and scanning electron microscopy characterizations, it was found that the molecular weight of OCS did not affect the size significantly; the average diameter of the obtained nanoparticles is about 50-60 nm. It was shown that the change of weight ratio of OCS to TPP and pH influenced the stability notably, and the nanoparticles were not only narrow-distributed in size and dispersed well, but also not easy to dissolve at pH 6.

MEDI 251

Polyacrylate nanoparticles for potential delivery of chloroquine resistance reversal agents

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A very important target for drug discovery is Malaria, especially strands that are resistant to cheaper drugs for poverty stricken areas of the world. While the drug chloroquine is becoming increasingly outdated due to resistance, it remains a very good target due to its very beneficial characteristics. Previous work has been done to identify agents that reverse resistance of chloroquine however there is a broad area of work that needs to be done. Herein, we have applied our nanoparticle delivery system to these reversal agents in hope that this system will provide an alternative transport for these molecules, and allow us to help bring back a very important drug to many areas of the world.

MEDI 252

Structure of Karlotoxin-2, a toxin causing massive fish kills worldwide

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In an attempt to determine the cause of repeated fish kills in an estuarine aquaculture facility in Maryland, a toxin was isolated from Karlodinium veneficum with hemolytic, cytotoxic, and ichthyotoxic properties, which was referred to as karlotoxin-2. Its structure was elucidated by

means of detailed 1D and 2D NMR spectra including 2D INADEQUATE. The relative configuration of karlotoxin-2 was determined using J-based configuration analysis. As an example, Figure 2 shows the determination of the relative configuration of C14~C16 by 3JH,H, 2JC,H, and 3JC,H.

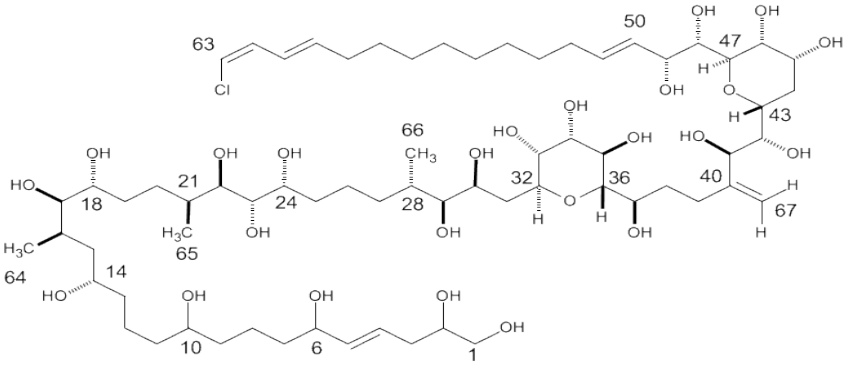

Figure 1. Structure of Karlotoxin-2

$^3J_{(H\text{-}14,\ H\text{-}15H)}$	3.3	$^3J_{(H\text{-}16,\ H\text{-}15H)}$	10.7
$^3J_{(H\text{-}14,\ H\text{-}15L)}$	9.7	$^3J_{(H\text{-}16,\ H\text{-}15L)}$	3.3
$^2J_{(C\text{-}14,\ H\text{-}15H)}$	-1.6	$^3J_{(C\text{-}64,\ H\text{-}15H)}$	3.1
$^2J_{(C\text{-}14,\ H\text{-}15L)}$	-5.4	$^3J_{(C\text{-}64,\ H\text{-}15L)}$	6.2

Figure 2. Relative configuration and the homo-and hetero-coupling constants

MEDI 253

Subtype-selective allosteric modulation of the M1 and M4 muscarinic receptors

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M1 and M4 subtypes of the muscarinic receptor represent attractive targets for many CNS disorders including Alzheimer's disease (AD) and Schizophrenia. Traditional muscarinic agonists lack efficacy and carry severe side effects due to non-selective activation of all mAChR subtypes, and absence of selective agents has hindered basic research into the respective roles of the M1 and M4 receptors in the CNS. We report the discovery and preliminary

characterization of novel muscarinic ligands that modulate either the M1 or M4 receptor in an allosteric manner with high subtype-selectivity. We also report the discovery of a highly potent M1 antagonist with unprecedented selectivity. Functional cell-based HTS and technology-enabled synthetic methods were used to identify and optimize a number of compounds. An identified allosteric agonist, TBPB, demonstrated disease modification potential for AD by decreasing Aβ secretion in an APP processing assay. TBPB also displayed in-vivo antipsychotic activity in rodent studies.

MEDI 254

Synthesis of subtype selective ligands and molecular modeling for alpha-5 containing GABAA/Bz receptors to treat memory deficits

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The α-aminobutyric acidA/benzodiazepine receptor (GABAA/BzR)-complex is the major inhibitory neurotransmitter system in the central nervous system (CNS). It has been proposed that the GABAA/BzR chloride channel is a pentameric protein polymer principally constructed from α, β and γ subunits. A total of 21 subunits (6α, 4β, 4γ, 1δ ,1ƒzπ, 1ƒzσ, 1ε and 3ρ) have been cloned and sequenced from the mammalian CNS. Studies in molecular cloning have shown that at least 1α, 1&beta and 1γ subunit are required to construct a fully functional recombinant GABAA/BzR chloride channel which mimics the biological, electrophysiological and pharmacological properties of a native GABAA/ BzR chloride channels. The distribution of various subunits in the brain was found to be distinct and regionally overlapping. From the recent work of Dr. Harry L. June it was demonstrated that RY024, the selective α5 ligand, is capable of antagonizing the reinforcing, motor impairing, and sedative effects of EtOH in Long-Evans rats. Three α5 subtype selective compounds have been used as lead compounds in recent research. The results will allow the mapping the binding sites in (GABAA/BzR)-complex subtypes as well as develop more potent and selective drugs with decreased side effects designed to treat memory deficits.

MEDI 255

N-Alkyl substituted-pyrrole 2-amino-3,5-dihydro-4H-imidazol-4-ones as potent, and selective BACE1 inhibitors

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Alzheimer's Disease (AD) affects an estimated four million people in the U.S. Its symptoms are a decline in cognitive functions leading to dementia. Studies have indicated that reduction of plaques formed from Ab deposition may slow the development of AD. Developing a potent orally active inhibitor of the Beta Amyloid Cleaving Enzyme (BACE1), an aspartic protease involved in

the generation of Ab, is the focus of this research. The previously disclosed (5S)-2-amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one (1) demonstrated high potency in the FRET and cell-based ELISA assays with IC50 values of 12 and 22 nM, respectively. Using X-ray crystallography and molecular modeling as a guide, we have found that replacement of the phenyl group of 1 residing at the S2' pocket of the binding site with N-alkyl-substituted pyrroles produced potent and selective BACE1 inhibitors (IC50 ~ 10 nM), which showed selectivity against Cathepsin D and BACE2. Key interactions between the pyrrole group and amino acid residues in the S2' region of the binding pocket have been identified. These interactions contribute to the potency and selectivity of the ligand. Herein we will describe the synthesis and biological activity of these compounds.

MEDI 256

2-Substituted-pyrrole 2-amino-3,5-dihydro-4H-imidazol-4-ones: Highly potent, and selective BACE1 inhibitors

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Alzheimer's Disease (AD) is a progressive, degenerative disease of the brain and most common form of dementia. One primary theory on the etiology of AD is that in AD patients, amyloid precursor protein (APP) is processed in the brain and converted to beta amyloid protein, a precursor to amyloid plaques. β-Secretase (β -site APP cleavage enzyme or BACE-1) and γ-secretase are two important enzymes involved in the amyloid synthetic cascade. Inhibition of secretases responsible for Aβ formation may stop or slow AD progression by preventing its production. The design and synthesis of highly potent, selective and orally active inhibitors of β-secretase (BACE-1) was based on the HTS hit 2-amino-3-methyl-5,5-diphenyl-3,5-dihydro-4H-imidazol-4-one (IC_{50} = 3 μM). With help from Xray crystallography we employed structure based design to develop a new series of pyrrole substituted 2-amino-3,5-dihydro-4H-imidazol-4-ones that are potent (IC_{50} <10 nM) and selective (>1000x vs Cathepsin D) inhibitors of BACE-1. Molecular modeling showed that we could access key interactions in the S2' sub-site of BACE-1 by substituting on the 2-position of the pyrrole ring. This afforded compounds with high affinity in cell-based assays (<10 nM). These potent and selective BACE1 inhibitors will contribute toward the understanding of APP processing, as well as the development of potential disease-modifying AD therapeutics.

MEDI 257

Rigid analogs of 4,4-diaryl-iminohydantoins as potent inhibitors of Beta-secretase

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive loss of memory and cognitive function. The disease currently affects 45 million people worldwide and this number in expected to rise dramatically over the next decade. At present no disease modifying therapy exists for AD. Palliative treatments, such as AChE inhibitors and NMDA receptor antagonists, afford modest, short-term improvement of symptoms.

Beta-secretase (BACE-1) is an aspartyl protease responsible for cleaving amyloid precursor protein to liberate amyloid beta (Ab), which aggregates leading to neurotoxic oligomers that are implicated in Alzheimer's disease. Inhibition of BACE-1 would prevent production of Ab thereby halting the progression of AD. We have previously disclosed a series of 4,4-diphenyl-imidazolones that have demonstrated promising activity for the BACE-1 enzyme

It has been shown that a rigid structure can often improve intrinsic activity and receptor specificity over related structures with rotatable bonds. Notable examples are the steroids. We will report the synthesis and biological activity of a series of conformationally restricted BACE-1 ligands for the potential disease modifying treatment of Alzheimer's disease

MEDI 258

Syntheses and biological properties of carbocyclic substituted aminohydantoin derivatives

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β-Amyloid deposits and neurofibrillary tangles are two major pathologic hallmarks associated with Alzheimer's Disease (AD). β-Amyloid deposits are predominately an aggregate of Aβ peptide, which is a product of the proteolysis of amyloid precursor protein (APP). Aβ peptide is generated in response to the sequential cleavage of APP at the C-terminus by γ-secretase, and at the N-terminus by β-secretase (BACE). Inhibition of secretases responsible for Aβ formation may stop or slow AD progression by preventing its production. We have reported that the aminohydantoin derivatives displayed potent BACE1 binding activities in previous presentations. Here we will report a novel synthesis of the carbocyclic substituted aminohydantoins and their biological properties as BACE inhibitors. SARs of the S3 sub-pocket will be addressed in this presentation.

MEDI 259

Substituted-pyrrole 2-amino-3,5-dihyro-4H-imidazol-4-ones as highly potent BACE1 inhibitors: Optimization of the S3 pocket

Ping Zhou[1]*, Yinfa Yan*[1]*, William F. Fobare*[1]*, Michael Malamas*[1]*, William R. Solvibile*[1]*, Rajiv Chopra*[1]*, Kristi Yi Fan*[1]*, Yun Hu*[2]*, Jim Turner*[2]*, Eric Wagner*[2]*, Ronald L Magolda*[1]*, Magid A Abougharbia*[1]*, Peter Reinhart*[2]*, Menelas Pangalos*[3]*, Jonanthan Bard*[2]*, and Albert Robichaud*[1]*. (1) Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, Fax: 732-274-4505, zhoup@wyeth.com, (2) Neuroscience, Wyeth Research, (3) Discovery Neuroscience, Wyeth Research, Princeton, NJ 08543*

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the brain that is the leading cause of dementia. Although the cause of AD is still unclear, increasing evidence implicates the β-amyloid peptide (Aβ, 39-43 residues) (most likely in multimeric forms such as oligomers) in the neurodegenerative pathogenesis. Aβ is produced from cell membrane-bound β-amyloid precursor protein (APP) by sequential proteolytic cleavage by β-secretase (BACE1) and γ-secretase. The Aβ peptide is neurotoxic and the principal component of the neuritic plaque found in the brains of AD patients. Therefore, inhibition of secretases responsible for Aβ formation may stop or slow AD progression by preventing its production. In this poster we will present novel substituted-pyrrole 2-amino-3,5-dihyro-4H-imidazol-4-ones as highly potent BACE1 inhibitors. X-ray crystal structure of pyrrolylaminohydantoin compound in complex with BACE1 demonstrated that the aminohydantoin moiety interacts with the two aspartic acids in the catalytic domain of BACE1, while some substituted groups have hydrogen bond interaction with tryptophan W76. The optimization of the S3 pocket via parallel synthesis approach led to many potent compounds. The synthesis, SAR and x-ray structure of the series will be presented.

MEDI 260

De novo design and SAR of cyclic hydroxyethylamine-based BACE1 inhibitors

Heinrich Rueeger[1]*, Clive McCarthy*[2]*, Jean-Michel Rondeau*[1]*, Henrik Moebitz*[1]*, Ulf Neumann*[3]*, Michele Chiesi*[3]*, Anne-Lise Jaton*[3]*, and Albert Enz*[3]*. (1) Global Discovery Chemistry, Neuroscience, Novartis Institutes for Biomedical Research, WKL-136.622, Basel CH-4002, Switzerland, Fax: ++41 61 696 24 55, heinrich.rueeger@novartis.com, (2) Global Discovery Chemistry, Oncology, Novartis Institutes for Biomedical Research, Switzerland, (3) Neuroscience, Novartis Institutes for Biomedical Research, Switzerland*

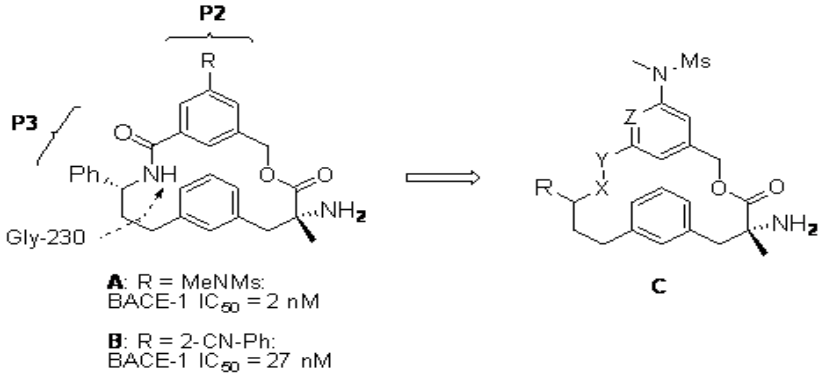
Beta-secretase is a leading target for the development of therapies to treat Alzheimer's disease. Despite intense research over the past decade, only recently have potent drug-like inhibitors of beta-secretase emerged. However, central efficacy in animal models has been difficult to achieve due to poor intrinsic permeability and active efflux by P-gp. In this poster we will present a de novo design approach which was selected due to a lack of CNS drug-like hits and to evade the poor property space inherent in a peptide-mimetic approach. The design, originating from X-rays of co-crystallization of macrocyclic ethanolamine inhibitors with BACE1, synthesis and early SAR of novel cyclic hydroxyethylamine BACE inhibitors will be presented.

MEDI 261

Strategies toward improving the brain penetration of macrocyclic tertiary carbinamine BACE-1 inhibitors

***Keith P. Moore**, Department of Medicinal Chemistry, Merck Research Laboratories, WP 14-3; 770 Sumneytown Pike; PO Box 4, West Point, PA 19486-0004, Fax: 215-652-3971, keith_moore2@merck.com*

Alzheimer's Disease (AD) is a progressive, degenerative brain disorder leading to dementia and death. Beta-Secretase (BACE-1), a transmembrane aspartyl protease, occupies a pivotal role in the proteolytic processing of APP (amyloid precursor protein) to A-beta (amyloid beta). Recently we disclosed the discovery and optimization of tertiary carbinamine derived inhibitors of BACE-1. This poster will describe replacements for the P3 amide moiety present in previously reported tertiary carbinamine macrolactones. Although P-gp efflux issues associated with these amide-macrolactones were solved and full brain penetration was measured, potency was compromised in the process.



MEDI 262

Aggregation and clearance of mutant huntingtin protein

***Alison Rinderspacher**[1], Yidong Liu[1], Shi-Xian Deng[1], Gangli Gong[1], Yuli Xie[1], M. Laura Cremona[2], Ai Yamamoto[2], Caty Chung[3], Nathalie Aulner[2], Udo Többen[2], Dušica Vidović[3], Stephan Schürer[3], Deborah H. Smith[2], Lars Branden[2], James E. Rothman[2], and Donald W. Landry[1]. (1) Department of Medicine, Columbia University, 630 West 168th Street, New York, NY 10032, ar2230@columbia.edu, (2) Department of Physiology and Cellular Biophysics, Columbia University, New York, NY 10032, (3) Scientific Computing, The Scripps Research Institute, Jupiter, FL 33458*

The neurodegenerative illness Huntington's disease reflects an abnormal intracellular accumulation of protein, and activators of autophagy-mediated clearance of mutant huntingtin protein (mHtt) are of potential therapeutic value. Using a stable HeLa cell line that conditionally expresses the first 17 amino acids of Htt followed by a polyglutamine (polyQ) stretch of 103 residues, encoded by repeating units of CAGCAGCAA, we screened a 10K subset of the NIH MLSCN chemical compound library and identified a class of quinazoline activators. Structure-

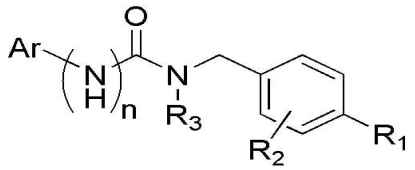
activity relationship studies revealed a novel potent inhibitor of aggregate formation (EC50=100nM) suitable for in vivo testing in models of Huntington's disease. A small molecule promoter of aggregate formation was also identified for studies of aggregate formation and the pathogenesis of accelerated Huntington phenotypes.

