



Division of Medicinal Chemistry
Scientific Abstracts
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The Division of Medicinal Chemistry
San Francisco Program at a Glance

MEDI: Division of Medicinal Chemistry	Sun	Mon	Tue	Wed	Thu
ACS-AFMC Joint Symposium		A			
An Update on Modulating Beta-Amyloid Production as a Method to Treat Alzheimer's Disease		A			
Beyond Amides: The Next Generation of Peptide Therapeutics				A	
Design of Multi-targeted Ligands for the Treatment of Complex Diseases				A	
Direct Approaches for Identifying all of the Cellular Targets of Small Molecule Drugs, and Mapping their Binding Cavities		P			
First Time Disclosures	P				
General Oral Session	A		P		D
General Poster Session	E			E	
Lean Thinking and Six Sigma: How Has It Affected Drug Discovery?		P			
MEDI Awards Symposium**			P		
Medicinal Chemistry in Rare, Orphan and Neglected Diseases	A				
Mimicking the Effects of Bariatric Surgery for Type 2 Diabetes			P		
NPC1L1 and Second Generation Cholesterol Absorption Inhibitors		A			
Sci-Mix		E			
Selective CCK Receptor Modulators					A
Selective Targeting of Thyroid Hormone Action for Novel Metabolic Disease Therapeutics			A		
Synthesis of Prodrugs: Strategies to Improve Drugability				P	
Update on Nuclear Hormone Receptor Based Drug Approaches: A Tribute to Ron Magolda				P	
Co-sponsored Symposia: Selecting a co-sponsored symposia will take you outside of the current Committee, Secretariat or Division					
Fragment Based Drug Design: Success Stories due to Novel Computational Methods Applications*(CINF)				D	
New Drug Targets*(BIOL)			A		
Undergraduate Research Poster Session*(CHED)		P			

Legend

A = AM; **P** = PM; **D** = AM/PM; **E** = EVE;

AE = AM/EVE; **DE** = AM/PM/EVE; **PE** = PM/EVE;

*Cosponsored symposium with primary organizer shown in parenthesis; located with primary organizer.

**Primary organizer of cosponsored symposium.

+Probationary division.

MEDI 1

Review of rare diseases research and orphan products development activities

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The need and opportunity for Therapeutics for Rare and Neglected Diseases (TRND) are enormous. A new congressionally mandated TRND program is in place at the NIH to encourage and speed the development of new drugs for rare and neglected diseases. A rare disease is defined as a condition affecting fewer than 200,000 people; neglected are diseases lacking substantial therapeutic development activity. Many genetic diseases are both rare and neglected, there are more than 6,000 rare and neglected diseases affecting over 25 million Americans. The TRND program will focus on the preclinical stages of drug development that currently separate basic research from human testing of new drugs. TRND is a collaborative program developed by the NIH Chemical Genomics Center of the NHGRI and the Office of Rare Diseases Research.

MEDI 2

Medicinal chemistry annotation of leads in rare, orphan and neglected diseases

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Hits or Leads in Rare, Orphan & Neglected Diseases can arise from phenotypic or mechanistic screening against commercially available screening libraries. Often the screening efforts arise in an academic setting. Because of the disconnect between academic biology and expert medicinal chemistry it is essential to carry out a medicinal chemistry annotation of putative hits or leads before expenditure of significant drug discovery effort. The early stages of the annotation process can be done using known filters and guidelines for acceptable chemistry functionality. A more detailed analysis asking questions about the chemistry of the hit or lead, and what is known biologically and chemically about substructures and similar compounds to the hit or lead currently requires a medicinal chemistry expert and takes on average about 20 minutes per compound. The in depth data available through CAS SciFinder was used in the annotation of 64 putative tools and probes from the NIH Roadmap MLSCN effort. Progress being made towards public sector tools for chemistry annotation might allow for a more affordable and accessible process in the future.

MEDI 3

mGluR5 Antagonists as potential symptomatic therapy for Fragile X Disorder

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Fragile X Syndrome (FXS) is caused by a single gene defect resulting in the loss of FMRP (fragile X mental retardation protein). FMRP acts as a translational repressor of proteins synthesis involved in neurotransmitter-mediated synaptic maturation and plasticity. Functionally, the lack of FMRP in mice results in enhanced mGluR5-mediated long-term depression in the hippocampus. mGluR5 antagonists are expected to counteract this deficit and thus may offer an improved symptomatic treatment of FXS. We will present the identification, the characterization and the development of mGluR5 antagonists for the treatment of Fragile X.

MEDI 4

Discovery of Ataluren: A novel chemical entity that targets genetic disorders caused by nonsense mutations

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Ataluren (PTC124) is an orally delivered, small molecule that promotes ribosomal read-through of premature stop codons in mRNA. In patients with Duchenne muscular dystrophy due to a nonsense mutation, Ataluren may overcome the basic cause of the disease. Ataluren was identified through a high-throughput screening program to identify molecules with the ability to allow ribosomes to selectively read-through nonsense mutations in mRNA, allowing production of full-length functional protein. Chemical optimization of the hits in the HTS screen was performed to identify compounds with high potency in the read-through assay. These compounds were further optimized for pharmaceutical properties, in vivo activity, and toxicological profile and Ataluren was identified. Preclinical testing in the mdx mouse has documented that Ataluren induces production of full length functional dystrophin protein in muscle, decreasing eccentric contraction injury and reducing muscle derived creatine kinase (CK) in the serum. A Phase 2a study enrolled 38 boys with Duchenne/Becker muscular dystrophy (DMD/BMD) to receive 28 days of Ataluren treatment. The study demonstrated Ataluren related increases in in vitro and in vivo dystrophin expression and statistically significant reductions in serum concentrations of muscle derived CK. Ataluren is currently under investigation in pivotal clinical trials for DMD and Cystic Fibrosis.

MEDI 5

Phenotypic screening and medicinal chemistry: Potent quinoline-based antibacterials effective against replicating, nonreplicating persistent and drug-resistant *Mycobacterium tuberculosis*

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Tuberculosis (TB) remains as a global pandemic that is aggravated by a lack of health care, the spread of HIV, and the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains. TB is caused mainly by *Mycobacterium tuberculosis* (*Mtb*), which is considered to be one of the most successful pathogens known to mankind, infecting one-third of the world's population. New anti-TB drugs are urgently required to shorten the long 6–12 month treatment regimen and to battle drug-resistant *Mtb* strains. In addition, since TB is a common HIV co-infection, anti-TB drugs that are compatible with the current AIDS/HIV retrovirals are needed. In this study, we identified several potent quinoline-based anti-TB agents, bearing an isoxazole containing side-chain. The most potent compounds exhibited submicromolar activity against the replicating bacillus (R-TB), with minimum inhibitory concentrations (MICs) of 0.77 and 0.9 μM , respectively. In general, these compounds also had low micromolar activity against the non-replicating persistent bacteria (NRP-TB) and did not show toxicity on Vero cells up to 128 μM concentration. These compounds were shown to retain their anti-TB activity against rifampin, isoniazid and streptomycin resistant *Mtb* strains. Details of this work and related studies directed toward finding improved anti-TB drugs will be presented.

MEDI 6

BMP type 1 receptor inhibition for the treatment of fibrodysplasia ossificans progressiva (FOP)

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A general description of bone morphogenetic protein (BMP) cell signaling would be presented. Next, structure-activity relationship studies of compounds that inhibit SMAD phosphorylation by BMP type 1 receptor kinases ALK2, 3, and 6 would be presented. In addition to potency, optimization of selectivity, metabolic stability and oral bioavailability would also be addressed. Efficacy of optimized compounds in a newly developed animal model of FOP would be described. Finally, the potential utility of BMP signaling inhibitors in other non-rare disease indications, such as anemia of chronic disease, would be highlighted.

MEDI 7

Development of novel small molecule analogs as SMN2 promoter activators for the potential treatment of spinal muscular atrophy

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Spinal Muscular Atrophy (SMA) is an inherited neuromuscular disorder caused by deletion of the telomeric copy of the survival motor neuron (SMN1) gene with loss of SMN protein. SMN2, the centromeric copy, which differs from SMN1 by a translationally silent single nucleotide mutation (C->T), leads to mis-splicing of the SMN2 mRNA and consequently mostly truncated SMN protein is produced, although some full-length protein is produced as well. Increasing the activity of the SMN2 gene, by producing additional full-length SMN protein, provides a promising strategy for the treatment of SMA. Utilizing a cell-based SMN2 promoter assay, a series of 5-substituted 2,4-diaminoquinazoline analogs were identified as druggable chemotypes. deCODE's medicinal chemistry team has utilized ligand-based design strategy, in-vitro ADMET assays focused on identifying and overcoming potential barriers to development. This approach led to identification of a series of nM potent, metabolically stable compounds. Several of these analogs possess desirable pharmaceutical and pharmacokinetic properties providing oral bioavailability and significant brain penetration. Recently, utilizing ¹²⁵I-labeled potent C5-quinazoline derivative, screening of protein microarray resulted in the identification of mRNA decapping scavenger enzyme (DcsP) as the molecular target for this series of analogs. X-ray crystal structures of several Ligand-Dcsp complexes have also generated. During this presentation, a brief background of the SMA, highlights of the medicinal chemistry effort towards lead optimization, improving ADMET, pharmacokinetic properties, identification of the DcsP molecular target and selected cocrystal structures of key quinazoline analogs, and preliminary in-vivo data will be presented.

MEDI 8

OSI-906, a selective, orally available dual inhibitor of IGF-1R and IR currently undergoing clinical testing in a phase III clinical trial in ACC patients

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Adrenocortical carcinoma (ACC) is a rare and aggressive cancer of the adrenal glands. Mitotane is the only approved drug for ACC, however, its efficacy is limited (5-30% response rates) and it causes significant neurological, gastrointestinal and endocrinological toxicities, highlighting the need for safer and more effective therapies. The insulin-like growth factor receptor (IGF-1R) is a receptor tyrosine kinase implicated as a key driver of tumor growth and survival in several hematologic and solid cancers, including ACC. Over 90% of ACC tumors overexpress IGF-2, an activating ligand for both IGF-1R and IR. Our drug

discovery efforts, including structure-based design and empirical medicinal chemistry efforts have resulted in the discovery of OSI-906, a potent, selective and orally available inhibitor of both IGF-1R and IR. In addition to its activity in preclinical models, OSI-906 has recently shown preliminary activity in ACC patients and is currently in a Phase III clinical trial in ACC.

MEDI 9

Development of procaspase activating compounds as potential personalized anticancer Drugs: Structure-activity relationship of PAC-1, and its cellular localization with caspase-3

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Evasion of apoptosis is a hallmark of cancer. The resistance to natural apoptotic signals is often due to the aberrant expression and mutation of upstream apoptotic proteins that prevent activation of procaspase-3 and initiation of apoptosis. Surprisingly, procaspase-3 is upregulated in many cancers. A personalized anticancer strategy might involve the direct activation of this proapoptotic protein downstream of any roadblocks in the cascade. We have reported PAC-1 as a small molecule that directly activates procaspase-3 to caspase-3 *in vitro* and induces apoptosis in cancer cell lines. PAC-1 has also shown efficacy in multiple mouse models of cancers. Recent experiments in our laboratory have found that PAC-1 activates procaspase-3 by sequestering inhibitory Zn²⁺. In this paper we report 1) the design and synthesis of 25 PAC-1 derivatives for structure-activity relationship studies; 2) the “click” of Alexa Fluor 350 to PAC-1 for investigating the subcellular localization of PAC-1 in cancer cells by confocal microscopy; 3) the modification of the chemical structure of PAC-1 to avoid blood-brain barrier permeability. Currently, we are assessing a PAC-1 derivative in a clinical trial of dogs with spontaneous lymphoma. The success of the experiments proposed herein will lead to more potent anticancer agents, and validate direct activation of procaspase-3 to caspase-3 as an effective personalized anticancer strategy.

MEDI 10

Progesterone receptor partial agonists: A novel approach for the treatment of endometriosis

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The progesterone receptor (PR) regulates proliferation of endometrial tissue through opposition of estrogen in the uterus and is therapeutic target for endometriosis. Progestins are effective in treating endometriosis but have numerous side effects such as weight gain and breakthrough bleeding that are associated with their full agonist activity and poor steroidal selectivity. A selective PR partial agonist that can suppress the action of estrogen in the uterus may be void of these side-effects and offer value as a treatment for endometriosis. Multiple classes of PR ligands including pyrrolidine amides, carbamates, sulfonamides, and pyrrolidinones, all derived from the pyrrolidine-based series, were identified as potent and selective PR partial agonists. These ligands had improved steroidal selectivity, hERG channel blocking, and PK profiles compared to the pyrrolidine series. In addition, several pyrrolidinones demonstrated potent *in vivo* activity in the rat OVX model. This presentation will describe optimization of these different series of compounds.

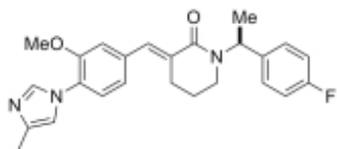
MEDI 11

Novel iminohydantoins as γ -Secretase modulators for the treatment of Alzheimer's disease

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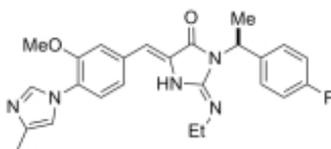
While the true cause of Alzheimer's disease is not known, it has been hypothesized that formation of amyloid plaques is key to the development and progression of the disease. Essential components of the amyloid plaques are the A β peptides, which are formed by γ -secretase and range in length from 37-42 amino acids. A β_{42} fragments are more prone to forming plaques, and therefore are considered to be more toxic and likely to cause Alzheimer's disease. γ -Secretase modulators shift the cleavage site to form shorter A β peptides, without inhibiting the enzyme. As a result, γ -secretase modulators hold the promise of treating Alzheimer's disease, while avoiding the Notch toxicity associated with γ -secretase inhibitors. A novel series of iminohydantoin γ -secretase modulators, incorporating pharmacophoric elements found in E-2012, were developed as potential treatments for Alzheimer's disease. The *in vitro* and *in vivo* γ -secretase

modulating profiles of these monocyclic and bicyclic iminohydantoins will be presented.



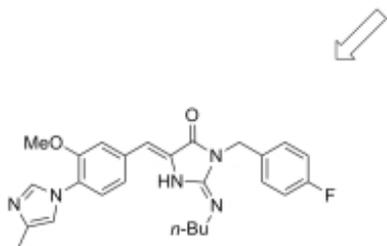
E-2012

$A\beta_{42} IC_{50} = 64 \text{ nM}$
 $A\beta_{Total} IC_{50} / A\beta_{42} IC_{50} = 226$



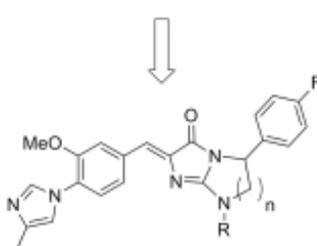
1

$A\beta_{42} IC_{50} = 158 \text{ nM}$
 $A\beta_{Total} IC_{50} / A\beta_{42} IC_{50} = 130$



2

$A\beta_{42} IC_{50} = 85 \text{ nM}$
 $A\beta_{Total} IC_{50} / A\beta_{42} IC_{50} = 70$



3

$n = 1, 2, 3$
 $R = \text{H, alkyl}$

MEDI 12

Discovery of indole and azaindole-7-carboxamides as potent and orally bioavailable HIV attachment inhibitors

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The process of HIV-1 entry into host cells begins with the attachment of the viral envelope glycoprotein gp120 to the host cell receptor CD4. This essential step can be inhibited by a class of indole or azaindole-oxoacetic piperazinyl benzamides. Clinical proof-of-concept for this inhibition mechanism was achieved with the azaindole BMS-488043. As part of the SAR development for this class of HIV-1 inhibitors, substitution at the C7 position of the early indole-based lead, 4-fluoroindole BMS-705, with amide moieties was explored. Inhibitors incorporating heteroaryl carboxamides at C-7 exhibited pM potency in a primary cell-based assay using pseudotyped virus expressing the JRFL-envelope. However, a simple methyl amide analog provided more favorable HLM stability and permeability which translated into improved animal pharmacokinetic properties compared to the early azaindole clinical candidate, BMS-378806. Substantial

improvement in the antiviral activity of the methyl amide against viruses in cell culture was achieved in a 4-methoxy-6-azaindole analog which possessed overall *in vitro* and *in vivo* profiles that compared favorably to BMS-488043. In this presentation, various aspects of the SAR of the C7 amide series leading to the improved analogs, as well as *in vitro* profiles and animal pharmacokinetic properties of key compounds will be described.

MEDI 13

Identification of novel potent Opioid inverse agonists

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Beginning in the early 1970s with the observation that systemic administration of the opioid antagonist, naloxone, significantly reduced food intake, the role for the endogenous opioid system in the modulation of ingestive behavior has been studied. Antagonists of the opioid receptors have been shown to reduce body weight in obese rats. In recent years a number of opioid antagonists have been disclosed in literature, but the search continues for more effective agents having an overall benefit to the patient with little or no major side effects. We have developed a new series of potent opioid inverse agonists that are efficacious in rodent models of obesity. The structure activity relationships and drug discovery process that led to the selection of a clinical compound will be discussed.

MEDI 14

Synthesis and SAR of 2-pyridinylbenzimidazoles as human histamine H4 antagonists

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A series of 2-phenylbenzimidazoles were evaluated as human histamine H4 receptor ligands following an initial hit from a high throughput screening campaign. During the course of this investigation, the optimal placement of the key distal piperazine nitrogen from the central phenyl ring was elucidated. Further analysis determined analogues with a distal piperazinyl ring behaved as functional agonists whereas deletion of the internal nitrogen to give a piperidine afforded functional antagonists at the H₄ receptor. While this series was promising, certain analogues demonstrated strong affinity for the hERG channel and undesirable PK properties. It was hypothesized that a reduction in overall lipophilicity may reduce these liabilities. Therefore, a series of 2-pyridylbenzimidazoles was investigated. Optimization of this series led to the discovery of a potent antagonist which demonstrated reduced affinity for the

hERG channel and *in-vivo* efficacy in several models of inflammation after oral administration in rodents. The synthesis, SAR, and corresponding functional activities of the 2-pyridylbenzimidazoles will be presented.

MEDI 15

Identification of the 3,3-diarylpropionamide structural motif as a minimal pharmacophore for glucocorticoid receptor modulation

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There is intense interest in the identification of glucocorticoid receptor (GR) ligands which modulate the activity of the receptor in a pathway-selective manner, ultimately maintaining the anti-inflammatory and immunosuppressive activity of steroidal glucocorticoids while minimizing the extent of side effects associated with their chronic administration. A series of dihydro-9,10-ethanoanthracene carboxamides served as the starting point for our efforts to identify such modulators ("dissociated agonists"), leading to the identification of a 3,3-diarylpropionamide structural motif as a minimal, highly tractable GR pharmacophore. Ligands in this class which demonstrate a favorable pharmacology in rodent models will be described.

MEDI 16

Oral GSK-3 inhibitors for the treatment of neurodegenerative diseases

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This presentation will outline the discovery, using structure based drug design, of potent and selective GSK-3 inhibitors that only modulate a subset of the enzyme's effects with favorable consequences for safety. These compounds preferentially inhibit GSK-3 tyrosine autophosphorylation (pTYR) over GSK-3 Ser/Thr kinase activity against substrates such as β -catenin. The inhibition of GSK-3 p-Tyr results in partial inhibition of enzymatic activity (~90%) resulting in selective downstream effects. Using E16 hippocampal neurons cultured *in vitro*, we demonstrate that inhibition of GSK-3 at levels that selectively affect TYR residue autophosphorylation, results in increased branching of both axons and dendrites and a reduction in the levels of phospho-CRMP-2. These findings suggest that such inhibitors may provide benefit in neuroregeneration following injury. Having demonstrated that partial inhibition of GSK-3 at p-TYR

concentrations correlates with mechanisms that are beneficial to neurorepair, we examine the effects of our inhibitors in an MCAO model of stroke.

MEDI 17

Studies directed toward identification of second generation HCV candidate: Investigation of novel P₃ cyclic sulfone caps

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HCV infections are the primary causes for hepatocellular carcinoma and liver transplantations. The slow progression of the disease and lack of visible symptoms make hepatitis C a silent epidemic. Even though newer blood screening techniques have greatly reduced infection rates, ~; 3% of the world population have been infected with HCV and urgently need effective treatments. Peginterferon in combination with ribavirin is the current standard of care which is effective in ~; 40% of patients infected with genotype-1 infections. Development of new drug candidates have been focused on inhibition of vital enzymes involved in life cycle of HCV replication. NS3, a serine protease is a pivotal enzyme involved in the development of mature HCV virions. The virus on internalization into the hepatocytes codes for a single polyprotein of ~; 3000 amino acids which is post translationally modified with the help of NS3 protease. It catalyzes the cleavage of downstream proteins at NS3-NS4A, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions to produce mature protein. Inhibition of this vital enzyme has demonstrated potent antiviral activity in humans. Many novel candidates targeting this enzyme are currently undergoing clinical trials. We recently disclosed the identification and development of boceprevir, a ketoamide compound that is currently undergoing phase III clinical studies. Towards the identification of a potential second generation candidate for clinical development we investigated various modifications for Boceprevir. One of the series we investigated extensively was the cyclic sulfone derivatives which resulted in compounds with improved cellular potency and PK compared to our first generation compound. In this presentation we would like to discuss the identification and SAR of cyclic sulfones towards the goal of identifying a second generation HCV protease inhibitor.

MEDI 18

Discovery of a novel and selective phosphodiesterase 9 inhibitor with excellent brain penetration for the treatment of Alzheimer's disease

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Phosphodiesterase 9 (PDE9), a cyclic guanosine monophosphate (cGMP) specific phosphodiesterase, has extensive distribution in rodent and human brain. We have shown that selective, brain penetrant inhibitors of PDE9 are able to enhance cognition in rodent models, suggestive of potential efficacy in treating Alzheimer's disease. Medicinal chemistry efforts afforded an initial clinical candidate (PF-04447943) with low human dose and clearance projections. The main focus of the talk will be on efforts to identify a structurally diverse back-up compound with excellent physicochemical and brain penetration properties. Key themes of structure-based drug design, innovative applications of parallel chemistry to rapidly drive SAR, and utilization of design concepts focused in CNS drug properties will be discussed.

MEDI 19

Fragment-based design of orally bioavailable CDK inhibitors

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Astex has previously described the discovery of AT7519 a novel, efficacious cyclin dependent kinase (CDK) inhibitor suitable for intravenous dosing, which was identified via fragment screening and subsequent structure-based drug design[1]. Here we will briefly outline Astex's approach to fragment-based drug discovery, then describe the medicinal chemistry strategies we used for developing compounds with suitable properties for oral dosing. This program ultimately led to the discovery of AT9311, the structure of which we will disclose for the first time. AT9311 possesses a differentiated kinase inhibitory profile with respect to AT7519, has good pharmacokinetic properties and efficacy in a mouse tumour model when dosed orally.

[1] *J. Med. Chem.*; **2008**, *51*, **4986-4999**

MEDI 20

Discovery of selective Nav1.8 modulators for the treatment of chronic mixed pain

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My presentation will discuss the role of voltage-gated sodium channels (NaVs) in pain signalling and the development of selective NaV1.8 modulators. In particular, I will focus on the origin of the Pfizer series and how a non-selective 3-phenylpyridine lead was optimised into two series of highly selective NaV1.8 modulators. Both series have good rat and dog oral pharmacokinetics, predicting for once-daily dosing in man. Two candidates have been nominated and they work well in pain *in vivo* models at free concentrations below 50nM. Unfortunately, during toxicity assessment both candidates displayed some unexpected findings and further work is underway to identify compounds with a cleaner toxicological profile.

MEDI 21

Discovery of a new thyroid hormone receptor-coactivator antagonist by using qHTS

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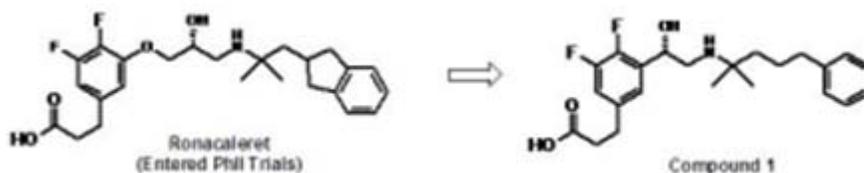
Thyroid hormone receptors (TR) are ligand-dependent transcription factors regulating development, growth, and metabolism of target genes. In the absence of thyroid hormone, TR/RXR hetero dimer is associated with corepressor protein and suppresses basal transcription. Upon binding of thyroid hormone, TR undergoes a conformational change, releasing corepressor proteins and recruits coactivator for gene transcription. The coactivator have highly conserved LXXLL motifs; termed NR-boxes, in their nuclear receptor interacting domain (NID). We have reported that short peptidomimics consisting of the LXXLL motif and used these coactivator peptide fluorescently labeled for discovery of small molecule inhibiting the interaction between TR β and coactivator by using high throughput method. Here we report the result of a quantitative high throughput screening for new antagonist of TR β -coactivator interaction. One class of inhibitors indentified in this screen was nitro sulfonylbenzoate. These compounds were validated by the secondary assay such as reporter gene assay and alpha screen assay. The mechanism study revealed that the compound can covalently modify a cystein residue in the binding pocket through aromatic nucleophilic substitution reaction. The compound also showed inhibition of thyroid hormone signaling in the cellular system.

MEDI 22

Discovery of novel aminoalcohol antagonist of calcium sensing receptor

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The calcium sensing receptor (CaR), located in the parathyroid gland, functions as the principle regulator of parathyroid hormone (PTH) secretion. Increased levels of endogenous PTH levels are implicated in formation of new bone. PTH, either in its truncated form ([1-34], Forteo[®]) or as full length ([1-84], Preos[®]), has been clinically validated as a bone forming agent, and both peptides are used to treat osteoporosis. However, both forms require *daily* subcutaneous injection. An alternative approach would be an orally bioavailable small molecule antagonist of the calcium-sensing receptor (CaR) which would be expected to stimulate secretion of endogenous PTH as a potential treatment for osteoporosis.



Ronacaleret, a aminoalcohol based lead analog recently reached PhII trials. Analysis of the PhI data of Ronacaleret revealed that the profile of the biomarkers is indicative of bone growth and are comparable to Forteo. However, high-dose administration of Ronacaleret was required. A back up program was initiated to improve oral efficacy of second generation analogs of Ronacaleret. These efforts resulted in identification of "truncated linker" containing analogs. The synthesis and SAR of this series of compounds, culminating in the identification of (1), will be presented.

MEDI 23

Discovery of a novel series of [3.2.1]azabicyclic pyridazinones as α 6 nicotinic acetylcholine receptor (nAChR) agonists with robust activities in antipsychotic models

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α 6-containing nAChRs are preferentially expressed in catecholaminergic neurons of the central nervous system (CNS) and regulate dopamine (DA) and norepinephrine (NE) release in several brain regions. There is a growing interest in these receptors as a potential drug target for neurological disorders involving dopamine signaling, such as Parkinson's Disease, addiction and schizophrenia. Here we report a novel series of [3.2.1]azabicyclic pyridazinones as dual α 6* β 4 / α 3 β 4 nAChRs agonists with high in vitro potencies, functional selectivities over other nAChR subtypes and excellent pharmacokinetic properties. The lead compounds demonstrated robust efficacies in mouse spontaneous and methamphetamine-stimulated locomotor, prepulse inhibition (PPI), mescaline-induced scratching (MIS), and conditioned avoidance responding (CAR) assays, similar to that of clinically effective antipsychotic agents. The design, synthesis and SAR development of the [3.2.1]azabicyclic pyridazinones and related series as well as their in vivo profiles will be discussed in detail in this presentation.

MEDI 24

First synthetic agonists of FFA2: Discovery and SAR of phenylacetamides as allosteric modulators

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Free fatty acid receptor 2 (FFA2) is a G-protein coupled receptor for which only short chain fatty acids (SCFAs) have been reported as endogenous ligands. We describe the discovery and optimization of phenylacetamides as allosteric agonists of FFA2. These novel ligands can suppress adipocyte lipolysis *in vitro* and reduce plasma FFA levels *in vivo*, suggesting that these allosteric modulators can serve as pharmacological tools for exploring the potential function of FFA2 in various disease conditions.

MEDI 25

Identification of quinolizidinone carboxylic acids as CNS penetrant, selective M1 allosteric receptor modulators

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Identification of new mechanisms to treat the complex neurodegenerative effects of Alzheimer's disease (AD) represents a major unmet medical need. One avenue to ameliorate the cognitive decline in AD has been to target the neurons

of the basal forebrain cholinergic system via activation of the M₁ muscarinic receptor. A number of non-selective M₁ muscarinic agonists have previously shown positive effects on cognitive behaviors in AD patients, but were limited due to cholinergic adverse events thought to be mediated by activation of other muscarinic receptors. One approach to confer selectivity for M₁ over the M₂ to M₅ sub-types is the identification of positive allosteric modulators of the M₁ muscarinic receptor, which would target an allosteric site on the M₁ receptor rather than the highly conserved orthosteric acetylcholine binding site. We have previously reported the quinolone carboxylic acid BQCA as a highly selective M₁ positive allosteric modulator with good pharmacokinetic and in vivo properties. This presentation will focus on the identification of novel quinolizidinone carboxylic acid scaffolds via replacement of the quinolone ring system, leading to M₁ allosteric modulators with higher plasma free fraction, enhanced CNS exposure, and improved efficacy in a rodent in vivo model of cognition.

MEDI 26

Design, synthesis, structure-activity relationships, and biological evaluation of AMPA positive allosteric modulators (PAMs)

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AMPA positive allosteric modulators (PAMs) are compounds that potentiate the action of glutamate on AMPA receptors by slowing the rate of receptor deactivation and/or desensitization. Numerous *in vitro* and *in vivo* studies have demonstrated the ability of AMPA PAMs to enhance long-term potentiation and, as such, are hypothesized to exert positive effects on memory in elderly and schizophrenic patients. Accordingly, we are seeking novel AMPA PAMs for the treatment of the cognitive deficits associated with schizophrenia. Initial efforts were focused on developing proprietary series with potent functional activity through exploration of HTS hits, as well as literature agents such as LY451646 and GSK. Our team has identified a number novel series of AMPA PAMs with suitable PK, ADME, and safety profiles. Several of these PAMs have shown very promising functional activity and display excellent ADME properties. The design, synthesis, *in vitro* binding and functional activity, as well as ADME properties will be presented.

MEDI 27

Discovery of AP24534, a pan-inhibitor of BCR-ABL including the T315I gatekeeper mutation for Chronic Myeloid Leukemia

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Resistance to the BCR-ABL kinase inhibitor imatinib in patients with chronic myeloid leukemia (CML) is associated with emergence of BCR-ABL point mutations that preclude effective drug binding. Although most mutants are effectively inhibited with the second generation compounds dasatinib and nilotinib, neither compound inhibits T315I which represents 15-20% of all clinically observed mutants. Through our program of structure-guided design, we have identified AP24534, a potent orally available multi-targeted kinase inhibitor active against the T315I gatekeeper mutation and other BCR-ABL mutants. The structure-activity-relationship (SAR) evolution and insight provided by key X-ray co-structures leading to the identification of AP24534 will be detailed in addition to a summary of supporting in vitro, in vivo, and ADME data. AP24534 is currently in a Phase I clinical trial in patients with refractory or resistant CML and other hematological malignancies.

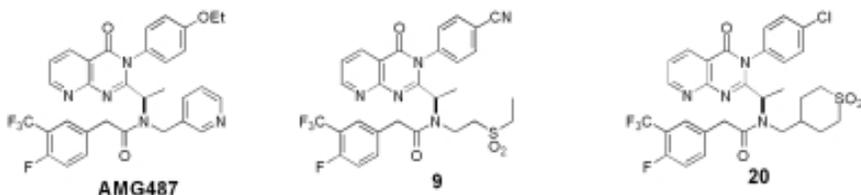
MEDI 28

Discovery and characterization of potent and bioavailable CXCR3 antagonist

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AMG 487 is a potent, selective, and orally bioavailable CXCR3 antagonist. However, in a multiple ascending dose Phase 1 clinical study, unexpected dose- and time-dependent changes in pharmacokinetic behavior were observed that

suggested a potential for time-dependent inhibition (TDI) of CYPs responsible for AMG 487 clearance. Subsequent medicinal chemistry effort was carried out to identify analog **9** with CN substitution to replace OEt group was synthesized. This compound binds CXCR3 with high affinity, IC₅₀ of [125I]-IP-10 in buffer and [125I]-IP-10 in the presence of human serum are 10 nM and 18 nM respectively. Unfortunately, compound **9** showed positive chromosomal aberration. Further SAR studies identified analog **20** which inhibits [125I]-IP-10 binding to CXCR3 with an IC₅₀ of 12 nM in the presence of human serum. Compound **20** tested negative in the chromosomal aberration assay. Also, **20** exhibited moderate to high oral bioavailability (44-69%F) in mice, rats, and cynomolgus monkeys.



MEDI 29

Spirotetrahydro β -carbolines: A new class of potent and orally efficacious compounds for the treatment of malaria

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Malaria continues to be a significant global health problem with an estimated 247 million infections and nearly one million deaths in 2006 alone. In light of increasing resistance to many current antimalarials, and the growing concern over reduced effectiveness of artemisinin-combination therapies, there is an urgent need for new drug candidates for the treatment of malaria. The antimalarial activity of a series of spiro-tetrahydro- β -carbolines identified from a whole cell screen on *Plasmodium falciparum* is described. Structure activity relationships for the optimization of the lead compound including the identification of the active enantiomer and elimination of metabolic liabilities will be discussed. Improvement of the pharmacokinetic profile translated to exceptional oral efficacy in the *Plasmodium berghei* infected malaria mouse model where full cure was achieved with a single 100 mg/kg dose or three daily doses of 30 mg/kg.

MEDI 30

Discovery of potent nucleoside inhibitors of heat shock protein Grp78 (BiP)

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Hsp70, Hsc70 and Grp78 belong to the 70kDa Heat Shock family of molecular chaperones which are known to play a role in cancer development and progression. Hsp70 and Hsc70 are found in the cytosol, while Grp78 is in the endoplasmic reticulum. Over expression of Grp78 in multiple tumor types protects cells from a wide variety of chemotherapeutic drugs, making Grp78 an interesting target for cancer therapies. The synthesis of novel nucleoside inhibitors for Hsp70/Hsc70, guided by docking and crystallography, has been recently reported by Vernalis. X-ray crystal structures of submicromolar inhibitors revealed a network of pi-stacking interactions between the protein and ligand. We now report the identification of nucleoside inhibitors targeting the ATPase domain of Grp78. Binding has been characterized by surface plasmon resonance, isothermal titration calorimetry, and X-ray crystallography. Differences in the binding sites observed between the Hsp70 and Grp78 crystals will be discussed with regards to selectivity.

MEDI 31

Discovery and optimization of multiple scaffolds of selective S1P₁ receptor agonist

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Herein, we wish to describe hit to lead and lead optimization on two scaffolds derived from the natural monoterpene (+)-3-carene and 2-oxo-2H-chromene-3-carboxylic acid amide. The compounds from the latest series demonstrated excellent DMPK properties and good efficacy in relevant animal models such as Experimental Autoimmune Encephalomyelitis (EAE), a model for multiple sclerosis. In parallel to this scaffold optimization, we developed a common pharmacophore model defining the minimal structural requirements needed for design of potent and selective S1P₁ receptor agonist.

MEDI 32

Dihydropyrrolopyrimidines and related heterocycles as potent GPR119 agonists

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GPR119 is a recently discovered GPCR expressed in pancreatic beta-cells and intestinal L-cells. Activation of this receptor delivers significant glucose control via at least two mechanisms of action: incretin and GI hormone release, and nutrient-stimulated insulin secretion. In addition, some GPR119 agonists have been reported to inhibit gastric emptying, reduce food intake and promote weight loss. Taken together, it appears that agonists of GPR119 modulate the enteroinsular axis and improve glycemic control, and may have utility in the treatment of type 2 diabetes and possibly offer beneficial effects on body weight. We identified a novel class of compounds, dihydropyrrolopyrimidine derivatives, that was shown to be potent agonists of GPR119. The detailed actions of a representative of this class, GSK252A, have previously been reported. Herein, we describe the discovery and structure-activity relationships (SAR) of this class of compounds in addition to the SAR of some related, novel heterocycles.

MEDI 33

Discovery of a selective CSF-1R inhibitor

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Stimulation of the M-CSF/Colony-stimulating factor-1 Receptor (CSF-1R, a receptor tyrosine kinase) signaling pathway leads to differentiation, proliferation, migration and survival of macrophages and osteoclasts of monocytic lineage. Aberrant activation of osteoclast activity due to bone metastasis causes osteolysis leading to skeletal-related events and severe pain in cancer patients. Our research has focused on the discovery of highly selective inhibitors of CSF-1R kinase activity to suppress tumor-induced osteolysis consistent with the receptors essential role in osteoclastogenesis. Here we describe the discovery and characterization of a selective, orally bioavailable CSF-1R inhibitor.

MEDI 34

Identification of SAM-531 (WAY-262531), a selective 5-HT₆ antagonist for the treatment of cognitive dysfunction associated with schizophrenia and Alzheimer's disease

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The 5-HT₆ receptor is the most recent addition to the 14-member serotonin receptor family. Isolated in 1993 from rat striatal tissue, this G-protein coupled receptor (GPCR) is positively coupled to adenylate cyclase and is localized primarily in the central nervous system. Extensive investigation has shown that these receptors are expressed in brain regions known to be associated with anxiety and cognition. The wealth of possibilities for potential drug candidates in this area has created a considerable effort focused on the identification of novel selective compounds, both as agonists and antagonists. Through an extensive drug discovery program, we have identified a portfolio of ligands with potency at the 5-HT₆ receptor and efficacy in a number of preclinical models of cognitive dysfunction. Herein, we report the identification of the clinical development entity, SAM-531 (WAY-262531), a selective 5-HT₆ antagonist for the potential treatment of cognitive disorders associated with schizophrenia and Alzheimer's disease. The SAR that led to the identification of SAM-531 along with the preclinical and selected clinical data will be presented.

MEDI 35

Discovery of AZD2624: A potent and selective NK3 antagonist to test the NK3 hypothesis in schizophrenia

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There is a mixture of preclinical and clinical data supporting the hypothesis that NK3 antagonists could be useful for the treatment of schizophrenia. Two structurally diverse NK3 antagonists, Osanetant and Talnetant, have progressed to phase II clinical studies and have shown some positive results before being stopped. These results in particular have enticed many companies to develop their own NK3 antagonists, including our efforts, which are the subject of this presentation. After describing our progress leading to AZD2624 we will describe the structure, NK3r antagonist potency, selectivity, pharmacokinetic properties

and in vivo pharmacodynamic activity of this clinical compound. In addition, the clinical trial results relating to safety and efficacy from phase I & II studies with AZD2624 will be discussed. Finally, the interpretation of these results and how they impact the NK3 hypothesis will be discussed.

MEDI 36

Inhibition of sphingosine-1-phosphate lyase for the treatment of autoimmune disorders

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Research dedicated to the study of sphingosine signaling pathways in knockout (KO) mice led to the identification of Sphingosine-1-Phosphate Lyase (S1PL) as an important enzyme involved in the metabolism of bioactive lipids important to the regulation of the immune system. We will present the discovery of the small molecule compounds LX2931 and LX2932, inhibitors of S1PL in vivo, for the treatment of autoimmune disorders. This will be the initial disclosure of LX2931 and LX2932, the first clinically studied inhibitors of S1PL. We will demonstrate the correlation of biology and biomarkers observed in the KO mouse with the pharmacology observed in preclinical in vivo models of inflammation and rheumatoid arthritis. Ultimately, we will present how these observations extend to human data obtained in Phase I clinical trials and the design of Phase 2 studies now underway in patients with rheumatoid arthritis.

MEDI 37

Discovery of MK-4305: A novel orexin receptor antagonist for the treatment of insomnia

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Orexins are neuropeptides secreted by hypothalamic neurons that project into regions of the brain that modulate sleep and arousal. Two receptors respond to

orexin signaling, Orexin 1 Receptor (OX1R) and Orexin 2 Receptor (OX2R) with partially overlapping brain distributions. Genetic and pharmacological studies suggest orexin receptor antagonists could provide benefit for insomnia and other disorders in which sleep/wake cycles are disrupted. We have identified MK-4305 as a potent, dual orexin receptor antagonist with excellent brain penetration and robust in vivo activity. The development and optimization of lead compounds along with the profile of clinical candidate MK-4305 will be presented.

MEDI 38

Discovery of BMS-650032, an NS3 protease inhibitor for the treatment of Hepatitis C

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HCV NS3/4A protease is an essential enzyme for viral replication that has been validated as a target for anti-HCV therapy in clinical trials. This presentation will focus on our recent discovery efforts in the NS3 protease arena. Design and optimization of the acylsulfonamide motif, a critical BMS development that provides access to both potent and selective tripeptide inhibitors of NS3 protease, will be highlighted. Optimization of this series for potency, ADME properties and toxicology profile yielded our first clinical compound, BMS-605339. This compound demonstrated promising antiviral activity upon administration to HCV infected patients, but was discontinued due to adverse events. Subsequent discovery efforts culminated in the identification of BMS-650032, which transitioned to clinical development based on its favorable preclinical profile. Details as to program evolution, the discovery of BMS-650032 and its early clinical profile will be described.