MEDI 263

Aryl amides and ureas: Novel leads for notch sparing gamma-secretase modulators

***Dai Lu**, Han-Xun Wei, Jing Zhang, Yong-Li Gu, Pamela Osenkowski, Wenjuan Ye, and Corinne E. Augelli-Szafran, Laboratory for Experimental Alzheimer Drugs (LEAD), Center for Neurological Diseases, Harvard Medical School and Brigham and Women's Hospital, 77 Avenue Louis Pasteur, Harvard Institutes of Medicine 750, Boston, MA 02115, dlu@rics.bwh.harvard.edu*

Alzheimer's disease (AD) is a neurodegenerative disease of which amyloid plaques and neurofibrillary tangles are recognized as two causative factors. Abnormal production and aggregation of amyloid proteins A&beta40 and A&beta42 are pivotal in the formation of amyloid plaques. Two enzymes, beta- and gamma-secretases, are directly involved in the production of the pathogenic A&beta40 and A&beta42. Inhibiting and modulating these secretases effects the production of A&beta40 and A&beta42 and hence are considered possible novel strategies for the treatment of AD. These approaches have led to several drug candidates that are currently in clinical trials. Our efforts are focused on the modulation of gamma-secretase that has multiple physiological important substrates, in addition to APP. A prominent substrate of gamma-secretase is the Notch receptor which is vital to cell differentiation. Sparing Notch processing is a key requirement for gamma-secretase inhibitors or modulators. We describe herein our exploratory work on aryl amides and ureas as gamma-secretase modulators that do not interfere with Notch signaling.



n= 0, 1

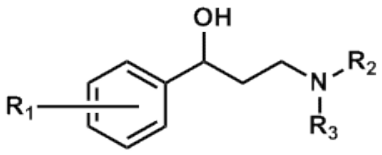
MEDI 264

β-Amino alcohols as notch sparing γ-secretase modulators

***Han-Xun Wei**, Dai Lu, Vivien Sun, Jing Zhang, Yongli Gu, Pamela Osenkowski, Wenjuan Ye, and Corinne E. Augelli-Szafran, Center for Neurological Diseases, Harvard Medical School and Brigham and Women's Hospital, 77 Avenue Louis Pasteur, Harvard Institute of Medicine 750, Boston, MA 02115, hwei@rics.bwh.harvard.edu*

Abstract: β-Amyloidal protein, a major component of the cerebral plaques found in the brains of Alzheimer's patients, and it is believed to play a key role in the development of Alzheimer's

disease. It is generally accepted that g-secretase cleaves amyloid precursor protein (APP) to generate a peptide that is 39 to 42 amino acids in length, with Aâ40 as the most common isoform and Aâ42 as the most susceptible to conformational changes that lead to amyloid fibrillogenesis. One therapeutic approach for Alzhemier's disease is to inhibit the cleavage of the APP protein by g-secretase. During the course of our recent studies, it was found that b-amino alcohols possess g-secretes modulatory activity. A new one-pot synthesis of b-amino alcohols and the structure-activity relationship of these analogs will be discussed.

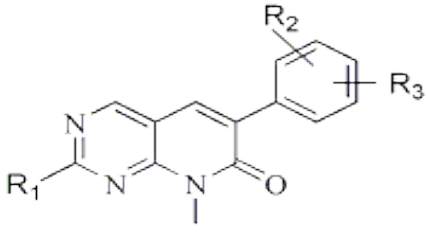


MEDI 265

Synthesis and structure-activity relationship of 2-substituted pyridopyrimidines as a possible therapeutic application for Alzheimer's disease

Jing Zhang*, Dai Lu, Han-Xun Wei, Yong-Li Gu, Pamela Osenkowski, Wen-Juan Ye, and Corinne E. Augelli-Szafran, Center for Neurological Diseases, and Harvard Medical School and Brigham Women's Hospital, 77 Avenue Louis Pasteur, Harvard Institute of Medicine 750, Boston, MA 02115, jzhang2@rics.bwh.harvard.edu*

The pathogenesis of Alzheimer's disease (AD) involves the abnormal accumulation and deposition of β-amyloid in the brain. Amyloid β-peptide (Aβ) as the major component of β-amyloid is formed by a series of cleavage of the amyloid protein precursor (APP) by β- and γ-secretases. It is hypothesized that the excessive cleavage of APP by γ-secretase finally leads to the overproduction of Aβ. 2-Substituted pyridopyrimidines (I) were focused to seek for potential γ-secretase inhibitor or modulator. The synthesis and structure-activity relationship of this series of compounds will be discussed.



(I)

MEDI 266

Design, synthesis, and biological evaluation of both conformationally flexible and rigid analogs of 7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalenols as dopamine D2/D3 receptor ligands: Development of a four point pharmacophore model for interaction with the D2 and D3 receptor subtypes

Dennis A. Brown[1]*, Prashant Kharkar*[1]*, Ingrid Parrington*[2]*, Maarten Reith*[2]*, and Aloke Dutta*[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48201, (2) Department of Psychiatry, New York University, New York, NY 10016*

Parkinson's disease (PD) is a neurological disorder that is characterized by the degeneration of the nigrostriatal dopaminergic pathway. Recent estimates suggest that at least 1% of the population over the age of 55 have PD, but the actual number may be much higher. In an effort to develop selective and potent ligands for the dopamine D3 receptor, our group has produced a class of hybrid 7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ols that exhibit both potency and selectivity for the D3 receptor subtype. A series of benzo[f] and benzo[g] quinolines, as well as conformationally flexible open chain analogs were synthesized and their D2/D3 binding affinities assayed. In an attempt to rationalize the binding affinities of these compounds, a molecular modeling study was undertaken, with particular emphasis on developing a pharmacophore model. A set of active molecules representative of the various chemotypes of these compounds along with the D2/D3 selective agonists R(+)-7-OH-DPAT, S(-)-5-OH-DPAT, dopamine, and (+)-PD128907 was chosen. A four point pharmacophore model based on these molecules is proposed and the differences in the observed binding affinities for these analogs are discussed.

MEDI 267

Design of mixed–ligand Zinc–(metal chelator) coordination species toward the treatment of neurodegenerative diseases and in vitro studies by single crystal X–ray diffraction, DOSY NMR and UV–vis spec

Zhenbo Ma*, Shuangbing Han, Russell Hopson, and Brian Moulton, Chemistry Department, Brown University, 324 Brook Street, Providence, RI 02912, Zhenbo_Ma@brown.edu*

Oxidative stress has been considered to be associated with the pathophysiology of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. And redox active protein bound Fe/Cu cations play an essential role in catalyzing the generation of reactive oxygen species (ROS). Traditional therapeutic options to relieve oxidative stress include the use of antioxidants and metal chelator. However, most anitoxidants have limited clinical evaluations; and chelation therapy often results in systemic metal depletion. Thus, “An ideal therapeutic drug would involve a compound that is relatively selective for metal ions, such as Cu, Fe.” (A. I. Bush etc. Annals New York Academy of Sciences.2000, 920, p292.) We prepared a series of mixed-ligand Zinc-(metal chelator) coordination species. The stability of as-prepared coordination species in water phase were studied by DOSY NMR analysis. And UV-vis spectra suggested Cu^{2+}/Fe^{3+} can substitute Zn^{2+} from the mixed ligand Zinc-(metal chelator) coordination species, while other metal ions such as Ca^{2+} and Mg^{2+} retain in water solution. The introduction of proper ancillary ligands can tune the lipophilicity of the as-prepared coordination species which makes it possible for the Zinc-(metal chelator) coordination species to penetrate the blood brain barrier

(BBB). Our preliminary in vitro data indicate that zinc-(metal chelator) coordination species could potentially be substituted by Cu^{2+} and Fe^{3+} without causing systemic metal depletion.

MEDI 268

Discovery of a novel series of biphenyl benzoic acid derivatives as potent, selective and orally bioavailable human beta 3 adrenergic receptor agonists with a long duration

Masashi Imanishi[1], *Yasuyo Tomishima*[1], *Shinji Itou*[1], *Hitoshi Hamashima*[1], *Yutaka Nakajima*[1], *Minoru Sakurai*[1], *Kenichi Washizuka*[1], *Shigeo Matsui*[2], *Emiko Imamura*[2], *Koji Ueshima*[3], *Takao Yamamoto*[2], *Kaori Hamada*[2], *Fujiko Takamura*[4], *and Kouji Hattori*[1]. *(1) Chemistry Research Laboratories, Astellas Pharma Inc, 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan, masashi.imanishi@jp.astellas.com, (2) Pharmacological Research Laboratories, Astellas Pharma Inc, (3) Applied Pharmacology Research Laboratories, Astellas Pharma Inc, (4) Analysis & Pharmacokinetic Research Laboratories, Astellas Pharma Inc*

Recently studies have indicated that activators of the beta 3–adrenergic receptor (beta 3-AR) are recognized as potential drugs for not only the treatment of obesity, non-insulin dependent (Type-II)diabetes, but also overactive bladder (OAB).

In our laboratory, a novel class of biphenyl analogues containing a benzoic acid moiety have been identified which displayed on excellent balance of high beta 3-AR potency, high selectivity for beta 1-AR and beta 2-AR and good pharmacokinetic profiles. In addition, several analogues were evaluated and shown to be efficacious for carbachol-induced increase of intravesical pressure (IVP), such as in an OAB model in anesthetized dogs. This represents the first demonstrated result dealing with beta 3–AR agonists. The synthesis and structure-activity relationships of these compounds will be presented.

MEDI 269

Discovery of a novel hyaluronic acid-MTX conjugate (DK226) for Osteoarthritis

Akie Honma[1], *Haruhiko Sato*[1], *Akira Okamachi*[1], *Takashi Emura*[1], *Takenori Ishizawa*[1], *Tatsuya Kato*[1], *Tetsu Matsuura*[1], *Shigeo Sato*[1], *Tatsuya Tamura*[1], *Yoshinobu Higuchi*[1], *Tomoyuki Watanabe*[1], *Hidetomo Kitamura*[1], *Kentaro Asanuma*[1], *Tadao Yamazaki*[1], *Masahisa Ikemi*[2], *Hironoshin Kitagawa*[2], *Tadashi Morikawa*[2], *Kazuaki Maeda*[2], *Koichi Takahashi*[2], *Kenji Nohmi*[2], *Noriyuki Izutani*[2], *Makoto Kanda*[2], *and Ryochi Suzuki*[2]. *(1) Research division, Chugai Pharmaceutical Co., Ltd, 1-135, Komakado, Gotemba, Shizuoka 412-8513, Japan, Fax: +81-550-87-5219, honmaake@chugai-pharm.co.jp, (2) Research Center, Denki Kagaku Kogyo K. K, Machida, Tokyo 194-8560, Japan*

Intra-articular injection of hyaluronic acid (HA) has been licensed worldwide for the treatment of osteoarthritis (OA). Joint pain and inflammation are major hallmark symptoms of OA. Current HA can reduce pain, but not fully control inflammation. Oral methotrexate (MTX) provides a very effective treatment for rheumatoid arthritis (anti-proliferative plus anti-inflammatory). However, systemic adverse events, such as pneumonitis, liver fibrosis and myelosuppression, are frequently associated. Intra-articular injected HA can accumulate in synovium and be incorporated into synovial cells.

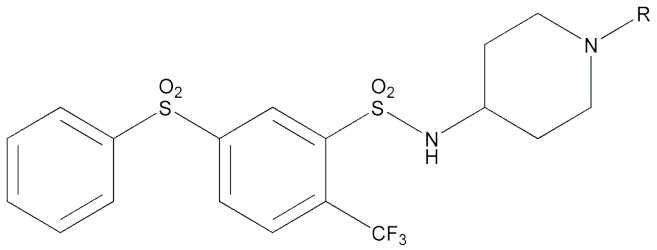
We therefore designed HA-MTX conjugates to combine the efficacy of the two arthritic drugs (pain reduction & anti-inflammatory effect), avoiding the risk of MTX by introducing HA as a DDS carrier for MTX. Here we show the optimization of peptide, linker, binding ratio of MTX, molecular weight of HA. We also show the detail of scientific rationale and in vitro and in vivo experimental data of DK226.

MEDI 270

Diaryl sulfone sulfonamides as Secreted Frizzled-Related Protein-1 (SFRP-1) inhibitors: SAR and optimization of substituted piperidine derivatives

Jeffrey C. Kern[1]*, William J. Moore*[1]*, Thomas J. Commons*[1]*, Richard P. Woodworth*[1]*, Matthew A. Wilson*[1]*, Gregory S. Welmaker*[1]*, Eugene J. Trybulski*[1]*, Keith Pitts*[2]*, Girija Krishnamurthy*[1]*, Barbara Stauffer*[3]*, Ramesh Bhat*[3]*, and Peter V. N. Bodine*[3]*. (1) Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, Fax: 484-865-9398, KernJ@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, (3) Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA 19426*

Activation of the canonical Wnt signaling pathway has been shown to increase trabecular bone formation by stimulating osteoblast activation and differentiation. SFRP-1 is a negative regulator of the Wnt pathway and deletion of the SFRP-1 gene in mice results in osteoblast activation, proliferation, and differentiation resulting in increases in trabecular bone. Therefore, small molecule inhibitors of SFRP-1, which promote Wnt signaling, are promising candidates for the treatment of bone related diseases such as osteoporosis. In previous disclosures piperidine sulfonamide I (R = H) was introduced as a SFRP-1 inhibitor with a good in vitro pharmaceutical profile. This communication will focus on piperidine substitution leading to inhibitors with improved binding and functional potency.



(I)

MEDI 271

Design, synthesis and biological evaluation of Benzamide Derivatives as tissue-selective androgen receptor modulators

Barbara A. Hanney*, Medicinal Chemistry Department, Merck & Co., Inc, 770 Sumneytown Pike, P.O. Box 4, West Point, PA 19486-0004, Fax: 215-652-7310*

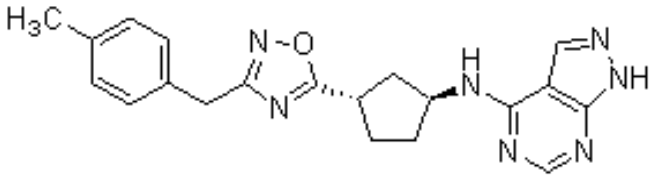
It is well-documented that androgens stimulate bone formation in post-menopausal women. Despite this beneficial effect, use of androgens for treating post-menopausal osteoporosis is limited due to unwanted virilizing effects such as facial hair growth. Thus, a tissue selective androgen receptor modulator (SARM) that stimulates bone formation, without eliciting virilizing effects, would be a desirable therapeutic agent for the treatment of post-menopausal osteoporosis. Toward this objective, we have identified a novel benzamide series as tissue selective androgen receptor modulators. We will report the SAR-guided library approach as well as, the biological profiles for key compounds in this structural class.

MEDI 272

Development of potent NR2B subtype selective NMDA receptor antagonists

***Michael J. Kelly III**, Department of Medicinal Chemistry, Merck Research Laboratories, WP14-3; 770 Sumneytown Pike; PO Box 4, West Point, PA 19486-0004, Fax: 215-652-3971, michael_kelly7@merck.com*

N-methyl-D-aspartate (NMDA) receptors are ligand-gated, ionotropic glutamate channels that are expressed throughout the CNS. NR2B subtype selective NMDA antagonists may be useful for the treatment of neuropathic pain and Parkinson's disease. In this poster the optimization of a novel series of amino-cyclopentanes as highly potent and selective NR2B antagonists is described. Compound A showed efficacy in animal models of pain and Parkinson's disease following oral administration.



Compound A

MEDI 273

Synthesis of ring fluorinated capsaicin analogs and their interactions with the vallinoid receptor

***Chaya Pooput**, Patrina Pellett, Jorge Heredia-Moya, and Kenneth L. Kirk, Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, 8 Center Drive, Bldg 8, Rm B1A06, Bethesda, MD 20892, Fax: 301-402-4182, pooputc@niddk.nih.gov*

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the main pungent component in hot chili peppers. It binds to the vanilloid receptor subtype 1 (VR1), an ion type channel responsive to heat, physical abrasion or acidic pH, explaining the hot or burning sensation perceived after consumption. Because of increased interest in the utilization of this receptor system for applications of pain alleviation, we have undertaken an investigation of the effects of fluorine

substitution on the aromatic moiety of capsaicin on the receptor affinity (a “fluorine scan”). With the successful synthesis of fluorinated capsaicin analogues substituted on the 2-, 5- and 6-positions, binding assays are performed with the natural capsaicin and the fluorinated analogues on the rat vallinoid receptor subtype 1 (rVR1). The results allow us to compare the differences in the binding affinities between fluorinated and non fluorinated capsaicins and to study the effects of the change of polarity and phenolic acidity, due to the presence and the position of fluorine, on the interactions with the vallinoid receptor.

MEDI 274

Comparison of calculated aqueous solubility and permeability to experimental data for a fragment based screening set

***Anthony Macherone**, Analytical and Bioanalytical Services, ASDI, 601 Interchange Blvd, Newark, DE 19711, amacherone@asdi.net, and Michael W. Wagaman, Department of Chemistry, ASDI, Inc, Newark, DE 19711*

In today's paradigm of drug discovery, aqueous solubility and passive permeability are two physiochemical properties that are critical in the selection, synthesis and screening of new chemical libraries. Many in silico algorithms exist to predict these properties a priori and numerous experimental tools have been utilized to measure these properties in the lab. Fragment screening, a relatively new approach in drug discovery, requires aqueous solubility around 1 millimolar and permeability around 50 micromolar. We have calculated the intrinsic aqueous solubility and polar surface area of fragment libraries using commercially available software and compared these results to experimental solubility data – determined using light scattering – and PAMPA permeability respectively. The experimental data allowed us to refine the calculations to provide more accurate predicted values. This information was then used to guide the selection of cores for the design and synthesis of new fragment screening sets.

MEDI 275

Modification of scutellarin for improved solubility by PEGylation

***Juan Lu**, Guoan Luo, Changmei Cheng, and Yiming Wang, Department of Chemistry, Tsinghua University, Beijing, China, j-lu06@mails.tsinghua.edu.cn*

Scutellarin has remarkable curative effect for treatment of heart and cerebrovascular disease, but the poor bioavailability due to the low solubility of scutellarin in water restricts its application seriously. For improving its solubility, modification of scutellarin with polyethylene glycol mono-methyl ether (mPEG) of different molecular weights (400-2000) was made and a series of modified compounds with enhanced solubility were obtained. The analytical sample was purified by silica gel column chromatography and the structure of these conjugates was confirmed by 1H NMR, MS. The physicochemical properties and the stabilities under different conditions were also investigated.

MEDI 276

Investigating the manipulation of Jak/Stat protein-protein interactions in cytokine signaling through multivalent small molecule recognition agents

*Steven Fletcher and **Patrick T Gunning**, Department of Chemical and Physical Sciences, University of Toronto, 3359 Mississauga Rd. North, Room 2038D, Mississauga, ON L5L 1C6, Canada, Fax: 001-905-569-4929, steven.fletcher@utoronto.ca, patrick.gunning@utoronto.ca*

Reversing a protein's aberrant role, via molecular manipulation of protein complexation offers significant value as a novel molecular therapeutic. We have developed compounds that artificially down and up-regulate specific gene expression profiles via manipulation of Jak/Stat protein-protein interactions, inducing therapeutically beneficial cellular responses in malfunctioning human cells. Protein-protein interactions remain a daunting target for small molecules due to their large interfacial areas and often non-contiguous contact points. However, protein-protein interfaces contain compact, centralized regions of residues, known as 'hot spots' that are crucial for interaction. Molecular modulation of specific Jak and Stat3 protein-protein interactions offers a dynamic approach to artificially regulate aberrant protein activity in human disease. We have investigated the potential of applying sophisticated, functionalized recognition scaffolds as molecular therapeutics.

MEDI 277

Novel α-helix mimetics with increased water solubility

***Christopher Gerald Cummings** and Andrew D. Hamilton, Department of Chemistry, Yale University, 225 Prospect Street, P.O. Box 208107, New Haven, CT 06520, Fax: 203-432-6144*

α-helices are common protein secondary structures involved in numerous protein-protein interactions. Disrupting these interactions, utilizing synthetic mimetics, is a route to regulating such cellular activities as proliferation and apoptosis. Earlier α-helix mimetics, such as the terphenyl and terpyridine scaffolds, are inherently disadvantaged because of poor solubility while others, based on the terephthalamide and trispyridylamide scaffolds, rely on hydrogen-bonding networks to maintain a correct orientation. Herein we describe new scaffolds that overcome these drawbacks by replacing six-membered aromatic end-units of earlier designs with water-soluble five-membered heterocyclic groups.

A crystal structure of our basic heterocyclic scaffold confirms the extended shape of the molecule and mimicry of side chain projections of α-helices. Increased water solubility and markedly shortened syntheses make these inhibitors attractive for targeting protein-protein interactions. One important potential target in this work is the Tiam1/Rac1 complex. Our design will mimic the i, i+4, and i+7 residues of the Tiam1 α-helix bundle.

MEDI 278

Design, synthesis and in vivo efficacy of mGluR5 positive allosteric modulators derived from a series of functionalized 4-(phenylethynyl)benzamides

***Richard Williams**, Department of Pharmacology, Vanderbilt Program in Drug Discovery, 802 Robinson Research Building, Nashville, TN 37232-6532, Fax: 615-343-6532, Richard.williams.1@vanderbilt.edu*

An iterative analogue library synthesis strategy rapidly developed comprehensive SAR for a series of 4-(phenylethynyl)benzamides and delivered 20f, the most potent, efficacious and highest affinity mGluR5 positive allosteric modulator (PAM) ever reported. Analogues in the series demonstrated in-vivo efficacy in rodent behavioural models in non-toxic vehicles, thereby respresenting a major advancement in the mGluR5 PAM field.

MEDI 279

Synthesis and biological evaluations of peptide nucleic acids as siRNA mimics

***Belhu B. Metaferia**, Young Song, and Javed Khan, Pediatric Oncology Branch/Oncogenomic Section, National Cancer Institute, 8717 Grovemont Circle, Gaithersburg, MD 20877, belhum@mail.nih.gov*

Since the discovery of siRNAs, efforts are directed towards the development of these molecules as therapeutic agents for a wide variety of diseases. The ability to stop the expression of a target gene by blocking the translation of mRNA has an immense potential to utilize the human genome for early diagnosis and discovery of effective therapeutics. The stability of siRNAs and delivery across the plasma membrane however remain a major bottle-neck for in vivo therapeutic application. Peptide nucleic acids (PNAs) have emerged as a good choice for such applications due to their stability towards enzymatic degradation, high affinity towards complimentary DNA and ease of synthetic manipulations. In this report, the synthesis of cell-permeable peptide nucleic acids and their biological sequence specific antisense effect will be discussed.

MEDI 280

Autophosphonylating peptides as the scavengers of nerve gas agents

***Zhengxiang Zhu**, Shi-Xian Deng, Joanne Macdonald, Michael Vinogradov, and Donald W. Landry, Department of Medicine, Columbia University, 650 W. 168th St. BB1019, New York, NY 10032, zz2141@columbia.edu*

Organophosphorus-based inhibitors of the serine esterase acetylcholinesterase, long used as agents for chemical warfare, are extremely toxic. Butyrylcholinesterase (BuChE) is the leading clinical scavenger of nerve agents but low enzymatic turnover rates and a high equivalent weight as a stoichiometric scavenger render maintenance of sufficient BuChE blood levels difficult. We now report development of autocatalytic, low molecular weight peptide-based stoichiometric scavengers. Serine-containing single-peptide-per-bead combinatorial libraries

were screened by FACS sarin labeled with Oregon Green as the fluorescent probe. Twenty-four hits were identified and sequenced. Synthesis of soluble peptide, observed reaction with a non-volatile sarin analog and independent synthesis of the products confirmed the hit.

MEDI 281

Synthesis and biological activity of meperidine analogs as selective serotonin reuptake inhibitors

Xiaobo Gu[1]*, Sari Izenwasser*[2]*, and Mark L. Trudell*[1]*. (1) Department of Chemistry, University of New Orleans, 2000 Lakeshore Drive, New Orleans, LA 70148, Fax: 504-280-6860, guxbo1@gmail.com, (2) Department of Psychiarty and Behavioral Sciences, University of Miami School of Medicine, Miami, FL 33136*

A series of meperidine analogues were synthesized and exhibited high affinity (nM) for serotonin transporters. The compounds were selective for serotonin transporters over dopamine and norepinephrine transporters. The 3, 4-dichlorophenyl, 4-iodophenyl, the biphenyl and 2-naphthyl aryl analogues have been identified as important structural moieties for molecular recognition at serotonin transporters. Furthermore, the N-demethylated benzyl ester congeners were found to be more potent and selective for serotonin transporters than the ethyl ester meperidine derivatives. The synthesis and structure activity relationships of these novel serotonin uptake inhibitors will be presented.

MEDI 282

Protein-ligand interactions: How universal is the pharmacophore assumption?

Haipeng Hu[1]*, Tiao Xie*[2]*, and Jim Snyder*[1]*. (1) Department of Chemistry, Emory University, 1515 Dickey Drive, atlanta, GA 30322, hhu2@emory.edu, (2) Dept. of Chemistry and Cherry L. Emerson Center for Computing, Emory University, Atlanta, GA 30322*

With increasing knowledge about the interaction between proteins and ligands, many theories and computational approaches have been developed to guide molecular design. A well-established methodology, structure-based design, depends on the existence of a protein X-ray structure ideally incorporating a suitable bound ligand [1-4]. In such a framework, ligand modifications and novel analogs are often based on the assumption that the novel structures populate a pharmacophore common to the experimentally bound ligand. Thus, either the protein target undergoes no significant conformational change upon ligand binding, or the macromolecular structure varies uniformly independent of ligand type. In other words, ligands that bind to a common protein binding site generally share a similar pharmacophore; that is, they display closely related binding poses.

A striking exception to the latter assumption was recently reported for the binding of three inhibitors to the active site of phosphodiesterase 5 (PDE5). Sildenafil and Vardenafil are very similar structurally and bind the protein with nearly identical poses as determined by X-ray crystallography. The structurally divergent Tadalafil exhibits an alternative binding pose in the same pocket but blocks PDE5 with similar potency. In this case, the above assumption fails to hold. We have inquired as to how universal is the common site – common pharmacohore

assumption might be. basic structural assumption? When it lapses, in what way does it do so? To investigate these questions, a protein-ligand interaction survey has been carried out. The work will discuss cases in which the assumption is not satisfied and the extent to which they occur.

MEDI 283

A synthesis of resveratrol using palladium-catalyzed carbon-carbon bond formation

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Resveratrol has received much interest in the popular press recently due to its favorable biological effects including but not limited to its use as an anticancer compound, an anti-obesity compound, antioxidant, and potential prevention of cardiovascular disease. The current synthetic routes utilizing Grignard addition are efficient but are not stereospecific as both the cis and trans isomers are formed. The preparation of an arylacetylene from the corresponding aldehyde utilizing Corey-Fuchs chemistry followed by elimination and the Sonogashira coupling of the alkyne to an aryl halide would lead to dehydroresveratrol. At this point stereoselective reduction (hydrogenation on Lindlar's catalyst or metal-ammonia reduction) would give rise individually to the possible stereoisomers.

MEDI 284

Design and synthesis of potent curcumin analogs using microwave chemistry as anticancer agents

***Ashutosh Pal**[1], David Maxwell[1], Zhenghong Peng[1], Bokyung Sung[2], Lan V. Pham[3], Archie Tamayo[3], Richard Ford[3], Bharat B. Aggarwal[2], and William Bornmann[1]. (1) Diagnostic Imaging, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, Fax: 713-563-0084, apal@mdanderson.org, (2) Experimental Therapeutics, University of Texas M. D. Anderson Cancer Center, Houston 77030, (3) Hematopathology, University of Texas M. D. Anderson Cancer Center, Houston 77030*

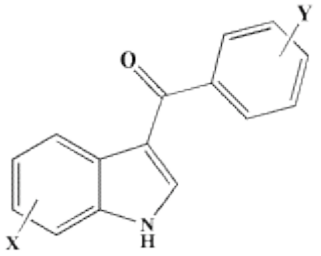
Curcumin, (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione/diferuloyl methane), the main yellow pigment of the Curcuma longa L, has been reported to have antioxidant, antiproliferative and other interesting biological properties. We have designed curcumin analogs and synthesized over 20 new compounds by microwave chemistry. Six of these new compounds were tested for cytotoxicity against the Mino (classic mantel cell lymphoma) and Z-138 (blastoid mantel cell lymphoma cell) cell lines. In those two cell lines, most of the analogs have better activity then curcumin. Nineteen compounds were tested against the KBM-cell line and six of those compounds had better activity with complete blocking and two compounds were found more potent then curcumin with incomplete blocking. The study establishes a structure-activity relationship that will be used to guide further design of newer and more potent curcumin analogs.

MEDI 285

Design, synthesis and biological study of 3-aroyl indoles

Balaiah Akula[1]*, Stephen C Cosenza*[2]*, Venkat R Pallela*[2]*, Nabisa Iqbal*[2]*, E. Premkumar Reddy*[2]*, and MV. Ramana Reddy*[2]*. (1) Medicinal Chemistry, Onconova Therapeutics Inc, 375 Phesant Run, Newtown, PA 18940, balu@onconova.us, (2) Fels Institute for Cancer Research, Temple University School of Medicine, Philadelphia, PA 19140*

During cell division microtubules play a prominent role in segregation of chromosomes. Microtubules are hollow tubes formed by polymerization of α-and β-tubulins. Many drugs that interfere with the dynamics of microtubule formation generate abnormal mitotic spindles thereby inducing cell cycle arrest in mitosis and finally apoptotic cell death. A variety of natural products, such as paclitaxel, epothilone A, colchine, combretastatin A4 and their synthetic analogs interfere with microtubule formation by changing the dynamics of polymerization and depolymerization of tubulins. Recently it has been shown that some of the tubulin inhibitors such as combretastatin A4 selectively target the formation of new vasculature at tumor site. This process irreversibly shut down the blood flow to neoplastic cells while leaving the blood supply to healthy cells intact. More recently a new series of aroyl indoles have been reported as a new class of synthetic antitubulin compounds possessing high potent cytotoxicity against human tumor cells. In this presentation, we are reporting a novel method for the synthesis of 3- aroyl indoles and their cytotoxicity towards human leukemic, breast, prostate, lung, uterine and intestinal cancer cells. The method described here provides a very practical alternative for the preparation of aroyl indoles. The reagents are stable and react under mild conditions with great purity and high yield of the product.



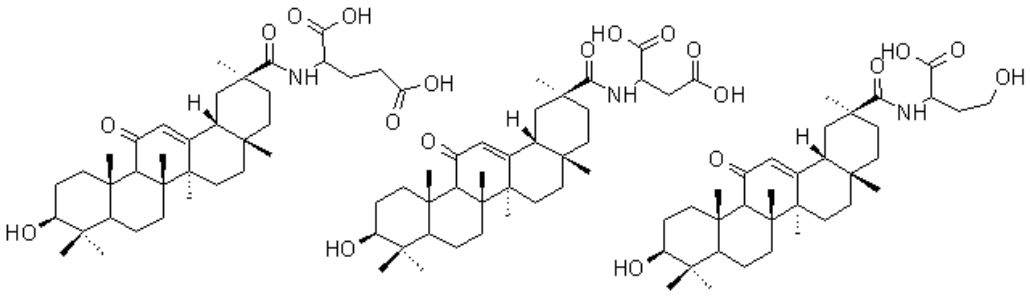
MEDI 286

Design, synthesis and screening of novel inhibitors of HMGB1/DNA complex formation

Sivakumar Annadurai*, Natalia Krynetskaia, Evgeny Krynetskiy, and Daniel J Canney, Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 3307 N Broad Street, Philadelphia, PA 19140*

High mobility group box-1 (HMGB1) protein is a ubiquitous nuclear protein that binds DNA and plays a crucial role in transcriptional regulation. Extracellularly it acts as a pro-inflammatory cytokine contributing to the pathogenesis of diverse inflammatory and infectious disorders. Small molecule inhibitors of this protein are of experimental interest and may find clinical application. Glycyrrhizin (GZ) has been reported as a weak inhibitor of HMGB1/DNA binding.

Molecular docking studies reveal interactions of the triterpene moiety of GZ in a binding site of HMGB1. In the present work the design and synthesis of novel GZ analogs are described. Attempts are made to improve the affinity of this triterpene lead for HMGB1 by appropriate structural modifications. Newly designed ligands were screened for their ability to inhibit the HMGB1/DNA interaction using Capillary electrophoresis mobility shift assay. The results of those assays and SAR data for this novel series of ligands will be discussed.



MEDI 287

Hazardous reactions: Safe production of multiton pharma products

James A. Schwindeman[1]*, Nikolaos H. Petousis*[1]*, and Ivo Hubacek*[2]*. (1) Dottikon Exclusive Synthesis AG, 773 Bloomfield Avenue, Verona, NJ 07044, Fax: 973-857-3874, james.schwindeman@dottikon.com, (2) Dottikon Exclusive Synthesis AG, Dottikon, Switzerland*

With product life cycles getting shorter and market launches more expensive industrial players are experiencing new challenges. For instance the pharmaceutical industry is facing a twofold challenge today. How can drug development be shifted towards more specific drugs and how can costs be reduced by innovation and by improving quality at the same time.

When developing new products both pharma and chemical industry try to avoid reactions they regard to be associated with process risks. The reason for this behavior is the perception that hazardous reactions cannot be run on scale safely. The result of such strategies, are efforts to circumvent chemical operations regarded to involve hazardous reactions. Usually such an approach ends up with: (i) additional chemical steps; (ii) vigorous reaction conditions resulting in less favorable impurity profiles and therefore additional purification operations; (iii) use of expensive and more starting materials. All these factors result in higher production costs and longer time to market for new chemical entities. This is in sharp contrast with the challenges those industries are facing.