MEDI 39

Discovery of a potent and selective S1P₁ receptor agonist for the treatment of rheumatoid arthritis

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Sphingosine 1-phosphate (S1P), an extracellular ligand at five cognate GPCRs (S1PRs) and a consequential intracellular lipid intermediate, affects diverse cellular processes including migration, growth and survival. S1P regulates function and trafficking of immune cells as well as survival and migration of cancer cells and has been implicated as an important mediator in pathogenesis of cancer, autoimmune and allergic diseases. Modulation of S1P/S1PR signaling axis has proven therapeutic potential as FTY720, a non-selective S1P receptor agonist, has been efficacious in preventing allograft rejection in renal transplant patients and in reducing disease burden in patients with relapsing-remitting multiple sclerosis (MS). While the function of each S1PR has not been definitively characterized it has been established that the S1P₁ receptor plays a critical role in T-cell regulation and trafficking. As such, developing orally active agents that act as S1P₁ receptor agonists has been an area of intense research activity. In this presentation, we will disclose some of our findings towards the development of a new potent and selective S1P₁ agonist for the treatment of autoimmune disorders. We will focus on key pre-clinical data that led to our compound selection as well as report early human clinical data.

MEDI 40

Testing the pharmacophore model for the system Xc- transporter: One less carbon

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We recently reported a common pharmacophore model for the system Xc- transporter, an obligate exchanger of glutamate and cystine, implicated in dysfunctions such as stroke, addiction and glioma. Our initial Structure activity relationship (SAR) studies indicate that lipophilic groups in the C-5 position of the isoxazole increase transporter binding at the expense of GluR2 receptor binding (i.e., the AMPA receptor). In addition to complementary sites for the alpha amino acid and gamma carboxylate or their functional equivalents, the pharmacophore model indicates the presence of a substantial lipophilic pocket. The developing SAR suggested that for the isoxazole series of analogs, a shorter linker between the carboxylates and lipophilic moiety could lead to enhanced activity. The target molecules designed considered both pi-pi and cation-pi stacking interactions, and

novel palladium catalyzed cross-coupling of the hetero benzylic halides was required. We will report on the scope and limitations of the palladation, which represents a facile solution to the synthetic challenge, and progress on the SAR for ligands at the System Xc- Transporter will be discussed.

MEDI 41

Iron porphyrin-loaded liposomes: Anticancer nano-drug delivery systems and their evaluation of anticancer properties

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Novel design of anticancer nano-drug delivery systems of iron porphyrin-loaded liposomes (FePor/Liposomes) and their evaluation of anticancer properties are reported. The FePor/Liposomes are composed of cationic iron porphyrin such as 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrinatoiron and negatively charged liposomes such as DPPC-PEG liposome and pH-sensitive liposome containing sodium oleate. A lack of cytotoxicity of the FePor/Liposome and an efficient generation of toxic hydroxy radical from superoxide anion radical through the iron-catalyzed dismutation and the Fenton reaction allow for targeted necrosis of tumor cells where the superoxide anion radical concentration is locally increased as a result of reduced activity of superoxide dismutase and catalase in the cells. Significant damage to such impregnated tumor cells due to FePor/Liposomes is observed in comparison with cisplatin and mitomycin c. Animal tests reveal that the FePor/Liposomes exert an effective antitumor activity to suppress tumor growth in mice in clear comparison with cisplatin and mitomycin c.

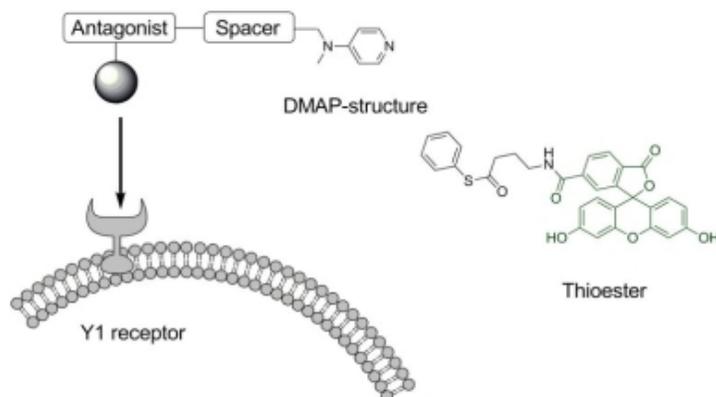
MEDI 42

Investigations on the catalytic staining of a G-protein coupled receptor

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Neuropeptide Y (NPY) is a highly conserved peptide that plays an important role as a neurotransmitter in the central and peripheral nervous system. In humans, four receptor subtypes, referred to as NPY Y1, Y2, Y4 and Y5 receptors, mediate the biological effects of NPY. Fluorescent probes for the NPY Y1 receptor (Y1R) are already available, but exhibit only a weak signal to noise ratio and bind reversibly to the receptor. All of these compounds are derivatives of the potent Y1R antagonist BIBP 3226. The catalytic staining of the G-protein coupled Y1R could enhance the fluorescence signal and still allows ligands to bind to the Y1R binding pocket. The catalytic staining is caused by the reaction of a ligand

tethered DMAP moiety and a reactive fluorescent acyl-derivative (thioester). The fluorescent moiety is then transferred to any nucleophile near the binding pocket.



MEDI 43

Exo-methylene γ -butyrolactone natural products: Can they be made into drugs?

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Exo-methylene- γ -butyrolactone natural products are abundant in nature that display broad biological profiles, among them high tumor activity. Despite their generally high cytotoxicity, these compounds are nevertheless considered to be unsuitable for drug development, due to their high but unspecific reactivity with biological nucleophiles. We present a strategy to combine the title compounds with carrier peptides that are able to selectively recognize specific cancer cells, followed by their internalization. Suitable modification of the potential drug molecules with an internal trigger finally allows their targeted release from the carrier. Thus, following our approach we believe that a large body of biologically highly potent, but greatly neglected natural products and analogs might become promising for drug development in medicinal chemistry.

MEDI 44

Enhanced mammalian cell adhesion and signaling induced by squaramides

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In this paper, we report an efficient synthesis of a new class squaramide based RGD mimics in two steps. Some of this library of RGD mimics are 5-fold more potent than natural RGD ligand at inhibiting mammalian cell adhesion in solution.

By immobilizing a squaramide ligand on a bio-inert surface that presents non-specific cell adhesion, we demonstrate that squaramide mediates mature mammalian cell adhesion. This work demonstrates that the high binding non-natural ligands drastically change the intracellular structures (the focal adhesion and stress fibers) of adhered mammalian cells. More importantly, we demonstrate that squaramide ligands induce more expression of proteins responsible for cell adhesion than natural linear RGD tripeptide. This suggests that the molecules aimed for treating the cell adhesion related diseases may be promoting the disease due to undesired cell signaling induced by the drugs. We believe that our work highlights the need for developing novel approaches to control cell adhesion.

MEDI 45

PET imaging of large molecule pharmacokinetics with Iodine-124

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With the growing number of large molecules and small molecule-carrying nanoconstructs entering preclinical and clinical studies, quantitative imaging of their pharmacokinetics (PK) is playing an increasingly important role. PET is a fully quantitative imaging modality most suitable for PK research in vivo. The intrinsically slow in vivo transfer of many large molecules requires labeling of the drug candidate with radionuclides that have long physical half-lives. Among all currently available positron emitters suitable for PET, ¹²⁴I has the longest physical half-life (4.2 d). The objective of this study was to determine whether ¹²⁴I, known as “non-pure” positron emitter, translate into data quality suitable for PK studies. Imaging was performed using MicroPET P4 (Siemens/Concorde Microsystems). Spatial resolution (full width at half maximum, FWHM) was studied using a line ¹²⁴I source (Ø=0.19 mm) in water. A 51x127 mm cylindrical phantom was used to evaluate the count-rate performance and coincidence detection. The transaxial and axial spatial resolutions in the center of the camera were satisfactory and higher for iterative image reconstruction protocols than for back projection (2.4 vs. 3.4 mm, and 3.1 vs. 3.6 mm, respectively). A good linearity of the positron count-rate was observed up to 1.2 mCi in the camera. Animal studies in rats and cynomolgus monkeys demonstrated excellent delineation and resolution of even small organs (e.g., single lymph nodes in rats, Ø<1 mm). The quality of numerical data was appropriate for PK analysis over at least 8 days. The results suggest that ¹²⁴I is an excellent label for quantitative investigation of slow as well as fast stages of the PK of large molecules and particles by PET.

MEDI 46

Neutron characterization of a sol-gel drug delivery system

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Here, we report the diffusive properties of model drugs within sol-gel drug delivery systems using a combination of quasi-elastic (QENS) and small-angle neutron scattering (SANS). The combination of SANS and QENS can potentially provide unheralded benefits in the characterization of both the structural and dynamic properties of drug delivery materials. Benzoic acid and Lovastatin were entrapped in a sol-gel matrix synthesized using diglyerosilane (DGS) as a bio-compatible sol-gel precursor. QENS analysis distinguished 3 dynamical components that could be related to the entrapped drug, glycerol that was released by hydrolysis DGS, and the solvent. By using SANS with contrast variation, it was possible to determine the effect of drug entrapment on the structural properties of the gels. This approach addresses a major scientific bottleneck in drug delivery research, namely the ability to characterize the distribution and diffusion of guest molecules in host carriers.

MEDI 47

Lilly PD² initiative: An invitation to open innovation in phenotypic drug discovery

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Lilly has established a panel of five phenotypic assay modules which represent therapeutic areas of long-term strategic interest such as oncology, neurological disorders, and metabolic diseases. ***Lilly now provides access to these assay modules to external investigators, at no cost to them, through the PD² website (pd2.lilly.com), Lilly's new collaborative initiative.*** Each assay module is composed of a phenotypic lead generation assay, followed by relevant biochemical and cellular follow-up assays, designed to define a compound's activity profile and early potential for further drug optimization. This presentation will present an overview of PD², the process by which institutions can become affiliated, a description of the phenotypic assay panel and accompanying secondary assays, and a summary of the results of a pilot project.

MEDI 48

Molecular dynamics simulations of lipid-based nanomedicines: Drug solubilization in PEGylated phospholipid nanocarriers

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Lipid-based nanosystems have a large potential for efficient and targeted delivery of anticancer drugs with limited water solubility and major side effects upon direct administration. Sterically stabilized phospholipid micelles (SSM), composed of PEGylated phospholipids, are particularly promising drug delivery nano-vehicles [1]. We model drug-loaded SSM nanomedicines by atomistic molecular dynamics simulations to predict the ability of SSM to carry and deliver anticancer drugs. We evaluate the Gibbs free energy profiles for typical anticancer drugs as a function of their distance from the micelle center. We show that SSM may accommodate drugs either at the periphery of the hydrophobic (alkane) and hydrophilic (PEGylated) regions or in a limited amount in the hydrophobic micelle core. Micelle loading capacities and drug retention times during nanomedicine circulation are predicted from the free energy profiles.

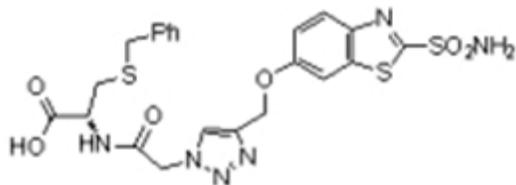
[1] A. Krishnadas, I. Rubinstein, H. Onyuksel, *Pharmaceutical Research* 20, 297, (2003).

MEDI 49

Synthesis of membrane impermeable high affinity carbonic anhydrase IX inhibitors through combinatorial click chemistry

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A focused library of 109 structurally diverse triazole sulfonamides was prepared using click chemistry in an effort to develop novel inhibitors of extracellularly expressed carbonic anhydrase-IX (CA-IX). 3 different alkyne scaffolds were combined with 40 structurally diverse azides. Several triazoles possessed K_d values ranging from 5 – 20 nM. The selectivity of these hits for CA-IX over CA-II in enzymatic assays was low (0.03-0.1 fold). Incorporation of charged functional groups, or moieties that undergo ionization in vivo, dramatically improved the CA-IX/CA-II selectivity. A potent CA-IX/CA-II selective benzene sulfonamide derivative containing a cysteine derivative ($K_d = 10$ nM), was the starting point for development of positron emitting tomography (PET) based tracers for detecting aberrant CA-IX expression in vivo.



C 21
Kd (CA IX) = 10 nM
Figure 1

MEDI 50

Synthesis of high-affinity thio and seleno derivatives of the TSPO ligand, PK 11195

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PK 11195 is the prototypical high-affinity non-benzodiazepine ligand for TSPO receptors (formerly known as PBR). [^{11}C]PK 11195 remains the most commonly used radioligand for imaging TSPO and associated inflammation in humans in vivo with positron emission tomography (PET). However, the receptor-specific binding signal is generally very low and challenging to quantify. Here we explored subtle structural modifications to PK 11195 in an effort to obtain superior TSPO PET radioligands. We prepared **1a-b**, a hindered analog of PK11195, in eight steps from a phthalimide ester, and aimed to increase the amide bond rigidity of this compound further by substituting the oxygen with either sulfur or selenium. In derivatives **2a-b** and **3a-b** these modifications allowed the amide rotamers to be observed and segregated by low temperature HPLC. Both **2a-b** and **3a-b**, retained high affinity for TSPO receptors.

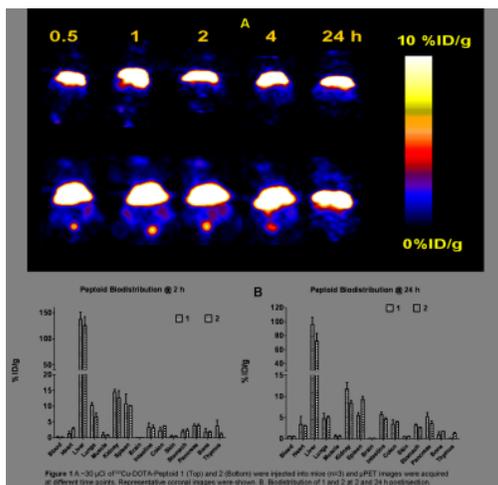
MEDI 51

Evaluation of in vivo distribution of peptoids using microPET

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Peptoids are novel emerging molecules for pharmaceutical development. A group of peptoids with antimicrobial and antitumor activities have been successfully discovered recently. However, there are very limited studies to understand the in vivo biodistribution of peptoids. In this study, the in vivo biodistribution of two antimicrobial peptoids and a control peptide were investigated using micro-positron emission tomography (μPET). DOTA

conjugated peptoids (named as 1 and 2) and the peptide were synthesized by a solid-phase peptide synthesizer. The purified compounds were labeled with a positron emitter, ^{64}Cu , and then evaluated by μPET and biodistribution assays in BALB/c mice. Excellent radiochemical purity and serum stability were obtained for all the radiolabeled complexes. The *in vivo* studies revealed high uptake and retention of radiopeptoids in liver, while low accumulation in kidneys



These findings provide the foundation and rationale for designing and applying biological active peptoids for diseases treatment.

MEDI 52

Ir-catalyzed asymmetric hydrogenation: An approach to the antidiabetic candidate drug PSN-GK1 and its analogs

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PSN-GK1 is a potential anti-diabetic drug, which has superior therapeutic effects than other categories of targeted anti-diabetic treatments by simultaneously increasing pancreatic insulin secretion and augmenting hepatic glucose metabolism. *In vivo*, only the *R*-configured drug (PSN-GK1) exerts the desired clinic actions while the *S*-enantiomer is completely inactive. The only available strategy to the asymmetric hydrogenation of the key intermediate was reported in 2006. However, this approach is far beyond optimum due to the high cost of both Rh catalyst and Mandyphos ligand.

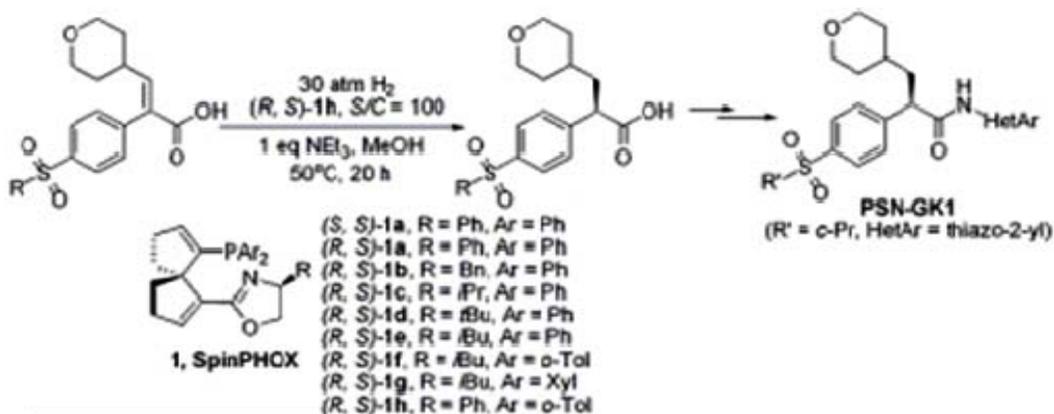


Figure 1

We recently developed a novel class of spiro[4,4]-1,6-nonadiene-based phosphine-oxazoline ligands (SpinPHOX, **1**), which was found highly efficient in the asymmetric hydrogenation of α -aryl- β -substituted acrylic acids. With the cationic iridium complex (*R, S*)-**1h**, a broad range of optically active acids were obtained with ee values of up to 96%. Complex (*R, S*)-**1h** was successfully employed in the catalytic asymmetric synthesis of PSK-GK1 and its analogues. Pharmacological evaluation of these analogs indicated that compound SOMCL-32 displayed good glucokinase activation, and was further investigated *in vivo*.

MEDI 53

Drug design from a new angle: Improving molecule design with demystified ADMET predictions

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Medicinal chemists are challenged to design New Chemical Entities (NCEs) with high biological activity. But good activity must be accompanied by acceptable ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) properties. Structure-based design tools provide chemists with insight into improving activity, but not ADMET; however, *in silico* predictions of ADMET properties are now sufficiently fast and accurate to allow chemists to consider both activity and many ADMET properties in drug design. The most accurate property prediction methods are based on sophisticated machine-learning methods such as artificial neural network ensembles that have been difficult to interpret. We have developed a Descriptor Sensitivity Analysis tool that provides molecule-specific insight into these complex models to identify structural aspects of NCEs that affect both activity and ADMET properties. This tool enables chemists to see the effects of various molecular descriptors on properties of interest. We demonstrate this approach with several examples.

MEDI 54

Radiosynthesis of [¹¹C]SU11274 for in vivo imaging of MET receptors

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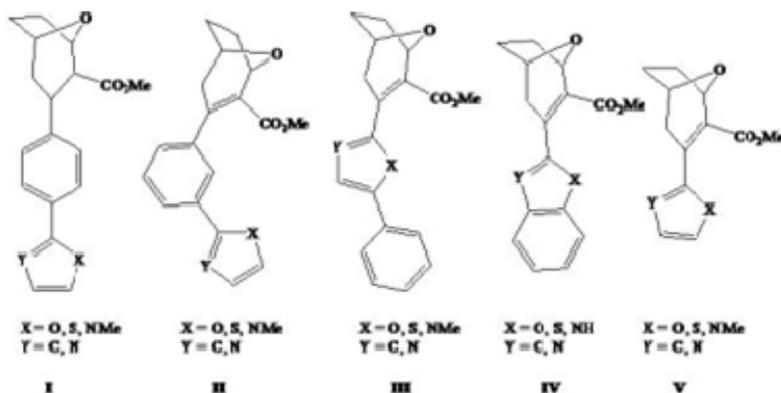
We report the multi-step radiosynthesis and evaluation of a molecular imaging probe, [¹¹C]SU11274, for quantification of MET receptors in human cancers *in vivo*. Following the synthesis of the precursor that was achieved in 10 steps with a total yield of 9.7%. [¹¹C]SU11274 was obtained through radiomethylation in a range of 5-10 % radiochemical yield and over 95% radiochemical purity. For *in vivo* microPET studies, two human lung cancer xenograft models were established using MET-positive NCI-H1975 and MET-negative NCI-H520. Quantitative [¹¹C]SU11274-PET studies showed that the tumor uptake of [¹¹C]SU11274 in the NCI-H1975 xenografts was significantly higher than that in the NCI-H520 xenografts, which is consistent with their corresponding immunohistochemical tissue staining patterns of MET receptors from the same animals. These studies demonstrated that [¹¹C]SU11274-PET is an appropriate imaging marker for quantification of MET receptor *in vivo*, which can facilitate efficacy evaluation in the clinical development of MET-targeted cancer therapeutics.

MEDI 55

Synthesis and structure activity relationship studies of 3-(biaryl)-8-oxabicyclo[3.2.1]octane-2-carboxylic acid methyl esters

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As part of an ongoing investigation to develop medications for cocaine abuse, synthesis and structure activity relationship studies of five series of 3-(biaryl)-8-oxabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters and their corresponding SmI₂ reduction products were investigated. The 3-biaryloctenes manifest binding potently and selectively to DAT versus SERT. The nature of the 3-aryl system in the oxatropane series studied is crucial for preferred interaction with DAT. Thus, the benzofuran, *benzothiophene*, *benzoxazole*, *benzimidazole* and indole groups (series **IV**) have the strongest interaction



with the binding site of DAT as compared to the other biaryl substituents (series **II**, **III** and **V**). Within this series sulfure heteroatom seems to have biggest influence on inhibition of WIN 35,438 with a remarkable DAT selectivity over SERT. The most potent analogues compound at DAT is benzthiophen derivative with an IC_{50} value of 13 nm for DAT and 177-fold selectivity over SERT (SERT: IC_{50} 2,300 nm). Indole (DAT: IC_{50} 336; SERT: IC_{50} 17,000, 50-fold selectivity) and benzofuran (O-2551) (DAT: IC_{50} 349; SERT: IC_{50} 35,000, 100-fold selectivity) derivatives are also notably potent at and selective for DAT. Potency among the Sml_2 reduction products is the highest with the chair diastereomer of benzthiophen substituent with a less pronounced DAT selectivity DAT: IC_{50} 9; SERT: IC_{50} 10). On the other hand, the corresponding boat diastereomer manifests DAT selectivity (DAT: IC_{50} 18, SERT: IC_{50} 79).

MEDI 56

Synthesis and SAR of potent and selective quinazoline inhibitors of PDE1

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A file screen yielded three distinct substituted quinazolines with good inhibitory activity against phosphodiesterase 1, and with excellent physicochemical properties predictive of good bioavailability including CNS exposure. X-ray crystallography and molecular modeling aided SAR expansion via library synthesis and traditional medicinal chemistry approaches. The discovery and synthesis of these molecules will be discussed along with select biological activity data.

MEDI 57

Synthesis of new carbon-11-labeled 3,3a,4,5-tetrahydro-2H-benz[g]indazoles as PET agents for imaging of necroptosis

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Apoptosis is the programmed cell death involved caspase activation, and necroptosis is a regulated caspase-independent cell death. A new series of tricyclic heterocycles (3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazoles) have been recently developed as potent necroptosis inhibitors. New carbon-11-labeled 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazoles were designed and synthesized as radiotracers for biomedical imaging technique positron emission tomography (PET) to image necroptosis. Unlabeled 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazoles were synthesized from 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one in multiple steps with moderate to excellent yields. The target tracers (3*R*,3*aS*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-2-carbaldehyde, (3*R*,3*aR*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-2-carbaldehyde, 1-((3*R*,3*aS*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)ethanone, 1-((3*R*,3*aR*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)ethanone, 1-((3*R*,3*aS*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)propan-1-one, 1-((3*R*,3*aR*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)propan-1-one, 1-((3*R*,3*aS*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-2-methoxyethanone and 1-((3*R*,3*aR*)-*rel*-8-methoxy-3-(4-[¹¹C]methoxyphenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-2-methoxyethanone were prepared from their corresponding hydroxyphenyl precursors with [¹¹C]methyl triflate ([¹¹C]CH₃OTf) under basic conditions through O-[¹¹C]methylation and isolated by a simplified solid-phase extraction (SPE) method in 50-70% radiochemical yields and 222-296 GBq/μmol specific activity at the end of bombardment (EOB).

MEDI 58

Synthesis of carbon-11-labeled quinoline-2-carboxamido and quinoline-3-carboxamido as new PET agents for imaging of breast cancer resistance protein

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Breast cancer resistance protein (ABCG2) is an attractive target for the development of therapeutic agents for use in breast cancer treatment, and diagnostic agents for use in breast cancer detection by the biomedical imaging technique positron emission tomography (PET). Quinoline-2-carboxamido and quinoline-3-carboxamido are two potent and selective inhibitors of ABCG2. This study was designed to develop carbon-11-labeled quinoline-2-carboxamido and quinoline-3-carboxamido as new PET agents for imaging of ABCG2. Unlabeled

reference standards, methyl 4-((4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-2-carboxylamino)benzoate and methyl 4-((4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-3-carboxylamino)benzoate, and their acid precursors, 4-((4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-2-carboxylamino)benzoic acid and 4-((4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-3-carboxylamino)benzoic acid, were synthesized from the starting material 2-(3,4-dimethoxyphenyl)ethylamine in multiple steps with moderate to excellent yields. The target tracers, [¹¹C]methyl 4-((4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-2-carboxylamino)benzoate and [¹¹C]methyl 4-((4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl)ethyl)phenyl)aminocarbonyl)-2-(quinoline-3-carboxylamino)benzoate, were prepared from their corresponding acid precursors with [¹¹C]methyl triflate ([¹¹C]CH₃OTf) under basic conditions through O-[¹¹C]methylation and isolated by a simplified solid-phase extraction (SPE) method in 50-60% radiochemical yields and 111-185 GBq/μmol specific activity at the end of synthesis (EOS).

MEDI 59

PEG-Scutellarin prodrugs: Synthesis and pharmacokinetics

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Scutellarin (4', 5, 6-trihydroxyflavone-7-glucuronide) is an active ingredient extracted from traditional Chinese medicine *Erigeron breviscapus*(vant) Hand-Mazz, which has been clinically used to treat acute cerebral infarction and paralysis induced by cerebrovascular diseases such as hypertension, cerebral thrombosis, cerebral haemorrhage in China since 1984. However, its clinical application was limited due to low solubility, poor bioavailability, low anti-infarct activity and short half-life in vivo. To overcome these disadvantages, mPEG with different molecular weight (400-3000) was used to modify the phenolic hydroxyl groups of scutellarin. Five PEG-scutellarin conjugates were synthesized. The analytical sample was purified by silica gel column chromatography and the structure of these conjugates was confirmed by ¹HNMR, ¹³CNMR and MS. The water solubility of the prodrugs was increased remarkably. The half life (15.8 min) of scutellarin that was released from the prodrug was significantly longer than that of scutellarin (3.0 min).

MEDI 60

N²-Alkyl-8-oxo-2'-deoxyguanosine: A solution to siRNA off-target effects

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One challenge facing siRNA therapy is off-target effects that may be either sequence dependent or sequence independent. A significant contributor to off-target effects appears to be diversion of siRNAs to nonproductive protein binding such as PKR or other proteins with a double-strand RNA binding motif (dsRBM). Most of these interactions occur in the minor groove of the siRNA. Hence, introduction of a sterically bulky group at minor groove positions of siRNA should prevent its interaction with dsRBM proteins. *N*²- Alkyl-8-oxo-2'-deoxyguanosines are one such modification that can introduce a steric blockade in the minor groove but also adopt a different conformation when binding to target mRNA in the RISC. Modifications introduced at different positions in the strand could prevent or minimize unwanted protein interactions without affecting the knockdown capability of siRNA. In the current work, a series of *N*²-alkyl-8-oxo-2'-deoxyguanosines has been synthesized and incorporated into one, two and three positions of siRNA that is optimized to knockdown caspase-2 gene expression. *T*_M studies indicated that the introduction of the modified bases did not affect the duplex stability significantly. Gene knock down studies in HeLa cells have shown that most of the modified siRNAs exhibit comparable activity as unmodified siRNA. Importantly, base modifications introduced at the cleavage site and in the seed region of siRNA show retention of gene knockdown ability. The results obtained will be utilized in further optimization of better siRNAs with fewer off-target effects.

MEDI 61

T3P[®]: The green, high performance reagent of choice for amide/peptide bond formation

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Propane Phosphonic Acid Anhydride (T3P[®]) is an exceptional reagent for amide/peptide bond formation. It is very easy to use and provides excellent selectivity, low epimerization and high yields with simple product isolation by extraction. Because of its properties, hazardous additives such as explosive HOBt, are not required. Additionally, the T3P[®] reagent is really "green" - nontoxic, non-allergenic/non-sensitizing, and the only waste products are phosphate salts, in sharp contrast to most other coupling reagents. These salts are readily removed via an aqueous wash at the conclusion of the reaction. T3P[®] is well established at large scale for liquid phase peptide coupling reactions where its advantages translate into high quality products and improved economics. Numerous examples of the application of T3P[®] in the formation of amide bonds and peptide couplings will be presented. In particular, utilization of T3P[®] in the synthesis of highly sterically hindered amides will be highlighted. The ease of use of this reagent will also be detailed.

MEDI 62

Human P2Y₁₄ receptor agonists: Truncation of the hexose moiety of uridine-5'-diphosphoglucose and its replacement with alkyl and aryl groups

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The P2Y₁₄ receptor, a G protein-coupled receptor in the neuroimmune system, is activated by uridine-5'-diphosphoglucose (UDPG). Substitution of the terminal glucose moiety of UDPG with small alkyl or aryl groups, or its truncation to uridine-5'-diphosphate (UDP), is tolerated in P2Y₁₄ receptor recognition and leads to highly potent agonists in HEK-293 cells stably expressing the human P2Y₁₄ receptor. UDP derivatives in the series of native uracil and synthetic 2-thiouracil were potent and selective P2Y₁₄ receptor agonists, such as 2-thio-UDP (EC₅₀ 1.92 nM, 224-fold selectivity in comparison to the P2Y₆ receptor) and its *b*-propyloxy ester. The *b*-methyl ester of UDP and its 2-thio analogue displayed EC₅₀ values at the P2Y₁₄ receptor of 2.73 μM and 56 nM, respectively. A *b*-*t*-butyloxy ester of 2-thio-UDP was 11-fold more potent than UDPG. Either *b*-aryloxy groups or larger, branched *b*-alkyloxy groups, such as cyclohexyl, reduced P2Y₁₄ receptor potency in comparison to UDPG. Replacement of the ribose moiety of UDP with a rigid methanocarba (bicyclo[3.1.0]hexane) group, either in a North or South conformation, abolished P2Y₁₄ receptor agonist activity. *a,b*-Methylene and difluoromethylene groups were well tolerated at the P2Y₁₄ receptor and are expected to provide enhanced stability in biological systems. *a,b*-Methylene-2-thio-UDP (MRS2905) displayed an EC₅₀ of 0.92 nM and 2160-fold selectivity versus the P2Y₆ receptor. Thus, these nucleotides and their congeners may serve as important pharmacological probes for the detection and characterization of the P2Y₁₄ receptor.

MEDI 63

Synthesis of phenanthropiperidine scaffold allowing for novel molecular modification

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The phenanthropiperidine alkaloids are a class of more than 60 plant isolates primarily found in the *Asclepiadaceae* plant family. These natural products have consistently shown impressive therapeutic potential such as anti-inflammatory, anti-viral, and anti-fungal activity, although their most remarkable feature is their potent and uniform cytotoxicity. Despite their medicinal properties, however, these compounds have received little attention as they are known to cause ataxia and disorientation when administered *in vivo*. It is hypothesized that more polar

analogues would avoid such adverse side effects by preventing blood-brain barrier penetration. Thus, novel methodology invented in the Georg lab was utilized to achieve syntheses of two phenanthropiperidine scaffolds in a viable manner. We report herein the syntheses both scaffolds which incorporate reactive functionalities to append ADMET improving moieties. In order to achieve a more convergent synthesis, a novel aryl-alkene oxidative coupling reaction was introduced to the synthetic pathway.

MEDI 64

Small-molecule modulation of transcription via the KIX domain of the CREB-binding protein

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Precise regulation of transcription is essential for normal cellular function. Transcriptional activators are key elements in regulating this process. We have developed a small-molecule isoxazolidine (iTAD **1**) that, when localized to DNA, reconstitutes both the function and mechanism of natural transcriptional activators. Through photocrosslinking and NMR studies we have identified the KIX domain of the CREB-binding protein (CBP) as a target of this small-molecule. CBP is a node in many transcription pathways and is involved in cell growth and differentiation, learning and memory, and cellular metabolism. Further studies are currently underway using a several iTAD variants to explore the SAR of this small-molecule transcriptional modulator. Additional investigation has shown that both iTAD **1** activation and repression is dependent upon CBP expression, demonstrating the utility of this class of small-molecules as mechanistic probes of transcription pathways and forging the way towards the development of small-molecule transcription-based therapeutics.

MEDI 65

Synthetic approaches to 5,7-disubstituted imidazo[5,1-*f*][1,2,4]triazin-4-amines

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Receptor tyrosine kinases (RTKs) represent a class of growth factor receptors that serve as important signal regulators for a variety of cellular functions including differentiation, proliferation, and apoptosis. Our group identified a series of novel 8-amino-1,3-disubstituted-imidazo[1,5-*a*]pyrazines, such as 1-[3-(benzyloxy)phenyl]-3-cyclobutylimidazo[1,5-*a*]pyrazin-8-amine (**1**), as potent

inhibitors of the insulin-like growth factor-I receptor (IGF-1R). In seeking to optimize this system for potency and metabolic stability, we became interested in the closely related bio-isostere, 5-[3-(benzyloxy)phenyl]-7-cyclobutylimidazo[5,1-f][1,2,4]triazin-4-amine (**2**). Herein we describe our initial linear preparation of compound **2** starting from methyl amino[3-(benzyloxy)phenyl]acetate, as well as the development of two convergent routes that allow for late-stage analoging at the 5-position *via* Pd-catalyzed transformations.

MEDI 66

Nanopore filters for dialysis machine for treatment of end stage renal disease

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Dialysis machines are the most widely used temporary lifesaving invention for patients with end-stage renal disease. Hemodialysis machines are described as large stationary hydro-mechanical devices. Blood urea nitrogen is a waste product in the liver as the end product of protein metabolism. It is removed from the blood by the kidneys in the Bowman's capsule along with creatinine a waste product of creatinine phosphate as energy storing molecule produced largely from muscle breakdown. The disease is caused by the loss of filtering capacity of the nephrons. Dialyzer filters are made of cellulose acetate, polysulfone or similar materials and sterilized with a solution of ethylene oxide, bleach or formaldehyde. Dialyzer filters have just one membrane pore size with a cut-off point larger than creatinine at 113.1 amu. Removed with creatinine is urea at 60.1 amu, water and essential electrolytes such as Na, K, Ca, Mg are removed by the dialyzer but not replaceable during dialysis. Phosphorous molecules at 123.9 amu are not removed by dialysis and large amounts are deadly to the patient. The pore size of the filter can be found from the Staverman reflection coefficient and sieving coefficient using numerical methods. The Staverman reflection coefficient varies with the solute radius as a 7th degree polynomial.

MEDI 67

On radial diffusion issues in design of bioartificial pancreas for treatment of insulin dependent diabetes mellitus

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Bioartificial pancreas can be used to treat insulin dependent diabetes mellitus, IDDM. Diabetes Mellitus is the one of the most prevalent causes of death by disease in USA next to cardiovascular and neoplastic disease. Microencapsulation of tissue cells such as islets of Langerhans which are injected into the human anatomy has led to interesting results. Poly-L-lysine can

be used for microencapsulation. According to Colton et. al. (1) the number of islets required to reverse diabetes is up to 5000 islets/kg. One of the salient considerations in the design of bioartificial pancreas self-contained miniaturized **implant** from which the islets are replenished after a certain period of time was patented by University of Utah (2). This device is extravascularly implantable and rechargeable. It comprises of a refillable immunoprotective membrane pouch containing an islet-polymer matrix. The polymer is soluble below human anatomy temperatures and insoluble above human anatomy temperatures. They exhibit **LCST** behavior. reas using hybrid materials is to prolong the cell life within the system. The artificial pancreas comprises of a pouch membrane that requires minimal space while affording optimal implant volume. The implant consists of islets suspended in polymers that exhibit LCST behavior.

MEDI 68

On study glycolytic Oscillations using control theory during design of bioartificial pancreas

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The dynamics of glucose induced secretion of insulin can be expressed as the sum of the proportional response to the step change and a derivative response to the rate of change in the glucose concentration. Each of them have a first order lag time. The lag times can be obtained by use of nonlinear regression of islet release-rate experimental data. Pharmacokinetic models have been developed to describe glucose and insulin metabolism. Insulin formed in human anatomy have been found to exhibit two kinds of oscillations: i) a rapid oscillation with a time period of 10-15 minutes and small amplitude; ii) longer or ultradian, damped oscillations with a period of 100-150 min and larger amplitude. 4 negative feedback loops form the proposed model involving glucose and insulin interactions: i) insulin formation is triggered when glucose levels become more than tolerable limit; ii) increase in insulin level increases the utilization of glucose and hence reduces the glucose levels; iii) rise in glucose level inhibits production of glucose; iv) increase in glucose levels stimulates its utilization. The glucose and insulin never reach stable equilibrium. The proposed model includes two time delays that are critical in describing the observed oscillatory dynamics. The suppression of glucose levels by insulin production is captured by one time delay and the correlation of biological action of insulin with insulin concentration is captured by another time delay in interstitial compartment. Six differential equations are used to describe the system.

MEDI 69

Development of “fragmenting hybrid” small-molecule antimalarials

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Artemisinin combination therapies (ACT) represent the current standard of care for treatment of uncomplicated malaria. Combination therapies for malaria are intended to mitigate the development of resistance and address the problem of recrudescence associated with artemisinin mono-therapy. We are exploring single-molecule hybrid therapeutics consisting of an artemisinin-inspired synthetic trioxolane linked to an antimalarial agent of a distinct therapeutic class. The nature of the chemical linkage in these hybrids is such that only upon exposure to iron (II) in the parasite food vacuole is the second agent released in its native (active) form. This novel form of targeted delivery is intended to reduce systemic drug exposure and associated toxicity. The technology may also enable the safe delivery of particularly potent agents that could not be employed as mono-therapies. We present here the synthesis and biological activities of prototypical trioxolane-quinoline and trioxolane-protease inhibitor hybrids.

MEDI 70

Formation of the Southwest Comprehensive Center for Drug Discovery and Development: New technologies, organization, work flow and projections

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The poster describes the recent formation of the Southwest Comprehensive Center for Drug Discovery and Development made feasible by the National Institute of Health (NIH) via a \$7.5 million grant to fund infrastructure and staff build up as part of the federal economic recovery act (RC2 – GO grant). As such, chemical technologies to rapidly establish a Southwest screening collection, using a novel chemical informatics platform, Chemtech™ will be discussed. Organizational aspects of the Unit- based Center will be presented, along with work flow associated with file enhancement and high-throughput screening spanning two institutions. The Center is projected to employ a more industrialized and high-throughput approach to medicinal chemistry, with an already established portfolio of targets that span a multitude of therapeutic areas.

MEDI 71

Novel nitroaromatic heterocyclics as potential anti-trypanosomal drugs: II

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Chagas' disease or American trypanosomiasis, is caused by infection with the parasite *Trypanosoma cruzi* and is the cause of an estimated 14,000 deaths per year and 8 million new cases, with 100 million at risk of infection in 21 Latin American countries. Drugs currently used in the treatment of Chagas disease are old, active mainly in the acute stage of the disease, require a long treatment period with significant dose-dependent toxicity and there is no treatment for chronic disease. We have synthesized several 3-nitro-1,2,4-triazoles and 2-nitroimidazoles and screened them against various trypanosomatids to establish structure-activity-relationships. Our data demonstrate that the nitro-group is necessary in the triazole ring for activity against *T. cruzi* amastigotes. Twelve out of 14 nitrotriazoles were active against *T. cruzi* and 4 of them were also active against *T. b. rhodesiense*. Ten out of the twelve active nitrotriazoles against *T. cruzi* were 2.2 to 9.6-fold more potent than the ref. drug benznidazole (Bnz), at nanomolar concentrations, and 8 of them demonstrated a selectivity index (toxicity to L6 cells/toxicity against *T. cruzi* amastigotes) > 100. There was a good correlation between pKa values and potency against *T. cruzi* in the nitrotriazole-series. Thus, nitrotriazoles with pKa >7 were the most potent ones. There was a decent correlation between logP values and toxicity in a subset of nitrotriazoles that did not include the acridinic derivatives. The most selective nitrotriazoles (selectivity >300) had logP values ranging from 2.5 - 3.5. In addition, six out of 20 nitroimidazoles were active against *T. cruzi* but 5 of them were also toxic in rat skeletal myoblasts (L6 cells). In conclusion, novel nitrotriazoles with activity against African and South American trypanosomes have been identified.

MEDI 72

Acetylenic fatty acids inhibit plasmodial FAS-II enzymes and arrest erythrocytic and liver stage *Plasmodium* infections

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The 2-, 5-, 6-, and 9-hexadecynoic acids were synthesized and their activity against blood stage *Plasmodium falciparum* was determined. In combination assays, the 2-hexadecynoic acid and the 9-hexadecynoic acid remarkably reduced the IC₅₀ value of artesunate. 2-Hexadecynoic acid potently inhibited *P. falciparum* type II fatty acid elongation enzymes, PfFabI and PfFabZ, and arrested the growth of liver stage *P. yoelii* infection. Enzyme kinetics and molecular modeling studies revealed valuable insights into the binding mechanism of 2-hexadecynoic acid on the enzymes. All hexadecynoic acids showed trypanocidal and leishmanicidal effects. This study indicates chemotherapeutic potential of the hexadecynoic acids against various protozoa for the first time, and hints that PfFAS-II enzymes may underlie the malarial liver stage growth inhibitory effect, which could be useful for malaria prophylaxis.