Illustrative examples of development and scale up using hazardous reactions including assessment of hazard potentials and determination of appropriate measures will be disclosed and discussed on the poster.

A set of proprietary process hazard tests has to be routinely performed in dedicated process safety laboratory. The execution of these tests leads to quantification, assessment and adjustment of critical reaction parameters as well as to the definition of limits for safe process operation. This guarantees full control of residual hazard potentials. Combination of hazardous reactions with a state of the art technology platform lays ground for process designed

equipment set-up and large scale manufacture of high purity cGMP pharma and chemical products.

MEDI 288

Synthesis and characterization of 4-tert-butylphenylboronic acid

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4-tert-Butylphenylboronic acid was synthesized with trimethyl borate and Grignard reagents which was prepared with 1-Bromo-4-tert-butylbenzene and metal magnesium as raw materials under nitrogen. An optimized process was obtained by investigating the influence of the temperature, reaction time and reactant proportion on the yield as following: Trimethyl borate /1-Bromo-4-tert-butylbenzene 1:1(mol), 223K, 140 min. The final yield is 69.5%. The products were identified by mass spectrum and HNMR.

MEDI 289

Synthesis of Tetramic acid derivatives with the use of protecting groups

***Subramanya Ravi K Pingali**, Chemistry, University of new orleans, 102 CSB, 2000 LAKESHORE DR, New Orleans, LA 70148, srkiran1@gmail.com, and Branco S. Jursic, Department of Chemistry, University of New Orleans, New Orleans, LA 70148*

Natural products containing tetramic acid moieties continue to attract the interest of chemists, biologists, and physicians due to their challenging structures and to the wide range of biological activities they display. A short overview of laboratory syntheses of β-keto acids and α, β unsaturated amino acids will be presented through this poster It is not possible to envision a synthesis that includes the preparation of any complex organic molecule without envisioning the use of protection groups on key functional elements of such molecules. We have designed a new protection group for acids and alcohols known as the MPBI protecting group utilized by us for the synthesis of β- keto acids and hence tetramic acids. This protection group in our synthesis is not just used for the stated purpose but is also used as a tag which serves as a synthetic equivalent of a resin. The β-keto acids and α, β unsaturated amino acids thus produced can be used to prepare the desired tetramic acids.

MEDI 290

Controlled microwave-assisted amination of quinolone

***Shahnaz Ghassemi**, Biotage, 1725 Discovery Drive, Charlottesville, VA 22911, Fax: 434 979-4743, SGhassemi@biotage.com*

A quick and general method of microwave–assisted amination of 7-halo-6-flouroquinolone-3-carboxylic acid in excellent yield is descried. Bounded reagents have been used for quick purification.

MEDI 291

Cytotoxic effect of crude extracts or synthetic hedysarimcoumestans on tumor cells

***Yean-Jang Lee**[1], Tsui-Hwa Tseng[2], and Chia-Fu Chang[1]. (1) Department of Chemistry, National Changhua University of Education, 1 Chieng-Derg Rd., Changhua 50058, Taiwan, Fax: 886-7-211190, leeyj@cc.ncue.edu.tw, (2) Department of Applied Chemistry, Chung Shan Medical University, Taichung, Taiwan*

Natural products provide an unparalleled source of chemical diversity for discovery of important and interesting biologically active molecules. As part of a recent search to prepare new biologically active substances, we were attracted to the coumarins and benzofuran family whose members are widely distributed in biologically important natural products and pharmaceutical agents. Recently, Liang et al. have reported that ten coumestans were isolated from the roots of Hedysarum multijugum, which is a plant in Hedysarum Linn. of the family Leguminosae used as a folk herbal drug in northwest China. Coumestans comprise a class of naturally occurring products with a variety of biological activities including phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects. For instance, hedysarimcoumestans, demethylwedelolactone, and wedelolactone are natural products and characteristic members of the coumestan family. Herein, we present our studies on the crude extracts or synthetic hedysarimcoumestans and analogueos on the tumor cells. First, a concise route to hedysarimcoumestan B has been achieved in which the longest linear sequence is only eight steps in 50% overall yield from commercially available phloroglucinol. This synthesis is high yielding and easily applied to give access to a variety of different hedysarimcoumestan A and coumestan analogues, especially, demethylwedelolactone and wedelolactone, which were afforded from bromocoumarin in high 55% and 47% yields, respectively. Finally, we have evaluated the cytotoxicity of the crude extracts or synthetic hedysarimcoumestans and analogueos on HL-60 cells.

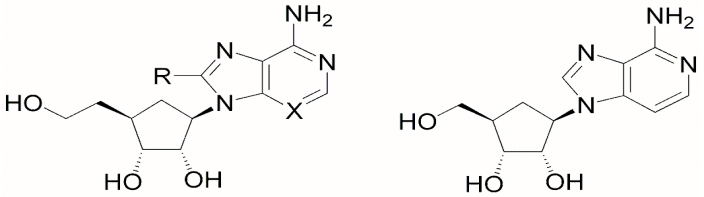
MEDI 292

Design and synthesis of 5'-homoaristeromycin derivatives

***Qi Chen** and **Stewart W. Schneller**, Department of Chemistry and Biochemistry, Auburn University, 179 Chemistry building, Auburn, AL 36849, chenqi1@auburn.edu, schnest@auburn.edu*

Significant effort has been directed toward the synthesis of purine carbocyclic nucleosides modified in the cyclopentyl ring. Within this category, a particular noteworthy example is 5'-homoaristeromycin (**1**). In the rational design of derivatives of **1**, as a means to improve upon its antiviral scope, substituents at the C-8 position have been identified as important targets for two reasons: (1) the meaningful antiviral properties of C-8 substituted ribofuranosyl derived nucleosides and (2) as probes for the conformational preferences around the N-9 purine/C-1' cyclopentyl linkage. Also, 3-deazaaristeromycin (**2**) has found its place among antiviral structural units as a consequence of its inhibition of S-adenosylhomocysteine hydrolase. Thus, 8-methyl-5'-homoaristeromycin (**3**) and 8-methyl-5'-homo-3-deazaaristeromycin (**4**) became target compounds. The successful preparation of **3** and **4** and their antiviral properties will be reported. This research was supported by funds from DHHS (AI 56540)

Figure 1



1, R=H; X=N
3, R=Me; X=N
4, R=Me; X=CH

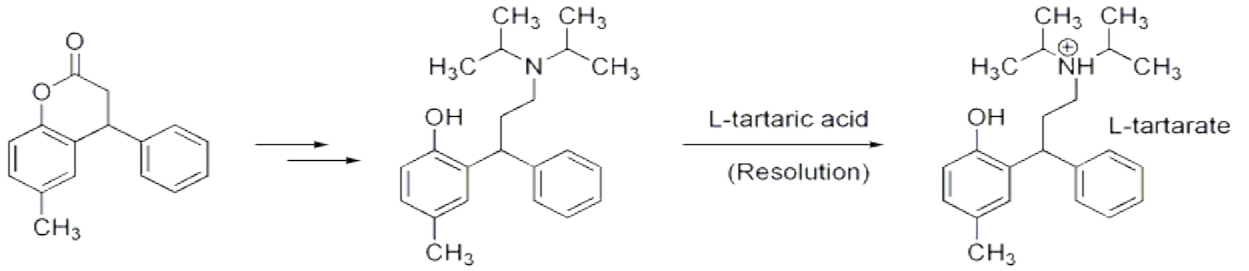
2

MEDI 293

Efficient synthesis of racemic tolterodine

Joo Hi Kang[1]*, Jong Hyoup Lee*[2]*, Young Jun Park*[2]*, Kyoung Soo Kim*[2]*, and Jae Yeol Lee*[1]*. (1) Department of Chemistry, Kyung Hee University, 1 Hoegi-Dong, Dongdaemun-Gu, Seoul 130-701, South Korea, Fax: 82-2-966-3701, sweetyguy1@gmail.com, (2) Chirogenix Co., Ltd, Whasung, Kyunggi-do 445-743, South Korea*

The synthesis of racemic tolterodine (1), a precursor of (+)-(R)-tolterodine as an important urological drug, was efficiently performed via 4 steps from 6-methyl-4-chroman-2-one in high purity and yield. This process is suitable for large-scale commercial production by avoiding hazardous reagents and high pressure of hydrogen gas.



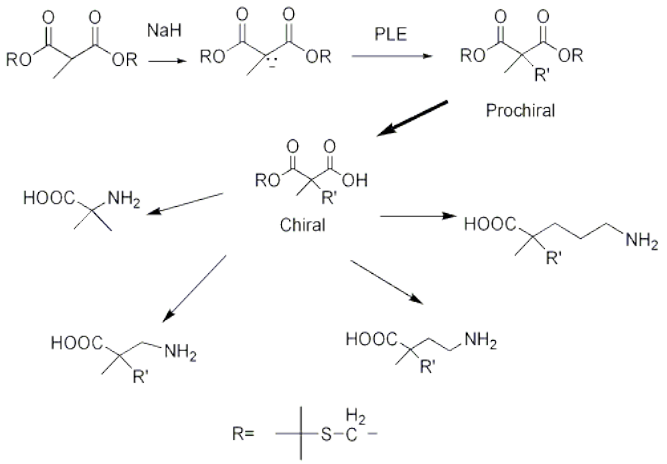
2 **Tolterodine (1)** **(+)-(R)-tolterodine L-tartarate**

MEDI 294

A novel method to synthesize unnatural cysteine analogs

Kinkini Roy *and Douglas S. Masterson, Department of Chemistry and Biochemistry, University of Southern Mississippi, Hattiesburg, MS 39406, Kinkini.roy@usm.edu*

It has been shown that incorporation of unnatural amino acids into protease specific sites in small peptides (somatostatin) increases the in vivo half-life of the peptide. Much attention has been given to the so called α-, β-,and γ-peptides which are composed of &alpha-,&beta-, &gamma- amino acids. The current interest in these unnatural peptides has provided an opportunity for chemists to design amino acid preparation which are simple, efficient, and general. There is a lack of general syntheses which can be used to prepare a wide variety of amino acid classes from simple, high yielding transformations. As it currently stands, the preparation of each class of amino acids requires its own special procedures. The currently used syntheses make it extremely difficult to prepare several homochirally similar amino acids simultaneously. This presentation will illustrate our efforts to develop syntheses which can be used to construct a wide variety of cysteine analogues α-, β-,and γ) from a common intermediate.



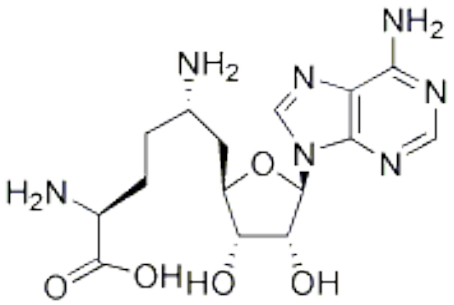
MEDI 295

An improved synthesis of Sinefungin

*Xueqiang Yin[1], **Weikuan Li**[2], and Stewart W. Schneller[2]. (1) Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36830, xqyin@yahoo.com, (2) Department of Chemistry and Biochemistry, Auburn University, 179 Chemistry Building, Auburn University, Auburn, AL 36830*

The significant broad-spectrum antiviral activity of sinefungin (1) is accompanied by unacceptable toxicity. To ascertain the structural components of 1 that could be varied to shift this therapeutic ratio to a more favorable level, a synthesis of 1 more convenient than those currently available was desired. In that direction a facile route to 1 will be reported that is built around a chiral C-6' Brown allylation and a Schöllkpf auxiliary for the amino acid moiety. This

research was supported by funds from the Department of Health and Human Services (AI 56540).



1 sinefungin

MEDI 296

Bacterial siderophore: New versatile synthesis and stoichiometry of vulnibactin

Raymond J. Bergeron, Medicinal Chemsitry, University of Florida, Gainesville, FL 32610, ***Shailendra Singh****, Medicinal chemistry, University of Florida, Gainesville, FL 32603, singhss@ufl.edu, and Neelam Bharti, Medicinal Chemistry, University of Florida, Gainesville, FL 32610*

Siderophore are low molecular weight Fe (III) specific transport agents, which are produced by both prokaryotic and eukaryotic microbial species under conditions of low iron stress. They are of particular interest as possible drugs for use both in the treatment of iron overload and for conditions of both acute and chronic metal toxicity. Vulnibactin (from Vibrio vulnificus) and Vibriobactin (from Vibrio cholerae) are hexacoordinated catecholamide iron chelators predicated on polyamine backbone. A short, high-yield, flexible synthesis is described for accessing vulnibactin and related siderophores, e.g., vibriobactin analogues and homologues. Job's plot of the ferric complex of vulnibactin suggested 1:1 ligand-to-metal stoichiometry.

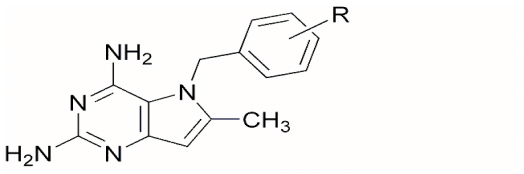
MEDI 297

Design, synthesis and biological evaluation of 5-substituted-6-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamines as dihydrofolate reductase inhibitors

Aleem Gangjee[1], ***Wei Li****[1], and Sherry F. Queener[2]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, liwei7054@hotmail.com, (2) Department of Pharmacology and Toxicology, Indiana University, Indianapolis, IN 46202*

A series of eight novel nonclassical 5-substituted-6-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diamines **2-9** were synthesized as potential inhibitors of dihydrofolate reductase (DHFR) and as antitumor agents. The analogues contain various electron donating and electron withdrawing substituents on the phenyl ring of side chain. The synthesis of **2-9** was accomplished via a 8-step sequence which involved the synthesis of 2-amino-6-methyl-3,5-dihydro-4*H*-pyrrolo[3,2-

d]pyrimidin-4-one **15** in four steps from commercial available 3-aminobut-2-enenitrile and diethyl aminomalonate hydrochloride. Protection of the 2-amino group of **15** and chlorination at the 4-position followed by N5-benzylation with different benzyl bromides under basic conditions afforded corresponding intermediates **18-25** which were then converted to final compounds **2-9** by nucleophilic displacement of the chloro group with ammonia. The design, synthesis and biological evaluation of compounds **2-9** will be presented and discussed.



2-9

2. R= 4-Fluorophenyl
3. R= 4-Chlorophenyl
4. R= 4-Methoxyphenyl
5. R= 4-Trifluoromethoxyphenyl
6. R= 3,5-dibomophenyl
7. R= 3-Methoxyphenyl
8. R= 2-Methoxyphenyl
9. R= 3,5-Dimethoxyphneyl

MEDI 298

Design, synthesis and evaluation of inhibitors for the IL-2/IL-2Rα interaction

Ishu Saraogi *and Andrew D. Hamilton, Department of Chemistry, Yale University, 225 Prospect St, PO Box 208107, New Haven, CT 06520-8107*

Interleukin-2 (IL-2), which plays a key role in the generation of an immune response, acts by binding to its heterotrimeric receptor (IL-2R) composed of α, β and γ chains. Immunosuppressive therapy by inhibiting the IL-2/IL-2Rα interaction is of interest in treating forms of leukemia, organ transplant rejection and autoimmune diseases like multiple sclerosis. Small molecules capable of inhibiting this protein-protein interaction are highly desirable as potential therapeutic leads. We have developed a new α-helix mimetic scaffold that mimics key residues located at the *i*, *i*+4, *i*+7 positions on an α-helical domain in IL-2 and has shown promising results in an *in vitro* ELISA assay.

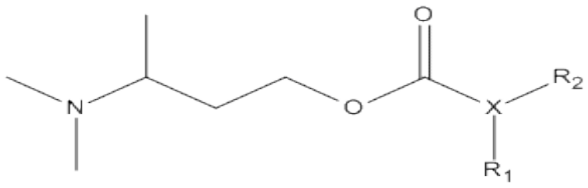
MEDI 299

Design, synthesis and pharmacological characterisation of novel acetylcholine and carbamoylcholine analogs

Camilla Petrycer Hansen*, Anders A. Jensen, Tommy Liljefors, and Bente Frølund, Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark, cph@farma.ku.dk*

Ligands for the nAChR have been designed to achieve selectivity and potency at the various nAChR subtypes. The structures of nicotine and epibatidine have to a great extent been used as lead structures, whereas acetylcholine has been given limited attention. Recently, we

synthesized a series of carbamoylcholine and acetylcholine analogues, which showed very interesting pharmacological properties. Generally, the analogues displayed nanomolar binding and high selectivities to the α4β2 nAChR. The selectivity was most pronounced for the analogue 3-((3-methylazetidine-1-carbonyloxy)-1-methylpropyl)-dimethylamine, which displayed high affinity binding to the α4β2 subtype (Ki=2.1 nM), a Ki ratio of 11,000 between the α4β2 and α3β4 subtypes and no affinity to the α7 subtype. Ligand-protein docking using homology models of the α4β2 and the α3β4 nAChR identified the residues Val109(β2)/Ile109(β4), Phe117(β2)/Gln117(β4) and Thr148(α4)/Ser148(α3) as key determinants of the selectivity displayed by the analogues.



X= C or N
R_1,R_2= various alkyl/aryl groups

MEDI 300

Design, synthesis, and antiangiogenic effects of a series of potent novel Fumagillin analogs

Young Min Kim*, Yong Sang Yoo, Hong Woo Lee, Sung Kwon Kang, and Soon Kil Ahn, Research Institute, Chong Kun Dang Pharmaceutical Corp, 15-20 Osaekdang-ri, Seonggeo-eup, Cheonan, South Korea, Fax: 82-41-558-3004, kimymin@ckdpharm.com*

Angiogenesis, the process by which malignant tumors visualizes, is essential for the growth and metastasis of tumors. Endothelial cells respond to angiogenic signals produced by tumors by proliferating and migrating to neighboring tissues. After undergoing differentiation, endothelial cells generate the inner lining of blood vessels that provide oxygen and nutrients to a growing tumor.

Fumagillin, a natural product from Aspergillus fumigatus, was discovered serendipitously and found to inhibit angiogenesis by blocking endothelial cell proliferation.

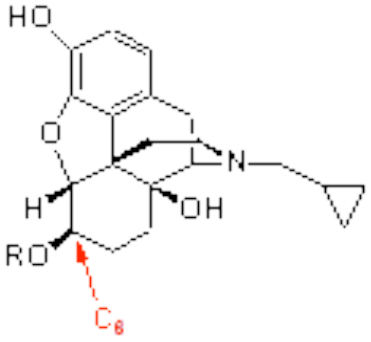
We have previously reported that CKD-732, a fumagillin analogue, elicits good inhibitory activity on cell proliferation. The goal of our program was to explore the tolerability of MetAP-2 toward inhibitors with lower cytotoxicity and better solubility than CKD-732. Therefore we focused our efforts on the modification of side chain of CKD-732. As a result, a series of new fumagillin analogues containing C6-substituted cinnamoyl moiety were designed, synthesized, and evaluated for antiangiogenic activity. Among them, 4-hydroxyethoxy-cinnamoyl fumagillol and 4-hydroxyethoxy-3,5-dimethoxycinnamoyl fumagillol exhibited more potent anti-proliferation activity in CPAE and HUVEC cells with low cytotoxicity in vitro. The compounds are currently under further pharmacological evaluation studies.

MEDI 301

Design, synthesis, and evaluation of 6ß-Naltrexol analogs in in vitro opioid receptor models

Amy M. Deveau[1], *Edward J. Bilsky*[2], *Wolfgang Sadée*[3], *Ryan M. Smith*[2], *and Andrea L. Pelotte*[1]. *(1) Chemistry & Physics Department, University of New England, College of Arts and Sciences, 11 Hills Beach Road, Biddeford, ME 04005, adeveau@une.edu, (2) Pharmacology Department, University of New England, Biddeford, ME 04005, (3) College of Medicine and Public Health, The Ohio State University, Columbus, OH 43210*

The opiates 6ß-naltrexol and 6ß-naltrexamide function as neutral antagonists in *in vitro* and *in vivo* systems previously exposed to morphine, and are under investigation as improved treatments for narcotic dependence. We are currently studying the specific structural characteristics that differentiate inverse agonists from neutral antagonists at the mu opioid receptor. In this research, we synthesized carbamate and sulfonate derivates of 6ß-naltrexol that do not contain a protic group at C_6, and characterized these derivatives using ^{1}H and ^{13}C NMR, IR, and mass spectrometry. Data on *in vitro* receptor subtype selectivity of the carbamate and sulfonate derivatives will also be reported. In conclusion, the data obtained further directs the design of improved analogs for the treatment of narcotic dependence, and enhances our understanding of opioid molecular pharmacology.



β-Naltrexol, R=H

MEDI 302

Efficient regioselective synthesis of 5′−*O*−lauric 5−azacytidine catalyzed by *Candida antarctica* lipase B

Xi Yu Chen, ***Wen-Yong Lou****, Min Hua Zong, and Hong Wu, Laboratory of Applied Biocatalysis, South China University of Technology, Wushan Street 381#, Tianhe District, Guangzhou 510640, China, Fax: +86-20-2223-6669, cxy.scut@yahoo.com.cn, wylou@scut.edu.cn*

Enzymatic acylation of 5−azacytidine, an analogue of natural pyrimidine nucleoside cytidine used for the treatment of myelodysplastic syndrome, was successfully conducted with vinyl laurate using an immobilized lipase from *Candida antarctica* (Novozym 435). The acylation was highly regioselective, giving high purity (99%) 5′−*O* −lauric 5−azacytidine, which is more lipophilic and might be more bio-available than 5-azacytidine. The enzymatic acylation

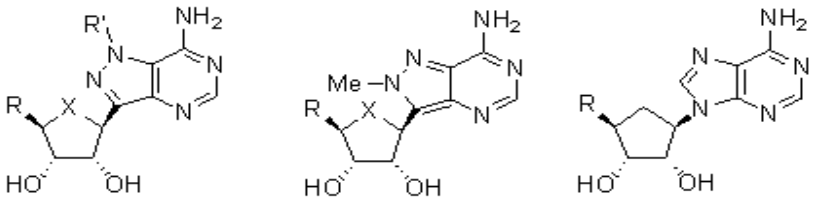
proceeded more rapidly by switching from pure pyridine to hexane-pyridine (40/60, v/v) co−solvent as a reaction medium to substantially diminish enzyme inactivation caused by very polar pyridine. Additionally, several key influential factors on the reaction were examined. The optimal initial water activity, molar ratio of vinyl laurate to 5−azacytidine and reaction temperature were 0.07, 15:1 and 50 ^{o}C, respectively, under which the substrate conversion and the regioselectivity were as high as 97.5% and >99%, respectively, within 1.5 h.

MEDI 303

Enatioselective synthesis of N-1 and N-2 methylated carbocyclic 5'-orformycin analogs

Mingzhu He[1]*, Jian Zhou*[2]*, Xueqiang Yin*[3]*, and Stewart W. Schneller*[2]*. (1) Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849, Auburn, AL 36849, hemingz@auburn.edu, (2) Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849, (3) Auburn University, Auburn, AL 36849*

The C-nucleoside formycin (1) has shown potentially significant antiviral properties. However, the usefulness of 1 is limited by its inhibition of cellular DNA and RNA synthesis as a consequence of formation of its 5'-nucleotides. Also effecting the biological properties of 1 is its metabolism by adenosine deaminase. Of its methylated analogues, N-1-methylformycin (2) was highly resistant to enzymatic deamination; N-2-methylformycin (3) exhibited high activity against vaccinia virus and did not affect cellular DNA and RNA synthesis. Both 2 and 3 were non-cytotoxic. A carbocylic nucleoside analogue of 1 is aristeromycin (4), whose biological properties are also limited by its 5'-phosphorylation. We found the activity of 4 is improved with its 5'-nor derivative 5. This report describes combining the structural components of 5 and 2/3 resulting in N-methylated carbocyclic 5'-norformycins 6/7. This research was supported by funds from the Department of Health and Human Services (AI 56540).



1, R=CH_2OH; X=O; R'=H
2, R=CH_2OH; X=O; R'=CH_3
6, R=OH; X=CH_2; R'=CH_3

3, R=CH_2OH; X=O
7, R=OH; X=CH_2

4, R=CH_2OH
5, R=OH

MEDI 304

Mild, efficient and regioselective synthesis of fatty ester derivatives of 5-fluorouridine via lipozyme TL IM-catalyzed acylation in cosolvent mixtures

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A facile synthesis of 5'-O-monoesters of 5-fluorouridine, more powerful antitumor drugs, was successfully performed for the first time using enol esters as acyl donors and lipozyme TL IM as the biocatalyst in tetrahydrofuran-acetone co-solvent mixture system. The alkyl chain length of the enol esters had an obvious effect on the reaction rate, but had little effect on the substrate conversion and regioselectivity (> 98.0% and > 99.0%, respectively in all cases assayed). The acylation of 5-fluorouridine with vinyl laurate was used as a model to explore the influence of various factors on the reaction with respect to the initial rate, the maximum substrate conversion and the regioselectivity. The polarity of the co-solvent mixture had a strong relation to the reaction rate. Additionally, the acylation was dependent on the tetrahydrofuran content, the water activity and reaction temperature as well, with 15% (v/v), 0.07 and 40 °C being the optimal reaction parameters, respectively, under which the maximum substrate conversion was 98.6%. The high efficient, facile and mild nature of the procedure makes it promising for industrial application.

MEDI 305

Synthesis of beta-methylthioaspartic acid and derivatives

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Beta-Methylthioaspartic acid occurs at position 88 in E. coli ribosomal protein S12, a position that is a mutational hotspot resulting in both antibiotic-resistant and antibiotic-sensitive phenotypes. In bacteria, S12 binds to 16S rRNA in regions associated with the fidelity of codon recognition. This posttranslational modification is highly conserved phylogenetically and thus should be both structurally and functionally important. Research designed to determine the biological function of beta-methylthioaspartic will involve elucidation of the enzymology of this modification. Critical to this work is having available synthetic beta-methylthioaspartic acid as well as derivatives designed for peptide incorporation. We report here the synthesis of beta-methylthioaspartic acid and derivatives. The installation of the beta-methylthio moiety into the aspartic acid structure was accomplished by electrophilic sulfenylation of N-protected-L-aspartic acid derivatives with 2,4-dinitrophenyl methyl disulfide. Following this key transformation, we were able to prepare beta-methylthioaspartic acid as well as the protected amino acid suitable for peptide coupling.

MEDI 306

Synthesis of new polyhydroxylated pyrrolidine alkaloids and their future as biological inhibitors

Morgan E Shirley*, Department of Biochemistry, IREU, Texas A&M IREU, 8201 W100th Terrace, Overland Park, KS 66212, mshirly1@ku.edu, and Wei-Chieh Cheng, Genomics Research Center; IREU, Primary investigator to Morgan Shirley during the IREU, Taipei, 115, Taiwan*

A breakthrough in the fields of both biology and chemistry has been the advent of chemical genetics by means of synthesizing small molecules that can act as effectors on proteins and

genes. With the understanding of the structure- activity- relationship (SAR) among small molecules and their molecular interactions with proteins and biological pathways the structure and function of these target areas can be further understood, and fields of drug discovery can be explored. A chemical library based on a polyhydroxylated pyrrolidine core is being synthesized from several aldo and ketopentose monosaccharides including xylose, lyxose, arabinose, and ribose with the purpose of inhibition of glycosidase and sialic acid formation. Synthesis of the library is nearly finished and the imino-sugars already synthesized have been verified by H1 and C13 NMR analysis. Upon completion of the library biological assays with the cooperation of biological specialists will begin with the intent of restoring function in the lysosome with respect to misfolded proteins and maximizing lysosomal function, along with sialic acid formation in tumor cells, and the functionality of GlcNac 2-epimerase.

MEDI 307

Synthesis of nonhydrolyzable pyrimidine and purine nucleotide analogs

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Cell surface oligosaccharides are biosynthesized by glycosyltransferase enzymes that catalyze the transfer of a carbohydrate from a sugar nucleotide donor to a glycosyl acceptor. For this reason, glycosyltransferase inhibitors are of potential therapeutic value for the treatment of diseases associated with glycosyltransferase regulation. Many nucleoside polyphosphates, including reaction products of these glycosylation reactions are known to be inhibitors of glycosyltransferases. However, natural nucleotides are easily degraded and do not readily pass across biological barriers due to the presence of pyrophosphate bridges in the structure. It is thus of interest to design and synthesize analogs of nucleotides with increased biological stability and membrane permeability. We have focused our attention on using sulfones as neutral phosphate analogs that are capable of mimicking phosphate-metal interactions. In this context, we focused our attention in synthesizing neutral analogs of GTP, GDP, ATP, ADP, UTP and UDP.

MEDI 308

Synthesis and characterization of aplysinopsin analogs

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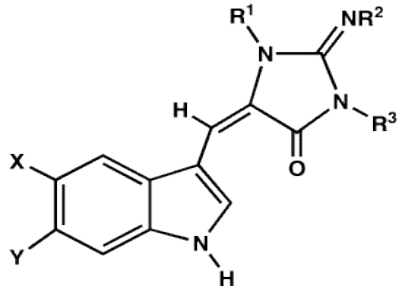
Aplysinopsin (**1**) was first isolated from a marine sponge in 1977. Since the initial discovery several aplysinopsin derivatives have been isolated from marine organisms. Some of the naturally occurring aplysinopsins have been shown to selectivity bind to 5-HT2C over 5HT2A

serotonin receptor subtypes (Hu, *et. al., J. Nat. Prod.* **2002**, *65*, 476). In the present work, three aplysinopsin analogs (**2-4**) were synthesized by reacting indole-3-carboxaldehydes with creatinine or 2-imino-1,3-dimethyl-imidazolidin-4-one. Single crystal structures on the 5-bromoaplysinopsin (**2**) and the 5-fluoroaplysinopsin (**4**) analogs have been determined. The crystal structures of **3** and **4** demonstrate that they exist in the E configuration. The X-ray structure of **4** shows that the imine double bond in the imidazolidin-4-one ring exists in the endocyclic tautomeric form.



1: X = Y = R^2 = H; R^1 = R^3 = CH_3
2: X = Br; Y = R^2 = R^3= H; R^1= CH_3
3: X = Br; Y = R^2 = H; R^1 = R^3 = CH_3
4: X = F; Y = R^2 = H; R^1 = R^3 = CH_3

MEDI 309

Polymer assisted, high throughput methods for Petasis and Ugi reactions

Paul A Boguszewski[1]*, John W Davies*[1]*, Peter A Marsh*[2]*, and Matthew Williamson*[1]*. (1) Polymer Laboratories Ltd, Now a part of Varian, Inc, Essex Road, Church Stretton, Shropshire SY6 6AX, United Kingdom, Fax: (+44) 01694 722171, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd, now a part of Varian, Inc, Church Stretton, Shropshire SY6 6AX, England*

Multiple component condensation reactions (MCRs) are highly attractive processes for parallel synthesis as libraries of compounds with drug-like structures and diverse substitution patterns can be synthesized in one step, often under mild reaction conditions. Two such examples are the Petasis (boronic Mannich) reaction and the Ugi reaction. One variant of the Petasis reaction, which uses glyoxalic acid, a boronic acid and an amine, is a facile route to unnatural aryl amino acid derivatives without the need for a cyanide based Strecker synthesis. The Ugi reaction is perhaps the most famous of the multicomponent reactions, allowing access to peptidomimetic species with a broad range of biological activity. One potential issue with MCR's is that the end purification can be non-facile. We describe polymer-assisted versions of the Petasis and Ugi reactions, employing resin-bound scavengers, reagents and novel polymeric SPE materials. These methods offer significant advantages in final compound purity and integrity.

MEDI 310

Optimized methods for the synthesis of peptides containing an N-Ethylamide terminus

Paul A Boguszewski[1], *John W Davies*[1], *Peter A Marsh*[2], *Graham Margetts*[2], *and Matthew Williamson*[1]. *(1) Polymer Laboratories Ltd, Now a part of Varian, Inc, Essex Road, Church Stretton, Shropshire SY6 6AX, United Kingdom, Fax: (+44) 01694 722171, SPS@polymerlabs.com, (2) Polymer Laboratories Ltd, now a part of Varian, Inc, Church Stretton, Shropshire SY6 6AX, England*

There are a number of biologically synthetic peptides which contain an *N*–ethylamide terminus. One well–known example is Leuprolide (Lupron®). With current interest in this particular type of peptide functionality, novel, robust methods for their synthesis are very attractive. We describe the development of two new indole based linkers for use in solid phase peptide synthesis. A proprietary manufacturing method means that the loading and efficacy of these supports is very consistent. These supports contain the pre–cursor *N*–ethylamine functionality which can be easily functionalized using standard Fmoc peptide synthesis protocols. The resulting *N*–ethylamide peptide can then be cleaved under mild acid conditions. The synthesis of several peptides is described.

MEDI 311

Synthesis and evaluation of á-amidoboronic acids for their ability to interact with carbohydrates

Shan Jin*, Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, atlanta, GA 30303, wang@gsu.edu*

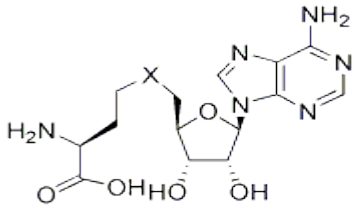
Boronic acids are known to form tight complexes with diol-containing compounds, which forms the basis for the design and synthesis of boronic acid-based carbohydrate sensors. However, essentially all such studies were done with arylboronic acids, which sometimes have water solubility and stability problems. á-Amidoboronic acids form an important class of boronic acids with high stability, high water solubility, and known affinity for diols. They could potentially be very useful in fluorescent carbohydrate sensor design. However, there has never been a systematic effort to study their binding with diols in a quantitative fashion. Aimed at achieving some fundamental understanding of amidoboronic acid-diol interactions, we synthesized and studied the binding of a model á-amidoboronic acid with various carbohydrates and other diol-containing. As expected, this compound showed good water-solubility. In this presentation, we will discuss the quantitative binding affinity data of amidoboronic acid binding with various diols.