MEDI 73

Synthesis and evaluation of novel visible light activated type 1 photosensitizers for phototherapy

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Photodynamic therapy (PDT), a Type 2 process, is mediated through singlet oxygen generated by excited photosensitizers and is used in certain types of cancer and ocular disease treatment. A Type 1 process operates via direct energy or electron transfer from the photosensitizer to the cellular components, and despite its considerable potential, has not been widely investigated. Herein, we report the synthesis of several compounds containing fragile motifs like azido ($-N=N=N-$), azo ($-N=N-$), and oxaza ($-N-O-$) functional groups that undergo photo-fragmentation by visible light. All the photosensitizers caused cell death in the presence of light compared to the controls in a concentration and time dependent fashion against U397 leukemia cell line. Moreover, conjugates of these photosensitizers with targeting vectors (e.g. leukemia cell binding peptide and folic acid) caused significant selective cell death, thus clearly indicating the usefulness of this approach in various phototherapeutic applications.

MEDI 74

Removal of TFA from Prep-LC fraction: Isolation of purified free-base product

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Medicinal compounds are often isolated and purified from reaction mixtures using preparative scale liquid chromatography (Prep-LC). In many cases, acidic modifiers such as trifluoroacetic acid (TFA) are used in the Prep-LC separations.

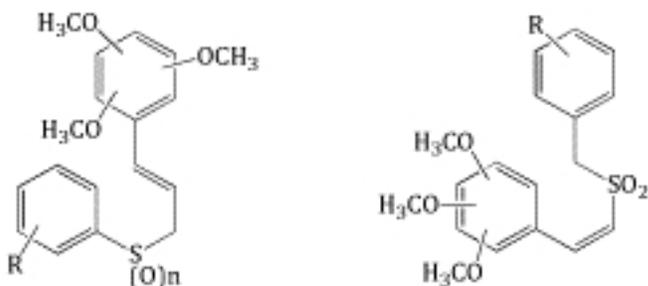
Simply removing the mobile phase from the collected fraction will leave an equivalent amount of TFA associated with any basic compound synthesized; the compound is recovered as a TFA salt. Residual TFA has been linked to degradation of basic compounds synthesized for medicinal investigation. This poster will show a simple post Prep-LC fraction cleanup, removing mobile phase and residual TFA. The fraction is collected in a volatile solvent for rapid evaporation which yields a basic compound as a free-base product.

MEDI 75

Stereospecific synthesis and biological evaluation of (E) and (Z)-styryl benzylsulfides, sulfoxides, and sulfones

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Many antimetabolic agents that interfere with polymerization / depolymerization of α and β -tubulins have been successfully used for cancer treatment. These agents cause dynamic instability of microtubules resulting in cell cycle arrest in the M-phase, forming abnormal mitotic spindles. Agents such as vincristine and paclitaxel have gained wide clinical use for the treatment of various cancers, they suffer from undesired side effects, particularly neurotoxicity and are substrates various efflux mechanism leading to drug resistance. More recently, alternative components of the mitotic machinery have been targeted in an attempt to develop novel anti cancer agents. These include critical signaling kinases such as the Plk, Aurora, wee1 and the Cdk-2 kinases. In an attempt to identify potent inhibitors of tumor cell progression, a series of novel cell cycle inhibitors, styryl benzyl sulfides, sulfoxides and sulfones were synthesized and evaluated their activity in tumor cell cytotoxicity assay. This led to the identification of ON 01370, as a potent cytotoxic agent that kills tumor cells and sparing normal cells at much higher concentration. Further modification of ON 01370 led to analogs with enhanced potency and bioavailability. The stereo-specific synthesis, structure-activity relationships and biological activity of this series of compounds will be discussed.



MEDI 76

Synthesis and reactions of oxetan-3-*tert*-butylsulfonimine for the preparation of substituted oxetan-3-amines

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The replacement of a geminal dimethyl group with an oxetane ring is a potentially useful practice in medicinal chemistry. While exhibiting a similar van der Waals volume to a dimethyl group, an oxetane ring can be more stable to oxidative metabolism and has decreased lipophilicity, which can confer an enhanced pharmacokinetic profile. The decreased lipophilicity can also mitigate undesirable off-target effects, such as hERG channel binding and hPXR activation. We were interested in preparing a 3-aryl-3-amino-oxetane while exploring structure activity relations during a medicinal chemistry program, and found that this structural motif had not been reported. A straightforward approach involving condensation of oxetan-3-one with *tert*-butylsulfonimine to generate an isolable oxetan-3-sulfonimine, followed by addition of an aryllithium reagent and acid-promoted deprotection of the intermediate sulfonamide was successful in generating 3-aryl-3-amino-oxetanes. The reactivity of this novel oxetan-3-sulfonimine towards a variety of nucleophiles was explored, and a wide array of diversely substituted oxetan-3-amines is now easily accessible from a single intermediate.

MEDI 77

Designing treatments for leishmaniasis: Employing computational tools to examine biological affinity and mechanisms of arylimidamides

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Parasites that cause leishmaniasis are difficult to treat and vaccines have not been successful. Traditional drug treatments require intravenous or intramuscular administration due to poor oral bioavailability and these treatments often result in severe toxicity. Our studies employ computational tools to examine a biological dataset of synthetic heterocyclic arylimidamides with respect to experimental findings. The most potent of these arylimidamides display activity similar to that of the clinically used antileishmanial agent amphotericin B. Results will aid in the design of novel analogs that retain or improve activities, eliminate harmful side effects and have good oral bioavailability.

MEDI 78

Diol columns – pretend they're normal phase

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Diol columns are useful as an intermediate polarity media between C18 and silica. Diol derivatived media are less polar, may have different selectivity, and are reusable compared to bare silica. Diol is particularly useful to chromatographers because it can be used with a wide range of solvents. This flexibility is confusing since phrases such as “normal phase mode” and “reverse phase mode” are commonly used. These terms cause confusion when developing methods for MPLC or flash chromatography. Treating the diol column as if it were normal phase for all solvents simplifies method development for these columns. Diol columns can readily be converted between solvent systems and are reusable. Examples of method development using thin layer chromatography and columns are detailed.

MEDI 79

Method development strategies for amine bonded phase columns for medium pressure liquid chromatography

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Amine is a useful alternative to silica gel because it is less polar and has a basic character. Compounds that require basic mobile phase modifiers such as triethyl amine or ammonia on silica can be purified without these additives on amine columns, simplifying the purification. Amine columns can be run as a normal phase or reverse phase column, which cause confusion for method development. Treating the amine column as if it were normal phase for all solvents simplifies method development for these columns. Amine columns can be changed between solvent systems and are reusable, facilitating method development. Examples of method development using amine TLC and columns are provided.

MEDI 80

Synthesis, SAR, and pharmacological profile of analogs of the ASIC-3 inhibitor A-317567

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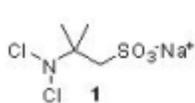
The quest for novel treatments for chronic pain and inflammation continues to be an area of intense research. Under conditions of acidosis, tissue damage can often result leading to acute or chronic pain. A number of receptors and ion channels expressed in neurons have been shown to be modulated by protons. Among them, the acid-sensing ion channel-3 (ASIC3) is representative of a proton-gated subgroup of degenerin/epithelial Na⁺ cation channel family. There is substantial evidence that ASIC3 serves as a pH sensor playing an important role in conveying the pain sensation resulting from tissue acidosis. Accordingly, small molecule inhibitors of the ASIC3 channels are of considerable interest to study the physiological role of ASIC3. In this paper, the synthesis, SAR, and pharmacological evaluation of analogs of the ASIC channel inhibitor A-317567 are reported.

MEDI 81

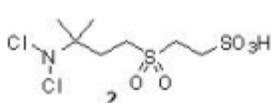
New *N*-Chloroamines: Chemical synthesis, solution stability and biological activity

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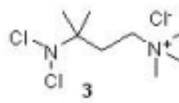
2-Dichloroamino-2-methyl-propane-1-sulfonic acid sodium salt (**1**) is currently a clinical candidate as a topical antimicrobial agent. Structure-activity relationships of its analogs were explored to achieve optimal antimicrobial activity with minimal mammalian toxicity while maintaining aqueous stability. All the analogs synthesized showed antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* in the range of 2- >256 µg/mL and cytotoxicity against mammalian L929 cells in the range of 0.03-5.8 mM. After systematically varying the distance between the dichloroamine and other functional groups, the ideal distances were determined for optimum aqueous stability and biological activity. This study has led to the identification of a new class of solution stable topical antimicrobial agents which have sulfones in the backbone (**2**) and quaternary ammonium salts (**3**) as water solubilizing groups.



E. coli - 2 ug/ml
C. albicans-32 ug/ml
S. aureus - 2 ug/ml
T₉₀ (pH 4) - >2 years
T₉₀ (pH 7) - >300 days



E. coli - 8 ug/ml
C. albicans-16 ug/ml
S. aureus - 2 ug/ml
T₉₀ (pH 4) - 226 days
T₉₀ (pH 7) - 69 days



E. coli - 2 ug/ml
C. albicans-64 ug/ml
S. aureus - 2 ug/ml
T₉₀ (pH 4) - > 281 days
T₉₀ (pH 7) - 195 days

Figure 1. Promising compounds from SSR/SAR studies in *N,N*-dichloroamine series.

MEDI 82

Diverse applications of flow technology in medicinal chemistry

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Flow technologies have been applied to many areas of medicinal chemistry. In this poster, two distinct methodologies will be illustrated using meso-scale flow technology. The first is a “droplet” based library synthesis method which allows for the preparation of a theoretically unlimited number of compounds using a single Teflon loop by employing immiscible solvents as spacers. The second methodology takes advantage of the inherent closed nature of flow systems to create noxious chemicals *in situ*, react them in a desired way, and then quench them in a continuous process. This methodology was demonstrated using isocyanides, reagents notorious for their unpleasant smell. Isocyanides were synthesized in one flow instrument, transferred directly via tubing to a second instrument to perform Ugi reactions, and then quenched without the user ever being exposed to their odor. Examples as well as future applications will be given for both methodologies.

MEDI 83

Steroid oxidation by cytochromes P450 from *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis (Mtb) is responsible for more than 2 million deaths each year and a third of the world's population is latently infected. The frontline drugs to treat Mtb are less effective due to the emergence of drug resistant strains, creating a need to identify new drug targets within this pathogenic bacterium. One of the challenges faced by Mtb during infection within the host is the need to obtain nutrients, and cholesterol has been implicated as an important source of energy. The Mtb genome encodes for 20 cytochrome P450 enzymes that are potential drug targets, including several that are likely to be involved in lipid metabolism. This presentation will report the first in-vitro study of the oxidation of steroids by three Mtb P450 enzymes (CYP124, CYP125 and CYP142) with clear demonstration of the oxidation of cholesterol and/or cholesterol metabolites. The data include the measurement of binding affinities, steady-state kinetic analysis of steroid oxidation, and product elucidation, including the regio- and stereochemical specificities of each enzyme that have

implications for their roles in host cholesterol metabolism. This work was supported by NIH grant AI74824.

MEDI 84

Exploration and expansion of hChAT promiscuity to generate ChEis

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Alzheimer's disease (AD) is a rising ailment of the elderly, causing loss of cognition and poor quality of life. Efforts to discover the cause are many, however the treatments are few. The fundamental goal of this project is to explore the promiscuity of human choline acetyltransferase (hChAT) for use as a tool in developing a novel high-throughput screen (HTS) searching for new cholinesterase inhibitors (ChEis) for the treatment of AD. We propose using the substrate and cosubstrate promiscuity of hChAT to chemoenzymatically generate acetylcholine analogs and develop a methodology to identify novel ChEis in a HTS fashion. To broaden the panel of chemoenzymatically synthesized acetylcholine analogs hChAT is mutated at several residues to broaden its cosubstrate and substrate promiscuity in addition to amplifying activity via posttranslational phosphorylation. We have found hChAT to accept a variety of choline analogs and a variety of acetyl-CoA analogs. We are currently testing mutants for activity and phosphorylated hChAT for greater activity.

MEDI 85

Transport of nitric oxide prodrugs through proline transporters

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O²-Vinyl 1-[2-(carboxylato)pyrrolidin-1-yl]diazene-1-ium-1,2-diolate (V-PROLI/NO) is a proline-based nitric oxide (NO) prodrug of the diazeniumdiolate class which has been shown to protect human liver cells from arsenic toxicity *in vitro*. Arsenic-based chemotherapeutic agents like arsenic trioxide have been shown to be very effective in acute promyelocytic leukemia and mitigation of arsenite's dose-limiting hepatotoxicity may augment the effectiveness at increased dosages. This cytochrome P450-activated prodrug was previously assumed to passively diffuse through the cellular membrane like its extensively studied analogue, O²-vinyl pyrrolidin-1-yl]diazene-1-ium-1,2-diolate (V-PYRRO/NO). Using

¹⁴C-labeled proline in a competition assay, we show that V-PROLI/NO is selectively transported through proline transporters into multiple cell lines. A fluorescent, NO-sensitive dye, 4-amino-5-methylamino-2',7'-difluorofluorescein diacetate (DAF-FM diacetate), and nitrite excretion indicated intracellular NO release after metabolism. These results also allowed us to predict and design a more permeable analogue, *O*²-Vinyl 1-[N-(carboxymethyl)-N-methylamino]diazene-1-ium-1,2-diolate (V-SARCO/NO). We report a proline transporter-based strategy for the selective transport of NO prodrugs that may enhance arsenic-based anti-cancer chemotherapeutics and in development of further NO prodrugs with enhanced permeability.

MEDI 86

Discovery of thioxothiazolidinones as novel inhibitors of purine nucleoside phosphorylase from *Schistosoma mansoni*: Structure-based virtual screening, hit optimization and mechanism of inhibition

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Schistosomiasis is a chronic and debilitating parasitic disease in several developing countries. *Schistosoma mansoni*, the causative agent of schistosomiasis, is unable to synthesize purine nucleotides de novo, which makes the purine salvage pathway enzymes attractive targets for the development of novel anti-schistosomal agents. In the present work, the enzyme purine nucleoside phosphorylase from *Schistosoma mansoni* (SmPNP) was investigated for the discovery and optimization of a new chemical class of inhibitors. Structure-based pharmacophore models and virtual screening methods were employed as rational drug design approaches for the identification of an innovative thioxothiazolidinone derivative with substantial inhibitory activity. Synthesis, biochemical evaluation and structure-activity relationships studies led to the discovery of a new series of competitive inhibitors of SmPNP with affinity values in the low micromolar range

MEDI 87

Nootropic potential of *Acorus calamus* after chronic administration

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Acorus calamus (Araceae), is a semi aquatic rhizomatous perennial herb, also known as sweet flag or Vacha. *A. calamus* is used in Indian traditional medicine for psychoneurosis, insomnia, hysteria, epilepsy and loss of memory, and is one of the common ingredients of numerous marketed herbal preparations e.g. BR-16A (mentat), Maharishi Amrit Kalash (MAK), Composite Indian Herbal Preparation (CIHP III). Single administration of nootropic agents exhibit minimal nootropic activity, however nootropic effect becomes prominent after their repeated administration of drugs. Different fractions of *A. calamus* methanol extract were evaluated for nootropic activity after chronic administration with the help of standard behavioral models. Acetyl-cholinesterase inhibition is suggested to be the most realistic mechanism of action for *Acorus calamus* to elicit anti-amnesic effects.

MEDI 88

Utility of metathesis reactions for developing novel nitric oxide donors

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Nitric oxide (NO) plays a vital role in many physiological processes. Diazeniumdiolate prodrugs, on activation, release up to 2 moles of NO per mole of the drug. They have versatile and significant biological applications. Future diazeniumdiolate drug development revolves around NO-donors with increased payload, and/ or combination of NO-donors with other biologically significant molecules. Increase in NO payload can be achieved by bifunctionalization of the diazeniumdiolate prodrug using the ruthenium-carbene catalyzed cross metathesis reaction. The ruthenium-carbene catalyzed metathesis reactions are widely used in organic synthesis, but to our knowledge not previously in conjunction with diazeniumdiolate chemistry. Metathesis reactions can also be used to tether the diazeniumdiolate prodrugs to different bioactive molecules. The poster will elaborate on the utility of these metathesis reactions for developing novel NO-releasing drug candidates.

MEDI 89

Preparation of *N*-diazeniumdiolated amidines as nitric oxide releasing prodrugs

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Under physiological conditions, many diazeniumdiolated compounds have been found to release nitric oxide (NO) which has been implicated in a wide variety of bioregulatory processes. Carbon-bound diazeniumdiolated amidines have previously been prepared by the reaction of amidines containing replaceable acidic α -hydrogen atom(s) with NO. Here, we report the reaction of amidines containing no α -hydrogen atom with NO to produce the amidinium salts of *N*-diazeniumdiolated amidines, which on treatment with sodium methoxide afford the corresponding sodium salts. The NO-release profiles of these *N*-diazeniumdiolated amidines have been monitored by chemiluminescence studies and they have been found to be significant NO donors at physiological pH in phosphate buffer at 37 °C. Several *O*²-derivatized prodrugs of *N*-diazeniumdiolated amidines have been prepared and their molecular structure has been elucidated by X-ray crystallographic studies. Funded in part by NCI Contract HHSN261200800001E.

MEDI 90

Properties determining nanoparticle clearance by primary human leukocytes

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Spherical gold nanoparticles have been used in medicine for almost 90 years. Recent research activities focus on surface modification as well as tailoring of particle shape which opens previously inaccessible applications. However, upon blood contact or generally after entry into the body, they are faced with the human immune system and may be internalized and subsequently removed by immune cells before they can reach their potential target site. Despite the central role of these primary human immune cells for successful drug-delivery applications involving nanoparticle technologies, nanoparticle-cell interaction studies are usually performed using non-primary cell-lines that differ significantly in their behaviour and ability to internalize nano-sized objects. Here, we present the first systematic evaluation of the impact of nanoparticle size, shape and surface chemistry on their clearance by defined sub-species of primary human leukocytes.

MEDI 91

Determination of fentanyl metabolite concentrations in decomposing and formalin-stored post-mortem liver tissue under anaerobic and aerobic conditions by gas chromatography and mass spectrometry

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Fentanyl is considered a powerful analgesic that is abused both by prescription and adding it to illegal drugs, mainly heroin. In previous research the concentration of fentanyl was studied over time. In this study, the concentration of metabolites of fentanyl will be studied over time in decomposing and formalin-stored pig liver samples. Two sets of the sample were used to analyze affects of fentanyl for liver stored under anaerobic and aerobic conditions. The samples will be spiked with fentanyl and analyzed over a period of six months. Pig liver samples will be used from previous research in order to analyze metabolites formed over a long period of time under anaerobic conditions. The analysis uses a purification process followed by gas chromatography/mass spectrometry to identify and quantify fentanyl metabolites. The most common metabolites seen are norfentanyl and despropionylfentanyl.

MEDI 92

Modifications of acyl carrier protein didomains with synthetic polyketide-based affinity labels

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Polyketides are a diverse class of natural products with a wide range of biological and pharmacological activities. Polyketides are biosynthesized by modular multienzyme complexes, polyketide synthases (PKSs), through sequential condensation of simple carboxylic acid building blocks. Due to multidrug resistant bacteria becoming a growing public health problem, there is increased interest to exploit these systems to produce novel molecules and drug leads through combinatorial biosynthesis. However, there is a lack of knowledge about the structure and mechanism of most catalytic domains in PKS systems. The objective of our research is to explore the substrate range of each catalytic domain, and to understand what structural features specify their chemical and stereochemical outcomes. Here we present, through synthetic chemistry, crystallography and biochemistry, the evaluation of affinity labels as probes for the structure and mechanism of thioesterase- and ketoreductase-containing didomains from the biosynthetic pathways for erythromycin, pikromycin, and tylosin.

MEDI 93

Benzil based inhibitors of carboxylesterases

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Carboxylesterase enzymes (CE) are ubiquitous proteins found in human and animal tissues and are responsible for the hydrolysis of carboxylic esters into their respective alcohol and carboxylic acid. Some of these carboxylic esters include clinically used drugs such as the anticancer agent CPT-11 (irinotecan). When hydrolyzed, CPT-11 is converted to its active metabolite (SN-38), which is responsible for killing tumor cells. However, because high levels of CEs are expressed in the intestine, high concentrations of SN-38 are produced, resulting in diarrhea, the dose limiting toxicity of CPT-11. Therefore, identifying specific CE inhibitors which could ameliorate the delayed diarrhea associated with this agent may have clinical utility. In past studies, benzil was found to be a potent inhibitor of CEs, in vitro and in mammalian cells. In this study, we have synthesized and determined the ability of benzil derivatives to inhibit CEs in vitro. By replacing the phenyl groups with alkyl chains of increasing length, increased potency of enzyme inhibition was observed. Additionally, by replacing only one of the phenyl groups with an alkyl chain, we obtained similar levels of enzyme inhibition to that observed with the alkyl. Finally, by inserting different atoms between the benzene ring and the 1,2-dione moiety, it was determined that the inhibitory power of these compounds depended upon both the polarity and hydrophobicity of the inserted atom. These inhibitors have also been used to assess intracellular inhibition of CEs. These studies demonstrated that enzyme inhibition could be achieved using a novel in situ assay with 4-methylumbelliferone acetate as a substrate. The alkyl diones were also potent inhibitors of human intestinal CE-mediated CPT-11 hydrolysis, with K_i values ranging from 24 - 140 nM. Potentially, these alkyl dione CE inhibitors represent a promising new class of compounds that could be used to reduce the intestinal toxicity of CPT-11.

MEDI 94

Progress towards the development of a fluorimetric diagnostic for the early detection of trypanosomatid diseases

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We are developing a new point of care diagnostic for the detection of trypanosomatid parasites, based on the fluorimetric detection of a trypanosomal

biomarker. Trypanosomal parasites cause three neglected human diseases including Chagas' Disease, Human African Trypanosomiasis, and Leishmaniasis. We are developing a new method for early diagnosis that is based on the detection of a parasite-specific metabolite. Our results show that a unique dye can be used to detect this metabolite from serum extracts by creating a fluorescent molecule upon conjugation suggesting the metabolite may be a good biomarker for the detection of trypanosomal diseases. This diagnostic has several attractive features, including a unique parasitological detection mechanism, low cost, and a low technology detection method that would require minimal technical training. We have synthesized a library of dyes to detect this metabolite and will report our efforts towards developing a diagnostic protocol for the detection of this biomarker.

MEDI 95

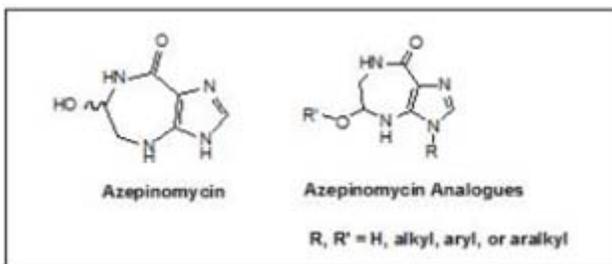
Synthesis and biochemical studies of azepinomycin and its analogs against the enzyme guanine deaminase (guanase)

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Reports of abnormally high levels of serum guanase activity in patients with liver diseases, multiple sclerosis, and in kidney and breast cancer tissue cells are well known. Studies for exploring the biochemical mechanisms of metabolic disorders and specific physiological role played by guanase are much needed.

Azepinomycin is a naturally occurring inhibitor of the enzyme Guanase.

Synthesis of azepinomycin and its IC_{50} value have been reported in literature but its actual K_i value against an isolated guanase is yet unknown. As a step toward designing a potent guanase inhibitor, we report here our synthetic strategies to access azepinomycin and its analogues, as well as our biochemical investigations to assess their K_i values.



MEDI 96

Imaging of infection foci using the ^{99m}Tc -labeled folate conjugate: EC-20

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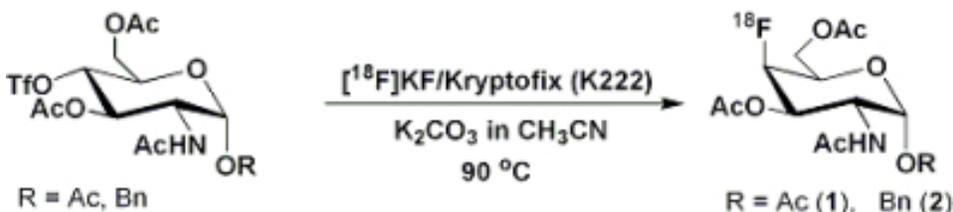
Rapid identification and localization of infection foci remains a significant clinical challenge. EC-20, a ^{99m}Tc based folate radio-imaging agent with high folate receptor binding affinity and rapid clearance (I.V. plasma $t_{1/2} \sim$; 4 min), has been evaluated for the diagnosis and staging of folate receptor (FR) positive malignancies (currently in phase II trials) and inflammatory conditions marked by FR+ macrophages. Recent evidence demonstrates the presence of FR+ macrophages in bacterial infections. On this basis, EC-20 was evaluated for the detection and localization of infection foci via selective uptake at sites of infection. Gamma scintigraphic imaging demonstrated accumulation of EC-20 at *Staphylococcus aureus* infection sites with a significant difference ($P < 0.0001$, $n = 12$) noted between the infected limbs of mice that received the EC-20 imaging agent compared to a control group injected with a 200 fold excess of free folic acid. A significant difference was also noted between the infected limbs versus the non-infected limbs within the same animals ($P < 0.0001$, $n = 12$). Taken together, these observations confirm both site specific and folate mediated uptake of the radiotracer. This study demonstrates for the first time the feasibility of detecting infectious disease using folate targeted imaging agents and may serve as a basis for future clinical applications.

MEDI 97

Synthesis of 2-Acetamido-2,4-dideoxy-4-[¹⁸F]fluoro-D-hexopyranoses

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Positron emission tomography (PET) is a powerful noninvasive technique for investigating physiological parameters (blood-flow, glucose metabolism, receptor binding, and drug metabolism). It is known that agents which inhibit binding between heparin sulfate proteoglycan and the amyloid precursor are effective anti-amyloid compounds both *in vitro* and *in vivo*. 2-Acetamido-2,4-dideoxy-D-glucosamine analogs have shown amyloid inhibitory properties *in vivo*. Accordingly, we designed and synthesized two novel radiolabeled fluorinated analogs of 2,4-dideoxy-D-glucosamine. We wish to report the synthesis of 2-acetamido-2,4-dideoxy-4-[¹⁸F]fluoro-D-hexapyranoses, **1** and **2**, using microfluidic techniques



MEDI 98

Imidazole-4,5-dicarboxylic acid libraries for the Molecular Library Small Molecule Repository

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One goal of the NIH Roadmap for Medical Research is the acquisition and screening of small molecules in order to identify useful molecular probes for studying the cell and biological phenomena. We have completed the synthesis of compound libraries totaling over 1000 members that are based on an imidazole-4,5-dicarboxylic acid (I45DA) scaffold, and submitted these compounds to the Molecular Library Small Molecule Repository. The compound libraries are in varying stages of screening, with the results of the bioassay data made publicly available via PubChem. The I45DA scaffold is readily modified with variations of alkanamines, anilines, alcohols, and amino acid building blocks. Our synthesized libraries were primarily monomeric in I45DA, while another segment of the library was oligomeric in I45DA. The final compounds, depending upon the structures under consideration, represent mimics of substituted purines as well as peptide secondary structures. The synthesis, purification, and characterization of these libraries will be presented.

MEDI 99

Synthesis and evaluation of novel human CYP3A inhibitors

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Ritonavir (RTV), an HIV-1 protease inhibitor (PI), is also a potent mechanism-based inhibitor of cytochrome P450 3A (CYP3A) and has been widely used as a pharmacokinetic enhancer. As a boosting agent for marketed PIs, it reduces pill burden, and improve compliance. Desoxy-ritonavir with a 1, 4-diamine core is a less potent HIV protease inhibitor. Herein we report the discovery of a novel series of CYP3A inhibitors that are devoid of antiviral activity. The synthesis and evaluation of novel analogs with extensive modifications of the 1, 4-diamine core will be presented. The structure activity relationships with respect to anti-HIV activity, CYP3A inhibitory activity, selectivity against other CYP enzymes and the human pregnane X receptor (PXR) will be discussed.

MEDI 100

Synthesis of novel vasodilatative molecules from marine natural product

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Although terrestrial plants and microorganisms are important sources in the development of clinical drugs, marine resources have recently received the attention of researchers in drug discovery because of their considerable biodiversity in the widespread oceans which cover over 70% of the earth. So, various marine natural products have been found to be useful tools for physiological and pharmacological studies and many researchers performed clinical trials or preclinical evaluation for cancer, pain, and inflammation. Because vascular-related diseases such as hypertension, stroke, subarachnoid hemorrhage and Alzheimer's dementia are a threat to the public health, the development of modulators that control vascular tone and then alleviate the symptoms is an urgent endeavor. In our marine-bio program of center for marine drug discovery (CMDDD), we discovered that two farnesylacetones isolated from *Sargassum siliquastrum* have a vasodilatation effect on the basilar and carotid arteries of rabbits. In this presentation, we describe an efficient synthesis of two farnesylacetones and the investigation on the vasodilatation effect of synthetic intermediates. The established synthetic route for these target lead compounds will be used in the synthesis of chemical mimics library for discovering the potential antihypertensive agents.

MEDI 101

Synthesis and biological evaluation of febrifugine analogs as potential antimalarial agents

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Febrifugine is a quinazoline alkaloid isolated from *Dichroa febrifuga* Lour and shows potent antimalarial activity against *Plasmodium falciparum*. Adverse side effects such as severe gastrointestinal irritation and liver toxicity have precluded febrifugine as a potential clinical drug. Nevertheless, the powerful antimalarial activity has encouraged medicinal chemists to investigate derivatives of febrifugine which may retain good antimalarial activity with an increased chemotherapeutic index. We have developed new and flexible synthetic pathways to febrifugine and analogues. Synthesized compounds were evaluated *in vitro* against chloroquine sensitive (D10) and chloroquine resistant (W2) *P. falciparum* strains and *in vitro* for potential cytotoxicity against a mammalian cell line. Initial mode of action studies of the febrifugine analogues have been undertaken. These results provide insight into the structure activity relationships

of the febrifugine analogues and may be valuable in the development of novel antimalarial drugs.

MEDI 102

Fluorescent inhibitors of trypanothione reductase based on mepacrine-conjugated diaryl sulfide scaffolds

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Trypanothione reductase (TR) is a flavoenzyme unique to trypanosomatid parasites and a target for lead discovery programs. Different inhibitor scaffolds have emerged in the past, exhibiting moderate affinity for the parasite enzyme. We showed that the combination of two structural motives of known TR inhibitors – diaryl sulfides and mepacrine - enables simultaneous addressing of two hydrophobic patches in the active site. The binding efficacy of these conjugates is enhanced compared to that of the respective parent inhibitors. They show K_{ic} values for the parasite enzyme down to $0.9 \pm 0.1 \mu\text{M}$ and exhibit high selectivity for TR over human glutathione reductase (GR). In vitro studies revealed IC_{50} values in the low micromolar to submicromolar range against *Trypanosoma brucei*, *Trypanosoma rhodesiense* and *Trypanosoma cruzi* as well as the malaria parasite *Plasmodium falciparum* not possessing a trypanothione metabolism. The inhibitors exhibit strong fluorescence which allowed visualization of the drugs in the parasite where high accumulation was observed by fluorescence.

MEDI 103

Library technique for the synthesis of ureas and carbamates from amines and CO₂ under mild conditions

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In the development of urea and carbamate containing pharmaceuticals, library synthesis is often employed to rapidly probe the structure activity relationships (SAR) and physical chemical properties of a given scaffold. This work describes a mild and efficient library synthesis technique for the synthesis of ureas and carbamates from carbamic acids derived from the DBU catalyzed reaction of amines and carbon dioxide gas. Primary amines were treated with catalytic amounts of DBU under an atmosphere of CO₂ to form the carbamic acid derivatives. The carbamic acids then reacted with Mitsunobu reagents to generate isocyanates *in situ* which were condensed with amines to afford the desired ureas. Using the methodology described, the syntheses of di- and trisubstituted ureas have been achieved in good yield. The method has proven

superior to existing methods for the generation of unsymmetrical ureas, as the symmetrical product has not been observed under these reaction conditions.

MEDI 104

Antioxidant activity of the dichloromethane extract of commercially available prunes on differentiated PC12 cells

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Neural cells are highly susceptible to oxidative damage. In this study, differentiated PC12 cells exposed to 0.05% hydrogen peroxide were used to investigate the antioxidant effects of a dichloromethane prune extract. Chromatographic and spectroscopic analysis of this extract revealed that the extract contained four major compounds that each possessed aromatic and carbonyl moieties. We first determined whether the extract alone was toxic to cells using the MTS cell viability assay. The extract was non-toxic to cells at biologically relevant concentrations (0.00001 to 0.01 mg/ml). Next, we examined the antioxidant activity of the prune extract in cells exposed to 0.05% hydrogen peroxide. At extract concentrations between 0.1 to 1 µg/ml, an increase in cell survival was observed for cells exposed to hydrogen peroxide. Therefore, results indicate that antioxidants found in prunes protect neurons from oxidative damage.

MEDI 105

Discovery of clinical candidate E6201 inspired from natural product, LL-Z1640-2(f152A1) through total synthesis

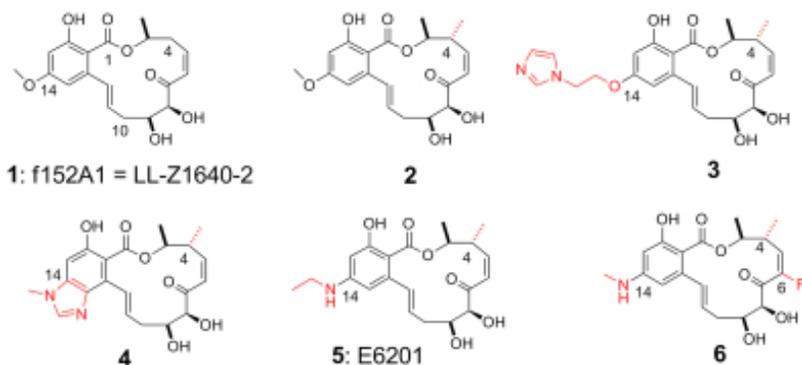
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The natural product f152A1 (**1**, LL-Z1640-2),¹ was found to exhibit potent anti-inflammatory activities *via* inhibition of MEK1 and MEKK1 *in vitro*, but it was rapidly inactivated in microsomes and plasma.² With development of effective synthesis, chemical modifications on C4 position and enone lead to an analog ER-803064 (**2**) with increased metabolic stability and somewhat reduced

potency.² Modification at C14 position lead to an *in vitro* and *i.v. in vivo* potent analog **3** (IC₅₀ = 12 nM *in vitro*; ED₅₀=6.5 mg/kg *i.v.*). But its mouse oral bioavailability was low (BA=4.1%). Further optimization at C13 and C14 positions led to **4** and E6201 (**5**) with improved BA in mouse. Introduction of C6-F resulted in **6** resulted in good BA in rat, with efficacy *in vivo* at 10 mg/kg. E6201 is undergoing phase I clinical trial for psoriasis and cancer.



MEDI 106

Predicting the flavonoids' inhibition activity towards Na,K-ATPase by computational approaches

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Flavonoids are polyphenol compounds that showed a wide range of biological activities and low toxicity. The inhibitory activity of flavonoids on Na/K-ATPase of cellular membranes is of great interest for biochemists. As it was proved earlier the mechanism of inhibition for flavonoids differs from the inhibitory action of commonly used cardiac glycosides. In this study, in order to find the significant factors for inhibitory activity and to understand the mechanism of Na/K-ATPase inhibition the 25 flavonoids are examined experimentally and theoretically. The inhibitory activity on brain Na/K-ATPase of rats has been measured for these flavonoids experimentally. A QSARs have been developed to predict the activity of these compounds by means of CoMFA, CoMSIA and other techniques. The docking studies were exhibited to reveal the observed difference in Na/K-ATPase inhibition at molecular level.

MEDI 107

Lead optimization of novel boron-containing small molecules for the treatment of human African trypanosomiasis

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Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, is a fatal disease caused by infection with the protozoan parasite *Trypanosoma brucei* (*T.b.*) that threatens millions of people in sub-Saharan Africa. The discovery and development of new, effective and safe treatments for HAT is urgently needed because current drugs for HAT are either toxic and/or complicated to administer, particularly in the treatment of patients who have progressed to Stage 2 disease, in which the parasite has migrated to the brain. Small molecule oxaboroles has been identified as a chemotype of interest for the treatment of HAT from the collaborative research between SCYNEXIS, Inc., Anacor Pharmaceuticals, Inc., Pace University and DNDi. Recently, our ongoing lead optimization efforts discovered another class of novel boron-containing molecules that inhibit *in vitro* growth of *Trypanosoma brucei brucei* with IC₅₀ in the range 80 ~; 200 nM, are not cytotoxic to mammalian cells (L929), exhibit good physicochemical and pharmacokinetic properties and demonstrate robust *in vivo* efficacy in both the acute (stage I) and chronic (stage II) mice models. The synthesis, structure-activity relationship (SAR), measured physicochemical and ADME properties, *in vivo* efficacy screening and evaluation of lead analogs will be reported herein.

MEDI 108

Benzoxaboroles for the treatment of human African trypanosomiasis

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Human African Trypanosomiasis (HAT), or sleeping sickness, is a fatal neglected disease that is transmitted through the kinetoplastid parasite *Trypanosoma brucei*. Unfortunately, current treatments are either inadequate, impractical to administer in the field or toxic. A collaborative research effort between SCYNEXIS, Inc., Anacor Pharmaceuticals, Inc., Pace University and DNDi has identified oxaboroles, and their analogs, as a potential treatment for HAT. Compounds of this class have been found to inhibit growth *in vitro* in *Trypanosoma brucei brucei*, *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. Select examples have been shown to be efficacious *in vivo* against both the acute and chronic stages of the disease. These oxaboroles have

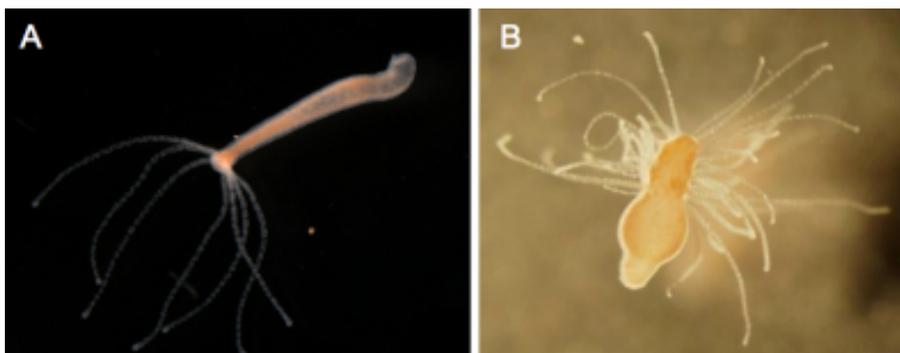
excellent physiochemical properties, are chemically and metabolically stable, and demonstrate low toxicity and good bioavailability. The synthesis, SAR, and ongoing evaluation of lead compounds in a model of Stage 2 (CNS) HAT will be disclosed.

MEDI 109

Structure activity relationship (SAR) studies of 6-(4-(dimethylamino)phenyl)-4-methylpyridin-2(1H)-one: Investigation of ectopic tentacle growth in *Hydra*

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The identification of small molecules that affect the growth and development of simple organisms, such as the cnidarian *Hydra*, can provide clues to understanding complex signaling pathways. One example is the Wnt signaling pathway, whose homologous pathway in humans is relevant in development and plays a crucial role in human disease. Random screening of a library of small molecules in a *Hydra* developmental assay produced a number of hits with varying effects; one of the most interesting observations was that a simple substituted pyridone induced reversible ectopic tentacle growth in *Hydra* without any deleterious side-effects, even with chronic exposure. SAR studies have been launched by preparing and assaying a series 4-methyl-6-aryl-2-pyridone derivatives, a structure that is readily produced in a single step using simple enoic acids and aryl nitriles as starting materials. In addition, attempts are being made to attach fluorescent or photoaffinity tags to the 2-pyridone core in order to identify the protein target in *Hydra* that is responsible for the observed effect.

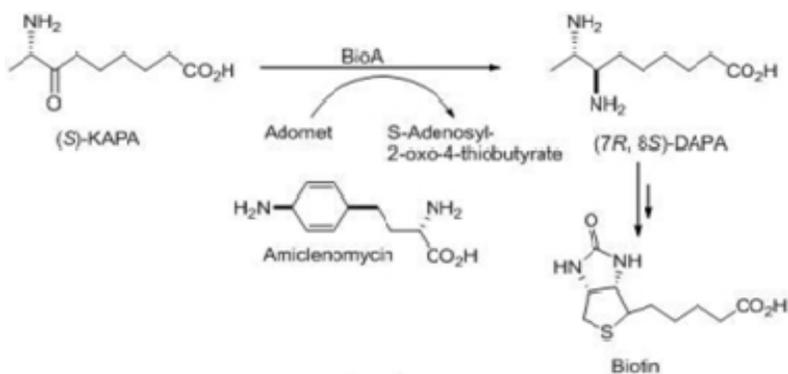


MEDI 110

Synthesis and evaluation of mechanism-based inhibitors of biotin biosynthesis in *Mycobacterium tuberculosis*

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Tuberculosis remains as one of the major bacterial infectious disease in the world. *Mycobacterium tuberculosis* (*Mtb*) the causative agent of tuberculosis has developed resistance to several antibiotics and hence, there is an urgent need for drugs with new mechanisms of action to treat this disease. Several lines of evidence have shown that biotin is essential for the survival of *M.tuberculosis*. Biotin biosynthesis is carried out by four enzymes (BioF, BioA, BioD, BioC). Our effort focuses on BioA due to availability of three dimensional structure of BioA, and amiclennomycin, a known inhibitor of BioA. BioA is a pyridoxamine phosphate dependent transaminase which catalyzes conversion of KAPA (7-keto-8S-aminopelargonic acid) to DAPA (7R,8S-diaminopelargonic acid) and concomitant oxidation of PMP (pyridoxamine-5'-phosphate) cofactor to PLP(pyridoxal-5'-phosphate).