MEDI 312

The 5'-oxa analog of S-adenosylhomocysteine

Weikuan Li *and Stewart W. Schneller, Department of Chemistry and Biochemistry, Auburn University, 179 Chemistry Building, Auburn University, Auburn, AL 36830*

S-Adenosylhomocysteine (SAH, 1) is a product feedback inhibitor of biomethylations dependent on its precursor S-adenosylmethionine (SAM) as the methyl source. This inhibitory control is moderated by the metabolism of 1 to adenosine and homocysteine by S-adenosylhomocysteine hydrolase (SAHase). In exploring variations of 1 that could mimic its properties and also be resistant to SAHase and, in turn, serve as selective inhibitors of viral SAM methyltransferases, the 5'-oxa analogue 2 was seen as a candidate for that purpose. The synthesis and biological properties of 2 will be presented. This research was supported by funds from the Department of Health and Human Services (AI 56540).



1 X=S, S-Adenosylhomocysteine (SAH)
2 X=S, Oxa-SAH

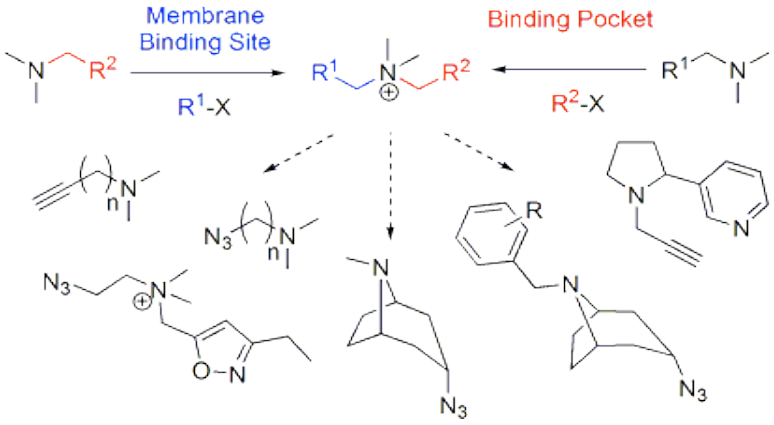
MEDI 313

Acetylcholine binding protein (nAChBP) ligands

Timo Weide[1]*, Joseph R. Fotsing*[1]*, Neil P. Grimster*[1]*, Todd T. Talley*[2]*, K. Barry Sharpless*[1]*, Palmer W. Taylor*[2]*, and Valery V. Fokin*[1]*. (1) Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, fokin@scripps.edu, (2) Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, CA 92093-0636*

Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand gated ion channels that are widely distributed throughout both the peripheral and central nervous system. The prevalence of nicotinic receptors in mediating physiological functions and diseases makes them attractive targets for the development of new therapeutic agents. Similar to the neurotransmitter core structures of acetylcholine and nicotine, a quaternary nitrogen or a nitrogen-containing aliphatic ring is characteristic for active compounds. Our approach is focused on a modular union of g-pocket binding groups A with newly designed membrane site binding units B. Therefore, different building blocks were synthesized, including those based on tropine derivatives and various azide or alkyne substituted amines, and coupled to different membrane side binding units B. Copper(I)-catalyzed azide-alkyne cycloaddition, which results in regioselective formation of 1,4-disubstituted [1,2,3]-triazoles and alkylation reactions on nitrogen were used as a simple and reliable tools to synthesize a library of potential ligands. Thus far, we have identified a number of high affinity binders (Kd < 1 nM) that demonstrate significant specificity.

Coupled with crystallographic data, these compounds are providing leads for the development of new molecular tools and therapeutics.

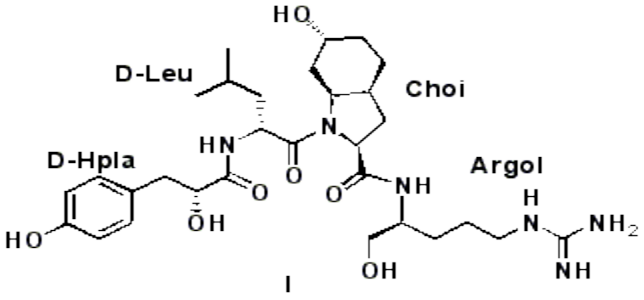


MEDI 314

Synthesis of aeruginosin 298-A analogs as thrombin inhibitors

Navneet Goyal, *Xiaoping Nie, and Guijun Wang, Department of Chemistry, University of New Orleans, 2000 lakeshore Drive, New Orleans, LA 70148, ngoyal@uno.edu*

Aeruginosins are a family of oligopeptides containing mostly non-proteogenic amino acids, including a common 2-carboxyoctahydroindole amino acid (Choi) as the core structure. More than twenty aeruginosins and related compounds have been isolated and identified so far. Several compounds in the family exhibit inhibition activity towards serine proteases in the blood coagulation cascade: thrombin and Factor VIIa. In order to understand the structure activity relationship (SAR) of the aeruginosins and to discover novel anticoagulants with potentially improved inhibitory and pharmacokinetic properties, we synthesized a series of novel analogs of aeruginosin 298-A (I), in which the Choi is replaced with L-proline or oxygenated Choi analogs, and the argol is replaced with various functionalities. The preparation of these compounds and their inhibitory activities against thrombin and trypsin will be presented.



I

Aeruginosin 298-A

MEDI 315

Unsymmetrical 1,3-diaryl ureas as conformationally rigid inhibitors of soluble expoxide hydrolase

*Preston A. Baecker, Zung N. Do, Heather Kay Webb, and **Richard D. Gless**, Arete Therapeutics, Inc, 3912 Trust Way, Hayward, CA 94545, rgless@aretetherapeutics.com*

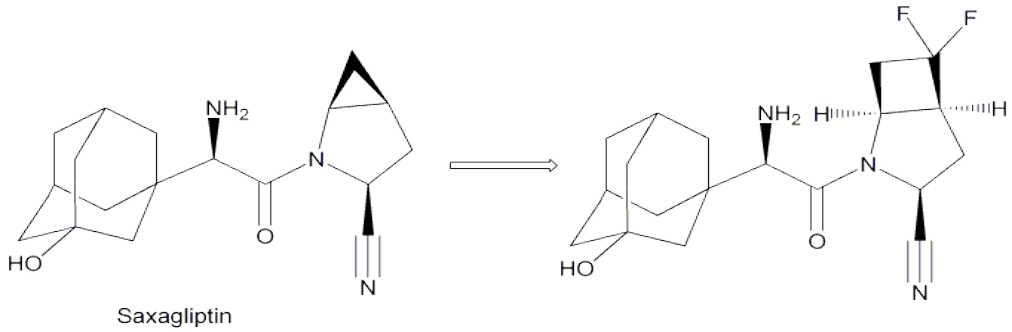
Soluble epoxide hydrolase (sEH, EC 3.3.2.3) appears to be a promising pharmaceutical target for the development of therapies in a number of disease indications including hypertension, heart failure, kidney disease, and inflammatory disease. sEH is found in a variety of mammalian tissues, with the highest activity measured in liver, kidney, intestinal and vascular tissue. Endogenously produced epoxides of arachodonic acids (epoxyeicosatrienoic acids or EETs) are known modulators of biological processes such as vasodilation. EETs are hydrolyzed by sEH to the corresponding diols (dihydroxyeicosatrienoic acids or DHETs) which have significantly diminished activity, suggesting inhibition of sEH as a new drug target. In order to generate more potent and metabolically stable inhibitors of sEH, conformationally rigid unsymmetrical 1,3-diaryl urea inhibitors were prepared. The synthesis and structure-activity relationships of this series as well as the pharmacokinetic properties of selected examples in rat will be presented.

MEDI 316

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

*TANG Peng Cho, LIN Zhi Gang, YANG Jia Liang, ZHAO Fu Qiang, WANG Yang, WANG Qian, **YANG Fang Long**, and LV He Jun, Shanghai Hengrui Pharmaceuticals Co. Ltd, 279 Wenjing Road, Shanghai 200245, China, tangpc@shhrp.com, yangfl@shhrp.com*

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 has showed clinical benefit as a novel mechanism for the treatment of type 2 diabets. A novel series of cyanocyclobutylpyrrolidine alpha-amino amides were synthesized and evaluated as inhibitors of dipeptidyl peptidase. The design, synthesis and inhibitory activities of these compounds will be discussed.



Saxagliptin

MEDI 317

Design and synthesis of hydroxy-alkynoic acid methyl esters as novel activators of BK channels

Shivaputra Patil[1]*, Anna Bukiya*[2]*, Wei Li*[1]*, Alejandro M Dopico*[2]*, and Duane D Miller*[1]*. (1) 1Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, College of Pharmacy, 847 Monroe Avenue, Room 327, Memphis, TN 38163, Fax: 901-448-6828, spatil3@utmem.edu, (2) Department of Pharmacology, University of Tennessee Health Science Center, College of Medicine, Memphis, TN 38163*

Physiological mediators and pharmacological compounds that activate large conductance, calcium- and voltage- gated potassium (BK) channels in vascular smooth muscle are effective vasodilators. Thus, BK channel activators can be considered potential therapeutic tools to treat cerebrovascular spasm and constriction. Lithocholic acid (5 beta-cholanic acid 3 alpha-ol) (LC) and other cholane derivatives dilate rat cerebral arteries through BK channel activation (Bukiya et al., 2007). However, LC clinical application may be constrained due to several LC actions (elevations of intracellular calcium, induction of apoptosis) that are thought to be related to LC steroidal structure. Based on data documenting that the alpha hydroxyl group at C3 is critical for LC to activate BK channels (Dopico et al., 2002), we now develop non-steroidal LC analogs and tested their effectiveness as BK channel activators in rat cerebrovascular myocytes. Computer simulation (MOE2006.08) of minimum energy conformation of LC in a lipid-protein interface establishes that the C3-C24 distance=10.36 Å. Then, C8 to C16 hydroxy-alkynoic acids and corresponding methyl esters were synthesized by coupling the bromoacids with alkynols in presence of sodium hydride, followed by acid-catalyzed methylation in methanol. Using standard patch-clamp techniques in the cell-free inside-out (I/O) configuration, we probed the action of these nonsteroidal LC analogs by applying each compound (150 μM) to the intracellular side of the I/O membrane patch at physiological [calcium]=3μM and membrane voltage=±40 mV. Data show that C9 and C10 hydroxy-alkynoic acid methyl esters (9.73 and 10.99Å in length) are the most effective BK channel activators, increasing steady-state activity (NPo; Dopico et al., 1996)×2 of control levels. Thus, these LC nonsteroidal analogs and related compounds should be considered potential vasodilators that might be free of side effects caused by the presence of a steroidal nucleus.

MEDI 318

Simple alkenes as nitric oxide vehicles through nitro-oximes

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Nitric oxide (NO) modulates a variety of physiologic processes including neurotransmission, blood clotting, and blood pressure control. NO binds to the heme group of soluble guanylyl cyclase (sGC) and activates cyclic guanylate monophosphate (cGMP) production. Many organic and inorganic compounds, such as nitroglycerin and sodium nitroprusside, find use as nitric oxide donors. FK409 is a biologically active natural product that spontaneously releases NO and nitrite. Using the functionality of FK409 as a model, a group of nitro-oximes were prepared as potential NO donors by purging solutions of simple alkenes with oxygenated NO. These

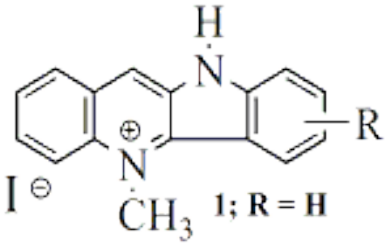
compounds undergo dimerization through the nitroso form and have been characterized by a variety of spectroscopic methods. Chemiluminescence detection shows the ability of these compounds to release NO and gas chromatographic studies may reveal the ability of these compounds to release nitroxyl (HNO). This work identifies this functional group as a new NO donating moiety.

MEDI 319

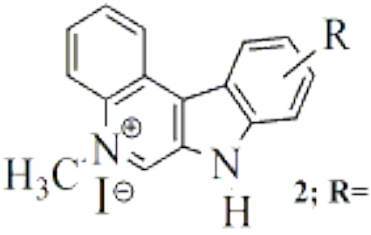
Angular indoloquinoline analogs as novel antiinfective agents against opportunistic pathogens

Seth Y. Ablordeppey[1], *Jagan R. Etukala*[1], *E. V. K. Suresh Kumar*[1], *Melissa Jacob*[2], *Shabana I. Khan*[3], *and Larry A. Walker*[4]. *(1) Basic Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, Fax: (850) 599-3934, seth.ablordeppey@famu.edu, (2) Research Institute of Pharmaceutical Sciences, University of Mississippi, University MS 38677, (3) National Center for Natural Products Research, The University of Mississippi, University, MS 38677, (4) National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, MS 38677*

Previous studies on the indoloquinoline alkaloid, cryptolepine (1) revealed that it has anti-bacterial, antifungal, antiprotozoal and anticancer activities. Using a new synthetic procedure to obtain quindoline, we discovered that angular indoloquinolines (2) were formed in addition to the linear quindoline structure. The main objective of this study was to conduct a comparative study of the linear and angular indoloquinoline ring systems and to evaluate their antiinfective properties in a search for new antiinfective agents. Preliminary results indicate that, the angular indoloquinolines constitute new anti-infectives with lower cytotoxicity than cryptolepine. The synthesis and antiinfective activities of some representative compounds will be presented. This research was supported in part by the Pharmaceutical Research Center NIH/NCRR grant 1 C06 RR12512-01 and by the Division of Research Resources, RCMI # G12 RR 03020. The research is also supported by NIGMS MBRS program, Grant # GM 08111 and a Title III award to SYA.



1; R = H



2; R= H

MEDI 320

Synthesis and antibacterial activities of S-heterosubstituted disulfides

Praveen Ramaraju *and Edward Turos, Department of Chemistry, University of South Florida, 4202 E. Fowler Ave CHE 205, Tampa, FL 33620, pramara2@mail.usf.edu*

This study describes the antibacterial properties of synthetically-produced heterosubstituted disulfide compounds as a means to control the growth of drug resistant *Staphylococcus aureus* and *Bacillus anthracis*. The mode of action of these compounds is likely similar to that of previously reported N-thiolated beta-lactams, which have been shown to create alkyl-CoA disulfides through a thiol-disulfide exchange within the cytoplasm, ultimately inhibiting fatty acid synthesis. These structurally-simple disulfides may serve as new leads to the development of effective antibacterials for drug-resistant staph infections and anthrax disease.

MEDI 321

Antiinfective secondary metabolites from marine sponges and microorganisms

MinKyun Na[1]*, Damaris A. F. Meujo*[1]*, Dion Kevin*[1]*, Matthew Anderson*[2]*, Russell T. Hill*[2]*, Raymond F. Schinazi*[3]*, and Mark T Hamann*[1]*. (1) Department of Pharmacognosy, School of Pharmacy, The University of Mississippi, University, MS 38655, nka@olemiss.edu, (2) University of Maryland Biotechnology Institute, Baltimore, MD 21202, (3) Medical research 151H, Emory university/VA Medical center, Decatur, GA 30033*

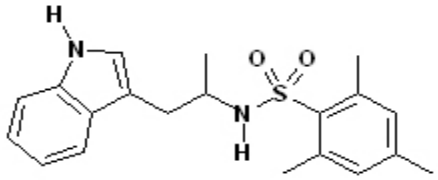
Bioassay-guided fractionation of a methanol extract from a new deep-water Alaskan sponge species of the genus Latrunculia resulted in the isolation of two new brominated pyrroloiminoquinones, discorhabdins X (3) and Y (6), along with six known pyrroloiminoquinone alkaloids, discorhabdins A (1), C (4), E (5), L (8), 3-dihydrodiscorhabdin C (2), and a benzene derivative (7). The major isolates 1, 2, and 4 displayed anti-HCV activity with EC50 values less than 10 μM, and showed antimalarial activity against both the chloroquine-susceptible (D6) and -resistant (W2) clones of Plasmodium falciparum, with IC50 values ranging from 22 to 1300 ng/ml, as well as exhibited selective antimicrobial activity against AIDS opportunistic pathogens, Methicillin Resistance Staphylococcus aureus (MRSA), Mycobacterium intracellulare, and M. tuberculosis. Our antimalarial screening of marine microorganisms from Hawaiian sediments yielded a Streptomyces sp. designated strain H668 with highly potent in vitro activity against P. falciparum without significant cytotoxicity to Vero cells. The antimalarial guided fractionation of the culture of H668 strain led to the isolation of a new polyether metabolite. The structure was determined by comprehensive NMR and MS assignments. This new metabolite showed in vitro antimalarial activity against both the chloroquine-susceptible (D6) and -resistant (W2) clones of P. falciparum, without cytotoxicity to normal cells (Vero) making it a promising first lead from this marine bacterium.

MEDI 322

From antagonist to agonist: Optimization of a nonsteroidal glucocorticoid receptor ligand

Darren DiSalvo[1], *Daniel Kuzmich*[2], *Raj Betageri*[2], *Joerg Bentzien*[3], *Alison Kukulka*[2], *Daniel R. Marshall*[3], *Gerald H. Nabozny*[4], *Richard Nelson*[3], *and David S. Thomson*[3]. *(1) Department of Research, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Road, Ridgefield, CT 06877-0368, (2) Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT 06877, (3) Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT 06877, (4) Department of Pharmacology, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT*

Glucocorticoids are among the most effective agents for the treatment of acute and chronic inflammatory diseases. For these therapeutic indications, it is necessary that a glucocorticoid receptor (GR) ligand functions as an agonist. One potential strategy for obtaining a class of GR agonists is to explore structural features that could switch a known class of antagonists to agonists. Previously we reported a series of ƒÑ-methyltryptamine sulfonamides exemplified by compound 1. Early hit-to-lead efforts focused mainly on sulfonamide substitution which provided a series with potent GR binding and weak antagonist activity. More recently focused SAR has targeted specific hydrogen bonding and lipophilic interactions within the GR binding site that has resulted in potent agonist activity. This poster describes the structural motifs that have allowed for the functional switching of a GR antagonist to an agonist in an effort to identify a new scaffold for lead optimization.



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MEDI 323

Synthesis and evaluation of novel polyaminocarboxylate-based antitumor agents

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Iron depletion using iron chelators targeting transferrin receptor (TfR) and ribonucleotide reductase (RR) is proven to be effective in the treatment of cancer. We synthesized and evaluated novel polyaminocarboxylate-based chelators NETA, NE3TA, NE3TA-Bn and their bifunctional versions C-NETA, C-NE3TA, and N-NE3TA for use in iron depletion tumor therapy. The cytotoxic activities of the novel polyaminocarboxylates were evaluated in the HeLa and HT29 colon cancer cell lines and compared to the clinically available iron depletion agent DFO and the frequently explored polyaminocarboxylate DTPA. All new chelators except C-NETA displayed enhanced cytotoxicities in both Hela and HT29 cancer cells compared to DFO and

DTPA. Incorporation of the nitro functional unit for conjugation to a targeting moiety into the two potent non-functionalized chelators NE3TA and NE3TA-Bn (C-NE3TA and N-NE3TA) was well tolerated and resulted in minimal decrease in cytotoxicity compared to NE3TA and NE3TA-Bn. Cellular uptake of C-NE3TA examined using confocal microscope indicates that the chelator is taken up to HT29 cancer cells.

MEDI 324

Mining the Magic Mountain for novel antibacterial agents: Slow onset inhibitors of the enoyl reductase enzymes from Mycobacterium tuberculosis and Francisella tularensis

Peter J. Tonge[1]*, Christopher am Ende*[1]*, Hao Lu*[1]*, Kathleen Bostrom*[2]*, Susan Knudson*[2]*, Nina Liu*[1]*, Todd J. Sullivan*[1]*, Francis Johnson*[1]*, Richard A. Bowen*[2]*, Sylvia Luckner*[3]*, Caroline Kisker*[3]*, and Richard A. Slayden*[2]*. (1) Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400, Fax: 631-632-7960, peter.tonge@sunysb.edu, (2) Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO, (3) Institute for Structural Biology, University of Wurzburg, Wurzburg, Germany*

Novel chemotherapeutics are needed for treating infectious diseases caused by pathogens such as multi-drug resistant M. tuberculosis as well as the category A agent Francisella tularensis (Ftu). Using structure-based drug design, we have developed a series of alkyl diphenyl ethers that are uncompetitive inhibitors of the fatty acid biosynthesis enoyl reductase enzymes (FabIs) from M. tuberculosis (Mtb; MtbFabI; InhA) and Ftu (FtuFabI). The compounds have been designed to cause ordering of the FabI active site loop, based on the premise that loop ordering is coupled to slow-onset enzyme inhibition. While several nanomolar inhibitors of either ftuFabI or MtbFabI were identified, those targeting ftuFabI were slow onset inhibitors while those targeting MtbFabI were not. The mtbFabI inhibitors inhibit the growth of both drug sensitive and isoniazid-resistant MTB strains with MIC90 values of 3-4 ìg mL-1. In addition, the slow onset ftuFabI inhibitors had MIC90 values of < 0.06 ìg mL-1 against the LVS strain of ftu. Significantly, the most potent compounds are highly active in the F. tularensis murine model of infection at 200 mg kg-1. The in vivo activity of the ftuFabI inhibitors is attributed, at least in part, to the fact that these compounds are slow onset inhibitors with increased residence time on the enzyme. Based on this knowledge, a second series of mtbFabI inhibitors have been developed that incorporate modifications designed to reduce the entropic penalty for loop ordering and enzyme inhibition. The results of these studies will be presented.

MEDI 325

Structure guided design, synthesis and characterization of inhibitors of the bacterial enoyl-ACP reductase Fab1

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There is a pressing need for new antibacterial agents that act via new targets. Bacterial fatty acid biosynthesis enzymes offer such an opportunity. In certain pathogenic bacteria the enoyl-acyl carrier protein (ACP) reductase FabI is responsible for the terminal step in fatty acid biosynthesis and its corresponding gene is essential (similar transformations in humans are

carried out by a single multifunctional enzyme designated FAS1). This has led to the pursuit of specific enoyl-ACP reductase inhibitors of FabI as novel antibacterial agents. Structure guided design and synthesis of a series of ene-amide inhibitors of FabI will be described. High resolution 3-dimensional structures of FabI from S. aureus and the Class A pathogen F. Tularensis provide a detailed understanding of the structural factors governing ligand recognition. The potent antibacterial activity of these compounds will be presented.

MEDI 326

Synthesis and activity of novel fatty acid synthase inhibitors

*Gil Ma[1], Robyn D. Richardson[2], Manuel Zancanella[1], Yatsandra Oyola[1], Wei Zhang[1], Jeffrey W. Smith[2], and **Daniel Romo**[1]. (1) Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, TX 77842-3012, romo@mail.chem.tamu.edu, (2) Cancer Research Center, The Burnham Institute, La Jolla, CA 92037*

Fatty acid synthase (FAS) is a multi-domain enzyme responsible for synthesis of cellular fatty acid. Mounting evidence suggests that FAS is a valid target for cancer given that this enzyme is upregulated in many types of cancer. Building on an initial observation made through activity-based profiling that the FDA approved anti-obesity drug, orlistat, is an inhibitor of FAS, we prepared a series of orlistat (tetrahydrolipstatin) derivatives with an aim of improving solubility and potency. Methods developed for the asymmetric synthesis of orlistat derivatives, the bioactivity of these derivatives, and related studies will be the topics of this seminar.

MEDI 327

Antisense approaches for antibiotic discovery: Discovery of platensimycin and platencin

***Sheo B. Singh**, Natural Products Chemistry, Merck Research Laboratories, 126 E. Lincoln Avenue, RY80Y-350, Rahway, NJ 07065, Fax: 7325946880, sheo_singh@merck.com*

FabH and FabF are essential enzymes in type II fatty acid synthesis and are promising targets for antibacterial drug discovery and development. A new approach using a xylose inducible plasmid to express antisense RNA (AS-RNA) in Staphylococcus aureus has been recently described. In order to identify FabF/FabH target specific cell permeable inhibitors from natural products, we developed an agar-diffusion two-plate differential sensitivity assay. Because both the fabH and fabF genes share the same operon, the increase in fabF AS-RNA levels decreases the expression of FabH and FabF proteins, making the cells more sensitive to FabF and/or FabH inhibitors.

Using this assay, we screened over 250,000 natural product extracts followed by confirmation in biochemical assays, giving a hit rate of 0.1%. We discovered all known FabH and FabF inhibitors that included cerulenin, thiolactomycin, thiotetromycin and Tu3010 from natural product extracts for the first time using a mechanism based screening approach. We discovered a number of novel natural products as FabF inhibitors including platensimycin and platencin. The details of discovery process, structures, biological activities, in vivo efficacy, mechanism of action and inhibitor bound X-ray crystal structure will be discussed.

MEDI 328

The mechanism of bioreduction of nitroimidazooxanes by Mycobacterium tuberculosis

Clifton E. Barry*, Ramandeep Singh, Richard Ledwidge, Young Hwan Ha, Ill-Young Lee, Ujjini Manjunatha, and Helena Boshoff, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, 12441 Parklawn Dr, Twinbrook II, Room 239, Rockville, MD 20852, clifton_barry@nih.gov*

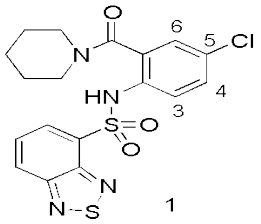
Bicyclic nitroimidazoles such as PA-824 and OPC-67683 are currently in clinical trials for the treatment of tuberculosis. We have previously shown that the protein Rv3547 is adeazaflavin-dependent nitroreductase involved in activation of some bicyclic nitroimidazoles; and that such activation is essential for these compounds to exert a lethal effect on mycolic acid synthesis and respiration. The deazaflavin-dependent reductase has the ability to transfer a hydride atom from coenzyme F420 to either the substrate nitro group or directly to the 5-position of the imidazole ring. The products of both reduction pathways have been characterized and confirmed by total synthesis and reduction using deuterated reductant or solvent has unambiguously identified the source of the hydrogens in the final products. A plausible mechanism for reduction will be presented.

MEDI 329

Discovery and SAR of a novel series of orally efficacious antagonists of the CCK-2/gastrin receptor that block gastric acid secretion in vivo

Michael Rabinowitz[1], *Brett D. Allison*[2], *Mark Rosen*[2], *Victor K. Phuong*[2], *Laura C. McAtee*[2], *Clogagh Prendergast*[3], *Xiaodong Wu*[4], *Magda F. Morton*[2], *Terrance Barrett*[5], *and Nigel P. Shankley*[2]. *(1) Department of Chemistry, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, 3210 Merryfield Row, San Diego, CA 92121, mrabinow@prdus.jnj.com, (2) Physiological Systems, Johnson and Johnson Pharmaceutical Research and Development, La Jolla, CA 92121, (3) Department of Physiology, University of Liverpool, Liverpool L69 3BX, United Kingdom, (4) Johnson & Johnson Pharmaceutical R&D, San Diego, CA CA, (5) Department of Biology, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, San Diego, CA 92121*

In the past few years there has been a renewed interest in CCK-2 (formerly gastrin/CCKB) receptor antagonists for the treatment of GI adenocarcinoma such as Barrett's metaplasia and pancreatic cancer based on evidence that gastrin, the cognate ligand for the CCK-2 receptor, is a potent trophic factor for these tumors. A high throughput binding assay screening of the J&JPRD compound collection against the gastrin receptor resulted in the identification of compound 1, which possessed promising ADME and pharmacokinetic parameters. Preliminary SAR investigations demonstrated the importance of the electronic structure of the heterocyclic sulfonamide ring system as well as its susceptibility towards CYP450-mediated oxidation. ADME-driven SAR studies identified alternative ring systems that retained receptor binding affinity but showed a greatly improved resistance towards oxidative metabolism. This presentation will focus on the preliminary structural optimization, pharmacokinetics and in vivo efficacy of this novel series of gastrin receptor antagonists, along with conformational modeling aimed at gaining an understanding of the active pharmacophore.



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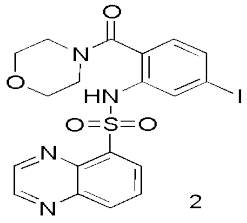

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MEDI 330

Identification of a new class of nonpeptidic inhibitors of cruzain

Katrien Brak[1], *Patricia S. Doyle*[2], *James H. McKerrow*[3], *and Jonathan A. Ellman*[1]. *(1) Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720-1460, katrien@berkeley.edu, (2) Department of Pathology, UCSF, San Francisco, CA 94158-2330, (3) Sandler Center for Basic Research in Parasitic Diseases, University of California San Francisco, San Francisco, CA 94158*

Chagas' disease, caused by the parasitic protozoan Trypanosoma cruzi, is the leading cause of heart disease in Latin America. Due to the toxicity of current chemotherapy and emerging drug

resistance, there is an urgent need for developing an effective therapy against Chagas' disease. Cruzain, the primary cysteine protease of the T. cruzi parasite, is essential for replication of the intracellular parasite. A novel class of potent nonpeptidic inhibitors of cruzain has been discovered. The inhibitors were identified by screening a library of protease substrates using the Substrate Activity Screening (SAS) method. Optimization of the substrate scaffold through structure-based design resulted in highly efficient substrates that were converted to potent aryloxymethyl ketone inhibitors of cruzain. This class of inhibitors cured mammalian cell cultures infected with T. cruzi and could lead to treatment agents for Chagas' disease.

MEDI 331

Bump-hole reoptimization of the tacrine pharmacophore achieves selective inhibition of *Anopheles gambiae* acetylcholinesterase

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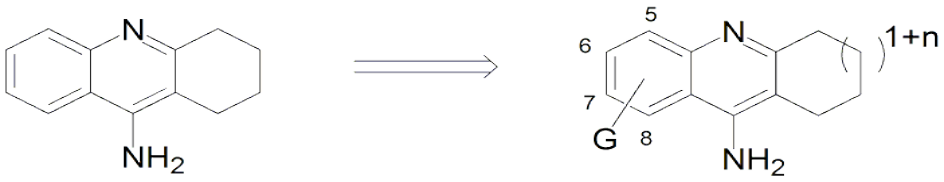
Acetylcholinesterase (AChE) inhibition can present therapeutic or toxic effects, depending on the degree of inhibition. 9-Amino-1,2,3,4-tetrahydroacridine (tacrine) was the first drug approved for the treatment of Alzheimer's-related memory loss; other AChE inhibitors have been used as pesticides and chemical warfare agents. With the goal of developing new insecticides to control the malaria-transmitting mosquito, *Anopheles gambiae*, we undertook a reoptimization of the tacrine pharmacophore to attain high selectivity for inhibition of mosquito AChE. By exploring structural modifications of tacrine known to reduce affinity for human AChE, we discovered an inhibitor that exhibits a greater than 100-fold selectivity for the mosquito enzyme over the human enzyme.



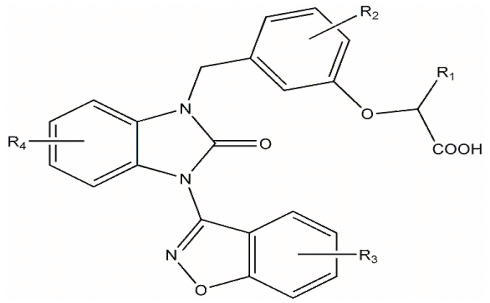
MEDI 332

Benzimidazolones: A new class of PPAR gamma selective modulators

***W-G. Liu**[1], K. Liu[1], T. E. Akiyama[2], M. Einstein[2], J. R. Thompson[2], C. H. Chang[2], M. E. McCann[2], J. P. Berger[2], H. B. Wood[1], and P. T. Meinke[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O.Box 2000, Rahway, NJ 07065, Fax: 732-594-9556, weiguo_liu@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ 07065-0900*

Peroxisome Proliferator-Activated Receptors compose a subfamily of ligand-activated nuclear hormone receptors that are involved in regulating nutrient storage and catabolism. There are three PPAR subtypes, commonly designated as PPAR-alpha, PPAR-gamma, and PPAR-delta.

Agonists of the gamma subtype have been studied extensively for their role in regulating glucose metabolism and insulin sensitivity. PPAR-gamma full agonists, such as rosiglitazone and pioglitazone have been developed for the treatment of type II diabetes (T2D). However, mechanism-based adverse effects including weight gain, edema and congestive heart failure has limited the therapeutic utility of currently available PPAR-gamma agonists. Recently, several reports in the literature, including work from our own laboratories, have demonstrated that selective PPAR-gamma modulators (SPPARgammaMs) could bind to the receptor in a distinct mode relative to full agonists. As a result, such ligands act as partial agonists in transcriptional activity assays and induce an attenuated adipocyte gene signature. In vivo, SPPARgammaMs retain anti-diabetic efficacy comparable to full agonists while displaying reduced mechanism-based adverse effects. Here, we report the design, synthesis, and structure activity relationship of a new class of PPAR-gamma ligands. These benzimidazole based analogs are SPPARgammaMs. They robustly reduce elevated glucose level in preclinical models for T2D with attenuated induction of weight gain and fluid retention in comparison with PPAR-gamma full agonists



MEDI 333

Crystalline packing: A crucial aspect for developing new cooling agents

***Stefan M. Furrer**, Ingredient Systems, Givaudan Flavors R&D, 1199 Edison Drive, Cincinnati, OH 45216, Fax: 513-948-3582, stefan.furrer.sf1@givaudan.com*

Until recently the flavor industry dealt mostly with volatile compounds and crystalline compounds were more an exception then a rule. More recently, efforts towards the discovery of new taste modulators, fueled by ground breaking discoveries in receptor technology and taste physiology, led us to focus on nonvolatile chemicals.

The water solubility as well as solubility in various oils was soon recognized to be a decisive factor for the development of active compounds.

In this presentation we will discuss the role played by crystalline packing and water solubility during the development of our newest generation of cooling chemicals. X-ray crystallography gave us essential clues on factors that stabilize or disrupt lattices and was further used for designing of new cooling compounds. The role of physicochemical structural properties governing aqueous and mint oil solubility and their application in the development of a new generation of cooling agents will be discussed as well.