While amiclennomycin is a potent inhibitor of Bio A, it suffers from poor chemical and metabolic stability. We will describe the design, synthesis, and evaluation of a series of mechanism-based irreversible inhibitors of BioA as a potential new class of antitubercular agent.

MEDI 111

First low μM SecA inhibitors

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SecA ATPase is a critical member of the Sec system, which is important in the translocation of membrane and secreted polypeptides/proteins in bacteria. Small

molecule inhibitors can be very useful research tools as well as leads for future antimicrobial agent development. Based on previous virtual screening work, we optimized the structures of two hit compounds and obtained SecA ATPase inhibitors with IC_{50} in the single digit micromolar range. These represent the first low micromolar inhibitors of bacterial SecA ATPase and will be very useful for mechanistic studies.

MEDI 112

Uracil nucleotides as human P2Y₂ receptor agonists: Probing the distal region of the oligophosphate moiety

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The P2Y₂ receptor is a G protein-coupled receptor (GPCR) that is activated by UTP and ATP to produce vasodilation and enhance fluid secretion in the epithelial cell layer of the lung. Uridine 5'-triphosphate analogues and 5'-tetraphosphate esters were shown to be full P2Y₂ receptor agonists in stimulation of phospholipase C in stably transfected 1321N1 astrocytoma cells. The structure activity relationship of aryl and alkyl phosphoesters (including sugar moieties) of Up₄ has been explored. Hydroxyl groups on a terminal glucose moiety were inverted or substituted with hydrogen or fluorine to probe the effect of hydrogen binding in molecular recognition. Up₄-[1]4'-deoxy-4'-fluoroglucose (MRS2928) displayed an EC₅₀ value of 0.62 μM. Aryl phosphoesters displayed greater selectivity than alkyl phosphoesters for P2Y₂ receptor in comparison to P2Y₄ and P2Y₆ receptors, and the delta-(3-chlorophenyl phosphoester) of Up₄ (MRS2921) displayed an EC₅₀ value of 0.84 μM. The chemical and enzymatic stability of selected derivatives was examined by HPLC. Molecular docking at the P2Y₂ receptor was performed to evaluate possible interactions of selected derivatives with the receptor. Our data indicate that the potency, selectivity, and stability of extended uridine tetraphosphate derivatives as agonists of the P2Y₂ receptor may be modulated by distal structural changes.

MEDI 113

Optimization of PSMA-targeted PET imaging agents

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Accurate and reliable imaging techniques for prostate cancer remain a challenge but encouraging results have been made in targeting the prostate cancer

biomarker, PSMA (prostate-specific membrane antigen). We have recently demonstrated that high-affinity, small-molecule inhibitors of PSMA outfitted with ^{18}F are effective in the selective targeting and imaging of prostate tumors in a mouse model. The focus of the current study is to optimize the P2 position of the peptidomimetic inhibitor core to enhance affinity for PSMA and to increase lipophilicity for reduced renal clearance. It is anticipated that the development of highly selective PET imaging agents for prostate cancer with improved clearance will allow for better detection of prostate cancer from early to late stages.

MEDI 114

Membrane fluidity and blood pressure of hypertensive and normotensive rats: The effects of flaxseed oil

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Systemic hypertension is known to be the major risk factor for coronary heart disease. Membrane fluidity of erythrocytes and cardiac muscle tissue were studied in spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats using spin labeling technique and EPR spectroscopy. The rats were administered flaxseed oil 0.1 mL/200 g 3 days/week for 4 weeks and blood pressure was measured once weekly, using tail-cuff method. The values of the maximum splitting parameter for a fatty acid spin-label (5-SASL) incorporated in erythrocyte and cardiac membranes from both SHR and WKY rats were compared. Our preliminary results suggest an increase in membrane fluidity and a decrease in blood pressure of SHR rats.

MEDI 115

Discovery of a series of benzoisothiazolone derivatives that are selective inhibitors of phosphomannose isomerase (PMI) for the treatment of congenital disorder of glycosylation

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Congenital Disorder of Glycosylation Type Ia (CDG-Ia) is a rare autosomal recessive metabolic disorder with multisystemic symptoms where patients have decreased activity of phosphomannomutase 2 (PMM2). This reduction in PMM2 activity impairs the conversion of mannose-6-phosphate (Man-6-P) to mannose-1-phosphate leading to defective N-glycosylation. There is currently no therapy for CDG-Ia patients and the prognosis is extremely poor. We hypothesized that CDG-Ia patients would benefit from dietary mannose supplementation combined with inhibition of PMI using small molecule inhibitors selective for PMI over PMM2 thus driving metabolic flux into the glycosylation pathway. Herein we

disclose the discovery and validation of benzoisothiazolone derivatives that are PMI-selective, cell-permeable, non-competitive inhibitors of human PMI. High-throughput screening (HTS) of a library of diverse small molecules led to the identification of hit compounds that were subsequently optimized for PMI potency and selectivity over PMM2. Representative analogues were also validated as PMI inhibitors using live cell-based PMI assays that measure metabolic flux of mannose into glycosylation vs. glycolysis. In addition, the optimized inhibitors were profiled in in vitro ADMET assays and display drug-like properties. These compounds are promising candidates for additional evaluation in vivo, and represent viable leads for the development of novel therapeutics to treat CDG-1a.

MEDI 116

Triazines as antiprotozoal agents: Design, synthesis, and structure-activity relationship analysis

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Amoebiasis is the second leading cause of death from the protozoan parasite, *Entamoeba histolytica* (*E. histolytica*) and affects more than 10% of the world's population. Globally, amoebiasis accounts for 50 million clinical cases and is responsible for 100,000 deaths annually. Metronidazole is currently the most effective anti-amoebic medication but it has several side effects including immunosuppression, mutagenic in bacteria and carcinogenic to rodents. Since the resistance to metronidazole in *E. histolytica* is also known, there is a clear need for new effective and safer amoebicidal agents. 1,2,4-Triazines are a well-known class of heterocyclic compounds and display significant biological activity especially with condensed heterocyclic systems. In this study, we synthesize a new series of triazine-thiosemicarbazide derivatives and tested them in vitro against *HM1:IMSS* strain of *E. histolytica* for their anti-amoebic evaluation. After structure-activity relationship analysis, two compounds have shown anti-amoebic activity comparable to the standard drug metronidazole. This study suggests thorough investigation of these molecules for a possibility to develop triazine analogues as potential drug candidates for amoebiasis.

MEDI 117

Competitive inhibition of α -glucosidase by novel styrylphenylurea

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The α -glucosidase plays a major role in glycoprotein processing and its inhibitors are predicted to have significant therapeutic potential as diabetic, antiviral and antitumor agents. Most developed α -glucosidase inhibitors except for azasugar derivatives show non-competitive or mixed type inhibitors. We have explored analogue of stilbene, which is a weak and non-competitive inhibitor. Modification of the stilbene side with urea derivatives to enhance inhibitory activity and change inhibition behavior led to the identification of styrylphenylurea(**1-10**), having a competitive inhibition behavior against α -glucosidase. Compound **1** bearing 2,4-difluorophenyl on urea displays 8.4 μ M of IC_{50} , four-fold increase in activity relative to that of the sugar derived α -glucosidase inhibitor, deoxynojirimycin ($IC_{50} = 39.4 \mu$ M). In kinetics study compound **1** showed the simple reversible slow binding model ($k_3 = 0.0028 \mu$ M⁻¹ min⁻¹, $k_4 = 0.00084$ min, and $k_i^{app} = 0.296 \mu$ M) against α -glucosidase.

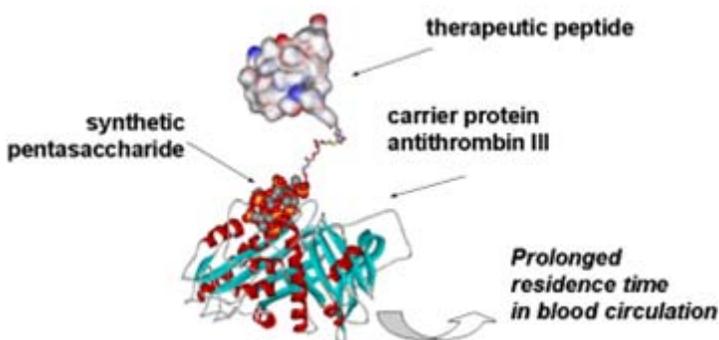
MEDI 118

CarboCarrier[®]: A novel technology to extend the half-life of small proteins and peptides

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A novel carrier technology has been developed to improve the pharmacokinetics of therapeutic peptides. The underlying principle is based on the high affinity of the unique pentasaccharide domain in heparin for antithrombin III (ATIII), a coagulation factor inhibitor that is abundant in the blood circulation. Synthetic ATIII binding glycoconjugates with enhanced PK/PD profiles have been obtained in which the strong binding of the pentasaccharide to ATIII is conserved. Previously developed (ATIII mediated) selective inhibitors of coagulation factor Xa such as fondaparinux (launched) and idraparinux (reached Phase III) require daily and weekly administration, respectively. The prolonged action of idraparinux is due to its strong interaction with target ATIII, thereby preventing renal clearance of the polar pentasaccharide. The developed CarboCarrier[®] technology is applicable to potent peptides and proteins for which the target receptor is readily accessible from the circulation. The half-lives are adjustable by changing the ATIII binding affinity of the pentasaccharide, approaching the pharmacokinetic profile of the long acting pentasaccharide idraparinux. The technology is exemplified with novel long acting antidiabetic peptide hormones (e.g. insulin) with glucose lowering activities extended by several hours in rats,

providing access to therapeutics that require less frequent injections and a lower dose.

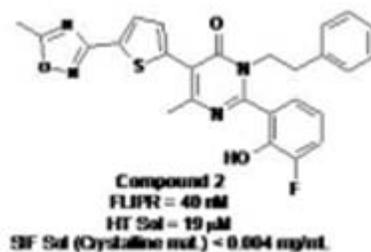
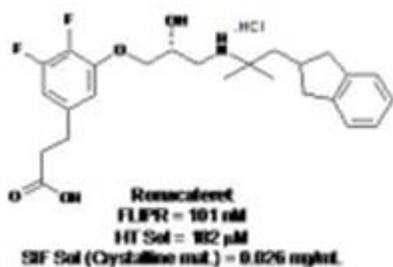


MEDI 119

Utility of small molecule X-Ray analysis in medicinal chemistry: Lessons learned in calcium receptor antagonist program

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The calcium sensing receptor (CaR), located in the parathyroid gland, functions as the principle regulator of parathyroid hormone (PTH) secretion. Increased levels of endogenous PTH levels are implicated in formation of new bone. PTH, either in its truncated form ([1-34], Forteo[®]) or as full length ([1-84], Preos[®]), has been clinically validated as a bone forming agent, and both peptides are used to treat osteoporosis. However, both forms of PTH require *daily* subcutaneous injection. An alternative approach would be an orally bioavailable small molecule antagonist of the calcium-sensing receptor (CaR) which would be expected to stimulate secretion of endogenous PTH as a potential treatment for osteoporosis.



Ronacaleret[®], which recently reached PhII clinical trials, is a small molecule antagonist of the CaR and belongs to the aminoalcohol class whilst compound 2 is a pyrimidinone. Both chemotypes have showed much low solubility from crystalline material in bio-relevant fluids despite reasonable (high in the case of Ronacaleret) solubilities in high throughput solubility screens. The poor solubility

of crystalline material is a major factor affecting the oral exposures of both chemotypes. Understanding of the crystalline forces and how they contribute to solubility/dissolution rates can have a profound influence on the developability of small molecules. Analysis of many examples from two different chemotypes were used and successfully applied in identification of two preclinical candidates. The key learnings from these endeavors will be presented.

MEDI 120

Minimizing purification bottlenecks using a multi detector approach to flash chromatography: A proactive lean strategy to reduce waste and rework in upstream and downstream processes

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Ever increasing productivity demands and cost reduction in discovery laboratories force the synthetic chemist to consider alternate isolation techniques that can reduce sample workup times without sacrificing purity or yield. The Reveleris flash chromatography system was designed using a Lean, Six Sigma philosophy to minimize or eliminate costly rework or non-value added steps evident in the chromatographic purification process in discovery settings. The RevealX™ detection technology utilizes multiple detector signals, including UV and ELSD, to trigger fraction collection and enable the chemist to eliminate the need for several, non-value added pre and post purification steps typically encountered with traditional UV only flash techniques. In addition to the time savings benefit, the chemist is able to submit samples for downstream testing and analysis with an increased confidence around sample purity

MEDI 121

General synthetic technology toward monofunctional curcumin derivates, biomimetic curcumin polyphenols, and soluble bioactive curcumin derivatives

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There has recently been tremendous interest in curcumin, [(1*E*, 6*E*)-1, 7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene 3,5-dione], because it has been shown to have antioxidant anticancer, anti-inflammatory, anti-Alzheimer's disease activity and antibiotic activity. Curcumin has poor bioabsorption and bioavailability due its poor water solubility. We have developed a general synthetic technology to produce mono-functional curcumin derivatives in which one of the phenolic groups of curcumin was chemically modified with reactive groups was recently developed. The approach involved direct one/two step covalent modification of curcumin to produce the mono-functional derivatives (with, azide,

alkyne, carboxylic acid and PEG groups) in good yields. The presence of at least one free phenolic group is necessary for the biological activity of many antioxidants like curcumin. We have exploited this synthetic technology to produce and dendritic curcumin polymers and water soluble curcumin conjugates with Anti-Cancer and potential Anti-Alzheimer's disease activity that is significantly better than the parent molecule.

MEDI 122

Fluoro macrocycles as potent HCV NS3 Protease inhibitors

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The hepatitis C virus (HCV) infection is the major cause of chronic liver disease. The HCV NS3 serine protease is essential for viral replication. It has been a target of choice for intensive drug discovery research in recent years. As an effort towards the development of a backup candidate for our clinical candidate Boceprevir, we have done research on various regions of the molecule. Macrocyclization was adopted as a tool for depeptidization and an SAR on the P1-P3 fluoromacrocycles is discussed. This class of HCV protease inhibitors had excellent potency in enzyme assay (e.g. $K_i^* = 7$ nM) and cell-based replicon assay (e.g. $EC_{90} = 40$ nM).

MEDI 123

Dithianes as alternate P2 substituent for the HCV NS3 protease inhibitors: SAR studies

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The hepatitis C virus is a major health hazard affecting over 170 million individuals worldwide and its infection is a leading cause of chronic liver disease and death from liver disease in the United States. The current standard of care treatment is a combination of subcutaneous pegylated interferon- α with oral nucleoside drug ribavirin. Response rates for HCV patients having genotypes 2 or 3 on a 24 week treatment of this are 80% whereas those with genotype 1 are less than 50%. The NS3 protease which is located at N-terminal portion of NS3 protein has a demonstrated vital role in the replication of the HCV virus. Many efforts have been focused on small molecules as NS3 serine protease inhibitors and the most advanced ones are the Boceprevir from Schering-Plough pharmaceuticals and Telaprevir from Vertex pharmaceuticals. In our search for an alternate P2 for the 2, 2-dimethylcyclopropyl proline **1**, dithianes of type **2**

emerged as one of the alternatives. Here in we report a brief summary of the identification, synthesis of some of thio P2 inhibitors and their biological activity.

MEDI 124

Inhibitors of HCV NS3 protease: Design and SAR elucidation of a series of 3-aryl-6-methoxy-isoquinolinyl tripeptides

L.-Q. Sun, sunl@bms.com, A. X. Wang, P. Hewawasam, M. Ding, Y. Tu, A. Sheaffer, F. Yu, D. Hernandez, D. Barry, H. Mulherin, M. Lee, J. Friberg, J. O. Knipe, K. Mosure, F. McPhee, A. Good, N. A. Meanwell, and P. M. Scola. Research and Development, Bristol-Myers Squibb, Wallingford, CT, United States

Hepatitis C (HCV) is a chronic viral infection which afflicts more than 200 million people worldwide. In the United States alone approximately 4 million people are infected, with 25,000 to 40,000 new cases reported annually. HCV is one of the most common causes of liver disease and has emerged as a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplants. The current standard of care for HCV patients involves treatment with pegylated interferon and ribavirin for a duration of 24 to 48 weeks, depending on viral genotype. This therapy demonstrates limited efficacy, while incurring significant side effects. Therefore, there is a clear unmet medical need to develop HCV specific antiviral agents. The HCV NS3 protease is essential enzyme for viral replication, and has been validated as a target in clinical trials. In previous disclosures, we have reported two series of potent acyclic isoquinolinyl tripeptides as HCV NS3 protease inhibitors. As part of a continued effort toward optimization of these leads, herein, we disclose a new class of 3-aryl-6-methoxy-isoquinoline derivatives as HCV NS3 protease inhibitors. SAR optimization in this series resulted in the identification of several compounds which demonstrated excellent potency (<10 nM) in both biochemical and whole cell replicon screens. Details as to the preparation, biological evaluation and structure-activity relationships of this series of inhibitors will be described.

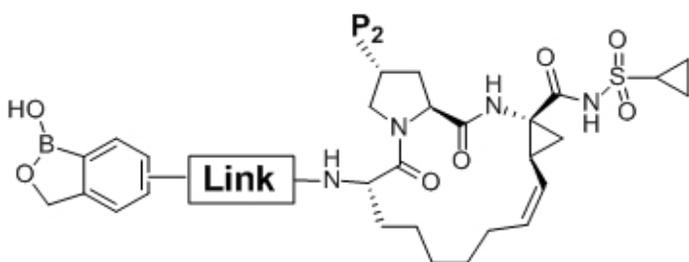
MEDI 125

Macrocyclic HCV NS3/4A serine protease inhibitors with benzoxaborole at P4 position: Design, synthesis and SAR

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HCV virus chronically infects more than 200 million people worldwide and current treatment options are very limited. In a HCV research program, one of the strategies we used for structural design is to link the stable and novel boron-containing moiety, benzoxaborole, to a macrocycle with variation at P2 site. Computer modeling suggests that benzoxaboroles with suitable orientation and linkage may interact with Ser122, Arg155 and Asp168 of HCV NS3/4A serine protease. This approach provides a class of new benzoxaborole-containing macrocyclic HCV NS3/4A serine protease inhibitors with good potencies both in enzymatic assay and cell-based replicon assay. Synthetic methodologies and structure-activity relationship (SAR) of this structure series will be presented at this conference.



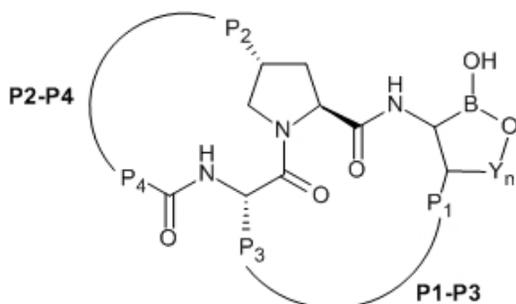
MEDI 126

Design, synthesis and SAR of cyclic boronate-containing macrocyclic inhibitors of HCV NS3/4A serine protease

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Hepatitis C virus (HCV) is the major cause of chronic liver disease such as cirrhosis, carcinoma, and liver failure. The HCV NS3/4A serine protease is an essential enzyme for the replication of the virus and has been a clinically validated target for intervention. We have discovered a novel series of cyclic boronates as HCV NS3/4A protease inhibitors. X-ray structural studies showed

that cyclic boronates inhibited NS3/4A serine protease by trapping Ser-139 hydroxyl group in the enzyme active site. To further improve enzymatic and replicon potency of these inhibitors, two macrocyclization strategies were explored through P1-P3 and P2-P4 residues, respectively. While the P1-P3 macrocyclization through the P1 cyclic boronate residue led to complete loss in inhibitor potency, the P2-P4 macrocyclization was found to significantly improve their enzymatic and replicon activities. The solution to synthetic challenges, biological activity and SAR for these macrocyclic inhibitors will be presented.



MEDI 127

Synthesis and anti-HCV activity of 3',4'-oxetane nucleosides

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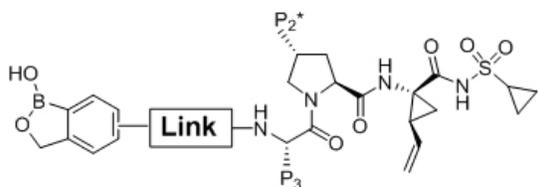
Hepatitis C virus (HCV) is a leading cause of chronic liver disease and liver transplant. Nearly 1.6% of the U.S. population and an estimated 180 million people worldwide are infected with HCV. The current standard of care, pegylated interferon alpha and ribavirin, is effective in only about half of the infected patients, and is associated with various adverse side effects. Moreover, no vaccine is available for HCV, and consequently, there is an urgent unmet need for the identification of new chemical entities to effectively treat chronic HCV infection. β -D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) is a potent nucleoside inhibitor of the HCV replication *in vitro* and its prodrug, RG7128, is currently undergoing Phase II clinical evaluation. As part of our continuing efforts to discover novel anti-HCV agents, conformationally constrained, 3',4'-oxetane cytidine and adenosine nucleosides were prepared and studied. The synthesis and structure-activity relationships of this series of novel nucleosides will be discussed in detail.

MEDI 128

Synthesis and SAR of novel acyclic tripeptides containing benzoxaborole at P4 position as HCV NS3/4A serine protease inhibitors

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Hepatitis C virus (HCV) has infected approx. 200 million people worldwide making it the leading cause of chronic liver disease such as cirrhosis and hepatocellular carcinoma. The current approved therapy, IFN-alpha and ribavirin, is only moderately effective and is associated with a range of side effects. Therefore, there is a clear unmet medical need for the development of new, effective therapeutics for the treatment of HCV infection. The NS3/4A serine protease of HCV has emerged as a popular target for HCV inhibition because it is essential for viral replication and has been validated in clinical trials. In this presentation, the synthesis and SAR of a series of novel acyclic tripeptide-containing P4 benzoxaborole inhibitors that exhibit excellent binding in an NS3 enzyme assay and activity in replicon cellular assays will be described. P4 benzoxaborole moieties may be involved in a hydrogen-bonding network with Ser122, Arg155 and Asp168 of HCV NS3/4A serine protease on the basis of computer modeling.



MEDI 129

Novel tetrazole type hepatitis C serine protease inhibitors

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Hepatitis C virus (HCV) is a major disease that infects over 170 million individuals worldwide. HCV NS3 protease is essential for cleavage of the viral polypeptide during the viral replication process. In our efforts to identify small molecule inhibitors of HCV NS3 protease, we discovered a novel series of

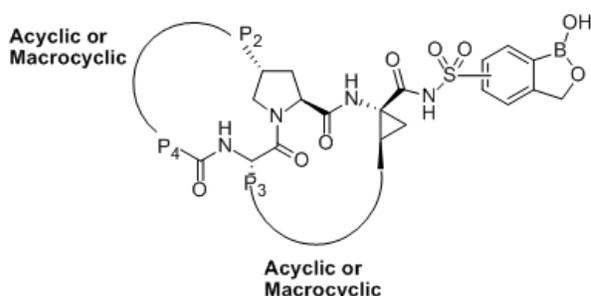
compounds featuring tetrazole groups as P*. We did systematic SAR study on both acyclic and macrocyclic compounds and were able to improve the antiviral activities dramatically based on the results. The optimal compound in this class is extremely potent against NS3 enzyme (IC50 = 0.4 nM) and showed excellent antiviral activity in genotype 1b replicon assay (EC50 = 0.8 nM). The compound also has very good bioavailability in rat PK studies. The details of synthesis and activities of these compounds will be presented.

MEDI 130

Synthesis and evaluation of novel inhibitors containing P1' benzoxaborole for HCV NS3/4A serine protease

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Hepatitis C Virus (HCV) infection continues to be a major cause of chronic liver disease, which affects more than 200 million people worldwide. Since current treatments have shown limited efficacy with significant side effects, there is urgent need for the discovery and development of new efficacious therapeutics. The HCV NS3/4A serine protease is an essential enzyme involved in HCV replication and has been a target of choice for intensive drug discovery research. We have designed new series of acyclic, P1-P3 and P2-P4 macrocyclic inhibitors that contain benzoxaborole at P1' prime region. Computer modeling suggests P1'-benzoxaboroles may potentially interact with Thr42, Lys136 and Arg109 of the enzyme. The resulting inhibitors show good enzymatic and replicon activities. Synthetic methodologies and SAR of these inhibitors will be presented.



MEDI 131

Design and synthesis of a novel series of 2-*N*-hydroxy-1-oxo-1,2-dihydro-isoquinoline-3-carboxylic acid derivatives as HCV NS5B RNA-dependent RNA polymerase inhibitors

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A series of substituted 2-*N*-hydroxy-1-oxo-1,2-dihydro-isoquinoline-3-carboxylic acid derivatives has been synthesized as a novel class of HCV NS5B polymerase inhibitors. These compounds were designed to have potential metal-chelating ability and thus could inhibit the catalytic activity of HCV NS5B polymerase that is mediated by two magnesium ions in the active site. This series of compounds inhibit NS5B in micromolar range, with moderate potency in HCV replicon cells and good selectivity over parent Huh7 cells. The predicted binding model using program GOLD illustrates that this series of compounds could form chelating interactions with the magnesium ions within the active site of the enzyme. The design, synthesis and structure activity relationship studies of this series of compounds will be presented.

MEDI 132

Introduction of P4 substituted 1-sulfonylmethylcyclohexyl groups into Boceprevir: A change in direction in the search for a second generation HCV NS3 protease inhibitor

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Hepatitis C virus (HCV) is the etiologic agent of non-A, non-B hepatitis leading to liver cirrhosis, hepatocellular carcinoma and liver failure in humans. An estimated 3% of the human population, including 4 million in the USA, is infected with HCV. Therapeutic potential of inhibiting HCV NS3 protease, vital for viral replication, has been evaluated in the clinic. Boceprevir, discovered in our laboratories, and Telaprevir are the most advanced HCV NS3 protease inhibitors that are currently undergoing phase III clinical studies in human. Since discovery of Boceprevir, the

major goal of our research program was to identify an improved (*in vitro* potency and pharmacokinetic properties), specifically-targeted, orally active compound that could be developed as a second generation HCV NS3 protease inhibitor permit once a day dosing and possibly increase virologic response. Steps involving comprehensive SAR studies, along with collaborative efforts between medicinal and structural chemistry, virology, and drug metabolism groups at SPRI culminated in the discovery of a novel, selective, potent, and orally bioavailable second generation NS3 serine protease inhibitors.

MEDI 133

Discovery of HCV replicon NS5A inhibitors: SAR and elucidation of potent dimeric components

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A high-throughput screening campaign and SAR studies identified the thiazolidinone derivative BMS-528824 as a potent inhibitor of HCV replication in a genotype 1b replicon assay ($EC_{50} = 6$ nM). The thiazolidinone exhibited an excellent therapeutic window (CC_{50}/EC_{50}) and resistance was mapped to the HCV NS5A protein. It was observed that under certain conditions, including incubation in cell culture, BMS-528824 underwent an intriguing structural transformation; however the inhibitory activity remained largely unchanged following 6 days of incubation. The structural transformation gave an oxidized and chemically stable product which was found to be devoid of inhibitory activity. Subsequently, HPLC biofractionation was performed upon cell culture media incubated with BMS-528824 in search of potentially active components. Fractions with highly potent inhibitory activity were obtained that mass spectral and NMR data analysis revealed to be dimer of BMS-528824. Information known from structure-activity studies was used to provide a prototype bibenzyl derivative which displayed excellent HCV inhibitory activity and became the basis for further SAR work. The HTS screening results, early SAR optimization to BMS-528824, biofractionation studies, and synthetic access to the prototypic inhibitor will be presented. A HCV NS5A inhibitor, BMS-790052, has provided proof-of-concept for HCV NS5A inhibition as a clinically-relevant mechanism for the control of HCV.

MEDI 134

Towards the back-up of Boceprevir (SCH 503034): Discovery of novel P₄-capped ketoamide inhibitors of hepatitis C virus NS3 serine protease with improved potency and favorable pharmacokinetic profiles in preclinical species

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Hepatitis C is the most prevalent liver disease. Viral hepatitis C (HCV), a small (+)-RNA virus, infects chronically 3% of the world's population. **Boceprevir (SCH 503034), 1**, our first generation HCV inhibitor, has already established proof-of-concept and is currently in late stage (phase III) clinical trials. In view of the positive data from our first generation compound, further work aimed at optimizing its overall profile was undertaken. Herein, we report that extension of our earlier inhibitor to the P₄ pocket by introducing a new sulphonamide moiety and optimization of the P₁/P₁' capping led to the discovery of a novel series of inhibitors of the HCV NS3 serine protease. Optimization of the P₁ residue significantly improved potency and selectivity. The combination of optimal moieties led to the discovery of new compounds which, in addition to being potent inhibitors of HCV subgenomic RNA replication, were also found to have good PK profile in rat, dog and monkey relative to **1**

MEDI 135

Optimization of benzofuran-3-carboxamide HCV polymerase inhibitors: Highly potent C-6 heteroaryl series

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Benzofuran-3-carboxamides have proven to be one of the most exciting advances in discovery of novel agents against viral Hepatitis-C. Two compounds from this series advanced to the clinic including HCV-796 which demonstrated clinical proof of efficacy. While HCV-796 and other benzofuran lead molecules feature a C6-N atom, we also investigated groups bearing a C6-Carbon atom. In this presentation, C-6 heteroaryl modifications and their SAR will be described. Leading molecules from this series have special advantages over the C6-N-analogs and possess single digit nanomolar potency in both polymerase and the whole cell sub-genomic HCV replicon screens.

MEDI 136

Development of new agents against AIDS-related opportunistic pathogens

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The incidence and severity of human opportunistic infections continues to be of grave concern in the developing countries and especially Sub-Saharan Africa. The AIDS epidemic combined with the use of powerful immunosuppressive agents for cancer chemotherapy and for organ transplantation has contributed to a significant increase in the number of people infected. With the increased incidences and resistance development to current drugs used in treating opportunistic infections, it is imperative that a search for new drugs to treat opportunistic infections be instituted. Previous studies in our laboratories and those of others have indicated that the indoloquinoline alkaloid, Cryptolepine, and its analogs possess interesting antiinfective activities. However, the toxicity profile of cryptolepine is less than desired. To improve the potency and toxicity profile of cryptolepine, we began to explore changes in its tetracyclic structure resulting in the identification of 3-substituted-quinolinium salts as a novel antifungal/antibacterial lead. Several analogs have been synthesized and evaluated for their anti-infective properties against several microorganisms including *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and Methicillin-Resistant *Staphylococcus aureus* (MRSA). The design, synthesis and evaluation of a representative example of the agents will be presented and discussed.

MEDI 137

Next generation orally bio-available HIV maturation inhibitors

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The continuing emergence of therapy-resistant forms of HIV-1 fuels the growing need for antiviral compounds with unique mechanisms of action. In this regard, HIV-1 maturation inhibitors represent a promising new class of antiviral therapeutics that prevent immature virus from transforming into infectious virions. One such compound, **MPC-4326**, is an orally bioavailable HIV-1 maturation inhibitor currently in advanced stages of clinical development. In an effort to further improve on both its antiviral activity and ADME properties, we embarked on discovery and development of next generation, oral HIV-1 maturation inhibitors. This presentation highlights the *in vitro* antiviral activity and rat pharmacokinetics data for **MPI-0461359**, a next generation maturation inhibitor currently in advanced stages of preclinical development.

MEDI 138

Construction of multivalent gp120 epitope mimics as platforms for HIV vaccine

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In 1997, a 15-mer mimotope recognized by IgG1b12, a potent virus-neutralizing and broadly reactive anti-HIV-1 MAb, was identified through phage display technology. This mimotope is a mimic of an epitope of gp120, which is known to be one of the antigenic sites of HIV. But because of the peptide's relatively small size, it may not be immunogenic on its own. Our group has designed and developed synthetic multivalent mimotope constructs of IgG1b12 as vaccine candidates. One of the constructs involves conjugation with a known potent, synthetic, "universal" helper T-lymphocytes (HTL) 13-mer epitope as an immunogenic carrier (IC). IgG1b12 mimotope and IC peptide were prepared using microwave-assisted solid-phase peptide synthesis (SPPS) using tentagel HMBA as the resin. The orthogonal amino acid side-chain deprotection and peptide cleavage allows on-bead immunofluorescent studies of deprotected peptide on the resin. The peptides were functionalized with different PEG-based linkers via microwave-assisted solid-phase amide coupling for multimerization experiments. Preliminary on-bead assays show that the 15-mer mimotope has low affinity binding towards IgG1b12. Hence, the different multivalent constructs were developed to improve binding. The synthesis involves chemically conjugating functionalized mimotope and IC peptide via 1,3 dipolar cycloaddition for multivalent presentation. Peptides and constructs were purified by RP-HPLC and characterized by SDS-PAGE and MS. These constructs will be evaluated for immunological response in animal models. Fully synthetic multivalent mimotope constructs were designed, prepared and characterized. These constructs are potential platforms for HIV vaccine development and have advantages in terms of safety, homogeneity and large-scale production.

MEDI 139

Discovery of TAK-442: A potent and orally active factor Xa inhibitor

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The coagulation enzyme factor Xa (FXa) is a promising target for the development of new anticoagulant agents. We first discovered an orally available imidazo[1,5-c]imidazol-3-one derivative with potent FXa inhibiting activity. However, metabolic amide bond cleavage of this compound was observed in human liver microsomes (HLM). In order to address the issue, our synthetic efforts were focused on replacement of the imidazo[1,5-c]imidazol-3-one ring in this series with other lactams to modulate the physicochemical properties of the compounds. As a result, TAK-442, a tetrahydropyrimidin-2(1H)-one derivative

with improved stability in HLM, optimal in vitro activity, and a favorable pharmacokinetic profile, was selected as the candidate for further development. The design, synthesis, structure-activity relationship (SAR), in vivo animal studies, and identification of TAK-442 metabolites will be presented.

MEDI 140

Structure based design and structure activity relationship of new reversible peptides inhibitors of thrombin derived from D-Phe-Pro-Arg substrate peptide

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By employing in silico structure-based design approaches, novel hexapeptides, pentapeptides and tetrapeptides were designed, new compounds that may be used as additives in the treatment of acute coronary diseases (ACD). Additionally, these new compounds were further tested for their ability to reversibly inhibit alpha thrombin using kinetics, thermodynamics, and platelets aggregation assays. Initial molecular docking experiments generated a candidate group of compounds with both L- and D- amino acids, including two classes of sequence spaces: 1-D-Phe(P3)-Pro(P2)-Arg(P1)-D-Pro(P1')-P2'-P3'-CONH₂ and 2-D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1'-P2'-P3'-CONH₂. D-Pro and D-Arg replaced Arg in the P1 and P1' positions, respectively, increasing the stability to proteolysis of the designed peptides. The P3 position was scanned for unnatural amino acids, such as Phe analogs. The P1' position contained L or D-isomers of the amino acids specific of this position, within the natural substrate of thrombin, and also other unnatural amino acids, such as L-2-thienylalanine. The newly-designed peptides competitively inhibited the alpha-thrombin induced cleavage of a chromogenic substrate, at 1,050-0.8 uM. Additionally, some lead compounds inhibited the thrombin-activated human platelets aggregation in the presence of its natural substrate, fibrinogen, effectively sustaining these peptides as powerful new anti-coagulants.

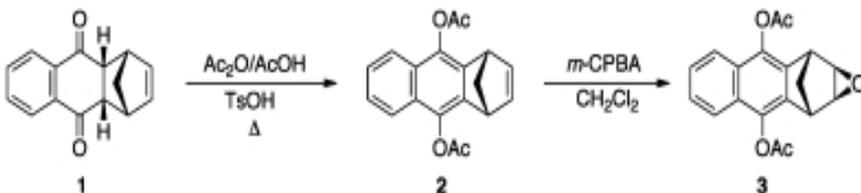
MEDI 141

New synergistic adjuvants of warfarin anticoagulant activity

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Warfarin (Coumadin®) is the only effective FDA-approved oral anticoagulant currently available for long-term prevention and treatment of thrombo-embolic problems. We have discovered a new class of compounds that exhibit no significant anticoagulant activity when administered alone, but exhibit synergistic potentiation of warfarin when co-administered. The title compounds are prepared

from the Diels-Alder adduct of 1,4-naphthoquinone and cyclopentadiene (**1**) by aromatization of the dione ring by (Ac₂O/AcOH/TsOH/D) to give the diacetate (**2**), which was oxidized (*m*-CPBA) to the *exo* epoxide (**3**). Co-administration of warfarin and (**2**) or (**3**) to rats shows that (**2**) is a modest agonist of warfarin anticoagulant activity. Compound (**3**), on the other hand, is a potent *antagonist* of warfarin activity after 4 days of co-administration, and a potent *agonist* of warfarin activity at 10 days. A model to rationalize the *in vivo* the activity of these compounds will be proposed.

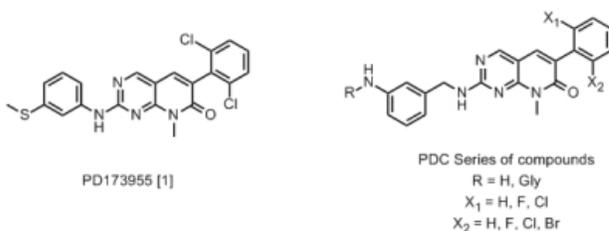


MEDI 142

Development and SAR of effective Abelson kinase inhibitors

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Substituted pyrido[2,3-*d*]pyrimidines are potent inhibitors of tyrosine kinases. Different substituted pyrido[2,3-*d*]pyrimidines vary in their specificities for different kinases. PD173955 (**1**), a member of this family, is a selective inhibitor of Abelson kinase. Abelson kinase (c-ABL) is constitutively activated when translocated to the genetic locus of the breakpoint cluster region (leading to the BCR/ABL fusion gene), thereby forming the causative pathogenetic event for the development of chronic myeloid leukemia. Clarkson and Duyster have shown that **1** and related compounds inhibited Bcr-Abl kinase activity with greater potency than Imatinib. Moreover, many of these compounds also inhibited kinase domain mutations of BCR-ABL that caused resistance to Imatinib. We have studied PD173955 and related compounds to increase the effectiveness of PD173955 by developing and testing new analogs, and to image cells *in vivo*.



MEDI 143

Design and synthesis of indolylpyridone derivatives for use as CHK1 inhibitors: A case study in structure based drug discovery

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Conventional chemotherapeutic agents such as gemcitabine, cisplatin or irinotecan induce DNA damage and activate cell cycle checkpoints. P53 defective tumors lack a functional G1 checkpoint and rely heavily on the S and G2 checkpoints, and the effector kinase Chk1, for protection against this DNA damage. Inhibiting Chk1 potentiates the anti-tumor effects of these cytotoxic chemotherapeutic agents. A number of Chk1 inhibitors, such as AZD7762, PF-00477736 and SCH-900776 have recently entered early clinical development. Using crystallographic fragment-based screening, we identified a pyridone scaffold from our kinase targeted fragment library that showed competitive binding to Chk1. Further elaboration using SBDD technology led to a series of potent compounds with increased activity. The poster will discuss the design, synthesis, and preliminary biological evaluation of the indolylpyridone series which led to the identification of VER158411, a novel small molecule inhibitor of Chk1. Representative Structures and xenograft data will be disclosed.

MEDI 144

Discovery and optimization of 1,3,5-triazine IGF-1R kinase inhibitors

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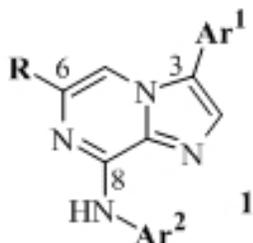
The insulin-like growth factor-1 receptor (IGF-1R) is an important oncology target that plays an essential role in the establishment and maintenance of the transformed phenotype in cancer cells. Monoclonal antibodies that target the extra-cellular binding domain of IGF-1R have advanced in the clinic validating this target. More recently, several small molecule inhibitors of IGF-1R have entered the clinic including NVP-AEW-541, OSI-906, XL-228, AXL-1717 and BMS-754807. This presentation describes the discovery of a new chemotype, 1,3,5-Triazines as IGF-1R inhibitors. Taking cues from the SAR of our recently disclosed clinical candidate BMS-754807, a 2, 4-disubstituted pyrrolo-triazine, the 1,3,5- triazines are optimized for *in vitro* cellular and *in vivo* efficacy profile. In addition to the ease of synthesis, representative examples from this chemotype offer other advantages such as metabolic stability and kinase selectivity.