MEDI 334

Giving the Rule-of-5 a more accurate twist

*Sanjivanjit Bhal, Ian G. Peirson, Karim Kassam, and **Greg Pearl**, Advanced Chemistry Development, Inc, 110 Yonge Street, 14th Floor, Toronto, ON M5C 1T4, Canada, sanji.bhal@acdlabs.com, greg.pearl@acdlabs.com*

The much publicized “Rule-of-5” (Ro5) has been widely adopted in the pharmaceutical industry as the first step in the virtual screening of compound libraries, to pre-emptively eliminate hits that are deemed to have poor physicochemical properties for oral bioavailability; and in lead optimization to filter out less suitable compounds.

LogP is a key parameter in the Ro5 and one that is inordinately familiar to medicinal chemists. Although it is useful, it fails to take into account variation in drug lipophilicity due to ionization under physiological conditions. Given that more than 95% of commercial pharmaceuticals contain an ionizable moiety, we propose that logD is a better descriptor for lipophilicity in the Ro5 (and similar filters).

In this presentation we will discuss the important differences between logP and logD, and results from screening a number of commercially-available libraries using an adapted Ro5 applying logD in place of logP.

MEDI 335

Synthesis and biological evaluation of novel cannabinoid receptor ligands

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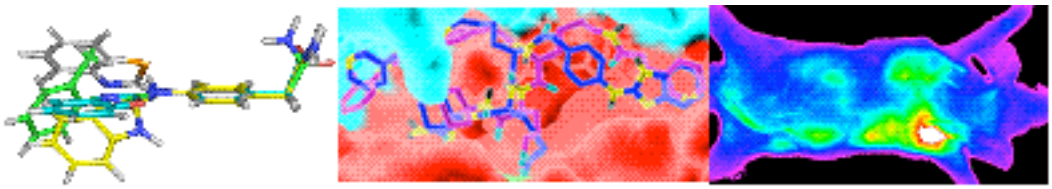
Cannabinoid receptor antagonists have been suggested to have potential utility as medications for cannabinoid abuse and psychostimulant addiction. Recent studies in our laboratories have shown that 1,5-diaryl-1,2,3-triazoles exhibit potent affinity (nM) for CB1 receptors. A series of 1,5-diaryl-4-substituted-1,2,3-triazole, 4,5-diaryl-1-substituted-1,2,3-triazole and 4,5-diaryl-2-substituted-1,2,3-triazole derivatives have been successfully synthesized and evaluated at CB1 receptors. The synthesis, binding affinity and structure activity relationships of these novel diaryl-1,2,3-triazoles will be presented.

MEDI 336

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

***Richard D. Carpenter**, Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616, rcarpenter@ucdavis.edu, Kit S. Lam, Department of Internal Medicine, University of California Davis Cancer Center, Sacramento, CA 95817, and Mark J. Kurth, Department of Chemistry, University of California Davis, Davis, CA 95616*

The ligand-radio conjugates LLP2A (IC50 = 37 pM) have shown utility as an imaging and therapeutic agent, however this conjugate has shown an inability to clear the kidneys. To circumvent this issue, we focused on preparing water-soluble benzimidazole, benzoxazole, and benzothiazole KLCA analogs that at physiological pH would be dianionic (2-bisarylamino N-H + carboxylic acid) and are less likely to be reabsorbed and more likely to be cleared. In silico modeling studies were performed to better comprehend the respective binding interaction and solution-phase conformation of the KLCA analogs with respect to LLP2A enabling the preservation of its picomolar potency. The benzimidazole KLCA7 (IC50 = 115 pM) and the benzothiazole KLCA12 (IC50 = 53 pM) were comparable to LLP2A in binding during competitive inhibition studies with known anti-á4â1 CS-1 peptide. Imaging data derived from the conjugate KLCA12-Cy5.5 will be shown, in addition to preliminary I-125 murine therapeutic studies.

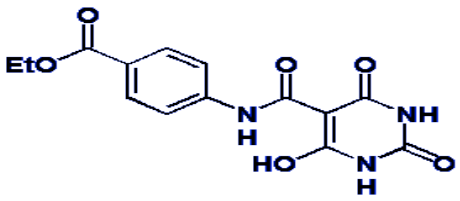


MEDI 337

Targeting the Polo Box Domain of Polo-like kinase 1 for therapeutics

Karen M. Carter *and Peter Wipf, Department of Chemistry, University of Pittsburgh, 10029 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15232, kmc4fb@gmail.com*

Polo like kinase-1 (Plk1) carries out key roles throughout cell cycle progression. Due to its exclusive function during mitosis, Plk1 has become a therapeutic target for cancer research. Plks are defined by two conserved regions; an N-terminal Ser/Thr kinase domain and a C-Terminal polo box domain (PBD). Although several Plk1 inhibitors have been reported, they target the highly conserved ATP kinase domain, and as such display limited selectivity over other protein kinases. The PBD is distinctive within the polo-like kinase family; therefore identification of small molecules targeting the PBD will afford inhibitors that are specific to polo-like kinases. A library screen for small molecule inhibitors of the PBD of Plk1 using a HT fluorescence polarization assay identified several lead structures, of which 861574 was selected for optimization. The synthesis of analogs of this lead compound, subsequent biological evaluation, and the results will be discussed.



861574

MEDI 338

Structure guided design of balanced dual PPARalpha/gamma agonists for the treatment of type II diabetes and dyslipidemia

Uwe M. Grether[1]*, Hans Hilpert*[2]*, Bernd Kuhn*[3]*, Hans Peter Marki*[2]*, Markus Meyer*[2]*, and Peter Mohr*[2]*. (1) Discovery Chemistry, PRBD-CM, F. Hoffmann-La Roche Ltd, Bldg. 92/7.64C, CH-4070 Basel, Switzerland, Fax: 0041-61-6889748, uwe.grether@roche.com, (2) F. Hoffmann-La Roche, Basel CH-4070, Switzerland, (3) Pharma Division, Preclinical Research PRBD, F. Hoffmann-La Roche Ltd, Basel CH-4070, Switzerland*

Information gained from studying ligand protein X-ray co-crystal structures with PPAR ligand binding domains of all three PPAR isoforms (PPARƒÑ, PPARƒ× and PPARƒÔ), both from in house and from public data, has provided growing insight into the factors controlling receptor binding and functional activation as well as isoform selectivity. Capitalizing on this knowledge and guided by modeling a set of tool compounds was synthesized from which highly promising starting points emerged: i) simple ƒÑ-alkoxy-phenyl-propionic acids. Optimization of this compound class resulted in potent and balanced dual PPARƒÑ/ƒ× agonists frequently characterized by higher PPARƒÑ than PPARƒ× affinity. ii) Specific modeling design, focusing on novel aromatic scaffolds that replace the central phenyl ring present in a large number of synthetic PPAR agonists, led to the identification of the indolyl-alkoxy-propionic acids [5]. Lead optimization delivered potent and balanced dual PPARƒÑ/ƒ× agonists which are selective against the PPARƒÔ receptor subtype also for this compound class. Both series show a wide range of PPARƒÑ/ƒ× ratios within a rather narrow structural space. Rationalization of the SAR within the protein structure context and the optimization of the relative PPARƒÑ/ƒ×/ƒÔ potencies will be discussed. Several X-ray co-crystal structures underline that subtle structural changes can exert a profound impact on the binding conformation. Representatives from both series have excellent physicochemical, pharmacokinetic and in vitro safety properties. Data of advanced compounds in animal models of T2D and dyslipidemia will be presented.

MEDI 339

Rational design and generation of novel bimodal bifunctional ligands for antibody-targeted radiation cancer therapy

Hyun-Soon Chong*, Hyun A Song, Thien Le, Dengfeng Cheng, Hyunbeom Lee, and Xiang Ma, Chemistry Division, Biological, Chemical, and Physical Sciences Department, Ilinois Institute of Technology, 3101 S. Dearborn St, LS 182, Chicago, IL 60616*

An antibody-targeted radiation therapy (radioimmunotherapy, RIT) employs a bifunctional ligand that can effectively hold a cytotoxic metal with clinically acceptable complexation kinetics and stability while being attached to a tumor-specific antibody. RIT holds great promise for treatment of many cancers, as evidenced by Zevalin" therapy (overall response rate of ~80%). However, active clinical exploration of RIT using a variety of antibodies and cytotoxic radionuclides has been challenged by the absence of adequate bifunctional ligands that can bind the radionuclides with clinically acceptable kinetics and in vivo stability and thereby allow for practical and large scale production of stable radioimmunoconjugates. To address this deficiency, the bimodal bifunctional ligands C-NETA, C-NE3TA, and 3P-C-NETA in a unique structural class possessing both a macrocyclic cavity and a flexible acyclic moiety were

designed. The practical, reproducible, and readily scalable synthetic routes to the novel bifunctional ligands were developed, and their potential as the chelators of diverse metals for RIT was evaluated in vitro. The new ligands were favorably compared to the most frequently employed bifunctional ligand C-DOTA for complexation kinetics and stability in vitro. The new ligands were also successfully conjugated to Herceptin, an antibody against HER2 receptor, a target of metastatic breast cancer drugs and possesses great promise for RIT applications.

MEDI 340

ABT-263, an orally bioavailable and efficacious inhibitor of Bcl-2 family proteins

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The involvement of Bcl-2 proteins in oncogenic processes collectively makes them an attractive target for cancer therapy, as small molecule inhibitors of anti-apoptotic Bcl-2 proteins that could mimic the function of various BH3-only proteins should bias the cell towards apoptosis. In this presentation, the SAR development towards the discovery of ABT-263, a BH3-only protein mimetic, will be disclosed. Our first generation Bcl-2 family protein inhibitor - ABT-737, was effective in various tumor models, but lacked oral bioavailability. Therefore extensive SAR studies were initiated in order to identify a second-generation compound that could be dosed orally, an effort that culminated in the identification of ABT-263. This compound is a best-in-class, orally bioavailable inhibitor of Bcl-2 family proteins with high affinities (Ki < 1 nM). Additionally, ABT-263 has excellent preclinical, single-agent antitumor efficacy in small cell lung cancer, lymphoma, and leukemia, and recently entered into several phase I clinical trials.

MEDI 341

Synthesis of bis-diazeniumdiolates and their in vitro activities toward cancer cell lines

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Diazeniumdiolate ions, also known as NONOates, are extensively used in biochemical, physiological and pharmacological studies due to their ability to slowly release nitric oxide (NO) and or its congeneric nitroxyl (HNO) in neutral media.

They can be alkylated at the terminal oxygen to produce charge neutral derivatives that are proving useful as potential drugs. Compounds of the O^2-aryl diazeniumdiolate family have shown noteworthy anticancer activity in a variety of model systems.

Encouraged by these results, we synthesized a series of bis-diazeniumdiolates derived from 1,5-difluoro-2,4-dinitrobenzene. We have used the HL-60 human leukemia cell line and two lung adenocarcinoma cell lines (H-1944 and H-1703) to determine the ability of these compounds to inhibit cell proliferation. The IC_{50} values for these bis-diazeniumdiolates were between 0.8-2.2 μM. Additionally, the most active compounds from this series were tested in a panel of ten cell lines derived from different human cancers (prostate, colon, ovarian).

MEDI 342

Synthesis of peptide-amiloride conjugates as prodrugs of urokinase (uPA) inhibitors

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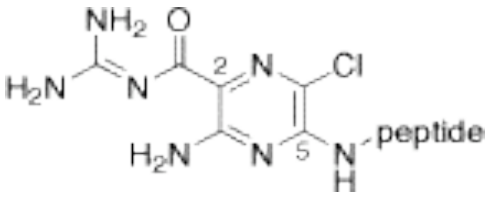
Urokinase plasminogen activator (uPA) is a serine protease synthesized within cancer cells. The secretion of uPA by cancer cells is a key step in tumor invasion and metastasis. We have designed and synthesized peptide-based amiloride conjugates as prodrugs of uPA inhibitors. Short peptides are attached to the C(5)-amino group of amiloride, a known uPA inhibitor. These peptides contain amino acid sequences that are recognized and selectively cleaved by uPA. The synthesized conjugates are inactive; however, peptide cleavage releases an active inhibitor of uPA. We will describe the solution- and solid-phase approaches used to prepare these peptide-amiloride prodrugs. The results of uPA cleavage studies also will be presented.



MEDI 343

Tumor homing peptide conjugated with cisplatin prodrug

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Many biologically active compounds are rendered ineffective, if they are not adequately administered and metabolized in the human body. We are exploring target delivery of cisplatin using identified peptide sequences that are capable of mediating delivery of therapeutic or imaging material. Various peptides have been shown to bind to integrins using phage display libraries, with some sequences residing preferentially in various tumor cell types. Cisplatin, like many anti-tumor drugs is one of the FDA approved drug widely used for treatment of many types of cancers. DNA is the biological target of cisplatin and formation of covalent bonds with N7 purine base results in subsequent interference with normal transcription, and/or DNA replication mechanisms followed by series of cellular events that lead to cell death. The specificity of this drug can be enhanced by efficient delivery of cisplatin and it's analogues to the nucleus of the cancer cells. In this study we present novel peptide–cisplatin conjugate to investigate the biological effect of the linker, tumor cell selective localization and cell uptake. Recent results on studies of peptide-cisplatin conjugate, synthesis, structure and function will be presented.

MEDI 344

Mycobacterial porins modified with Urokinase Cleavage Sequence make a potent, highly selective anticancer drug

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In the fight against cancer, researchers are always trying to discover agents that will distinguish between cancer cells and normal cells and are also very cytotoxic to the cancer cells. MspA, a porin isolated from Mycobacterium Smegmatis, shows promise on both fronts. In tests on the mammary cancer cell line, MDA 231, and Mat B III cells, MspA and various mutants show 100% cytotoxicity at nanomolar concentrations, thousands of times less than other cancer treatments. MspA has been modified with an attached peptide, which prevents its cytotoxicity. The peptide has a urokinase cleavage sequence embedded in it. Almost all solid tumors have elevated urokinase activity, which removes the peptide and activates the MspA's cytotoxicity. This renders MspA a highly selective anticancer agent.

MEDI 345

Antitumor celecoxib analogs that do not inhibit cyclooxygenase-2

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The initial development of celecoxib (Celebrex) as a selective inhibitor of cyclooxygenase-2 (COX-2) led to its clinical use as an anti-inflammatory agent for the treatment of various forms of arthritis and the management of acute or chronic pain. Subsequently, it was also discovered to be an effective antitumor agent and has been approved for the prevention of colon cancer in patients with familial adenomatous polyposis (FAP), while it is still been investigated for its chemotherapeutic potential in the therapy of several types of cancer. Recently, however, it has been shown that the ability of celecoxib to suppress tumor growth may be independent of any involvement of COX-2, and a number of alternative mechanisms for its antitumor properties have been investigated. Herein, we will present our own investigations of certain celecoxib analogs that retain and enhance its anticancer actions but do not inhibit COX-2. Studies on the development of new analogs and their possible mode of action will be described.

MEDI 346

Design, synthesis, and antidiarrheal properties of highly potent nonabsorbable multivalent CFTR inhibitors

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Secretory diarrhea, such as Cholera and Traveler's diarrhea, involves an increase in cyclic nucleotide levels in intestinal epithelium that leads to activation of CFTR chloride channels and fluid secretion. This provides rational basis for development of CFTR inhibitors for the treatment of secretory diarrhea. We synthesized non absorbable, externally acting, multivalent CFTR inhibitors by conjugation of malonic acid dihydrazide CFTR pore blocker (Sonawane et al. FASEB J. 2006, 20:130) via bifunctional crosslinker to PAMAM dendrimers and aminodextrans. In fluorescence cell-based assay, these conjugates showed dose dependant inhibition of CFTR mediated iodide influx. In short circuit current-electrophysiology experiments, these conjugates fully blocked forskolin induced CFTR chloride current with nanomolar potencies when added to the apical cell surface. Some of these conjugates at higher concentration also showed inhibition of calcium-activated chloride channels current (CaCC chloride current, in human epithelial cells) following stimulation by carbachol and ATP. These multivalent inhibitors exhibited excellent antidiarrheal efficacy in mouse models of cholera. Non absorbable, multivalent CFTR inhibitor-macromolecule conjugates may be may be useful as primary antisecretory therapy for a variety of secretory diarrheas. Nitin.Sonawane@ucsf.edu

MEDI 347

Effect of rhein on MDA-MB-435s breast cancer cells under hypoxic conditions

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Hypoxia-inducible factor-1 (a dimer of HIF-1α and HIF-1β), the major transcriptional factor activated by hypoxia, increases the invasion capacity, angiogenesis, and proliferation of MDA-MB-435s breast cancer cells. We have examined the effects of inhibiting HIF-1α activity on *in vitro* angiogenesis and breast cancer cell growth using rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid). Rhein inhibited endothelial cell tube formation, MDA-MB-435s cell viability, cell invasion, and migration under *in vitro* normoxic and hypoxic conditions. The levels of vascular endothelial growth factor (VEGF) secreted by MDA-MB-435s cells in normoxic and $CoCl_2$ conditions were measured by use of enzyme linked immunosorbent assay (ELISA). Rhein significantly reduced VEGF levels in cell cultures. Cytoplasmic and nuclear extracts of control and rhein-treated MDA-MB-435s cells were analyzed using western blot and ELISA, to determine the levels of HIF-1α and nuclear factor-κB. Our results show that rhein impaired *in vitro* invasive breast cancer cell angiogenesis and proliferation.