MEDI 145

Discovery of Aurora kinase inhibitors based on 3, 6, 8-trisubstituted imidazo[1,2-a]pyrazine scaffold

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The Aurora kinases are a family of three Ser/Thr kinases that are critical regulators of mitosis. They are over expressed in a variety of tumors which suggests that they would be promising targets for cancer therapy. In this poster, we will disclose novel dual inhibitors of Aurora kinases A and B based on the imidazo[1,2-a] pyrazine scaffold (**1**). Lead optimization efforts that identified a progression candidate and its in vivo target engagement and efficacy studies would be described.



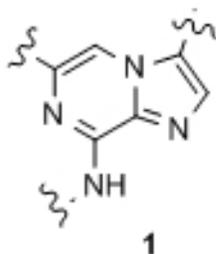
MEDI 146

Aurora kinase inhibitors based on the imidazolopyrazine core: Fluorine incorporation improves oral absorption and exposure

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Aurora kinases are cell-cycle regulated serine/threonine kinases and are required for cells to properly proceed through mitosis. Disruption of normal Aurora function impairs tumor growth and has potential for anti-tumor activity. We have identified

potent Aurora inhibitors based on the imidazolopyrazine core (**1**). However, these imidazolopyrazine-based Aurora inhibitors lacked oral bioavailability. Examination of the metabolic profile of **1** determined the sites of metabolism. Optimization led to the discovery of a series of fluoroamine analogues with improved oral bioavailability.



MEDI 147

Docking simulation study and kinase selectivity of f152A1 and its analogs

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f152A1 is known as a potent inhibitor of TNF α -transcription and in vitro kinase experimental data suggest that f152A1 and certain analogs have MEKK1 and MEK1 inhibition activities. f152A1 has highly reactive cis-enone moiety and flexible 14-membered benzoxacyclotetradecin ring. So, we performed conformation analysis and molecular orbital studies of f152A and its analogs, and the results indicate that i) the cis-enone is a Michael acceptor reactive with enzyme, ii) the active conformation is M1(8), in which the intermolecular hydrogen bond between 8-OH and the enone oxygen increases reactivity of the enone moiety and the 8,9-diol restrains the 14-membered ring conformation. The crystal structure of f152A1 with ERK2 was solved in 2007, and f152A1 covalently binds to the Cys166 at the ATP-binding site. Intermolecular docking studies were carried out for f152A1 with model structures of MEK1 and MEKK1. These docking simulation studies of f152A1 suggest it will bind at the ATP active site in the M1(8) active conformation. We will present our docking simulation results and consider these in light of the selectivity of f152A1 and its analogs for enzyme inhibition.

MEDI 148

Conformational analyses and MO studies of f152A1 and its analogs as potent protein kinase inhibitors

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f152A1 was isolated from a fermentation broth of *Curvularia verruculosa* and characterized as a potent inhibitor of TNF α transcription, with anti-inflammatory activity. f152A1 and several analogs displayed inhibitory activity against the MAP kinases ERK2 and MEK1 in *in vitro* kinase assays. Through SAR studies on f152A1 and analogs prepared via total synthesis, we have identified structural features which contribute to inhibitory activity. To rationalize these results and to aid in the discovery process, a combination of high temperature molecular dynamics and MOPAC AM1 semi-empirical molecular orbital method studies were used in studies that yielded a postulated active conformation, M1(8). The enone reactivity analyses suggested that these inhibitors were prone to Michael addition at the cis-enone moiety and might chemically react with cysteine residues in the ATP-binding site of MAP kinases. Reactivity of the cis-enone moiety and the M1(8) conformation make important contributions to the inhibitory activity on MAP kinases.

MEDI 149

Discovery and development of novel isoindolinone derivatives as JAK inhibitors

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Janus kinases (JAK) are non-membrane receptor tyrosine kinases that are activated by cytokine stimulation and have four subtypes: JAK1, JAK2, JAK3, and Tyk2. It is known that the JAK family phosphorylates signal transducers and activators of transcription (STAT) and thereby activates signals for cell growth, anti-apoptosis, etc. Activation of JAK/STAT pathway has been reported in myeloproliferative disorders (MPD) and several types of tumors. Inhibition assay for JAK2 identified 7-indolyisoindolinone derivatives as potent inhibitors. Utilizing information from an x-ray co-crystal structure, we varied substituents at the 5 position of the isoindolinone ring. The structural modification gave K454 which showed potent JAK2 inhibition and anticellular activity. Herein, we report the design, synthesis, biological activity and SAR of 5-substituted isoindolinone derivatives.

MEDI 150

Aminopyrazole inhibitors of selective c-Jun N-terminal Kinase 3 (JNK3)

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c-Jun N-terminal kinase 3a1 (JNK3a1) is a mitogen-activated protein (MAP) kinase family member expressed primarily in the brain that phosphorylates protein transcription factors, including c-jun upon activation by a variety of stress-based stimuli. In this study, we designed JNK3-selective inhibitors with >1000-fold selectivity over p38, closely related MAP kinase family member. We implemented High-Throughput-Screening (HTS) and traditional medicinal chemistry with structure based drug design. Aminopyrazole inhibitors such as **SR-3576** were found to be very potent and selective JNK3 inhibitors ($IC_{50} = 7$ nM) over p38 (>20 mM). In contrast, indazole based inhibitor **SR-3737** were potent both at JNK3 (12 nM) and p38 (3 nM). X-ray crystallographic results will be presented to explain this selectivity.

MEDI 151

Design, synthesis, and evaluation of bipolar biphenyl proteomimetics as ER α coactivator binding inhibitors

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A number of breast cancer therapeutics have effectively modulated tumor proliferation by inhibiting the binding of estradiol to the ligand binding domain of estrogen receptor alpha (ER α), however, prolonged treatment has unearthed side-effects and resistance mechanisms. Recent studies instead target the binding of coactivator proteins which bind the coactivator binding domain (CBD) through a conserved LXXLL motif, termed the NR box. Flanking the CBD are charged residues that clamp the coactivator in place by aligning with the intrinsic dipole of the peptide backbone. We have designed a novel series of coactivator binding inhibitors around a substituted bipolar biphenyl scaffold that mimics the steric and electronic properties of the NR box. This initial proteomimetic series was synthesized in a convergent manner from simple alkyl-substituted phenols using Suzuki coupling chemistry. Initial biological results support the ability of these compounds to compete for the ER α CBD. Synthesis of a broader library is currently underway, varying identity and position of hydrophobic substitution.

MEDI 152

Discovery of xanthene-based dissociated agonists of the glucocorticoid receptor

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The glucocorticoid receptor (GR) is a member of the nuclear receptor superfamily of intracellular transcription factors which includes ER, MR, AR, VDR and TR. Synthetic glucocorticoids (GCs) such as dexamethasone and prednisolone are among the most effective agents for the treatment of autoimmune and inflammatory diseases. Their long-term administration is complicated by a number of serious side effects which limits chronic dosing to only serious cases. There is significant unmet medical need for drugs which maintain the efficacy of GCs with improved risk-benefit ratios. Although the mechanisms by which GCs control signal transduction is complex, fundamental biological and pharmacologic studies have suggested that the molecular pathways primarily responsible for their anti-inflammatory effects (transrepression of transcription factors such as AP-1 and NFkB) and those responsible for side effects (transactivation) may be dissociated from each other. Described in this presentation is the synthesis and SAR of a novel class of xanthene-based dissociated GR ligands.

MEDI 153

Design, synthesis and biological evaluation of ortho-substituted phenethyl pyrazoles as selective glucocorticoid receptor modulators (SEGRMs)

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The human glucocorticoid receptor (GR) is a transcription factor and an important member of the superfamily of nuclear receptors that includes other steroid receptors such as androgen (AR), estrogen (ER), mineralocorticoid (MR) and progesterone (PR) receptors. The transcriptional activity of these receptors is influenced by complex interactions with a large number of co-regulatory proteins and also post-translational modifications. Glucocorticoids, such as dexamethasone and prednisone, are among the most widely prescribed drugs and most effective treatments for a wide range of inflammatory and immunological diseases, such as rheumatoid arthritis and asthma. However, the chronic oral dosing of glucocorticoids is associated with multiple undesirable side effects including adverse effects on metabolism (diabetes), bone tissue (osteoporosis), muscle tissue (myopathy) and skin atrophy. Therefore, there is a substantial medical need for glucocorticoids that retain the anti-inflammatory and immunomodulatory activity of traditional glucocorticoids but have a reduced risk of undesired effects.

MEDI 154

Novel non-steroidal glucocorticoid receptor modulators: Discovery of an agonist trigger in the dimethyl-diphenyl-propanamide series

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Recent interest in identifying glucocorticoid receptor (GR) ligands has mainly aimed at separating the two GR-mediated effects - transrepression and transactivation, based on the hypothesis that therapeutic effects are mediated to a major extent via a transrepression process, whereas side effects are predominantly mediated by transactivation. *De novo* design based on the previously reported GR agonist dihydro-9,10-ethano-anthracene carboxamides and SAR exploration led to the identification of the chemically tractable dimethyl-diphenyl-propanamides as potent GR ligands. Introduction of a hydroxyl group at the 4-position of the phenyl ring is critical. It acts as an agonist trigger of the functional activity in transrepression assays. Select compounds in this series showed favorable dissociation profile both *in vitro* and *in vivo* (rodent model). Modifications to improve the metabolic stability of the phenol moiety including *ortho/meta* substitutions and replacement with hydroxyl surrogates are also described.

MEDI 155

Synthesis and biological study of novel retinoids for APL (acute promyelocytic leukemia) therapy

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All trans retinoic acid (ATRA) is the treatment of choice for Acute Promyelocytic Leukemia (APL) and binds to the transcriptional repressor PML-RAR-alpha oncogene. The binding of ATRA to RAR-alpha relieves transcriptional repression and leads to induction of genes important for myeloid differentiation. The exact contributions of these structural components of ATRA in its clinically important binding to RAR-alpha receptor are not very well studied. In an effort to improve the therapeutic index and to study its binding mechanism, we synthesized novel retinoids.

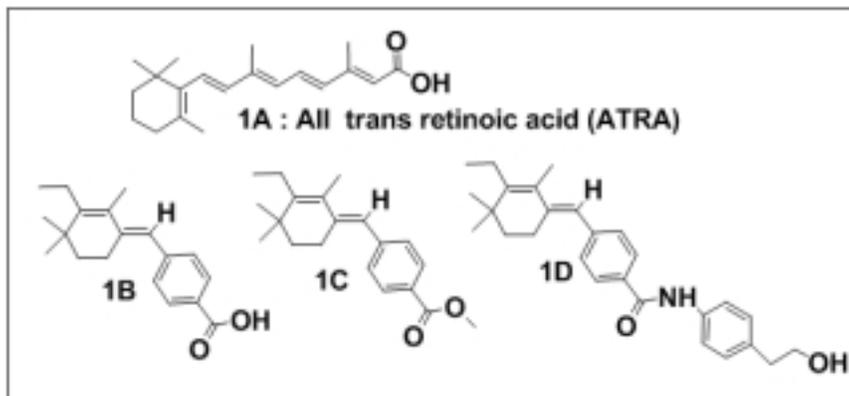


Fig 1A-D. Molecular Structures of ATRA and the synthesized retinoids 1B, 1C and 1D. ATRA consists of a cyclohexenylring with a polyene chain with four conjugated double bonds and a carboxyl group at position 15. 1B consists of a modified conjugated alkene backbone while keeping acid moiety intact (Fig 1B). 1C and 1D are characterized by modified conjugated alkene backbones and conversion of the acid group to either an ester (Fig 1C) or an aromatic amide (Fig 1D).

We tested the ability of these newer retinoids to bind to RAR-alpha as well as inhibit the proliferation of PML-RAR-alpha containing Acute Promyelocytic Leukemic cell line NB4. Our results demonstrate that both the acid moiety and conjugated double bonds are important in binding to RAR-alpha and the subsequent transcriptional repression by retinoic acid. These insights will be important in future efforts to improve the stability and efficacy of ATRA and also have implication in efforts focused on treating ATRA resistant cases of APL.

MEDI 156

Computational design of liver receptor homolog (LRH-1) antagonists based on helix-12 displacement

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Nuclear receptors (NR) are ligand-dependent transcription factors, which regulate the expression of responsive genes and thereby affect diverse biological processes including cell growth, development and metabolism. The activity of many NR superfamily members is controlled by lipophilic ligands such as steroid hormones, retinoids, vitamin D and thyroid hormone. In the ligand-dependent activation of NRs, a general and important feature revealed by X-ray crystal structures of several ligand binding domains (LBDs) is the ligand-induced re-folding of the loop to helix 12 (H12), an LBD substructure. In the apo-form, H12 takes an open conformation, while in the holo-form, it functions as a lid covering the ligand-binding pocket. The validity of the H12-folding inhibition hypothesis for molecular design of NR antagonists is also supported by X-ray crystal structures of LBD-bound antagonists. The liver receptor homolog-1 (LRH-1), a member of the NR subfamily V (NR5A), lays a critical role in embryonic development of the endoderm. In adults, it is expressed in the intestine, liver, exocrine pancreas and ovary. LRH-1 regulates the expression of genes involved in hepatic bile acid

biosynthesis and cholesterol homeostasis. Thus, the receptor may be an attractive target for drug design to treat cardiovascular disease. Its regulation of aromatase expression also suggests a possible utility in cancer therapy. Based on the H12-folding inhibition hypothesis, we have designed potential LRH antagonists by modifying known antagonists of nuclear receptors, especially SF-1. Due to the structural differences between LRH-1 and SF-1, antagonists of the latter show little or no inhibition of the former. The candidate LRH-1 antagonists are H12-folding inhibitors calculated to displace H12 from its position capping the LBD. The results offer opportunities for synthesis and biotesting of the proposed antagonists.

MEDI 157

NO-NSAIDs: Nitric oxide-releasing prodrugs of non-steroidal anti-inflammatory drugs with gastric-sparing properties

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Lately, a new class of gastric-sparing nitric-oxide-releasable non-steroidal anti-inflammatory drugs (NO-NSAIDs) is being studied as "Safe NSAIDs". As an extension of our novel disulfide linker technology,¹ we have designed, synthesized and evaluated 25+ novel NO-NSAID prodrugs of aspirin,² diclofenac,² naproxen, flurbiprofen, ketoprofen, indomethacin, sulindac and ibuprofen. Although amide-containing prodrugs did not show any bioavailability or antiinflammatory activity, the remaining types of prodrugs exhibited fair to excellent pharmacokinetic, anti-inflammatory and gastric-sparing properties. Among them, however, imide-containing NO-Aspirin, NO-Flurbiprofen and NO-Ketoprofen, ester-containing NO-Diclofenac, NO-Naproxen, NO-Sulindac and NO-Ibuprofen, and double ester-containing NO-Ketoprofen have shown promising pharmacokinetic, anti-inflammatory and NO-releasing properties and protected rats from NSAID-induced gastric damage which could be attributable to the beneficial effects of NO released from these prodrugs.

¹Satyam, A., *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 3196-3199. ²For a preliminary communication of this work, please see: Nemmani, K V S et al., *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 5297-5301.

MEDI 158

Development of new cathepsin B inhibitors containing argininal thiosemicarbazones

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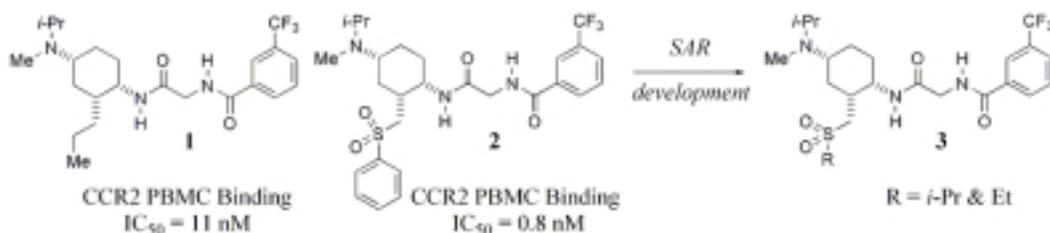
Cathepsin B has been proposed to be involved in the progression and metastatic spread of breast cancer. Associations have been made between high concentrations of cathepsin B and poor patient prognosis in primary breast cancer. Active cathepsin B localized to the plasma membrane has been shown in invasive bladder tumor cells, whereas non-invasive tumor cells have cathepsin B confined to the lysosomes. This suggests that membrane associated cathepsins may participate in tumor invasion. Specific proteinase inhibitors could lead to the development of therapeutic agents for treatment of many types of carcinomas. Described is the design and synthesis of inhibitors containing C-terminal argininal thiosemicarbazones. Inhibition data for these cathepsin B inhibitors is reported using N-Benzoyl-DL-Arginine-2-Naphthylamide hydrochloride (BANA) as the substrate.

MEDI 159

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

M. G. Yang, michael.yang@bms.com, D. G. Batt, R. J. Cherney, S. Mandlekar, M. Cvijic, Q. Zhao, J. C. Barrish, and P. H. Carter. Department of Research & Development, Bristol-Myers Squibb Company, Princeton, NJ, United States

We report the synthesis of 3-alkylsulfonylmethyl cyclohexylaminobenzamides (**3**) as CCR2 inhibitors for the potential treatment of inflammatory diseases. The *in vitro* structure-activity relationships of **3** are described. A number of the alkylsulfone-derived compounds display low-nanomolar binding IC₅₀s for CCR2.

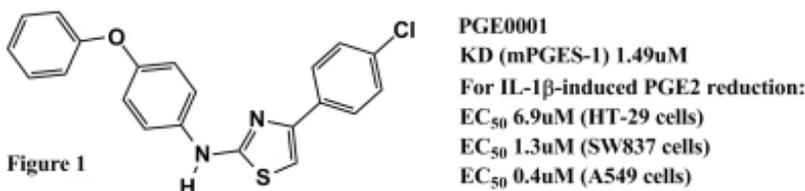


MEDI 160

Novel aminothiazoles as inhibitors of microsomal Prostaglandin E₂ Synthase-1 (mPGES-1)

E. Meuillet¹, H.-H. Chang¹, Z. Song¹, B. Smith², V. Gokhale², J. Dietrich², and C. Hulme², HULME@PHARMACY.ARIZONA.EDU. ¹Department of Nutritional Sciences and Molecular and cellular Biology, Arizona Cancer Center, The University of Arizona, Tucson, Arizona, United States, ²Department of Pharmacology and Toxicology, College of Pharmacy, The South West Comprehensive Center for Drug Discovery and Development, The University of Arizona, Tucson, Arizona, United States

Prostaglandin E2 (PGE2) plays an important role in cancer initiation and progression, where inhibition of its synthesis offers an attractive way to slow cancer cell growth. As such, most studies to date have concentrated on lowering PGE2 production by targeting cyclo-oxygenase-2 (COX-2), where small molecules have been discovered possessing anti-tumor activity in humans, with unfortunate cardiotoxicity liabilities when used in high doses. This poster presents an alternate mechanism for modulating PGE2 levels via inhibition of PGE2 synthase, in particular the isoform mPGES-1. Using *de novo* approaches utilizing a structural homology model and *in silico* screening, a series of novel amino-thiazoles have been discovered, exhibiting micromolar activity in cancer cells and promising anti-tumor activity in colon and lung cancer cell xenografts. The *de novo* approach, preliminary biochemical and functional SAR, coupled with anti-tumor properties will be discussed.



MEDI 161

Development of new cathepsin D inhibitors with hydroxyethylamine isosteres

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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 piperazines as the hydroxyethyl tertiary amine. K_i 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 162

Design, synthesis and in vitro biological evaluation of dual function inhibitors of relevance to chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a multi-factorial disorder that involves the interplay of multiple events and mediators, including an oxidant/anti-oxidant imbalance, apoptosis, a protease/anti-protease imbalance, and chronic inflammation. The molecular mechanisms which underlie the initiation and progression of the disorder are currently poorly understood, however, an array of proteases contribute to the pathophysiology of the disorder. The serine endopeptidase human neutrophil elastase and the macrophage-derived metalloprotease MMP-12 play a prominent role in the degradation of lung elastin and other components of the extracellular matrix. The multi-factorial nature of COPD suggests that a multifunctional molecule designed to disrupt the aforementioned cycle of events by inhibiting both HNE and MMP-12 or by inhibiting elastase while releasing an agent that abrogates apoptosis and/or moderates inflammation may be more effective in alleviating the disorder. Toward that end, the design, synthesis and in vitro biological evaluation of dual function molecules will be presented.

MEDI 163

Discovery of PF-610355, an inhaled once daily beta2 adrenoreceptor agonist for the treatment of COPD and asthma

D. A. Price, david.a.price@pfizer.com. PRGD, Pfizer, Groton, Connecticut, United States

The medicinal chemistry approach for the design and synthesis of a best in class, inhaled beta2 agonist for the treatment of COPD and asthma will be presented with a particular focus on ensuring biopharmaceutical properties and pharmacokinetics.

MEDI 164

Design, synthesis and biological evaluation of 2-(3*H*)-benzoxazolone and 2-(3*H*)-benzothiazolone dimers as potential antiinflammatory agents

A. H. Abdel Azeem^{1,2}, ahmed.pharm@yahoo.com, C. Mesangeau¹, S. Khan¹, K. Sufka¹, S. White¹, S. Abbas³, J. Poupaert⁴, and C. R. McCurdy¹. ¹Department of medicinal chemistry, University of Mississippi, Oxford, MS, United States, ²Department of Pharmaceutical Chemistry, Beni-Sueif University, Beni-Sueif, Egypt, ³Department of Pharmaceutical Chemistry, Cairo university, Cairo, Egypt, ⁴Department of Medicinal Chemistry, Université Catholique de Louvain, Brussels, Belgium

In an effort to develop potential anti-inflammatory agents using benzoxazolone and benzothiazolone as template blocks, two series of dimers were synthesized based on the concept of bivalent ligands. The first series (**I**) involved varying the carbon chain lengths extending from the piperazine core to the nitrogen atom of the dibenzo[*d*]oxazol-2(3*H*)-one or dibenzo[*d*]thiazol-2(3*H*)-one. The second series (**II**) was designed by isomerization at the attachment point. All compounds were examined for their *in vitro* activity on two targets, inducible nitrous oxide synthase (iNOS) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Eleven compounds showed significant activity on both targets. At the same time, these compounds were found to be devoid of cytotoxicity in a panel of cell lines. These results encouraged us to perform *in vivo* antinociceptive studies in rodent models of inflammatory nociception.

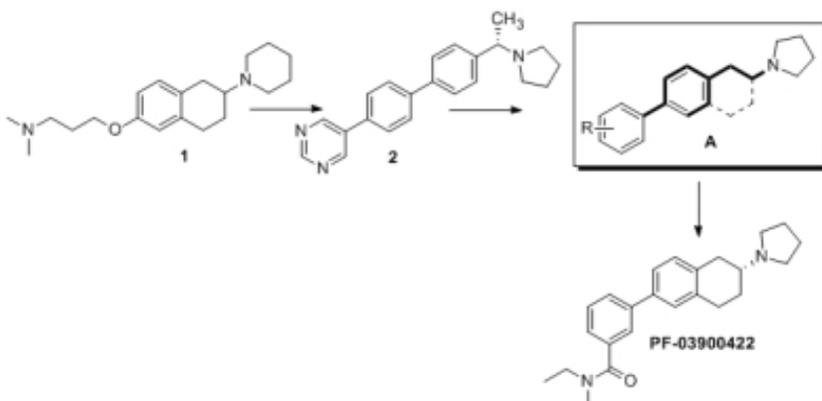
MEDI 165

Discovery of amino-tetralines as antagonist of the H-3 receptor

V. Parikh¹, vinod.d.parikh@pfizer.com, and S. McHardy², stanton.mchardy@swri.org. ¹CNS Research, Pfizer Inc., Groton, CT, United States, ²Southwest Research Center, United States

A very diverse set of structurally unique chemical series, which possessed the desired activity at the H3 receptor, were identified from both a HTS, as well as SBDD from known H3 antagonists. Unfortunately, a number of the series identified were plagued with both *in vitro* and *in vivo* toxicology findings that limited their further development. Since it is postulated that many of the undesired properties were a result of specific physical chemical and structural properties, an effort was made to move away from di-basic compounds such as compound **1**, while incorporating structural features of the mono-basic compound **2**. To this end, the general structure represented by compound **A** was targeted for synthesis. Furthermore, the compound **A** could be easily accessed and modified from the corresponding tetralone, which would allow for rapid, two-point SAR studies to be carried out using HSA. A number of variants of this pharmacophore were pursued, however the tetraline series below, highlighted by **PF-03900422**, which retain the di-aryl-phenylethyl amine core, seemed to have the most favorable activity profile for H3. The new mono-basic series, exemplified by **PF-3900422**, possesses high affinity for H3 receptor, good selectivity against other receptors, favorable pk and ADME properties, and was clean in a number of toxicology screens. The synthesis and structure-activity

relationships for binding and in vitro micronucleus data, as well as data on lead compounds such as PF-03900422 will be presented.

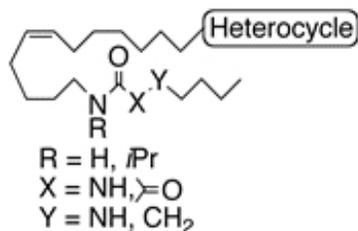


MEDI 166

14,15-Epoxyeicosa-5,8,11-trienoic acid (14,15-EET) in vivo surrogates: Influence upon vascular relaxation

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A series of heterocyclic 14,15-epoxyeicosa-5,8,11-trienoic acid (14,15-EET) agonist analogs designed to improve potency, bioavailability and half-life were synthesized and evaluated using in vitro vasorelaxation assays and animal models of hypertension. Several were sufficiently efficacious to be advanced towards clinical studies.



MEDI 167

Thienopyridone analogs as potent CDC7 inhibitors

M. Lindvall, C. McBride, M. McKenna, T. G. Gesner, A. Yabannavar, A. Walter, and **C. M. Shafer**, cynthia.shafer@novartis.com. Department of Global Discovery Chemistry/Oncology & Exploratory Chemistry, Novartis Institutes for Biomedical Research, Emeryville, CA, United States

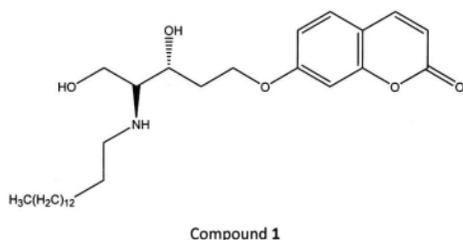
A series of 2-(heteroaryl)-6,7-dihydrothieno[3,2-c]pyridin-4(5H)-ones were designed as potent inhibitors of the serine/threonine kinase CDC7. Molecular modeling and medicinal chemistry techniques were employed to explore the SAR for this series. [abstractfigure]

MEDI 168

Synthesis of a fluorescent ceramide analog used in high-throughput screening (HTS) for the discovery of novel ceramidase inhibitors

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Ceramide, a mediator of apoptosis, is catabolized by ceramidase that has been found to be over-expressed in many cancers. Inhibition of ceramidase results in inhibition of tumor growth. Therefore ceramidase appears to be a druggable target. In order to identify novel drug-like ceramidase inhibitors, a fluorescent ceramide analog is required for HTS. Here we report an improved 6-step synthesis of compound **1**. Primary data have shown that compound **1** is suitable for HTS.



MEDI 169

Synthesis and SAR studies of 2-aryl-1,3,4-oxadiazole derivatives as human reticulocyte 15-lipoxygenase-1 (15-hLO-1) inhibitors

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Human reticulocyte 15-lipoxygenase-1 (15-hLO-1) is a nonheme, iron-containing enzyme, member of the human lipoxygenase isozyme subfamily with unique properties and functions. 15-hLO-1 has been implicated in various types of cancer and neurodegenerative diseases making it an attractive enzymatic target for pharmacological intervention. To date, few potent and selective inhibitors of 15-hLO-1 have been reported. As such, a quantitative high throughput (qHTS) screen of the molecular libraries small molecular repository (MLSMR) was performed at NCGC in collaboration with UCSC. Through these efforts we identified a 2-aryl-1,3,4-oxadiazole derivative as an attractive lead which exhibited in vitro potency in the nM range. Moreover, this chemotype showed remarkable selectivity vs. related human lipoxygenases (5-hLO, 12-hLO and 15-hLO-2). Through synthetic elaboration of this lead, we optimized potency and established an SAR profile which helped provide insight into the mode of inhibition.

MEDI 170

Discovery of a natural antagonist of macrophage migration inhibitor factor (MIF)

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MIF is a proinflammatory cytokine that plays a critical role in the pathogenesis of sepsis. Three-dimensional X-ray crystallography shows MIF has a homotrimeric conformation and we have determined that the hydrophobic cavity formed between two adjacent subunits of the homotrimer, is required for the pro-inflammatory activity of the molecule. We have designed several small molecules that fit into the site critical for the proinflammatory action of MIF, and confirmed the interaction by the crystal structure of the MIF-complex. Binding of MIF in this way inhibits its proinflammatory activity, improves the clinical outcome in several experimental models of autoimmune and inflammatory diseases. We have discovered a natural ligand, designated MIFn1 that binds the hydrophobic pocket of MIF with high affinity, and effectively modulates its activity. We examined several classes of endogenous small molecules and their metabolites and observed that MIFn1 binds to, and inhibits, the hydrophobic cavity of MIF in a dose-dependent manner with an IC₅₀ of 15.8 μM. Importantly, MIFn1 was a more potent inhibitor of MIF than ISO-1 (IC₅₀ 25 μM), the gold standard synthetic inhibitor of MIF. Therefore, we hypothesized that supplementation of this ligand during sepsis should compensate for its dramatic reduction and improve survival in our peritonitis model of sepsis in C57/Bl6 mice. Administration of MIFn1 improved the 7 day survival rate to 60% compared to 20% observed for the vehicle treated mice. Conclusion: Our data identify for the first time, the presence of a natural, ligand antagonist of MIF in plasma. This suggests that during severe sepsis, increased production and release of MIF leads to an imbalance of the MIF: MIFn1. A better understanding of the kinetics of

MIF/ligand regulation in patients with sepsis may lead to improved outcome in this devastating disease.

MEDI 171

Discovery and SAR of pyrimidine derived histamine H₄ receptor antagonists

B. M. Savall, bsavall@its.jnj.com. Johnson & Johnson Pharmaceutical Research and Development L.L.C., San Diego, CA, United States

The initial histamine H₄ receptor high throughput screening campaign identified a tricyclic pyrimidine series of low nanomolar inhibitors. Though potent, this series suffered from rapid in-vitro metabolism in human and rodent assays as well as narrow SAR around the diamine component. During the hit to lead campaign, we used a series of internal and literature observations to drive the program toward the discovery of the 6-alkyl-2,4-diamino pyrimidines. Subsequent optimization led to the discovery of a potent thiophene substituted histamine H₄ antagonist, with high selectivity over the other histamine receptors. This histamine H₄ antagonist has excellent PK properties with high bioavailability, good exposure and a reasonable volume of distribution and demonstrates efficacy in animal models. This presentation will discuss the SAR of the 6-alkyl-2,4-diamino pyrimidines as well as the profiling of representative analogs in PK and in-vivo efficacy models.

MEDI 172

Discovery of potent and selective prostanoid receptor antagonists: From high throughput screening to lead generation

J. R. Patel¹, jyoti.patel@abbott.com, Q. Shuai¹, G. Somal¹, R. Gum¹, P. Merta¹, L. Kifle¹, G. Grayson², T. Garrison², C. Hutchins³, J. Rohde¹, and J. Dinges¹.

¹Department of Hit-to-Lead Discovery, GPRD, Abbott Laboratories, Abbott Park, Illinois, United States, ²Division of Neurological Diseases Research, GPRD, Abbott Laboratories, Abbott Park, Illinois, United States, ³Department of Structural Biology, GPRD, Abbott Laboratories, Abbott Park, Illinois, United States

Prostaglandin E2 (PGE2) is a known pain sensitizer downstream of COX-1 and -2 in the arachidonic acid pathway. EP1 is one of four prostanoid GPCRs downstream of PGE2 and is a target for inflammatory and neuropathic pain. Selective EP1 receptor antagonists have the potential for equivalent efficacy and improved side-effect profiles relative to the COX inhibitors. In the literature, EP1 knockout mice and animals treated with small molecule EP1 receptor antagonists show decreased pain responses. We will discuss synthesis and SAR of a potent and selective novel series of small molecule antagonists of the EP1 receptor which was identified by high throughput screening. The data from human and rat EP1 functional assays will be presented. The data from selectivity assays against

closely related prostanoid receptors, metabolism and PK for representative compounds will also be presented.

MEDI 173

Discovery of novel thiazole EP2 antagonists

P. M. Roveto², proveto@amgen.com, A. Chen¹, Q. Cheng³, H. Dou³, T. Huang⁴, L. Jin⁴, F. Kayser², S. H. Olson², J. Treanor³, S. Wang³, S.-H. Xiao¹, G. Xu⁴, X. Zhao¹, and B. M. Fox². ¹Lead Discovery, Amgen, South San Francisco, California, United States, ²Medicinal Chemistry, Amgen, South San Francisco, California, United States, ³Neuroscience Research, Amgen, South San Francisco, California, United States, ⁴Pharmacokinetics & Drug Metabolism, Amgen, South San Francisco, California, United States

EP2 is a GPCR that is widely expressed throughout the body with PGE-2 as its natural ligand. The EP2 receptor is involved in diverse biological functions including ovulation, fertilization, salt-sensitive hypertension, bone remodeling, and activation of the innate immune response and concurrent oxidative damage. Initiated by an HTS hit, a novel collection of small molecule antagonists for the EP2 receptor has been developed. Extensive SAR work improved enzyme potency, microsomal stability, and selectivity against EP4. In addition, Cyp3A4 inhibition was decreased and there was a significant decline in hERG binding. The scaffold's structural requirements for efficient binding were elucidated through investigation of the spatial and electronic relationships between directly connected aromatic and heterocyclic rings, demonstrating the necessity of a hydrogen-bond donor, and exploring the electronic requirements of an amide-bound aromatic ring.

MEDI 174

Discovery of 1,3,4 -thiadiazole derivatives as H3 antagonists for treatment of obesity and type 2 diabetes

Y. R. Huang, ying.huang3@spcorp.com, A. Palani, anandan.palani@spcorp.com, Z. Liu, zhidan.liu@spcorp.com, X. Chen, xiao.chen@spcorp.com, R. Aslanian, robert.aslanian@spcorp.com, R. E. West, robert.west@spcorp.com, S. M. Williams, shirley.williams@spcorp.com, J. Hwa, joyce.hwa@spcorp.com, C. Sondey, christopher.sondey@spcorp.com, and J. Lachowicz, jean.lachowicz@spcorp.com. Schering-Plough Research Institute, Kenilworth, New Jersey, United States

The histamine H₃ receptor, predominantly expressed in brain, negatively regulates the synthesis and release of histamine directly. At the same time, it modulates other neurotransmitters, such as dopamine, norepinephrine, acetylcholine, glutamate and serotonin indirectly. As a result, intense research efforts were carried out in order to identify potent and selective H₃ antagonists as

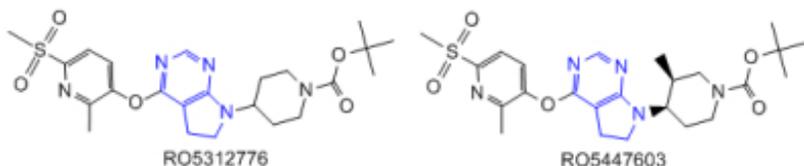
potential treatments for a variety of disorders, ranging from cognitive impairment, sleep disorder to energy homeostasis. This poster describes the design and synthesis of a novel class of 1,3,4-thiadiazole-based H₃ antagonists for potential treatment of obesity and type 2 diabetes. SAR optimization of this thiadiazole lead led to the discovery of a number of compounds with good binding affinity, high receptor occupancy, as well as improved pharmacokinetic profile.

MEDI 175

Discovery of GPR119 agonists for the treatment of Type 2 Diabetes: Part 2. Dihydropyrrolopyrimidines

R. Dominique, romyr.dominique@roche.com, S. Pietranico, K. Guertin, S. Erickson, K. Kim, K. George, Q. Qiao, Q. Zhang, L. Qi, B. Hennessy, W. McComas, C. Ma, R. Sarabu, J. Brinkman, J. Tilley, P. Gillespie, R. Goodnow, S.-S. So, P. Karnachi, V. So, C. Zwingelstein, R. Garippa, H. Salari, I. Hakimi, M. Dvorozniak, C. Spence, E. Hidalgo, K. Conde-Knape, A. Pamidimukkala, Y. Jiang, L. Guo, T. Yang, J. Racha, L. Shen, A. Railkar, and M. Myers. Discovery Chemistry and Metabolic Diseases, Roche, Nutley, New Jersey, United States

GPR119 is an α_s G-protein coupled receptor that is expressed in the pancreas and the intestines. Activation promotes insulin secretion from β -cells and stimulates the secretion of GLP-1 in the gut. Thus, small molecule agonists could be useful for the treatment of Type 2 Diabetes. The design, synthesis and SAR of a series of potent, drug-like, orally active dihydropyrrolopyrimidine GPR119 agonists will be described.



MEDI 176

Self organizing molecular field analysis based design, synthesis and *in silico* evaluation of novel 2, 4-thiazolidinedione derivatives as PTP 1B inhibitors for the management of diabetes

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Protein Tyrosine Phosphatase 1B (PTP 1B), an intracellular enzyme involved in down-regulation of receptor tyrosine kinase activity following stimulation of the insulin. PTP 1B inhibitors could potentially ameliorate insulin resistance and

normalize plasma glucose and insulin without inducing hypoglycemia, and could therefore be a major advance in the treatment of type 2 diabetes. Self Organizing Molecular Field Analysis (SOMFA), a novel 3D-QSAR technique, used in present case to study the molecular properties including both shape and electrostatic potential on reported series of 2, 4-thiazolidinediones having *in vitro* PTP 1B inhibitory activities. In the SOMFA study, a 40x40x40 Å grid originating at (-20,-20,-20), was generated around the aligned molecules. Master grid maps derived from the best model are used to display the contribution of electrostatic and shape molecular field. Based on master grid obtained, we have designed and synthesized some novel compounds having much higher activities *in silico*.

MEDI 177

Scaffold hopping of type III secretion inhibitors

M. K. Dahlgren, markus.dahlgren@chem.umu.se, C. T. Öberg, M. Hillgren, E. Wallin, P. Janson, and M. Elofsson. Department of Chemistry, Umeå University, Umeå, Sweden

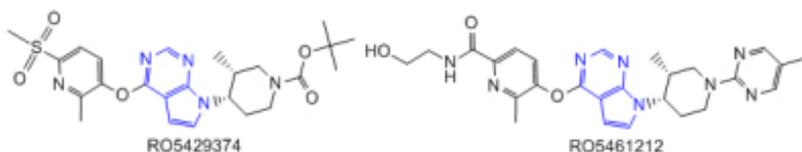
Salicylidene acylhydrazides are known inhibitors of type III secretion, an evolutionary conserved virulence system utilized by several gram-negative pathogens. In an effort to discover new inhibitors with higher potency, and higher metabolic and chemical stability scaffold hopping using the program SHOP has been performed. Two scaffolds have been identified and a number of analogs have been synthesized and evaluated biologically. The computational technique, synthesis and biological evaluation will be presented.

MEDI 178

Discovery of GPR119 agonists for the treatment of Type 2 Diabetes: Part 1. Pyrrolopyrimidines

K. George, kelly.george@roche.com, Q. Zhang, S. Pietranico, S. Erickson, K. Guertin, K. Kim, R. Dominique, C. Ma, B. Hennessy, L. Qi, Q. Qiao, W. McComas, R. Sarabu, J. Brinkman, J. Tilley, P. Gillespie, R. Goodnow, S.-S. So, P. Karnachi, V. So, C. Zwingelstein, R. Garippa, H. Salari, I. Hakimi, M. Dvorozniak, C. Spence, E. Hildalgo, K. Conde-Knape, A. Pamidimukkala, Y. Jiang, L. Guo, T. Yang, J. Racha, L. Shen, A. Railkar, and M. Myers. Department of Discovery Chemistry & Metabolic Diseases, Roche, Nutley, NJ, United States

GPR119 is an α_s G-protein coupled receptor that is expressed in the pancreas and the intestines. Activation promotes insulin secretion from β -cells and stimulates the secretion of GLP-1 in the gut. Thus, small molecule agonists could be useful for the treatment of Type 2 Diabetes. The design of potent, drug-like, orally active pyrrolopyrimidine GPR119 agonists will be described.



MEDI 179

3D-alignment and bioactive conformation hypothesis development for antagonists of the calcium sensing receptor for the treatment of osteoporosis

Z. Yang¹, Zheng.P.Yang@gsk.com, J. Ramajulu², L. N. Casillas², J. Jeong², P. A. Harris², R. Trout², Y. Lan², X. Dong², X. Chen², A. Rahman², and R. W. Marquis². ¹Computational and Structural Chemistry, GlaxoSmithKline Pharmaceuticals, Collegeville, PA, United States, ²Immuno Inflammation Center of Excellence in Drug Discovery, GlaxoSmithKline Pharmaceuticals, Collegeville, PA, United States

The vast majority of marketed drugs for the prevention and treatment of osteoporosis act as anti-resorptive agents. Another approach is to develop an agent that can elicit the secretion of endogenous parathyroid hormone (PTH), which is under the strict control of the calcium sensing receptor (CaR). The CaR is a family C G-protein coupled receptor (GPCR) and is the principle regulator of overall calcium homeostasis, capable of detecting minute variations in the extracellular $[Ca^{2+}]$. CaR small molecule antagonists, known as calcilytics, mimic low levels of extracellular $[Ca^{2+}]$ leading to the secretion of PTH. CaR antagonists should have an overall bone building effect provided that their exposure and subsequent parathyroid hormone profile is transient or pulsatile in nature. GSK has developed two distinct series of calcium receptor antagonists, with seemingly disparate shapes and distribution of chemical functionalities in 3-dimensional space. Given that no X-ray structure of a family C GPCR is available, a ligand-based drug design approach utilizing a flexible 3D alignment method has been used to develop a hypothesis regarding the correspondences between these chemical series and the bioactive conformation of each series. The hypothesis agrees with the SAR, as well as structure determination by small molecule X-ray crystallography and NMR spectrometry. More importantly, it has been successfully used to design novel templates with strong potency. Reference:

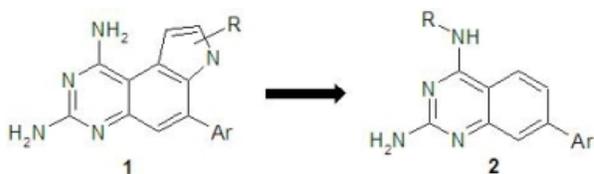
1. Robert W. Marquis, Amparo M. Lago, James F. Callahan, Robert E. Lee Trout, Maxine Gowen, Eric G. DelMar, Bradford C. Van Wagenen, Sarah Logan, Scott Shimizu, John Fox, Edward F. Nemeth, Zheng Yang, Theresa Roethke, Brian R. Smith, Keith W. Ward, John Lee, Richard M. Keenan, and Pradip Bhatnagar, "Antagonists of the Calcium Receptor I. Amino Alcohol-Based Parathyroid Hormone Secretagogues". *J. Med. Chem.* **2009**, *52*, 3982-3993.

MEDI 180

Aminoquinazolines: Novel and highly selective Protein Tyrosine Phosphatase 1B inhibitors

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Protein Tyrosine Phosphatase 1B is an intracellular enzyme that is involved in the regulation of insulin and leptin signaling. Mice lacking PTP1B have been shown to be lean and resistant to diabetes. Thus inhibitors of PTP1B should potentiate the effects both of insulin and leptin. We previously described a series of pyrido[2,3-d]pyrimidine-2,4-diamines **1** as PTP1B inhibitors and now report the SAR of a series of simpler and more selective diaminoquinazolines **2**. NMR data supporting the binding mode of members of this class to PTP1B and *in vivo* data for selective diaminoquinazolines **2** will also be presented.

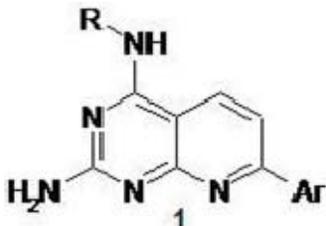


MEDI 181

Pyridopyrimidine: Novel and highly selective protein tyrosine phosphatase 1B inhibitors

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Protein Tyrosine Phosphatase 1B is an intracellular enzyme shown to be involved in the regulation of insulin and leptin signaling. Inhibitors of PTP1B would potentiate the effects of both leptin and insulin signaling, thereby, supporting the rationale that these compounds would have considerable therapeutic potential for the treatment of both obesity and Type 2 diabetes. We report here the synthesis and structural modification that led to identification of pyridopyrimidines **1** as PTP1B inhibitors. SAR and pharmacological studies of these compounds will be discussed



MEDI 182

Discovery of a potent and orally efficacious agonist of the G-protein coupled receptor 119

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GPR119 is a rhodopsin-type GPCR expressed in pancreatic β -cells and incretin releasing cells in the gastrointestinal tract. GPR119 agonists have recently gathered much attention as attractive antidiabetic therapies as these agents increase intracellular cAMP leading to increased glucose-dependent insulin secretion from pancreatic β -cells and incretin secretion from endocrine cells of the GI tract. Here we describe the SAR studies leading to the discovery of a potent and orally efficacious pyridopyrimidinone based GPR119 agonist.

MEDI 183

Discovery of [^{11}C]MK-4232 as a promising PET tracer for the calcitonin gene-related peptide receptor

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Calcitonin Gene-Related Peptide (CGRP), a potent 37 amino-acid neuropeptide has been implicated in the pathophysiology of migraine. Furthermore, clinical studies with the calcitonin gene-related peptide receptor (CGRP-R) antagonists olcegepant and telcagepant have demonstrated that blockade of CGRP-R is effective for relief of migraine headache, thus lending support that CGRP is a mediator in this process. CGRP and its receptor are found in both peripheral and central neurons. At clinically relevant plasma levels, olcegepant and telcagepant block CGRP-R in the periphery. In order to quantitate the level of central CGRP-R occupancy, we sought to identify a suitable CGRP-R PET tracer. The

chemistry and SAR pertaining to the development of [¹¹C]MK-4232 will be presented in detail

MEDI 184

Eleven amino acid glucagon-like peptide-1 receptor agonists with potent antidiabetic activity

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Glucagon-like peptide 1 (GLP-1) is a 30- or 31-amino acid peptide hormone that contributes to the physiological regulation of glucose homeostasis and food intake. Herein, we report the discovery of a novel class of 11 amino acid GLP-1 receptor agonists. These peptides consist of a structurally optimized 9-mer, which is closely related to the N-terminal 9 amino acids of GLP-1, linked to a substituted C-terminal biphenylalanine (BIP) dipeptide. SAR studies resulted in 11-mer GLP-1R agonists with similar *in vitro* potency to GLP-1. Further optimization studies identified 11-mers containing heteroaryl amino acids related to the BIP structure that have improved in-vivo activity and in-vivo pharmacokinetic properties relative to the initially discovered BIPs 11-mers. The 11-mers have a highly ordered structure and may shed light on the bound, active conformation of the N-terminal region of GLP-1. The described 11-mer GLP-1 receptor agonists represent new tools in further understanding GLP-1 receptor pharmacology.

MEDI 185

Aryl-heteroaryl ureas (AHUs) based on 4-aminoquinaldine as inhibitors of the insulin-like growth factor receptor

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The insulin-like growth factor system is an attractive target for the development of new anticancer drugs. The IGF system is composed of two ligands, IGF-1 and IGF-2, and their receptor, IGF-1R, which is a receptor tyrosine kinase. In addition

to its normal role for cell growth, IGF-1R is especially prevalent in breast and prostate cancers. PQ-401 is an aryl-heteroaryl urea (AHU) compound that is derived from 4-aminoquinoline and a substituted aromatic ring, which has been shown to inhibit IGF-1R with an *in vitro* IC₅₀ value of 15.5 μM. Our goal is to generate analogs of PQ-401 with improved potency against IGF-1R. Initially our work has focused on the homologation of an aryl methoxy group on the substituted aromatic ring. From there, we investigated the effects of the incorporation of an additional nitrogen into the quinoline ring, creating a class of heterocycles known as 4-aminonaphthyridines. This addition was proposed to exploit polar contacts in the ATP binding site, according to docking studies. Lastly, we explored analogs of PQ-401 with novel electron withdrawing substituents at the quinoline 2 position, namely analogs that incorporate 4-amino-2-trifluoromethylquinoline. Screening of our new class of inhibitors has indicated that the 2-trifluoromethylquinoline inhibitors have somewhat improved IC₅₀ values (3 μM). Additional optimizations of this scaffold are underway.

MEDI 186

Versatile, bifunctional bisphosphonates for treatment of skeletal diseases

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Skeletal diseases have a major impact on the world-wide population and economy. Around 1.5 million osteoporotic fractures are reported per year in the United States alone causing annual direct expenditures from \$12 to \$18 billion. Although several treatments are available for addressing bone diseases, bisphosphonates are the predominantly prescribed drugs. In this presentation, we will discuss the versatile nature of bifunctional hydrazine-bisphosphonates (HBPs), which are synthesized in our laboratory. *In vitro* apoptotic effects of HBPs were studied using the RAW 264.7 macrophage cell line and compared to the commonly used drug, alendronate. Cell apoptosis was studied by measuring caspase-3 activity and by visualizing the nuclear morphology using fluorescence microscopy. Additionally, enhanced affinities of HBPs to hydroxyapatite were measured and compared to alendronate and clodronate. Bifunctional HBPs were used for protein immobilization on hydroxyapatite to explore their application for drug delivery to bone tissue and for coating bone-implants.

MEDI 187

Discovery of pyridone and pyridazine heterocycles as gamma secretase modulators

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Alzheimer's Disease (AD) as an age related neurodegenerative disorder (cognitive impairment, loss of memory and language ability) is affecting millions of older people in the United States. It is very important to generate new therapies for this disease. γ -Secretase is a biochemically complex aspartyl protease-like enzyme which coupled with β -secretase can process APP to product $A\beta$ peptides. Soluble oligomeric forms of $A\beta$ peptides have been proposed as the neurotoxic agents. Inhibition of these enzymes would reduce production of $A\beta$ which should slow or halt the progression of cell death and cognitive decline. γ -Secretase cleavage of CTF β leads to $A\beta$ peptides of 37-42 amino acids of which $A\beta$ 42, the more hydrophobic form, is most toxic. γ -Secretase modulators shifts the γ -secretase cleavage towards short peptides by selectively inhibiting $A\beta$ 42 without blocking overall γ -secretase function. This will offer potentially better selectivity window over γ -secretase inhibitor – e.g. verses Notch processing. We have chosen to focus on the amino pyridone and pyridazone cores. Started with weak leads in this series, we quickly developed SAR and identified important lead compounds with good *in vitro* and *in vivo* activity and good $A\beta$ total/ $A\beta$ 42 selectivity.

MEDI 188

Novel heterocycles as γ -secretase modulators

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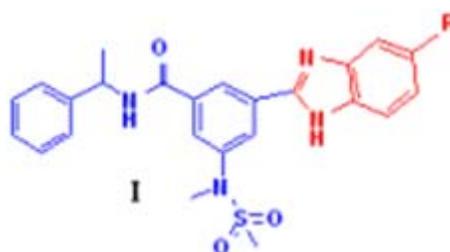
The pathogenesis of Alzheimer's disease (AD) is intimately related to the presence of neurotoxic amyloid- β peptide ($A\beta$) in the brain. Peptides $A\beta$ -40 and $A\beta$ -42 are produced by the proteolysis of amyloid precursor protein (APP), first by the membrane-associated aspartic protease β -secretase (BACE), and then further processed by γ -secretase. The development of γ -secretase modulators offers a potential therapeutic target which would shift the γ -secretase cleavage toward shorter $A\beta$ peptides resulting in selective inhibition of $A\beta$ 42 while decreasing $A\beta$ 42:40 ratio and increasing the production of shorter $A\beta$ peptides (e.g. $A\beta$ 37, $A\beta$ 38). Moreover, γ -secretase modulators offer a potentially better selectivity window than γ -secretase inhibitors since they do not block overall γ -secretase function (i.e. Notch processing). Our early studies of the synthesis and structure-activity relationships of several novel heterocycles as γ -secretase modulators will be detailed.

MEDI 189

Rational design and synthesis of potent isophthalic acid motifs as BACE1 inhibitors

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A key hallmark of Alzheimer's disease is deposition of aggregated b-amyloid peptides (Ab-40, 42) as plaques in the brain. Two proteases, b- and g-secretase have been identified to be involved in the sequential proteolysis of membrane-anchored amyloid precursor protein (APP).¹ In continuation of our efforts in finding lead compounds for inhibition of BACE1,¹ we describe herein new series of benzimidazole chromophores resident on isophthalic acid motifs (e.g. 1), as possible efficient inhibitors of this drug target. Such an approach retain the pharmacodynamic properties found in isophthalic acid derivatives described by many groups, but also may improve the pharmacokinetic properties for such motifs against BACE1 (figure 1).¹ Table 1 lists the calculated binding energy, Ki and ligand efficiency of our derivatives.



Compound	Glide Score	ΔG (kcal/mole)	Ki (nM)	Δg (kcal/mole)
Merck	-13.96	-63.62	1.11	1.55
1	-6.61	-38.79	1.07	1.21
2	-6.87	-35.68	1.06	1.08
3	-7.41	-37.57	1.07	1.10
4	-6.75	-44.24	1.08	1.30
5	-6.83	-32.72	1.06	0.96
6	-7.21	-37.39	1.07	1.04
7	-7.13	-35.39	1.06	1.01
8	-7.74	-44.48	1.08	1.24

1. (a) Al-Tel et al. *J. Med. Chem.* **2009**, 52, 6484. (b) Kortum et.al. *Bioorg. Med. Chem. Lett.* **2007**, 17, 3378.

MEDI 190

Unsymmetrical bis-styrylbenzene structure-activity relationship studies in β -amyloid plaque binding affinity and specificity

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Bis-styrylbenzenes have been studied for their capacity to bind with high affinity and specificity to β -amyloid ($A\beta$) plaques associated with Alzheimer's disease (AD). This class of compound has been studied as potential probes for early AD diagnosis using PET and MRI imaging. Most of the bis-styrylbenzene structure-activity relationship (SAR) is derived from data for symmetrical compounds; very little data is available for unsymmetrical compounds. To this end, we have developed a one-pot method for the efficient synthesis of unsymmetrical bis-styrylbenzenes. A library of 11 poly-phenolic unsymmetrical bis-styrylbenzenes were designed and synthesized based on the lead compound (*E,E*)-1,4-bis(4-hydroxy)styrylbenzene (DF-9). In this work we describe the expansion of unsymmetrical bis-styrylbenzene SAR with data from AD $A\beta$ plaque binding affinity and specificity assays, and radical scavenging activity using the DPPH assay.

MEDI 191

Pyrrolidine β -secretase inhibitors for treatment of Alzheimer's disease

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The Amyloid Precursor Protein (APP) undergoes sequential enzymatic cleavage by β -secretase (BACE) and subsequently by γ -secretase to form the $A\beta$ peptide; a hallmark of Alzheimer's disease (AD). BACE is a membrane bound aspartic acid protease found in the CNS. BACE is characterized by a large binding pocket designed to recognize 6-8 amino acid residues of APP. We have designed a series of pyrrolidine BACE inhibitors from observations of key structural features within the catalytic site followed by library chemistry to explore other key interactions. The design incorporated extension of known P1, P2 and prime side substituents from parallel efforts on hydroxyethylamine (HEA) inhibitors. These inhibitors are characterized by direct interaction between the basic nitrogen with the catalytic aspartic acids as well as well defined protein contacts on the prime and non-prime side of the enzyme. The implications of these features will be presented.

MEDI 192

Development of multi-target-directed organofluorine inhibitors as drug candidates for Alzheimer's disease

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Among the several factors responsible for Alzheimer's disease, self-assembly of amyloid- β ($A\beta$) peptide to oligomers and fibrils is considered to be of primary importance. According to the cholinergic theory, reduction of the acetylcholine (ACh) in specific areas of the brain may also aggravate the disease. Acetylcholine is hydrolyzed by its metabolic enzyme the acetylcholinesterase (AChE). Recent studies have also shown a complex formation between AChE and $A\beta$ peptide that induces amyloid fibrillogenesis. The urge for better therapeutic drugs has initiated efforts to synthesize multi-target-directed small molecule ligands. For this purpose, we have synthesized new organofluorine compounds that showed dual inhibition for the $A\beta$ fibril formation as well as the hydrolytic activity of AChE. The validation of the binding mechanism was carried out using molecular docking. The AChE inhibition was evaluated by Ellman's spectrophotometric method. The inhibitory activity of these molecules in fibril formation was determined by the standard Thioflavin T fluorometric assay, while atomic force microscopy (AFM) was used to follow the morphology of $A\beta$ aggregates. Our observations reveal that these small molecule organofluorine compounds are efficient dual inhibitors and block both the AChE activity and $A\beta$ fibril formation.

MEDI 193

Synthesis and evaluation of mefloquine analogs as affinity ligands to identify the target of mefloquine in *Mycobacterium tuberculosis*

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Mefloquine is a well-known anti-malarial drug that has recently been identified as also having potent antituberculosis activity. For the purpose of developing better anti-*Mycobacterium tuberculosis* agents with greater potency and less toxicity, determining the target of mefloquine in *M. tuberculosis* is crucial. In this regard we have synthesized mefloquine derivatives suitable for immobilization on a solid support. Such compounds may be specifically recognized and bound by bacterial proteins, enabling target identification by proteomic analysis. The (+) *erythro* form of mefloquine exhibits the greatest activity in vivo and accordingly, analogs were developed from both (\pm) and (+) mefloquine. Anti-mycobacterial

assays of these mefloquine derivatives revealed in vitro activity profiles similar to that of mefloquine standards and several of the analogs also retained submicromolar anti-plasmodium activity.

MEDI 194

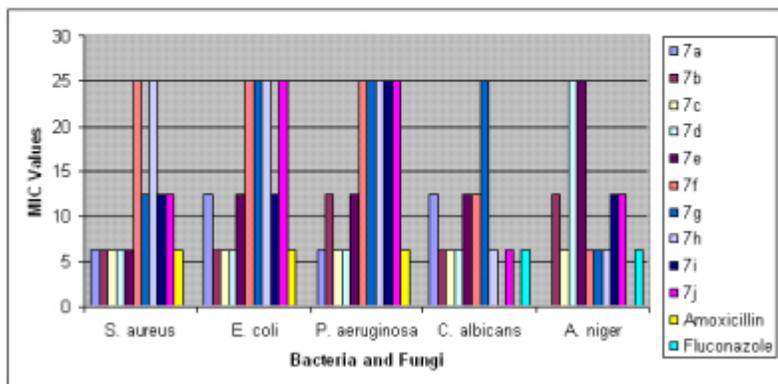
Design, synthesis, and in vitro antibacterial and antifungal activities of some novel spiro[azetidine-2, 3'-indole]-2, 4(1'H)-dione

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The present study deals with the synthesis of novel spiro[azetidine-2, 3'-indole]-2', 4(1'H)-dione derivatives (**7a-j**) from the reactions of 3-(phenylimino)-1,3-dihydro-2H-indol-2-one derivatives (**6a-j**) with chloroacetyl chloride in presence of triethyl amine (TEA).

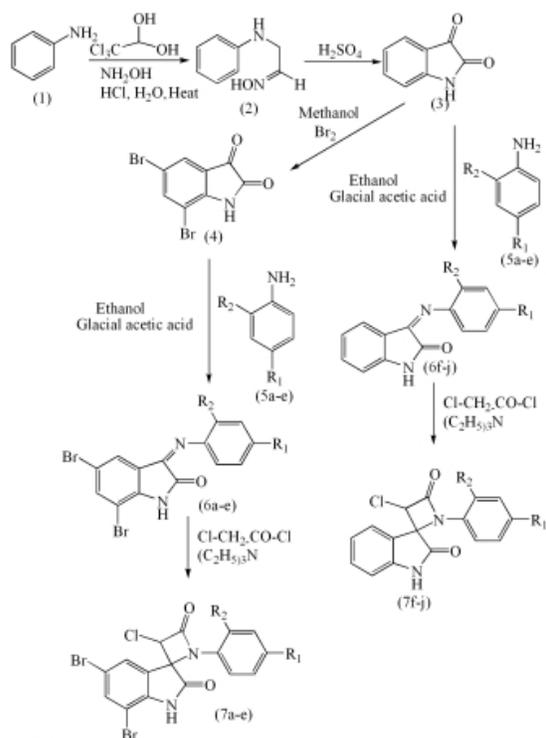
Figure 1

Comparison of MIC values (in µg/ml) of synthesized compounds (7a-j) and standard drugs against different bacteria and fungi.



All the compounds were characterized using IR, ¹H NMR, MS and elemental analysis. They were screened for their antibacterial and antifungal activities

Scheme - 1
Schematic representation for the synthesis of novel spiro[azetidino-2, 3'-indole]-2, 4(1'H)-dione



Where,

Comp. no.	R ₁	R ₂
7a	CH ₃	H
7b	H	CH ₃
7c	OCH ₃	H
7d	H	OCH ₃
7e	H	H

Comp. no.	R ₁	R ₂
7f	CH ₃	H
7g	H	CH ₃
7h	OCH ₃	H
7i	H	OCH ₃
7j	H	H

Results revealed that, compounds **(7a)**, **(7b)**, **(7c)**, **(7d)** and **(7e)** showed very good activity with MIC value of 6.25-12.5 µg/ml against three evaluated bacterial strains and the remaining compounds showed good to moderate activity comparable to standard drugs as antibacterial agents. Compounds **(7c)** and **(7h)** displayed equipotent antifungal activity in comparison to standard drugs. Structure-activity relationship study of the compounds showed that the presence of electron withdrawing group substitution at 5' and 7' positions of indoline ring and on ortho or para position of phenyl ring increases both antibacterial and antifungal activity of the compound.

MEDI 195

N-Thiolated β-lactams: Altering microbiological activity and bacterial cell targeting with C₃ ring functionality

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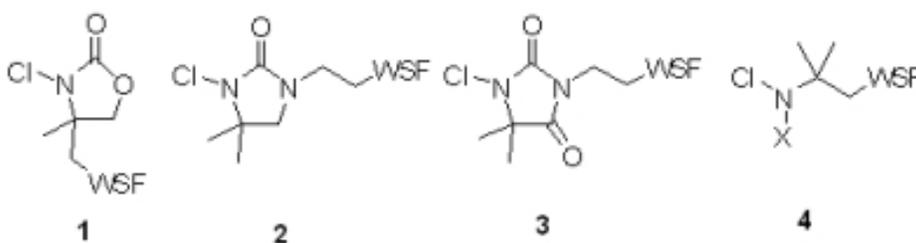
The main objective of this project is to check any change in inhibitor activity if the side chains were water-soluble polar groups like amino acids, sugar or PEG. This project also includes studying the effect of side chain structure and polarity at the C₃ position of N- Thiolated β-Lactams on solubility and antibacterial activity. Our primary objective is to see if there is a correlation between chain length and polarity at the C₃ position of N- Thiolated β-Lactams on the antibacterial activity. The project started to diverge and now we are looking at different moieties like carbohydrates and PEG attached to N-Thiolated β-Lactams.

MEDI 196

Water-soluble N-chloroheterocycles as topical antimicrobial agents

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N-Chloroamines are potent antimicrobial agents whose activity increases with decreasing pH. For applications in which physiological pH is required, compounds with pH-independent activity are desired. Water-soluble N-chlorooxazolidinones (**1**), N-chloroimidazolidinones (**2**) and N-chlorohydantoin (**3**) were synthesized and their antimicrobial activities assayed at pHs 4 and 7. All compounds are active against a diverse panel of Gram-positive bacteria (*S. aureus*), Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *S. marcescens*), and yeast (*C. albicans*). Like N-chloroamines (**4**), N-chlorinated heterocycles show good selectivity for microbes over human cells (therapeutic indices of 0.2-100). However, unlike N-chloroamines, N-chlorinated heterocycles showed 0.5-32 fold better activity at pH 7 compared to pH 4. WSF = water solubilizing functionality (SO₃⁻, NMe₃⁺, etc.)



MEDI 197

Computer-aided molecular design and synthesis of new inhibitors of bacterial RNA polymerase

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Structure-based drug design techniques including *de novo* molecular design (using SPROUT) and virtual high throughput screening (using eHiTS), have been used to discover novel inhibitors of bacterial RNA polymerase (RNAP). In the first series, a number of rifampicin derived inhibitors were designed to make additional contacts near the active site of RNAP. Following short and efficient syntheses and in keeping with the design predictions, one of the resulting inhibitors displayed an IC₅₀ of 17 nM against *E. coli* RNAP, in addition to possessing interesting bactericidal activity against a rifampicin resistant strain of *Staphylococcus aureus*. In the second series, a number of small molecule inhibitors (<10 µM), targeted to bind at the myxopyronin binding site on RNAP, have been discovered following the application of eHiTS. Detailed mode of action studies support RNAP as the target of these hit molecules. Further hit optimisation including x-ray co-crystallization trials are in progression towards development of a lead molecule as a potential new antibiotic.

MEDI 198

Modifying fluoroquinolones to overcome multi-drug resistance in methicillin-resistant *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a worldwide problem, and, increasingly, is no longer confined to hospitals. With the emergence of *S. aureus* with reduced susceptibility to vancomycin (VISA and VRSA), there is clearly a need for a pipeline of new antibiotics to combat the new MDR strains. The fluoroquinolones (FQs) are broad-spectrum antibiotics that are effective against *S. aureus*. Resistance to FQs can be due to either mutations at their target sites of DNA topoisomerase IV and DNA gyrase, or to export of the drug caused by overexpression of the efflux pump NorA. In this presentation we show a class of modified FQs which have shown excellent results against examples of both MRSA and VISA, while retaining their broad-spectrum activity

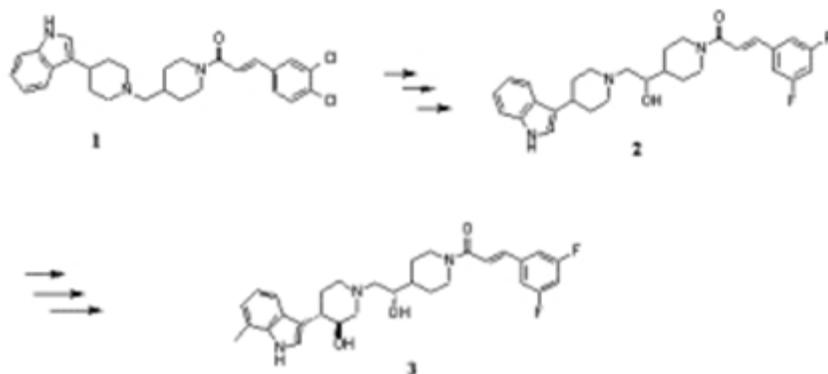
MEDI 199

Design and synthesis of a potent, selective CCR2 receptor antagonist as a potential treatment for atherosclerosis

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The CCR2 chemokine receptor and its primary ligand, monocyte chemoattractant protein-1 (MCP-1), play key roles in attracting monocytes to an inflammation site. Thus, a small molecule that blocks the CCR2 receptor may offer therapeutic benefit in treatment of inflammatory diseases. Here, we report our efforts toward the discovery of potent CCR2 antagonists starting from **1**. This led to the identification of a series of highly active CCR2 inhibitors (**2**) that display *in vivo* efficacy. Further optimization of this series resulted in the identification of **3** which was selected for advanced studies.



MEDI 200

Discovery of a series of imidazo[4,5-*b*]pyridines with dual action as angiotensin II type 1 receptor (AT1) antagonists and partial PPAR γ agonists

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Hypertension is commonly associated with an array of other risk factors for cardiovascular disease including obesity, insulin resistance, elevated plasma glucose, and dyslipidaemia. They are collectively referred to as the metabolic syndrome. Angiotensin II type 1 receptor blockers (ARBs) are clinically effective, well tolerated agents for the treatment of hypertension. Among the ARBs, telmisartan (Micardis®), an approved ARB with well documented efficacy in blood pressure reduction, demonstrated improvements in glucose and lipid metabolism in small clinical trials. This activity was associated with weak partial agonism of PPAR γ . Compounds possessing the dual pharmacology of AT1 receptor antagonist/partial PPAR γ agonist could potentially treat several recognized cardiovascular risk factors including hypertension, insulin resistance and hypertriglyceridemia in patients with metabolic syndrome. Our group recently

embarked upon a search of novel agents possessing this novel dual pharmacology. This presentation will describe the discovery, synthesis and in vitro evaluation of a series of imidazo[4,5-*b*]pyridines with the desired dual pharmacology. In addition, the in vivo pharmacology profile and the preclinical pharmacokinetic parameters of the compound selected as candidate for development will be provided.

MEDI 201

Ligand efficiency ranges of drugs and clinical candidates

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The calculation of ligand efficiency has proven to be a powerful tool in comparing the relative merits of compounds with varying sizes and potencies. It is one of several potency-based properties that have been proposed as a way of assessing chemical desirability. However, for lead-like and drug-like compounds, ligand efficiencies are generally related to the original theoretical threshold for a drug-like compound (0.29 kcal/mol/non-H atom, from Hopkins et al, Drug Discovery Today, 2004, 9, 430). Here, we describe our efforts to provide more realistic benchmarks for known drugs by using the GVK database to match known drug mechanisms of action to in vitro data. Issues in assembling this data set will be highlighted. We show that ligand efficiencies for known drugs are typically higher than the accepted threshold, and that there is a progressive improvement in ligand efficiency in moving from clinical candidates to marketed drugs.

MEDI 202

Optimization of the first generation Renin inhibitors

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The renin-angiotensin system (RAS) has been known for a long time as being a pivotal player in the regulation of blood pressure as well as in the maintenance of sodium and electrolyte balance. RAS blockers have demonstrated efficacy in hypertension, cardiac failure, and in renal protection. Recently we have disclosed a class of small molecule bicyclic inhibitors of renin, such as ACT-077825 (*IC*₅₀ buffer = 0.2 nM, *IC*₅₀ plasma: 19 nM), a highly potent renin inhibitor, but prone to

high plasma protein binding. In order to reduce plasma protein binding we have explored the introduction of polar functionalities at various positions of the bicyclic inhibitors. The introduction of a series of tertiary amines at the “linker” region and the replacement of the “central” phenyl moiety with a series of 5-membered heteroaryls and their activity *in vitro* and *in vivo* will be presented.

MEDI 203

New class of potent, nonpeptidic, orally active renin inhibitors

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The Renin-Angiotensin-Aldosterone system (RAAS) is widely accepted as an important regulator of cardiovascular, renal and adrenal function playing a major role in water and salt homeostasis, as well as blood pressure control. As a part of our renin inhibition program we recently published a new class of bicyclic 3,9-diaza-bicyclononenes (J. Med. Chem. 2009, 52, 3689). The most potent compounds in this series inhibited renin with $IC_{50} < 1$ nM (in buffer) and showed *in vivo* efficacy at 10 mg/kg in double transgenic rats (TGRs) expressing both the human angiotensinogen and the human renin genes. In order to explore the role of the CH_2-N-CH_2 bridge of the 3,9-diazabicyclononene moiety a series of other related bicyclic compounds with identical substituents at the key positions were prepared, i. e. 9-aza-3-oxabicyclononenes, 9-azabicyclononenes, 3,3-dioxo-3 λ 6-thia-9-aza-bicyclononenes, 3-oxo-3 λ 4-thia-9-aza-bicyclo[3.3.1]non-6-enes, and 8-azabicyclononenes. For comparison also the corresponding tetrahydropyridine analogs were designed and prepared. Among others, we identified the *first achiral, potent renin inhibitors*. Some of these compounds are efficacious after oral administration (10 mg/kg) in TGRs.

MEDI 204

Piperidines as potent, orally active renin inhibitors: Optimization of the amide substituent

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The Renin-Angiotensin-Aldosterone System (RAAS) is one of the major and most intensively studied regulating systems of the arterial blood pressure in humans. It plays a pivotal role not only in cardiovascular diseases, but also in

renal diseases, and other metabolic diseases as well. The RAAS consists of a two-step cascade. First, the aspartic proteinase renin cleaves its only known substrate, angiotensinogen, in the rate-limiting step to the decapeptide angiotensin I. In a second step, angiotensin I is cleaved either by the metalloproteinase angiotensin-converting enzyme (ACE) or by the serine proteinase chymase to the tensoactive octapeptide angiotensin II. The exclusive and rate-determining function in the RAAS makes renin an ideal pharmacological drug target. Recently, we have described rational design and the preparation of a new series of 3,9-diazabicyclo[3.3.1]nonene derivatives as potent, non-peptidic and bioavailable renin inhibitors (J. Med. Chem. 2009, 52, 3689). Based on this and previous knowledge (Farmaco 2001, 56, 21-27), we have designed a new series of potent, orally active renin inhibitors with a piperidine core structure. After optimization of the amide substituent and with the help of modeling based on X-ray structural analysis, we have prepared compounds with excellent potency against renin (in buffer and in plasma) and with very good selectivity profiles. These compounds were well absorbed and efficacious orally at 1 mg/kg in double transgenic rats (TGRs).

MEDI 205

Novel small molecule anti HBV compounds using click chemistry

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We have synthesized and tested a series of small molecules that interfere with the assembly of the Hepatitis B virus (HBV) capsid shell, as a strategy for the development of HBV-specific antiviral agents. Most commercial treatments for chronic HBV are nucleoside/tide analogs, usually applied as mono-therapies that inhibit HBV's reverse transcriptase. Alternative targets offer the opportunity for combination therapies and a more persistent effect on chronic infection. The HBV capsid plays roles in intracellular trafficking, viral nucleic acid metabolism, and protecting the viral genome. The capsid is an icosahedral complex of 120 copies of the homodimeric core protein (Cp). Cp has no known cellular homologs; thus its assembly is an attractive target for antiviral therapeutics.

Heteroaryldihydropyrimidines, HAPs, are a family of small molecules that inhibit HBV replication (1) by accelerating capsid assembly and inducing the formation of non-functional aggregate structures (2,3). Analysis of a low-resolution (5Å) crystal structure of HAP-capsid crystals shows that the bound HAP molecule is located at a Cp-Cp interface and is partly solvent exposed via a short "tunnel" between the two proteins (3). We have developed a series of HAPs and HAP dimers using 'click chemistry' to examine the structure-activity relationships in the assembly misdirection process, and have observed wide variations in the kinetics and thermodynamics of protein-protein interactions modulated by these small molecules.

1. Deres, Schroder, Paessens *et al.* Science 2003; 299:893-896.
 2. Stray, Bourne, Punna, *et al.* Proc Natl Acad Sci U S A 2005; 102:8138-8143.
- Bourne, Finn, Zlotnick. J Virol 2008; 82: 10262–10270.

MEDI 206

Arylpropenamide derivatives as inhibitors of hepatitis B virus replication

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Phenylpropenamides have been reported to be a unique class of non-nucleoside compounds that inhibit replication of the hepatitis B virus (HBV). We were interested in exploring this class of agents in order to develop potent anti-HBV agents that could be combined with any of several nucleoside/nucleotide analogs used as monotherapy, the current standard of care. To accomplish this objective a series of substituted arylpropenamide derivatives were prepared and evaluated against HBV *in vitro*. While exploring this chemotype, the stereoisomers were separated and their structures were characterized, revealing that, contrary to previous reports, the activity of this class of molecules resides in a single stereoisomer. Structure-activity relationship studies around the active single isomer revealed compounds that displayed potent antiviral activity against hepatitis B virus *in vitro*. Structure-activity relationships of this series and data supporting the structural assignment of the active isomer will be presented.

MEDI 207

Synthesis, biological evaluation and molecular modeling of nantenine as a 5-HT_{2A} receptor antagonist

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MDMA (3,4-methylenedioxy methamphetamine) is a psychoactive drug which is thought to act via stimulation of secretion as well as inhibition of re-uptake of large amounts of serotonin, noradrenaline and dopamine in the brain. MDMA also acts directly on a number of receptors, including 5-HT_{2A} receptors. There is considerable evidence that 5-HT_{2A} antagonists can modulate behavioral and physiological effects of MDMA in animals. Nantenine an aporphine alkaloid ex *Nandina domestica* has been reported to block and reverse a range of behavioral and physiological effects of MDMA in mice. It is known that nantenine has moderate 5-HT_{2A} antagonist activity. However, very little structure-activity relationship (SAR) studies have been performed on nantenine in relation to its

antagonist activity at the 5-HT_{2A} receptor. We have prepared a library of novel analogs to investigate the structural requirements for nantenine's 5-HT_{2A} activity. Our studies demonstrate that N-methyl group and structural rigidity of the aporphine nucleus are important for activity, but that appropriate substitutions on the aromatic aporphine core can improve 5-HT_{2A} antagonist activity. Further details of our SAR study as well as results of molecular docking experiments will be presented.

MEDI 208

Synthesis and CNS receptor affinity of Nantenine

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Nantenine, a naturally occurring aporphine alkaloid has been shown to block and reverse behavioural and physiological effects of the synthetic psychostimulant MDMA in mice. Our goal is to elucidate the role of various receptors in nantenine's MDMA antagonizing effects. Towards that end, we have engaged synthetic routes to prepare (±)-nantenine and have evaluated its receptor binding profile against a panel of 24 CNS receptors and transporters. (±)-Nantenine was prepared from tetrahydroisoquinoline precursors via two routes involving a PIFA-mediated oxidative biaryl cyclization and a direct biaryl coupling procedure as the key steps. For the key biaryl cyclization step, the direct biaryl coupling protocols provided a higher yield of aporphine, as compared to the PIFA-mediated coupling. Among the CNS receptors and transporters investigated, (±)-nantenine was found to have high affinity and selectivity for the α_{1A} adrenergic receptor. Further details of our synthetic and biological investigations will be presented.

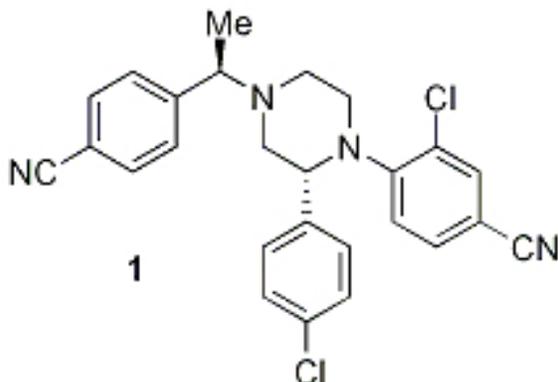
MEDI 209

Novel 1,2-diarylpiperazines as CB1 antagonists

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The blockade of the CB1 receptor has been demonstrated to decrease body weight by way of reducing food intake and increasing energy expenditure. Herein

we describe our novel 1,2-diarylpiperazines as CB1 antagonists. Our studies culminated in the identification of **1** as a potential recommendation candidate. Compound **1** was equipotent to rimonabant in animal models demonstrating the ability to reduce body weight and adiposity when dosed orally.

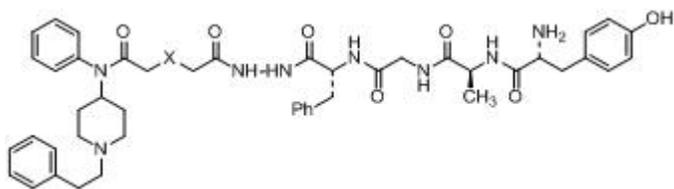


MEDI 210

Synthesis and biological evaluation of mixed peptide-nonpeptide analgesics: Biphaline/Fentanyl chimeras

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Biphalin is a unique dimeric opioid peptide, composed of two tetrapeptides connected “tail-to-tail” by a hydrazide bridge - [Tyr-D-Ala-Gly-Phe-NH]₂ has high analgesic potency both in vivo and in vitro and exhibits a high affinity at both μ and δ receptors. Most recent data show that Biphalin is unlikely to produce dependency use. There have been many attempts to modify its structure to obtain products unaffected by the action of enkephalinases, to enhance its antinociceptive activity, and to modify the BBB penetration. Assuming, that Tyr-D-Ala-Gly-Phe-NH- is the minimal fragment necessary to express the same biological activity profile as Biphalin, we undertook an attempt to create a hybrid peptide-nonpeptide “bivalent” liands composed from new Fentanyl derivatives synthesized by us and “half” Biphalin. Methods of synthesis and SAR results will be reported.

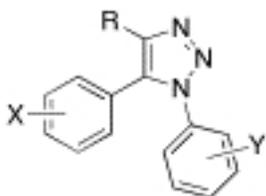


MEDI 211

Synthesis and biological evaluation of novel [1,2,3]triazoles at cannabinoid receptors

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A series of novel 1,5-diaryl-4-substituted[1,2,3]triazole derivatives has been synthesized and evaluated at cannabinoid receptors. The [1,2,3]triazole ring system was readily assembled using click chemistry to provide the unique 1,4,5-trisubstituted [1,2,3]triazoles in good yields. The synthetic details, in vitro binding affinity at CB1 receptors and in vivo efficacy of potent ligands will be presented.



MEDI 212

Design, synthesis and pharmacological evaluation of a series of 4-methyl-N-[(un)substituted phenyl]-N'-[phenyl/(pyridin-2-yl)]piperazin-1-carboxamidines as potential antipsychotic agents

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The present study deals with the synthesis of novel 4-methyl-N-[(un)substituted phenyl]-N'-[phenyl/(pyridin-2-yl)]piperazin-1-carboxamidines derivatives (**7a-c**, **9a-b**) from the reactions of S-methyl-N-[(un)substituted phenyl]-N'-[phenyl/(pyridin-2-yl)] isothiourea with N-methylpiperazine.

Figure 1

Dopamine receptor antagonistic activity of synthesized compounds on rat vas deferens

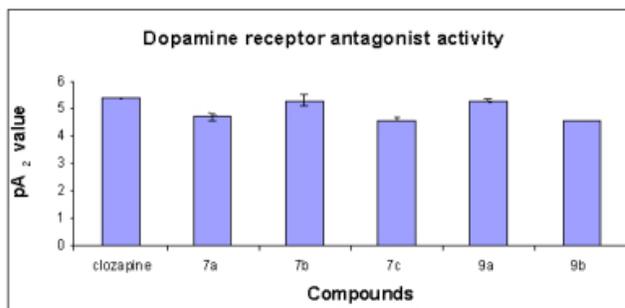
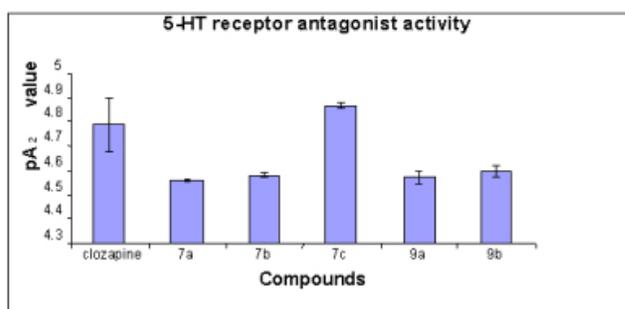


Figure 2

5-HT receptor antagonistic activity of synthesized compounds on rat vas deferens



All the compounds were characterized using UV, IR, MS, ¹H NMR and ¹³C NMR. They were screened for their dopamine and 5-HT receptor antagonistic activities. Results revealed that, compounds **(7b)** and **(9a)** showed potent dopamine antagonistic activity with pA₂ value 5.29 and 5.28 respectively. Moreover, all compounds **(7a-c, 9a-b)** showed no effect on 5-HT receptor. Structure activity relationship study of the compounds showed that replacement of phenyl with pyridine does not change the potency, while presence of electron donating group on second aryl ring exhibits most potent dopamine receptor antagonistic activity of the compound.

MEDI 213

Novel heterocyclic-azepine analogs as potent and selective 5-HT_{2C} agonists: Addressing issues with hERG inhibition

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As part of a programme to investigate the potential of 5HT_{2C} agonists for the treatment of metabolic disease we identified a new series of compounds based on a fused heterocyclic-azepine scaffold. SAR exploration and the identification of

an *in vivo* tool compound from this series will be described. During the optimisation of a series of analogues potent inhibition of the hERG ion channel was identified as an issue. The poster will discuss the design and synthesis of analogues devoid of significant hERG activity.

MEDI 214

Lithocholic acid-nitriles and tetrazoles as activators of large-conductance, Ca²⁺-activated K⁺ (BK) channels

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Activation of large-conductance, Ca²⁺-activated K⁺ (BK) channels in myocytes leads to vasodilation. Lithocholic acid (LC) and other bile acids activate vascular myocyte BK channels, LC being the most effective (Dopico et al., 2002). Accordingly, LC causes significant, endothelium-independent, cerebral artery dilation (Bukiya et al., 2007). The C3 α -hydroxyl and C24 carboxylate are both important for LC to activate BK channels (Dopico et al., 2002; Bukiya et al., 2008). We utilized the bioisosteric replacement of carboxylate to its equivalent tetrazole moiety to evaluate LC tetrazole analogs' efficacy on BK channel activation. Surprisingly, LC C24 and C25 tetrazoles reduced activity. However, their corresponding precursors, LC C24 and C25 cyano derivatives, activated BK channels at concentrations similar to those found effective with LC. The LC C24 cyano compound is the most effective activator of vascular myocyte BK channels among all the side chain analogs of LC. Support: HL077424 (AMD), Van Vleet Professorship (DDM).

MEDI 215

Potent, orally active fused bicyclic NK1 antagonists

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Our earlier lead NK₁ antagonist Sch 535353 suffered from *in vivo* degradation, which resulted in an undesired metabolite. We chose to address this problem by linking the key moieties to form one additional ring. The position of the second ring as well as its stereochemistry were investigated and optimal core structure was obtained. The advanced lead, Sch 714758, demonstrated excellent overall

profile without the liability in Sch 535353. A complete diastereoselective synthesis of Sch 714758 will also be presented.

MEDI 216

Design and syntheses of β -turn peptidomimetics of neurotrophins

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Protein-protein interactions are important in medicinal chemistry, and β -turns are parts of protein structures that are often involved in “hot-spots” for these interactions. We have synthesized many β -turn mimics that have led to the discovery of agonists and antagonists of nerve growth factor (NGF). Described here will be triazole-based mimics which have amino acid side-chains corresponding to the *i*+1 and *i*+2 residues in β -turns of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3). The mimics were coupled together to give high affinity bivalent systems that have the potential to interact at two β -turn hot-spots at once. Cell survival and western blot assays showed 6 hits from a library of 127 peptidomimetics.

MEDI 217

Modeling on various opioid ligands based on a novel backbone alignment concept

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In this study we have applied a novel backbone alignment concept to assess the structure-activity relationships (SARs) of various opioid receptor ligands. This concept was originated from a backbone match of the crystal structure of Leu-enkephalin to the scaffold of morphine and the match suggested that morphine is a close mimic of the backbone of L-Enk. Based on this information three backbone alignment models have been developed corresponding to the three different types of opioid ligands. These models appear to be applicable in assessing the SARs of a wide variety of opioid ligands.

MEDI 218

Discovery and SAR of benzoylpiperazines, a novel class of potent and selective GlyT1 inhibitors for the treatment of schizophrenia (Part 1)

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¹Pharmaceutical Research Basel, Discovery Chemistry, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ²Pharmaceutical Research Basel, CNS Disease Biology Area, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ³Pharmaceutical Research Basel, Non Clinical Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland

NMDA receptor hypofunction is suggested to be involved in the pathophysiology of schizophrenia. Thus, therapeutic intervention aimed at increasing NMDA synaptic tone is expected to show beneficial effect in schizophrenic patients. As glycine is an obligatory co-agonist at the NMDA receptor complex, one strategy to enhance NMDA receptor activity is to elevate extracellular levels of glycine in the local microenvironment of synaptic NMDA receptor. Glycine elevation can be achieved by inhibition of the glycine transporter 1 (GlyT1) which is co-expressed in the brain with the NMDA receptor. As a consequence, GlyT1 transporter inhibition has emerged as an attractive novel therapeutic strategy for the treatment of Schizophrenia. We have recently discovered benzoylpiperazines as a novel structural class of selective GlyT1 inhibitors. The structure activity relationship in this series will be discussed.

MEDI 219

Potent, orally active GlyT1 inhibitors: Optimisation of benzoylpiperazine class guided by the novel L-687,414 induced hyperlocomotion assay (Part 2)

E. Pinard¹, emmanuel.pinard@roche.com, A. Alanine¹, D. Alberati², E. Borroni², H. Fischer³, D. Hainzl³, S. Jolidon¹, J.-L. Moreau², M. Nettekoven¹, R. Narquizian¹, R. Norcross¹, H. Stalder¹, A. W. Thomas¹, and J. G. Wettstein².

¹Pharmaceutical Research Basel, Discovery Chemistry, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ²Pharmaceutical Research Basel, CNS Disease Biology Area, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ³Pharmaceutical Research Basel, Non Clinical Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland

GlyT1 transporter inhibition has emerged as an attractive novel therapeutic strategy for the treatment of Schizophrenia. We have recently discovered benzoylpiperazines as a novel class of selective GlyT1 inhibitors. So far the *in vivo* activity of GlyT1 inhibitors was traditionally assessed by measuring the increase of glycine in the CNS by microdialysis. However this *in vivo* model suffers from being low throughput, and therefore is not suitable for efficiently guiding lead optimisation in series of GlyT1 inhibitors. Recently, the novel L-687,414-induced hyperlocomotion assay, a very powerful and higher throughput model useful for the measurement of the *in vivo* activity of Glyt1 inhibitors was discovered at F. Hoffmann- La Roche. We report in this paper, on the impact of this assay on the optimisation of benzoylpiperazine class leading to highly potent and orally active compounds.

MEDI 220

Potent orally active GlyT1 inhibitors: Optimisation of brain penetration and selectivity vs. hERG in benzoylpiperazine series (Part 3)

E. Pinard¹, emmanuel.pinard@roche.com, A. Alanine¹, D. Alberati², E. Borroni², H. Fischer³, D. Hainzl³, S. Jolidon¹, J.-L. Moreau², M. Nettekoven¹, R. Narquizian¹, R. Norcross¹, H. Stalder¹, and J. W. Wettstein². ¹Pharmaceutical Research Basel Discovery Chemistry, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ²Pharmaceutical Research Basel, CNS Disease Biology Area, F. Hoffmann-La Roche Ltd, Basel, Switzerland, ³Pharmaceutical Research Basel, Non Clinical Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland

GlyT1 transporter inhibition has emerged as an attractive novel therapeutic strategy for the treatment of Schizophrenia. We report here on the strategies we developed to optimize brain penetration as well as selectivity against hERG channel activity in our series of benzoylpiperazines, leading to highly potent GlyT1 inhibitors having excellent safety profile.

MEDI 221

Novel enkephalin analogs designed as multivalent ligands for opioid receptors and cyclooxygenase 2 enzyme

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We have made novel multivalent ligands that will increase their analgesic efficacy in *in vivo* animal models. The idea is to evaluate the therapeutic effect of molecules that have two pharmacophore elements; cyclooxygenase 2 enzyme inhibitor activity and mu and delta opioid receptor agonist activity. In this study, we have taken the biphalin scaffold as a mu and delta opioid agonist pharmacophore, and celecoxib or the SC558 scaffold as a COX 2 pharmacophore. The novel molecules were docked to the COX2 enzyme in order to assess their inhibitory activity towards the enzyme. Further, solution phase and solid phase methodologies were used in the synthesis of these molecules. Pharmacological results reveal that these synthesized molecules have partial opioid agonism and moderate COX inhibitory activity.

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MEDI 222

Efforts leading to the identification of alkylsulphonylamino quinolines as NK3 receptor antagonists

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The Neurokinin-3 (NK3) receptor is regarded as a potential novel target for treating patients with schizophrenia. Multiple publications and patent applications suggest that a carboxyquinoline core provides a useful scaffold for compounds with NK3 activity. Here we report the drug discovery efforts leading to the identification of a novel series of C3-alkylsulfonylamino substituted carboxyquinolines as potent NK3 antagonists. These compounds demonstrated excellent NK3 functional activity, good selectivity and drug-like properties. Several key compounds have been shown to have excellent in vitro/in vivo DMPK characteristics and activity in the gerbil locomotor activity model.

MEDI 223

Alkylsulfoxide substituted carboxyquinoline as NK3 antagonists

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The Neurokinin-3 (NK3) receptor is regarded as a potential novel target for treating patients with schizophrenia. Compounds having a carboxyquinoline can tolerate a wide variety of substituents at the C3 position of the quinoline ring. Here we report the synthesis and SAR of a series of C3-alkylsulfoxide substituted quinolines as potent NK3 antagonists. These compounds have excellent NK3 functional activity, good selectivity and drug-like properties. Several key compounds have excellent in vitro/in vivo DMPK characteristics, and activity in a gerbil locomotor activity model.

MEDI 224

Novel conformationally restricted heterocyclyl amines as potent and selective 5-HT₆ receptor ligands

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The discovery of 5-HT₆ receptor antagonism as a target to address the cognitive disorders like Alzheimer's disease and Schizophrenia and metabolic disorders like obesity over the past decade and the discovery of the PET ligand at the receptor have given the necessary thrust to the research in this field. Also the indications of an additive or possibly the synergistic interaction of 5-HT₆ receptor antagonism and the inhibition of acetyl cholinesterases have enhanced the scope of current research. As a part of our contribution to the research in this field in

alleviating the human suffering, we at Suven Life Sciences Ltd, Hyderabad, have identified novel and conformationally restricted heterocyclamine derivatives as potent and selective 5-HT₆ receptor antagonists with good to excellent ADMET properties with minimal or no adverse effects. The novel molecules from this series are highly potent (with K_i in the range of 5 - 20 nM), selective and orally active in animal models of cognition like NORT and Morris Water Maze. Herein, we report the synthesis, physicochemical properties, *in-vitro* binding data, along with SAR and the pharmacological data of the molecules.

MEDI 225

Novel heteroaromatic sulfonamides as potent and selective 5-HT₆ receptor antagonists

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The emergence of positive clinical data for molecules like SB-742457, Lu AE58054 and SUVN-502 (from our laboratories) served as stimuli for additional research in the field of 5-HT₆ receptor antagonism, targeting cognitive disorders like Alzheimer's disease and Schizophrenia. There was an unending quest for the search of novel chemical entities, which can offer better physicochemical and ADMET properties with minimal or no adverse side effects in addition to good brain penetration and exposure levels. In view of the therapeutic importance of the target and in continuation of our own efforts in the field, the present study has been initiated to identify the molecules that can address the unmet medical need of the patient population. Herein, we report novel heteroaromatic sulfonamide derivatives as selective 5-HT₆ receptor ligands with K_i in the range of 3 - 10 nM, when tested by the *in-vitro* radio ligand binding techniques. The lead molecule from the series was found to be active in animal models of cognition, like Morris Water Maze and NORT at 1 mg/kg and 3 mg/kg (p.o). Details of synthesis, *in-vitro* binding data along with SAR and *in-vivo* data will be presented.

MEDI 226

Design, synthesis, and evaluation of novel biphenyl indanone-A (BINA) derivatives that are metabotropic glutamate receptor subtype-2 (mGluR2) positive allosteric modulators (PAMs): Incorporation of heteroatoms

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Modulation of metabotropic glutamate receptor subtype 2 (mGluR2) by small molecules represents a promising approach for the treatment of diseases caused by aberrant glutamatergic transmission such as schizophrenia, anxiety or drug addiction. Our ongoing program is focused on the design and synthesis of new brain penetrant, systemically active small molecule mGluR2 positive allosteric modulators (PAMs). We designed and synthesized focused libraries based on the mGluR2 PAM 3'-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid (biphenyl indanone-A, BINA) and this led to the identification of new analogues with optimized potency for mGluR2 and superior drug-like properties. In addition to being potent mGluR2 PAMs, several of these analogues are highly selective for mGluR2 vs. other mGluR subtypes. Furthermore, we found that incorporation of heteroatoms into the BINA scaffold led to analogues with significantly improved pharmacokinetic (PK) properties, providing compounds with excellent oral bioavailability and brain penetration. One compound was selected for in vivo studies of cocaine self-administration in rats, providing proof-of-concept for the use of mGluR2 PAMs for the treatment of cocaine dependence. Details of the structure activity relationships (SAR) of new potent and selective mGluR2 PAMs in this series will be presented.

MEDI 227

Design, synthesis, and evaluation of novel biphenyl indanone-A (BINA) derivatives that are metabotropic glutamate receptor subtype-2 (mGluR2) positive allosteric modulators (PAMs): Initial refinement of SAR

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Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that regulate synaptic strength in the central nervous system (CNS). Group II mGluRs (mGluR2 and mGluR3) are primarily localized presynaptically and modulate glutamate release. Small molecule modulators of Group II mGluRs have significant potential as therapeutic agents for several neurological and psychiatric disorders such as anxiety, depression, schizophrenia and drug addiction. While all of the orthosteric (competitive) agonists reported to date have similar affinities for mGluR2 and mGluR3, we and others have been successful in the design and synthesis of mGluR2-selective positive allosteric modulators (PAMs). Using the mGluR2 PAM 3'-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid (biphenyl indanone-A, BINA) as a starting scaffold we designed and synthesized new selective mGluR2 PAMs that are up to 5-fold more potent than BINA in vitro. Our lead optimization process

involved not only in vitro assays measuring potency for mGluR2, but also selectivity against other mGluR subtypes and evaluation in in vitro ADME/T assays that are helpful for predicting the drug-like properties of molecules. Based on the in vitro data, one analogue in the series of 3'-(aryloxymethyl)biphenylcarboxylic acid derivatives was chosen for comprehensive in vivo evaluation, including rat pharmacokinetic studies and a rat model of cocaine dependence. This presentation will discuss the design, synthesis and structure activity relationships (SAR) of new potent and selective mGluR2 PAMs.

MEDI 228

Novel bridged bicyclic NK₁ antagonists

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Designing novel, minimal sized core structure to accommodate pharmacophores is of unique value in improving CNS penetration. During the course of medicinal chemistry study of NK₁ antagonist, we designed and synthesized a series novel and compact bridged bicyclic piperidine core structure that was used to generate potent analogs. The lead compound in this series showed good overall profile.

MEDI 229

Chemical optimization of a novel class of orally available small molecules targeting Prion disease

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Creutzfeldt-Jakob Disease (CJD) is an untreatable and invariably fatal neurodegenerative condition caused by misfolding of the human PrP^C protein into an insoluble form denoted PrP^{Sc}. We recently reported on a high-throughput screen that identified 2-aminothiazole analogs which effectively lower PrP^{Sc} levels in a murine neuroblastoma cell line (ScN2a cells). Our subsequent structure-activity studies in this series have now afforded analogs with low-nanomolar potencies in the ScN2a cell assay. Concurrent optimization for *in vivo* properties has produced analogs that are both orally bioavailable and that achieve micromolar concentrations in the brains of animals. Here we will

describe the synthesis of novel 2-aminothiazole analogs, current structure-activity relationships pertaining to anti-prion activity, and also preliminary structure-brain exposure relationships gleaned from our in-life experiments.

MEDI 230

Novel NK3 antagonists for schizophrenia: Applications of knowledge-based screening and design

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NK3 antagonists have been investigated as potential treatments for schizophrenia based on preclinical models. Intense efforts in this afforded a wealth of available information from publications and patent applications. We sought to gain rapid entry into this field by maximally using this information. SAR and pharmacophore understanding were developed through analysis of more than 1100 described NK3 antagonists. This was used in a virtual screening model to select 15,000 compounds for biological analysis. The information served to refine our pharmacophore understanding leading to the selection of a 4-carboxyquinoline chemotype. Optimization efforts focused on improving physical properties while maintaining favorable biological properties. We systematically modified each region in the chemotype to define those that were critical for biological activity and those that were more tolerant to change to enable the needed property improvements. Focused alterations at the quinoline 3-position afforded a series of highly potent NK3 antagonists with improved physical properties.

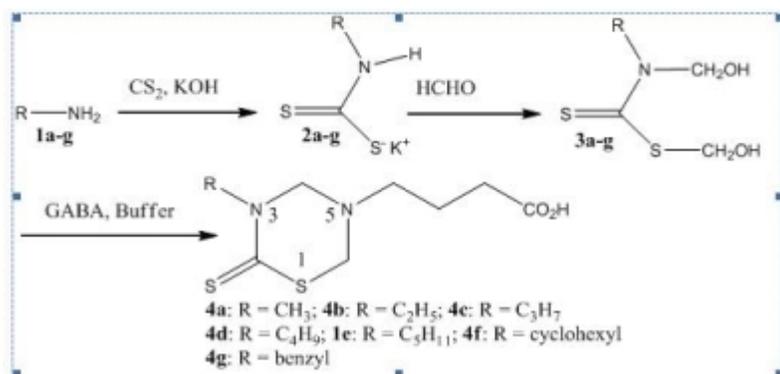
MEDI 231

Targeting γ -aminobutyric acid (GABA) carriers to the brain: Potential relevance as antiepileptic pro-drugs

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The search for antiepileptic compounds with more selective activity continues to be an area of intensive investigation in medicinal chemistry. 3,5-Disubstituted tetrahydro-2H-1,3,5-thiadiazine-2-thione (THTT) derivatives; **4a-g**, potential prodrugs incorporating the neurotransmitter; GABA were synthesized and studied for passing blood-brain barrier (BBB). Compounds were prepared from some selected primary amines and carbon disulfide to give dithiocarbamates **2a-**

g which upon reaction with formaldehyde provided *-in situ-* the intermediates **3a-g**. Addition of **3a-g** onto GABA furnished the title compounds **4a-g**. [figure 1]. The structures were verified by spectral data and the amounts of the compounds in the brain were investigated by using HPLC. The concentration profiles of the tested compounds in mice brain were determined and the *in vivo* anticonvulsant activity was measured.



: Synthesis of THTT pro drugs

MEDI 232

Pharmacological and biophysical properties of neuronal Ca_v3.1 (α_{1G}) T-type calcium channels studied with automated patch-clamp electrophysiology

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Low-voltage-activated neuronal T-type calcium channels are involved in a variety of normal physiological and pathophysiological processes in nerve tissues, and thus could be valuable therapeutic targets for drug discovery. However, there has been no selective blocker available for T-type calcium channels, demanding a need for the development of novel drugs acting on T-type calcium channels where a higher-throughput screening system is required. Here we present pharmacological and biophysical studies on recombinant Ca_v3.1 T-type calcium channels heterologously expressed in human embryonic kidney 293 cells using automated whole-cell patch-clamp recordings (Patchliner, Nanion Technologies). Various known T-type calcium channel blockers with different chemical structures were tested using automated patch clamp along with conventional patch clamp for comparison. The IC₅₀ values obtained from automated patch clamp were compared with the values measured with conventional patch clamp, showing a good correlation (correlation coefficient of 0.82). However, some biophysical characteristics of Ca_v3.1 T-type calcium channels including steady-state activation properties in automated patch clamp showed a discrepancy from those determined with conventional patch clamp. Thus, although the automated patch

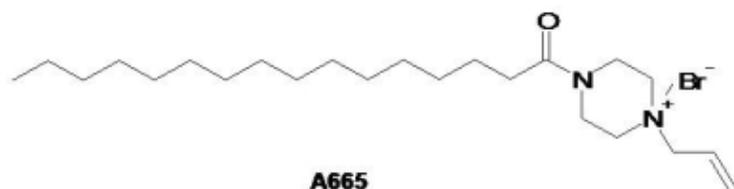
clamp is an efficient and reliable tool for ranking the drug potencies for T-type calcium channels, the accurate biophysical characterizations of T-type calcium channels still need to be conducted by a conventional method.

MEDI 233

Design, synthesis, and biological evaluation of novel RhoB modulators as antitumor agents

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Reactivation of suppressed RhoB is a critical step for the inhibition of cancer cell growth. The exact mechanism is still obscure, although some RhoB modulators were found which exhibited an anticancer effect. To this end, a novel RhoB modulator, **G02**, has been identified and evaluated. In the efforts to explore new chemical entities for novel RhoB modulators, we have identified a number of potent and selective antitumor agents for gastric and prostate cancer with excellent *in vitro* and *in vivo* profiles. Although analogs related to compound G02 had good cancer cell growth inhibition activities, poor *in vivo* tumor regression activities were observed due to the low plasma exposure. Therefore, the further optimization of various analogues was performed by an intravenous administration. Finally **A665** displayed excellent inhibitory activities on prostate and gastric cancer cells and no sign of toxicity. In this presentation, we will reveal structure-activity relationship (SAR) study, *in vitro* and *in vivo* data, and syntheses of a number of these novel RhoB modulators.



MEDI 234

Synthesis and antiproliferative activities of novel imidazole analogs

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A series of 2-Aryl-4-Benzoyl-Imidazoles (ABI) have been synthesized as a result of structural modifications based on previous reported 2-Aryl-imidazole-4-carboxylic amide (AICA) derivatives and 4-Substituted Methoxybenzoyl-Aryl-

Thiazoles (SMART). The antiproliferative potency of the ABI agents against melanoma and prostate cancer cells increased significantly from μM to nM when compared with AICA derivatives. The most potent compound has an IC_{50} value as low as 7.9 nM. The ABI series of compounds have substantially improved pharmacokinetic properties (water solubility and stability) compared with SMART series. The mechanism of action for these compounds is through inhibition of tubulin polymerization as demonstrated by a variety of biological studies.

MEDI 235

Targeting the JAK/STAT pathway in cancer with curcumin derivatives

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Curcumin is a structurally simple natural product isolated from the rhizome of *Curcuma longa*. It has been shown to have antioxidant, anti-inflammatory, antiangiogenic, and antiproliferative properties due to its interaction with numerous biological targets. Specifically, curcumin was recently shown to inhibit the JAK/STAT pathway in cancer cells. Using computational and synthetic chemistry we have designed and evaluated a series of curcumin analogues which display increased JAK/STAT inhibition and improved antiproliferative activity relative to curcumin itself. These compounds are predicted to act to some degree as dual JAK/STAT inhibitors, but most importantly interact with three key "hot-spots" which have been identified in our binding model of the STAT3 SH2 domain. Thus, synthetic modifications have been directed at developing potent and selective STAT3 inhibitors, as well as improving the solubility and stability of these compounds. Preliminary pharmacokinetic studies and in vivo assays have been carried out utilizing these lead compounds.

MEDI 236

Synthesis and antiproliferative evaluation of certain 6-arylindenoquinoline derivatives

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Recently, a number of condensed quinoline derivatives have been synthesized and evaluated for their topoisomerase I inhibitory activities. We have also synthesized certain indenoquinoline derivatives which were found to be more potent than camptothecin against the growth of AGS and A549. In continuation of our study to explore more potent anticancer drug candidates, we report herein the synthesis of certain 6-arylindenoquinoline derivatives and the evaluation of their antiproliferative activities. The preliminary results indicated that one of the

lead compounds, TCH-20 which exhibited GI_{50} of 0.60 and 0.68 micromole against the growth of Hep G2 and A549 respectively, was more active than the positive topotecan and irinotecan. TCH-20 was less toxic than topotecan against the growth of normal cell (MRC-5) and therefore, was selected for further evaluation. Results indicated that TCH-20 induce cell cycle arrest in G2/M phase, cause DNA fragmentation, and disrupt the microtubule network in A549 cells. The apoptotic induction may through the cleavage of PARP.

MEDI 237

Evaluation of substituted thieno[3,2-*b*]pyrrole[3,2-*d*]pyridazinones and substituted *N,N*-Diarylsulfonamides as activators of the tumor cell Specific M2 isoform of pyruvate kinase

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Pyruvate kinase operates at the final step of glycolysis that catalyzes the transfer of a phosphate group from phosphoenolpyruvate (PEP) to ADP, yielding one molecule of ATP and one molecule of pyruvate. There are four isozymes of PK (M1, M2, L and R) that are generated by two pyruvate kinase (PK) genes that each produce two different isozymes due to alternative splicing. The PKM2 isozyme is normally only found in undifferentiated embryonic tissues while PKM1 is found in normal adult tissue cells. Interestingly, PKM2 is found to replace PKM1 in all cancer cells examined to date. PKM2 is less active than PKM1 due to allosteric regulation of the former and recent studies have shown that the allosteric regulation of PKM2 shifts glycolysis to be a proliferative mode to make intermediates available for the biosynthesis that are necessary for cellular construction in rapidly proliferating cells. It is rationalized that pharmacological activation of PKM2, presumably to the levels found in normal PKM1 expressing cells, could impair the proliferative metabolic state of cancer cells and possibly yield a novel mechanism for cancer treatment. We have recently screened for PKM2 activators yielding two novel chemotypes; a series of substituted thieno[3,2-*b*]pyrrole[3,2-*d*]pyridazinones and substituted *N,N*-diarylsulfonamides. Both lead compounds were explored through synthesis, structure-activity relationship evaluations, and mechanism-of-action studies and their activity and selectivity were evaluated against the human PK isozymes.

MEDI 238

Importance of the glutamate moiety for folate receptor targeting and GARFTase inhibitory activity in classical thieno[2,3-*d*]pyrimidine antifolates

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We have recently reported a series of thieno[2,3-*d*]pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC₅₀ values. In addition, these analogs are not transported via the reduced folate carrier (RFC) into normal cells. Glycinamide ribonucleotide formyl transferase (GARFTase) was confirmed as the target. To further investigate the structural requirements of antifolates with respect to FR substrate activity and antitumor activity, a series of analogs with variations in the glutamate moiety were designed and synthesized. The synthesis and FR substrate and antitumor activity of these analogs will be presented.

MEDI 239

Classical and nonclassical 2-amino-4-oxo-5-arylthio-substituted-6-isopropyl thieno[2,3-*d*]pyrimidine antifolates as potent thymidylate synthase inhibitors

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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 human TS has long been considered as a useful mechanism for cancer chemotherapy. Gangjee et al. recently discovered the potent TS inhibitory activity of a series of 2-amino-4-oxo-5-arylthio-substituted-6-ethylthieno[2,3-*d*]pyrimidine analogues. In the present series, we have designed and synthesized classical and nonclassical 6-propyl substituted thieno[2,3-*d*]pyrimidines as homologues of our previous compounds. The synthesis and biological activities against TS of these analogs will be reported and discussed.

MEDI 240

Novel ERK1/2 substrate-specific inhibitors: Design and development toward anticancer agents

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Raf/MEK/ERK pathway plays important roles in controlling the fundamental cellular fate such as proliferation, differentiation, survival and apoptosis and this pathway has been demonstrated to have a strong link to the development of human cancers. Therefore small molecule inhibitors targeting this pathway would have potential to be targeted anticancer agents. However, the lack of specificity and the development of potential drug resistance make current inhibitors less ideal for further development. An alternative strategy in developing potential anticancer agents by targeting this pathway would be to develop substrate-specific ERK1/2 inhibitors that selectively disrupt the binding interactions of ERK1/2 with downstream substrate proteins given the unique position of ERK in controlling the signal distribution downstreams. In this report, a series of analogs of 3-(2-amino-ethyl)-5-(2-ethoxy-benzylidene)-thiazolidine-2,4-dione were designed, synthesized and biologically characterized in human leukemia U937 cells to define its pharmacophore and to search for more potent and selective ERK1/2 inhibitors. The results will be released in the poster presentation.

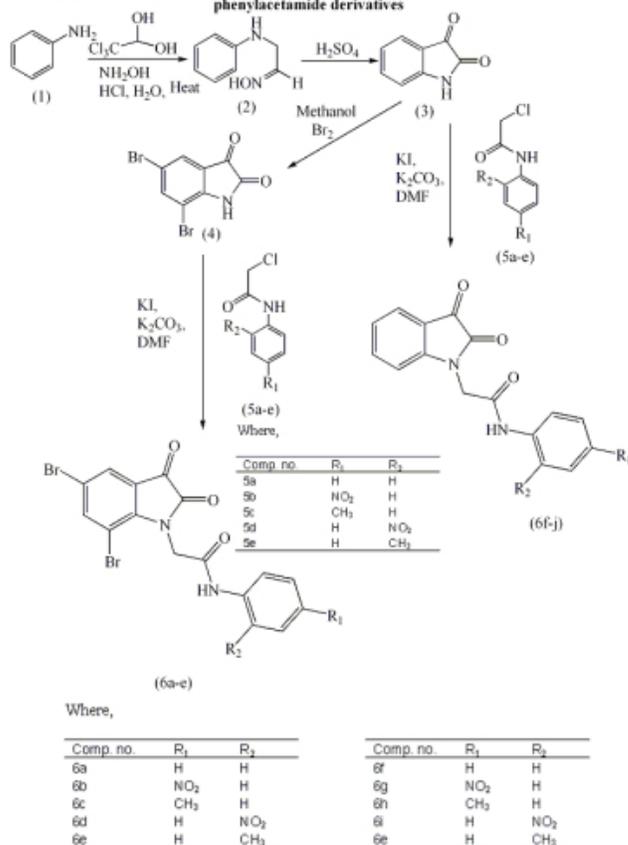
MEDI 241

Design, synthesis, QSAR and biological screening of novel 2-(2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-phenylacetamide as cytotoxic agents

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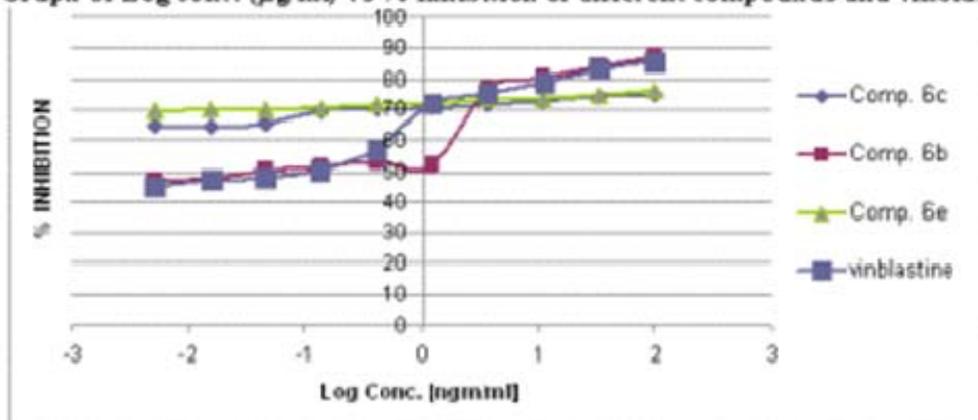
The present study deals with the synthesis of novel 2-(2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-phenylacetamide derivatives (**6a-j**) from isatin (**3**) and 5, 7-dibromoisatin (**4**).

Scheme - 1
Schematic representation for the synthesis of novel 2-(2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-phenylacetamide derivatives



All the compounds were characterized using IR, ¹H NMR, MS and elemental analysis and screened for their cytotoxic activity by XTT assay. Results of correlation of QSAR and *in vitro* assay indicates that electron withdrawing substitutions at para position of phenyl ring and increasing lipophilicity of the compound increased the cytotoxic activity. Most active compound in the synthetic series was 2-(5, 7-dibromo-2, 3-dioxo-2, 3-dihydro-1H- indol-1-yl)-N-(4-nitrophenyl)acetamide (**6b**) and demonstrated higher selectivity toward MCF-7 cell line. The LogIC₅₀ values were 0.044 µg/ml and 0.035 µg /ml for test compound (**6b**) and vinblastin (reference drug), respectively. This indicates compound (**6b**) may possess equipotent cytotoxic activity to vinblastine.

Graph of Log conc. ($\mu\text{g}/\text{ml}$) vs % inhibition of different compounds and vinblastine



Hence, we propose that 2-(5, 7-dibromo-2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-(4-nitrophenyl)acetamide may be used as lead for further development.

MEDI 242

Synthesis and biological activity of some new substituted purine derivatives in human cancer cells

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Purine nucleoside analogs represent a relatively novel group of cytotoxic agents with high immunosuppressive and antineoplastic activity¹. Fludarabine, cladribine and pentostatin were approved by FDA for the treatment of neoplastic diseases. In our present work, we report syntheses and *in vivo* cytotoxic activities of 8-substituted adenine and 6-substituted amino-9-cyclopentylpurine derivatives. The newly obtained purine and adenine compounds were evaluated by (NCI) anticancer drug screening method² with the aim of identifying chemical compounds with growth-inhibitory activity on HCT116 (colon), T47D (breast) and Huh7 (liver) cell lines. Among the tested purines, 8-(4-fluorophenyl)-9H-adenine had IC₅₀ values around 100 mM on HCT116 and T47D cells.

1. Robak T., Lech-Maranda, E., Korycka A., Robak, E., Purine Nucleoside Analogs as Immunosuppressive and Antineoplastic Agents: Mechanism of Action and Clinical Activity, *Current Medicinal Chemistry*, 2006, 13, 3165-3189

2. Shoemaker R.H., The NCI60 human tumour cell line anticancer drug screen, *Nat. Rev. Cancer*, 2006, 6(10), 813-23

MEDI 243

Syntheses and in vitro anticancer properties of novel radiosensitizer analogs

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Series of 4-(ethylsulfonyl)-1-halogen-2-nitrobenzene (**3a-e**) and 1-(4-halogen-3-nitrophenyl) propan-1-one (**5a-d**) analogs designed as novel radiosensitizers using bromonitropropiophenone and bromonitrobenzotrile as lead compounds were synthesized. The anticancer activities of the compounds were evaluated *in vitro* using human prostate cancer (DU-145) and breast cancer (MCF-7) cell lines and the MTT assay. From the series, 6 compounds (**3b-e**, **5b-c**) exhibited potent growth inhibitory effects against both cell lines. The most active, compound **3d**, is an iodosulfone was then compared with doxorubicin. It was more active than doxorubicin at the dose level of 10 μM against both carcinoma cell lines at 24, 48, and 72 h time points, but less active at the dose level of 1 μM and lower. The target compounds were designed to enhance cytotoxic effects of radiation. However, compound **3d** exhibited significant anticancer properties even without the radiation. Future studies include testing the compounds with radiation and *in vivo* studies.

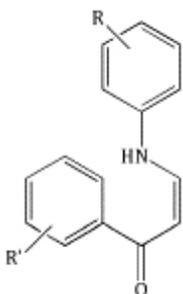
MEDI 244

(Z)-1-Aryl-3-(arylamino)prop-2-en-1-ones: A novel class of antitubulin agents

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Among the cellular structures necessary to maintain the growth and function of normal and malignant cells, the microtubules play a pivotal role. Microtubules are of particular importance for the formation of the mitotic spindle, which provides the structural framework for the physical segregation of chromosomes during cell division (mitosis). Many drugs that interfere with dynamics of microtubule formation generate abnormal mitotic spindles there by inducing cell cycle arrest in mitosis and finally apoptotic cell death. A variety of natural products, such as Paclitaxel, Etoposide, Vinorelbine, Colchicine, Combretastatin A4 interferes with microtubule formation by changing the dynamics of polymerization and depolymerization of tubulins. One of the most important antimitotic agents is Combretastatin A4 selectively target the formation of new vasculature at tumor site. This process irreversibly shutdown the blood flow to neoplastic cells while leaving the blood supply to healthy cells intact. Here, we describe a new class of small molecule antitubulin agents, which appear to satisfy many of the criteria for

successful development of new anticancer agents. These compounds belong to the enaminone family and could readily inhibit the polymerization of tubulins. They exhibit potent cytotoxicity against a wide spectrum of cancer cell lines. In this presentation we focus on the stereo-specific synthesis, structure-activity relationships and biological activity of these compounds.



MEDI 245

Synthesis of metal-cored photodynamic therapy anti-cancer agents

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BF₂ chelated azadipyromethene dyes have many potential applications in photodynamic therapy. When irradiated with near infrared light, in the presence of oxygen, these aza-BODIPY dyes react to form singlet oxygen species, which can lead to cellular damage and ultimately to cell death. A library of boron containing aza-BODIPY compounds has been synthesized via a four-step process, with varying substituents on the aromatic ring of the starting acetophenone and benzaldehyde. An *in vitro* study is also being conducted to test the degree of cell death in HeLa cells when irradiated, to evaluate their therapeutic effectiveness. Also, new agents that contain other metals were developed to see how they may possibly increase the effectiveness of these photodynamic therapy agents.

MEDI 246

Discovery and optimization of potent and selective triazolopyridazine c-Met inhibitors

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Deregulation of the receptor tyrosine kinase c-Met has been implicated in several human cancers and is an attractive target for small molecule drug discovery. We previously showed that O-linked triazolopyridazines can be potent inhibitors of c-Met. Herein, we report the discovery of a related series of N-linked triazolopyridazines, which demonstrate nanomolar inhibition of c-Met kinase activity. Moreover, the potent time-dependent inhibition of cytochrome P450 associated with the O-linked triazolopyridazines has been eliminated within this novel series of inhibitors. N-linked triazolopyridazines exhibited favorable pharmacokinetics and displayed potent inhibition of HGF-mediated c-Met phosphorylation in a mouse liver PD model. Once-daily oral administration of these inhibitors for 22 days showed significant tumor growth inhibition in an NIH3T3/TPR-Met xenograft mouse efficacy model.

MEDI 247

Development of new cytotoxic etoposide and doxorubicin derivatives using the EPiC platform for increased brain penetration

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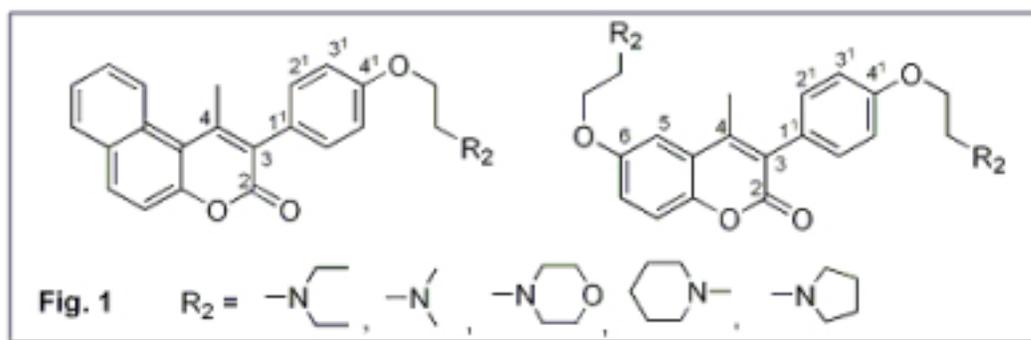
Chemotherapy for malignant brain tumors often has limited efficacy, largely due to restricted blood–brain barrier (BBB) permeability for chemotherapeutic drugs. Angiochem’s Engineered Peptide Compounds (EPiC) platform provides a non-invasive and flexible technology for designing novel drugs that cross the BBB efficiently, via the low-density lipoprotein receptor related protein. The most advanced EPiC anticancer drug, ANG1005, is currently completing two Phase 1/2 clinical trials for the treatment of brain tumors. Here, we are describing the syntheses and the preliminary biological characterization of two new anticancer drugs, ANG1007 and ANG1009 that consist of three doxorubicin and three etoposide molecules conjugated to one Angiopep-2 molecule, respectively. Both EPiC drugs show strong in vitro cytotoxic activity and exhibit dramatically higher brain transport rate across the BBB than the parental drugs. These results further support the potential of the EPiC platform to develop new chemical entities with increased brain penetration to treat brain diseases.

MEDI 248

Synthesis and antiproliferative activity of Coumarin-based benzopyranone derivatives containing antiestrogenic side chain against MCF-7 breast cancer cell line

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Breast cancer is the second leading cause of cancer death in American women behind lung cancer. Therapeutic agents preventing the biosynthesis and physiological action of estrogen have led to the development of SP500263, a novel Coumarin-based Benzopyranone Selective Estrogen Receptor Modulator (SERM), as therapeutic agents in the treatment breast cancer. Coumarins exhibit useful and diverse biological activities, resulting in a growing interest in their synthesis and possible applications for drug discovery. We herein report the synthesis of new analogs of coumarin-based benzopyranone derivatives containing antiestrogenic side chain at the C-4' of the phenyl group in the C-3-substituted position (monoalkylated compounds) and also in the C-3 and C-6-substituted positions (dialkylated compounds) of the benzopyranone ring



In vitro results indicated that coumarins possessing diethylaminoethoxyl- and piperidinoethoxyl- antiestrogenic side chains were the most potent showing significant growth inhibitory activities against MCF-7 human breast cancer cell line. Furthermore, their antiproliferative activities are comparable to that of tamoxifen, raloxifene and 4-hydroxytamoxifen (active metabolite of tamoxifen).

MEDI 249

DNA G-quadruplex ligands – anthraquinones and acridones: 3D - QSAR studies for a quantitative prediction of the telomerase inhibitory activity based on comparative molecular similarity indices analysis

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Telomerase enzyme, involved in immortalization of cancer cells is inhibited by stabilization of G-quadruplex at the ends of chromosomes. G-quadruplexes are higher-order DNA structures formed from guanine rich sequences that are built around tetrads of hydrogen-bonded guanine bases. For the design of potent and selective inhibitors and to understand the structural basis of anthraquinone and acridone derivatives as G-quadruplex ligands, a predictive 3D-QSAR model has been developed for the first time for telomerase inhibitory activity, employing Comparative Molecular Similarity Indices Analysis (CoMSIA). The protonated forms were analyzed considering that the basic nitrogens in these compounds should remain protonated at physiological pH. The contour maps obtained in 3D-CoMSIA study provided new insight into the biological requirements for anthraquinones and acridones to provide selective potent inhibitors. The actual predictive abilities of the QSAR model were thoroughly validated through an external validation test set of compounds. The statistics indicate a significantly high prediction power (r^2_{pred} 0.764) of the best model.

MEDI 250

Synthesis and bioactivity of flavaglines: A new class of anticancer natural products

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Flavaglines constitute a family of natural anticancer cyclopenta[*b*]benzofurans. We identified the first synthetic flavaglines that inhibit cell proliferation and viability (IC₅₀ ~ 1 nM) at lower doses than did the parent natural compounds. These synthetic flavaglines retain their potency against multiresistant cell lines and induce apoptosis independently of “classical” apoptosis pathways by triggering the translocation of Apoptosis Inducing Factor (AIF) and caspase-12 to the nucleus, suggesting that these compounds would retain their activity in cancers refractory to caspase activation (*J. Med. Chem.* 2009, 52: 5176–5187). Using a fluorescent probe, we demonstrated that the molecular target of flavaglines is located in the endoplasmic reticulum. The synthesis, biological evaluation and structure-activity relationships of newly synthesized flavaglines will be presented.

MEDI 251

Design, synthesis and evaluation of a novel DNA-interactive agent: A promising new class of cytotoxic molecules for use in antibody-drug conjugates

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A new class of DNA crosslinking/alkylating agents (IGNs) comprising of Indolino[1,4]benzodiazepine have been designed and efficiently synthesized. The lead compounds display high DNA binding affinity and sequence specificity.

These compounds are potent *in vitro* towards cancer cell lines, with IC₅₀ values in the sub-nano to pico-molar range. Linkable versions of the lead IGN compound were synthesized and conjugated to two different monoclonal antibodies directed against tumor-associated antigens. The Antibody-IGN conjugates displayed high antigen-specific potency *in vitro*, with antigen-negative cells being up to 1000-fold less sensitive to the conjugates. IGNs represent a promising new class of cytotoxic agents with a novel mechanism of action for use in the development of ADCs.

MEDI 252

Novel macrocyclic histone deacetylase inhibitors

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Histone deacetylases (HDACs) are enzymes responsible for the organization and functioning of nucleosomes, which means they influence gene transcription. Studies have shown that over-expression of HDACs in cells often results in improper realization of genetic information and suppression of cell cycle regulation, which leads to uncontrollable cell growth. Indeed, HDACs are usually over-expressed in cancer cells, which suggests that HDACs are potentially good chemotherapeutic targets. Among the five known classes of HDAC inhibitors, macrocycles, benzamides, ketones, small molecule hydroxamic acids, short chain fatty acids, macrocycles stand apart because they allow a broad array of variations and substitutions within their scaffold. The wide range of structures that can be synthesized with macrocycles may allow one to generate HDAC inhibitors that are specific to individual HDACs, thus selectively controlling cell death and toxicity. Our work describes the synthesis and biological evaluation of macrocyclic scaffolds that were designed to inhibit HDACs.

MEDI 253

Synthesis of the potent anti-cancer agent Largazole and its analogs

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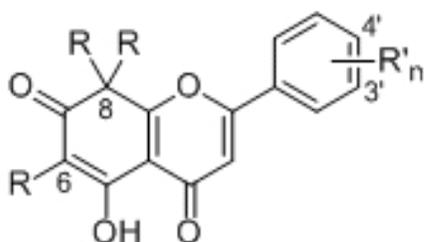
The discovery and development of anti-cancer agents with minimal or no adverse effects on healthy tissues necessitate the identification of new pharmacophores with novel mechanisms of action and with selective activity on cancer cells. Natural products have been a traditional and continuous source of many new anti-cancer molecules with novel mechanisms of action. A new anti-cancer natural product, largazole, a Class I Histone Deacetylase (HDAC) inhibitor, was reported recently by Luesch et al. It has potent and selective activity on highly invasive transformed human mammary epithelial cells (MDA-MB-231) and transformed fibroblastic osteosarcoma (U2OS cells). Development of largazole analogs as HDAC isoform selective inhibitors may lead to molecules with decreased toxicity with concurrent increase in activity. [figure 1] The identification of the structural elements responsible for the selective activity of largazole requires a detailed structure-activity relationship (SAR) study. Synthesis of largazole and its analogs for SAR study will be presented.

MEDI 254

Desmosdumotin-B analogs as promising cytotoxic antitumor agents to overcome MDR

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Desmosdumotin B analog **1** exerts selective in vitro cytotoxicity against the MDR tumor cell line KB-VIN (ED₅₀ = 0.15 µg/mL), with over 133-fold hyperactivity. Over 65 related analogs were synthesized and evaluated as MDR selective agents. Analogs **2-4** were potent selective inhibitors of KB-VIN replication (EC₅₀ = 0.03-0.04 µg/mL and hyperactivity up to 460-fold). The MDR selectivity was reversed by co-treatment with diverse P-gp inhibitors, suggesting dependence on efflux pump activity, and **1**-treatment induced apoptosis in KB-VIN cells.



Desmosdumotin B: R = Me, R' = H

1: R = Et, R' = H

2: R = Et, R' = 4'-Me

3: R = Et, R' = 4'-MeO-3'-Me

4: R = Et, R' = 4'-MeO-3'-F

MEDI 255

(E)-Styryl-N-aryl carboxamides: Novel antimetabolic agents

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Treatment of cancer cells with agents that interfere with microtubule assembly causes mitotic arrest and eventually cell death. Many antimetabolic agents that interfere with polymerization/depolymerization of α and β -tubulins have been successfully used for cancer treatment, especially for ovarian cancer. Ovarian cancer is the eighth most common cancer among women and accounts for about 3% of all cancers in women. It ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. The mitotic agents cause dynamic instability of microtubules resulting in cell cycle arrest in the M-phase, forming abnormal mitotic spindles. Agents such as vincristine and paclitaxel have gained wide clinical use for the treatment of various cancers, but suffer from undesired side effects, particularly neurotoxicity, and are substrates of various efflux mechanism leading to drug resistance. It is therefore desirable to discover novel antitubulin agents with fewer side effects, and better efficacy against MDR+ cancer cells. Here, we describe the synthesis, structure activity relationship, cytotoxicity and microtubule depolymerization studies of a new class of propenamides, small molecule antitubulin agents. They exhibit potent (IC_{50} of 25-500 nM) activity against a wide spectrum of cancer cell-lines including ovarian cancer cell lines and drug resistant cell-lines.

MEDI 256

Design, synthesis and evaluation of new monovalent BIR2 selective inhibitors of the anti-apoptotic protein XIAP

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Programmed cell death plays an essential role in development, typically occurring in animal species by a mechanism known as apoptosis. Defects in apoptosis are associated with many diseases characterized by either insufficient cell death (e.g. cancer) or excessive cell death (e.g. degenerative diseases). The Inhibitor of Apoptosis Family of Proteins (IAPs) contain ~70 amino acid motifs designated baculovirus IAP repeat (BIR) domains. The BIR domains are responsible for the anti-apoptotic activity of IAPs due to their ability to bind and inhibit distinct caspases, cysteine-aspartyl proteases critical for the initiation and execution phases of apoptosis. X-linked inhibitor of apoptosis protein (XIAP) is the most potent caspase inhibitor in the IAP family. XIAP contains three BIR

domains (BIR 1, 2 and 3) which exhibit specificity for different caspases. A short linker peptide that precedes the second BIR domain (BIR2) of XIAP forms identical interactions with caspase-3 and caspase-7, whereas the third BIR domain (BIR3) binds to caspase-9. Using structure-based design approaches we synthesized new small molecule XIAP inhibitors. In this presentation the design, synthesis and *in-vitro* evaluation of compounds that selectively bind to the BIR2 domain of XIAP will be described. In addition to their value as tools to understand cellular mechanisms of apoptosis, these small molecule probes are potential leads for the development of new cancer therapeutics.

MEDI 257

Design and development of piperazinedione derivatives as antitumor agents

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Compound HPW99-5, a piperazinedione derivative, was designed as cyclized dipeptide derivative of azatyrosinamide, previously developed in our lab. This compound exhibited cytotoxic activity (IC₅₀) within 10⁻⁷~10⁻⁸ M level in NCI60 cancer cell line panel. The NCI60 inhibition profile of HPW99-5 was correlated with genetic background of NCI60 cancer cell lines by Pearson correlation coefficient. According to clustering assay, leukemia cell lines (SR, RPMI-8226, K-562, HL-60, CCRF-CEM and MOLT-4) were shown to be most susceptible to HPW99-5 treatment. On the other hand, NCI60 profile of HPW99-5 was also submitted to public COMPARE website seeking for known compounds with the most similar NCI60 profile. The result of HPW99-5, along with the top 9 compounds from COMPARE analysis were further submitted to 3dMIND (<http://spheroid.ncifcrf.gov/spheroid/>) established by the Covell group, NCI-Frederick. According to the self-organizing map (SOM) result, all 10 compounds submitted were primarily lay within region M8 (M for mitosis). According to literature, 9 known compounds out of 10 of COMPARE result related to the process of tubulin polymerization, especially on the colchicine binding site. This was confirmed when HPW99-5 was subjected to in microtubule formation assay in HA22T hepatoma cells. The assay indicated that HPW99-5 3.3 μM could sufficiently inhibit the polymerization of tubulin to form microtubule, with effect similar to that of colchicines treatment (10 μM). *In vivo* efficacy of HPW99-5 was conducted with HA22T xenograft model. Tumor growth was significantly inhibited upon oral treatment of HPW99-5 (10 mg/kg/q2d/oral). These result suggested that HPW99-5 is a potent antitumor agent.

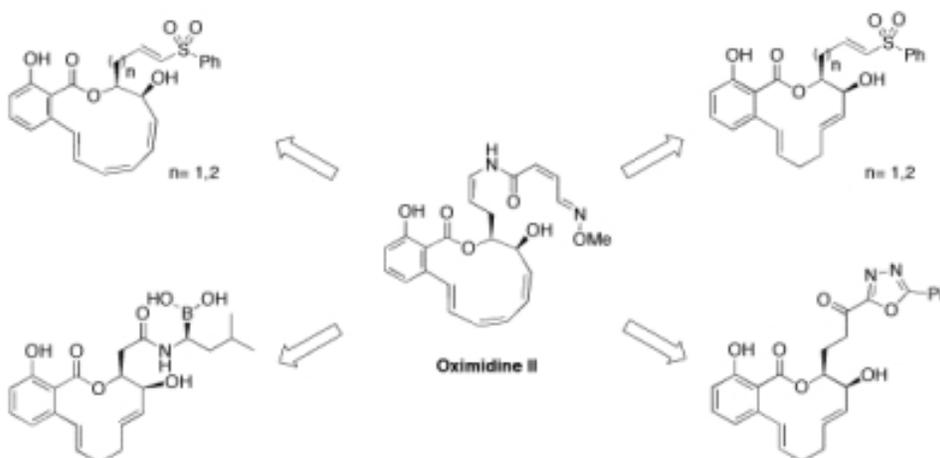
MEDI 258

Design, synthesis, and biological evaluation of novel oximidine analogs as anticancer agents

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The natural products oximidine I and II are potent and selective anticancer agents. Their structures and potent cytotoxicity are similar to the natural products salicylihalamides, apicularens, and lobatamides, which are members of the benzolactone enamide family. However, it is believed that the enamide, a crucial moiety for anticancer activity, will be labile under physiological conditions. *This has led to our hypothesis that the replacement of the enamide moiety with a stable warhead will allow the discovery of novel anticancer agents with improved pharmacokinetics.* We selected three different warheads that are likely to be stable under physiological conditions and that could undergo nucleophilic addition like the enamide. We prepared by total synthesis oximidine analogues that carry a vinyl sulfone, a boronic acid and an α -keto oxadiazole instead of the enamide side chain. Based on CoMSIA/QSAR analysis, we have also designed, prepared and evaluated analogs of oximidine II possessing a modified macrocyclic structure.



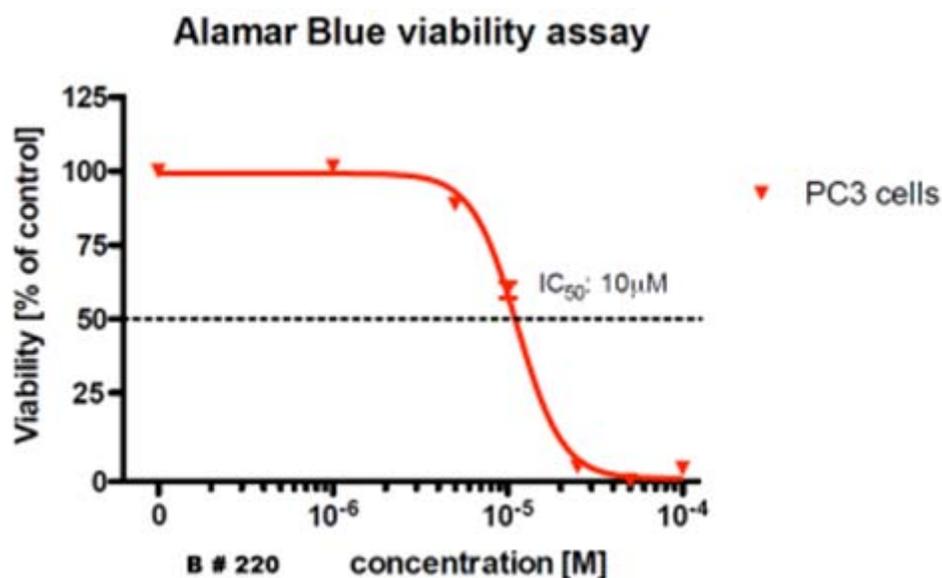
MEDI 259

Design and synthesis of novel retinoids for prostate cancer therapy

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Retinoids (retinol [vitamin A] and its biologically active metabolites) showed to promote differentiation, inhibit growth and induce apoptosis in many cancer cells. It is known that retinoids are required for the appropriate differentiation of normal prostate epithelial cells. Human prostate cancer cells contain much lower levels of vitamin A and its metabolites than those normal cells. The lower level of Vitamin A and its metabolites in prostate cancer cells due to the aberrant metabolism of vitamin A that affect the dysregulation of gene expression and related to the abnormal growth properties of the tumor cells. To avoid aberrant metabolism of Vitamin A, many novel retinoids have been synthesized and tested their biological activity, but so far nothing has been used for therapeutic use. So we synthesized novel retinoids, tested their biological activity against different prostate cancer cell lines PC3, DU145 and RM1.



We found our lead molecule B 220 shows IC₅₀ 10 micromolar in all 3 cell lines. The detail mechanism of action of this drug is currently undergoing in our lab to identify the receptor.

MEDI 260

Pheophorbide derivatives as potential agents for photodynamic therapy of cancers

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To enhance the efficacy of photosensitizers in photodynamic therapy (PDT) of cancers, pheophorbide-a derivatives were synthesized. The derivatives were prepared by a peptide coupling reaction using a series of amino acids. Proton

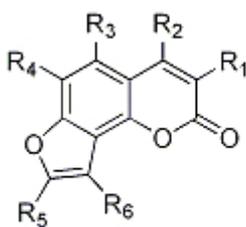
NMR spectra of the target compounds confirmed the formation of the desired products. UV-visible spectroscopy of the derivatives revealed red shifted fourth Q bands at 666 nm, which are used for PDT. Prostate cancer cell studies indicate that the target compounds co-localize to the mitochondria, lysosomes, and the ER. Initial PDT studies showed that at low light doses, eight minute light exposure, and low pheophorbide concentrations the cells exhibit features of apoptotic cell death, such as chromatin condensation and nuclear fragmentation. Although the target compounds have improved UV-visible properties and exhibit promising PDT results, their water-solubility is limited and may require a vehicle for cellular delivery. Current work involves the synthesis of pheophorbides that are water-soluble.

MEDI 261

Development of novel angelicin derivatives as anti-cancer agents

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Angelicin derivatives BPR2P series were discovered by National Health Research Institute as novel anti-cancer agents with activities within nano-molar range. More than 200 analogs from BPR2P series were synthesized for lead optimization. In order to improve the drug properties of BPR2P compounds, simplification of the chemical structure of BPR2P compounds was also attempted; for this purpose we synthesized coumarin derivatives and also benzofuran derivatives and checked their anti-cancer activities. The results showed that the furanocoumarin core structure was essential to maintain the anti-cancer activity. We also designed a novel synthetic route which can avoid the harsh Fries rearrangement synthesis pathway. In all, it takes 11 synthetic steps, with only five purification stages. By using this novel synthetic approach, several BPR2P analogs with sensitive substitutions were synthesized. These compounds are crucial in the SAR study of BPR2P compounds as anti-cancer agents. Further studies and lead optimization of these compounds is underway.



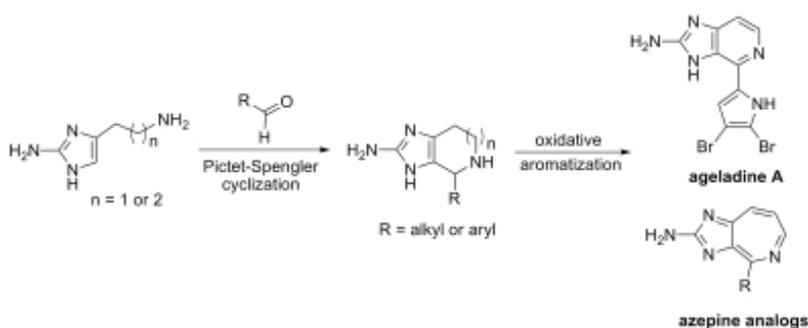
BPR2P series

MEDI 262

Synthesis and anticancer activities of ageladine A and structural analogs

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Ageladine A and a series of analogs that include 2-aminoimidazo[4,5-c]azepines (seven-membered ring) and 2-amino-3H-imidazo[4,5-c]pyridine (six-membered ring) derivatives have been synthesized. The synthesis of these analogs proceeds via a two-step pathway that involves a Pictet-Spengler reaction using 2-aminoimidazoles followed by oxidative aromatization of the resulting ring system. The choice of oxidizing reagents and conditions is highly dependent on the desired ring system. Details of the synthesis and analog evaluation for anticancer activities against several human cancer cell lines and MMP-2 inhibition will be presented.



MEDI 263

Anticancer mechanism of a bis-chelated gold diphosphine compound

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Organogold compounds were developed originally as analogues of platinum based cytotoxic drugs like cisplatin. Although their strong antiproliferative effect, such compounds failed to be advanced into clinical trials due to their severe toxicity issue. GC20, a novel bis-chelated gold(I) diphosphine compound has shown strong anticancer potential and low toxicity in cancer cells and animal models. Based on its structural characteristics and biological properties, we hypothesized that GC20 might specifically inhibit selenoprotein TrxR while it might also intercalate with DNA. Thus, GC20 has potential to be developed into a single anticancer agent possessing both cytotoxic and target specific activities. Here, we systematically investigated the molecular mechanism of GC20. We measured the inhibition activities of GC20 on the thiol (seleno)-containing-proteins (TrxR, hTrxRU498C, hGR and Trx), and the interaction with GSH, DTT and fish DNA. Our preliminary results support our hypothesis and lay the foundation for further structural optimization of the organogold compounds.

MEDI 264

Synthesis of lysine-substituted tetraphenylporphyrins for the use in photodynamic therapy of cancer

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To pursue the hypothesis that mitochondria-localizing porphyrins are better photosensitizers (PSs) for photodynamic therapy (PDT) of cancers, we synthesized and characterized amino acid-substituted tetraphenylporphyrins with properties, which promise to increase their photosensitizing efficacy and provide a sustainable addition to mainstream cancer therapies. Compound synthesis and yield were optimized using trifluoroacetic acid as catalyst. To determine efficacy, the PSs were incubated in androgen-sensitive human prostate adenocarcinoma *LNCaP* cells. Cell studies revealed that amino acid-substituted porphyrins that are positively charged in the slightly acidic medium of cancer cells allow for increased localization to mitochondria and lysosomes. Preliminary evidence suggests that these compounds are promising photosensitizers due to their increased amphiphilicity, acidic properties, and ability to provoke apoptotic cell death. These PSs reassure our attempts toward rational drug design and a sustainable cancer treatment due to their low-cost production, minimal need of additional resources, and convenient administration due to their water solubility.

MEDI 265

Cy5.5 and ⁶⁴Cu dual labeled Affibody molecule for PET and NIRF HER2 imaging

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Affibody proteins are small nonimmunoglobulin proteins with 58-amino acid residues and a three-helix bundle scaffold structure. High affinity and specificity Affibody proteins against a variety of molecular targets could be obtained using phage-display technology and affinity maturation. Recently, Affibody molecules have been extensively studied and used for imaging several important tumor targets such as the human epidermal growth factor receptor type 2 (HER2). Our goal in this research is to develop an Affibody based molecular probe suitable for the positron emission tomography and near infrared fluorescence (PET/NIRF) dual modality imaging. A dendrimer (PAMAM, G0) derivative coupled with both a NIRF dye Cy5.5 and a metal chelator DOTA was synthesized first, and it was

conjugated with an anti-HER2 Affibody ($Z_{HER2:342}$). The resulting bioconjugate (DOTA-Cy5.5-G0- $Z_{HER2:342}$) was then radiolabeled with ^{64}Cu . Finally, the dual labeled protein was further evaluated in vivo for PET/NIRF imaging of HER2 positive tumors. Excellent PET/NIRF tumor imaging contrasts were observed for ^{64}Cu -DOTA-Cy5.5-G0- $Z_{HER2:342}$. Our study demonstrated that the Affibody based probe for dualmodality imaging could be designed, synthesized and successfully used in vivo.

MEDI 266

Assessing mitochondria-targeting photosensitizers for improved photodynamic therapy

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Mitochondria are attractive targets in PDT, since they control apoptosis and could be used in tumor targeting. Two conjugates: TPP-Rh (a porphyrin-rhodamine B conjugate) and TPP-AO (a porphyrin-acridine orange conjugate), each possessing a delocalized lipophilic cation (DLC), were synthesized. Their ability to target mitochondria for PDT was evaluated in comparison to that of an unconjugated porphyrin (TPP-OH). Although fluorescence energy transfer (FRET) was observed in the conjugates, they generated singlet oxygen at rates comparable to TPP-OH. Biologically, both conjugates showed higher activities than TPP-OH. TPP-Rh was particularly interesting and showed a greater phototoxicity [IC_{50} , 3.95 μM : irradiation using 400-850 nm light (3 mW/cm^2) for 1 h] than TPP-OH (IC_{50} , > 20 μM) without significant dark toxicity at 20 μM . TPP-AO on the other hand showed some dark toxicity at 10 μM . TPP-Rh's improved photodynamic activity was attributed to its greater cellular accumulation, and preferential mitochondrial localization.

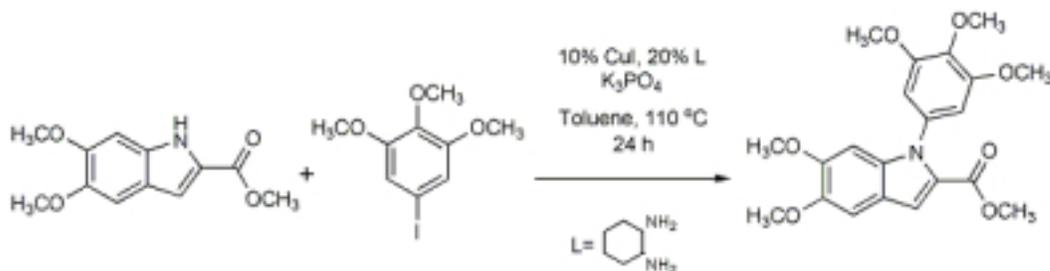
MEDI 267

Design and synthesis of indole-analogs of (-)-colchicine

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For many years, natural products such as (-)-colchicine have served as potential candidates for the treatment of numerous conditions such as cancer. (-)-Colchicine possesses the ability to disrupt the dynamics of microtubule assembly, arresting cell cycle progression at mitosis and leading to apoptotic cell death. Despite of such potential, the highly cytotoxic nature of (-)-colchicine continues to limit the application of this molecule. Consequently, there is a

continuing demand for the development of novel compounds that can exhibit the same activity as (-)-colchicine while possessing a larger therapeutic index.



Our laboratory has designed and synthesized a library of colchicine-like molecules, modeled on the perceived pharmacophore of (-)-colchicine. The compounds were synthesized by Cu-catalyzed Ullmann coupling reactions of aryl halides with substituted indoles. The compounds are being tested for biological activity through Lilly's PD² Program. Additionally, we are extending our library to the second generation.

MEDI 268

Development of 6-substituted purines as selective inhibitors of cyclin-dependent kinase 2 (CDK2)

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The Cyclin-dependent kinases (CDKs) are members of the serine-threonine protein kinase family, and are known to possess cell-cycle related functions. Aberrant cell cycle control may arise from the mutation or inactivation of tumour suppressor genes coupled with the frequently observed over-expression of CDK2, which has been validated as an attractive target for cancer chemotherapy. Previous structure-activity relationship investigations have indicated 2-aryl-amino-6-alkoxypurines are potent ATP-competitive inhibitors of CDK2 activity. One of the most potent and kinase-selective compounds in this series, NU6102 (CDK2; IC₅₀ = 5 nM), has been the subject of extensive studies to further improve selectivity by focusing on modification of the purine 6-position. A focussed series of 6-alkyl- and 6-arylpurines was synthesised by Suzuki cross-coupling in excellent yields. 6-Phenyl- and 6-(3-phenyl)phenyl-2-sulfanylpurines were potent inhibitors of CDK2 (IC₅₀ = 24 nM and 36 nM, respectively). Interestingly, the biphenyl compound exhibited excellent selectivity for CDK2 against a panel of kinases.

MEDI 269

Development of MMP-specific MRI contrast agent for ovarian cancer

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Despite intensive study and substantial research, ovarian cancer continues to take the lives of many women due to late detection. So there is a need to develop diagnostic tools for the early detection of ovarian cancer. In the past two decades, magnetic resonance imaging (MRI) has emerged as one of the most powerful imaging techniques available for the diagnosis of tumors. However, clinically approved MR contrast agents are toxic and have rapid blood-pool clearance and are non-specific resulting in low MRI sensitivity. To address these challenges, we have developed a safe, innovative, and stealth dual bioresponsive ultrasmall superparamagnetic iron oxide nanoparticles which will enable the early detection of ovarian cancer. The surface of the synthesized iron oxide nanoparticles were amine functionalized to facilitate the conjugation of a tumor-specific dual bioresponsive peptide to the contrast agent via a TEG linker. A PEG stealth layer was then attached to the other end of the peptide to sequester the bioresponsive elements within the brush layer of PEG. The synthesized dual bioresponsive nanoparticles were characterized for its functional and structural properties using energy dispersive spectroscopy (EDS), infrared spectroscopy (IR), and transmission electron microscope (TEM). However, its magnetic properties were characterized using MRI and SQUID. In addition, the tumor specificity of the dual bioresponsive peptide is demonstrated by incubating it with human matrix metalloproteinase (MMP).

MEDI 270

C-Lysine conjugates: pH-Controlled light-activated reagents for efficient double-stranded DNA cleavage with implications for cancer therapy

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Double-stranded DNA cleavage of light-activated lysine conjugates is strongly enhanced at the slightly acidic pH (<7) suitable for selective targeting of cancer cells. This enhancement stems from the presence of two amino groups of different basicities. The first amino group plays an auxiliary role by enhancing solubility and affinity to DNA, whereas the second amino group, which is positioned next to the light-activated DNA cleaver, undergoes protonation at the desired pH threshold. This protonation results in two synergetic effects which

account for the increased DNA-cleaving ability at the lower pH. First, lysine conjugates show tighter binding to DNA at the lower pH, which is consistent with the anticipated higher degree of interaction between two positively charged ammonium groups with the negatively charged phosphate backbone of DNA. Second, the unproductive pathway which quenches the excited state of the photocleaver through intramolecular electron transfer is eliminated once the donor amino group next to the chromophore is protonated. Experiments in the presence of traps for diffusing radicals show that reactive oxygen species do not contribute significantly to the mechanism of DNA cleavage at the lower pH, which is indicative of tighter binding to DNA under these conditions. This feature is valuable not only because many solid tumors are hypoxic but also because cleavage which does not depend on diffusing species is more localized and efficient. Sequence-selectivity experiments suggest combination of PET and base alkylation as the chemical basis for the observed DNA damage. The utility of these molecules for phototherapy of cancer is confirmed by the drastic increase in toxicity of five conjugates against cancer cell lines upon photoactivation.

MEDI 271

Infusing organic chemistry courses with anticancer research

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Underrepresented students at CSU have much interest in prostate cancer as they may have a family member affected by the disease. Through natural products research, students in STEM disciplines learn important techniques such as (i) experimental procedures for extraction and isolation of individual chemical constituents from medicinal plants, (ii) using combinatorial technologies as well as state-of-the-art solution- and solid-phase synthetic approaches to generate structurally diverse libraries of bioactive compounds, (iii) procedures for testing for selected bioactivity, (iv) explaining how molecular structures of the bioactive compounds may be determined using spectroscopic techniques, and (v) working (ethically) in a multicultural environment. Thus far, we have screened 75 synthetic and pure natural products against DU145, androgen-unresponsive (androgen-independent) human prostate cancer cells. To study the structure-anticancer activity relationships (SAR), novel derivatives of lead compounds have been synthesized and bioassayed. [figure 1] The variation in SAR was rationalized through quantitative structure-activity relationship (QSAR) models based on several molecular descriptors including van der Waals volume, molecular polarizability, dipole moment, and log *P*.

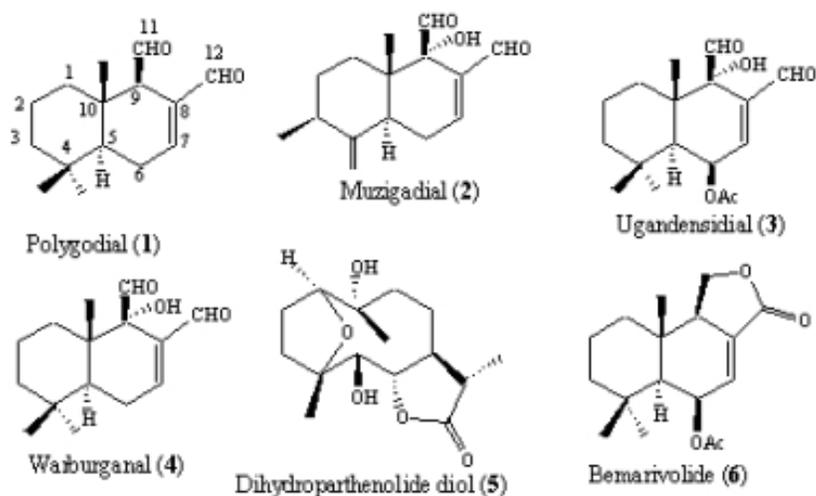


Figure 1. Novel Chiral Bioactive Compounds Isolated from Plants Endemic to Africa.

MEDI 272

New process for the rational design of protein interaction antagonists: Small molecule HDM2 and HDM4 antagonists and cocrystal structures

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Hot spots of protein protein interactions (PPIs) are offering an excellent opportunity for the rational design of low molecular weight antagonists. Herein we propose to excavate the amino acid with the highest buriedness from the PPI interface and to rename this amino acid side chain “anchor”. Next we impose this fragment on efficiently chemical-accessible scaffolds (multicomponent reaction chemistry - MCR) and to create virtual libraries based on several MCR scaffolds. These compound libraries are then docked into the PPI interface whereby the compounds “anchor” align with the protein “anchor” as a starting pose. Manual inspection of the docking results or automatic scoring functions are then used to choose compounds for synthesis and screening. This novel approach is validated by the discovery of several new classes of HDM2 and the first HDM4 antagonists as well as by dual-action HDM2/4 antagonists with nM potency and cell activity. HDM2 and HDM4 are key p53 regulators and comprise novel targets for the discovery of anti cancer treatments. Additional validation of our approach comes from several new cocrystal structures of molecules in HDM2 and the first cocrystal structure of a small molecule in HDM4. Advantages are ultra-fast chemistry from fragment to lead, multiple classes of tractable leads and high success rate.

MEDI 273

Discovery of RG1678: A potent and selective GLYT1 inhibitor for the treatment of schizophrenia

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GLYT1 is a selective transporter of the neurotransmitter glycine localized in the CNS in close vicinity with the NMDA receptor for which glycine is a co-agonist. As a result, GLYT1 inhibition provides a mechanism to potentiate NMDA receptor activity by elevating local glycine concentration. GLYT1 inhibition may thus deliver a completely novel therapeutic avenue in the treatment of schizophrenia for which NMDA receptor hypofunction is believed to be implicated. We have recently identified a novel structural class of GLYT1 inhibitors. The SAR studies as well as the Multi Dimensional Optimisation program that led to the identification of potent, selective and orally active GLYT1 inhibitors will be discussed. The discovery of RG1678, which is currently in clinical development for schizophrenia, will be presented.

MEDI 274

RG7128 and PSI-7851: The discovery and clinical efficacy of a unique class of 2'-F-2'-C-methyl nucleosides for the treatment of HCV

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Hepatitis C is a global health problem with over 170 million individuals infected with the hepatitis C virus (HCV). Infection with HCV is known to lead to chronic liver disease, cirrhosis and eventually hepatocellular carcinoma. Currently, the standard of care is a combination of interferon- α and ribavirin, however, this regimen has limited effectiveness and can be associated with debilitating side-effects. The search for direct acting antiviral agents has led to the discovery of several potent and selective nucleoside/tide inhibitors of the HCV NS5B polymerase. These inhibitors, RG7128 and PSI-7851, are members of the 2'-F-2'-C-methyl nucleoside class of direct acting antiviral agents. RG7128 has demonstrated exceptional potency and safety in the clinic against HCV genotype 1, 2 and 3 infected patients. In addition, PSI-7851, a nucleotide prodrug, showed increased liver exposure of the active triphosphate metabolite in laboratory animals and has also demonstrated antiviral activity in the clinic. The discovery and current state of development for these two agents will be presented.

MEDI 275

Discovery and clinical evaluation of JNJ26070109: A selective CCK2 receptor antagonist that blocks gastric acid secretion without causing acid rebound

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JNJ26070109 is a selective novel small molecule CCK2R antagonist that has completed Phase 1 clinical trials. It has been shown to be effective in reducing stimulated gastric acid secretion in healthy volunteers, with efficacy similar to that seen with PPIs but with faster onset of action. In addition to the discovery of 0109, we will present rodent data demonstrating the absence of rebound hyperplasia in comparison with a prototypical proton pump inhibitor using both acid secretion measurements as well as histological biomarker analysis. We will present the design and volunteer acceptance criteria for the phase 1 clinical trial conducted in Europe and Canada for 0109 and show both clinical pharmacokinetic data for the single dose and repeat dose studies. Clinical efficacy in the dose-dependent reduction in stimulated gastric acid secretion was observed in the multiple ascending dose arm and these data will be presented in comparison with those for omeprazole.

MEDI 276

Novel AChEI template for treatment of Alzheimers

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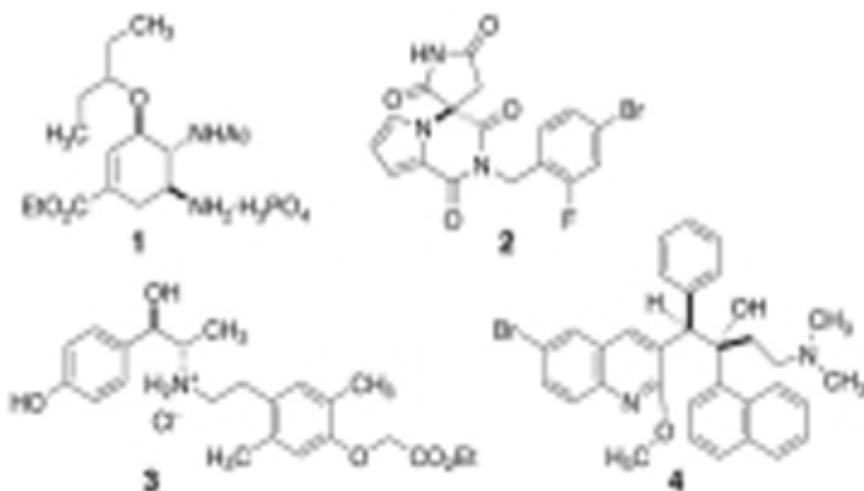
Visual Abstract: Macroxanton observed as a new drug template for treatment of Alzheimer. Our computational research showed structure-activity relation of new template with AChE active side. Macroxanton structure is evaluated by a force-field based docking programme which is embedded in MOE 2008. Acidic interaction between Asp 72 and Macroxanton was thought as a driver of AChEI activity.

MEDI 277

Catalytic asymmetric synthesis of pharmaceuticals and related molecules

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The concept of bifunctional catalysis, wherein both partners of a bimolecular reaction are simultaneously activated, is very powerful for designing efficient asymmetric catalysts. Catalytic asymmetric processes are indispensable for producing enantiomerically enriched compounds in modern organic synthesis, providing more economical and environmentally benign results than methods requiring stoichiometric amounts of chiral reagents. Extensive efforts in this field have produced many asymmetric catalysts, and now a number of reactions can be rendered asymmetric. We have focused on the development of asymmetric catalysts that exhibit high activity, selectivity, and broad substrate generality under mild reaction conditions. Asymmetric catalysts based on the concept of bifunctional catalysis have emerged as a particularly effective class, enabling simultaneous activation of multiple reaction components. Compared with conventional catalysts, bifunctional catalysts generally exhibit enhanced catalytic activity and higher levels of stereodifferentiation under milder reaction conditions, attracting much attention as next-generation catalysts for prospective practical applications. In this presentation, catalytic asymmetric synthesis of Tamiflu **1**, AS-3201 (ranirestat) **2**, β_3 -adrenoreceptor agonist **3**, and R207910 **4** is discussed.



MEDI 278

Elucidating SAR in atypical small molecule agonists of a stem cell cytokine, thrombopoietin (TPO)

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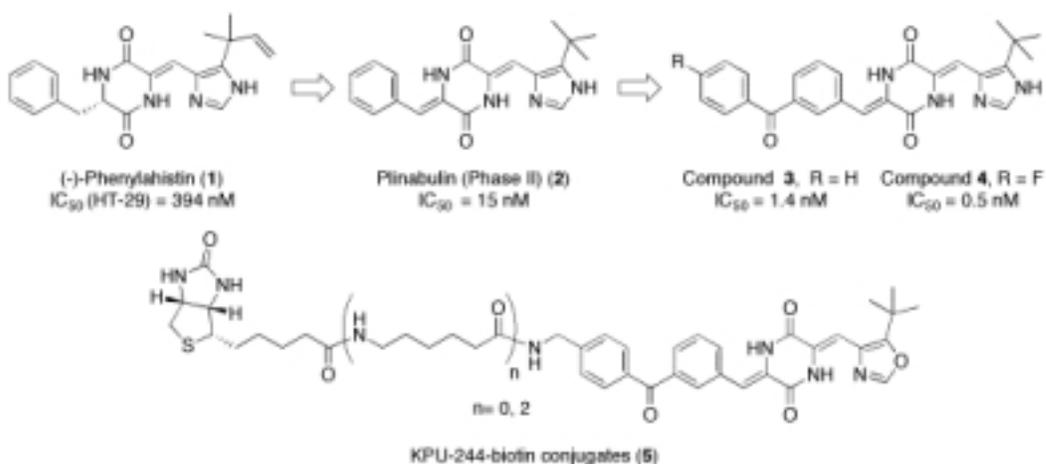
Human TPO is a circulatory cytokine that acts as a primary regulator of the proliferation and development of hematopoietic stem cells (HSCs) and megakaryocytes in the bone marrow, and platelets production. TPO binds to the extracellular domain of the human myeloproliferative leukemia virus oncogene (c-MPL) receptor. Thrombopoietic growth factors have been developed to treat thrombocytopenia, but difficulties administering protein therapeutics have stimulated research into orally active TPO mimetic drugs. Independent academic and pharmaceutical industry research groups have identified c-MPL agonists in a surprisingly diverse range of chemical classes. Subsequent work optimized the c-MPL agonist and pharmacokinetic properties to yield candidate drugs, Eltrombopag (SB-497115, Promacta[®]/Revolade[™]) and AKR-501. These drugs act by an unusual mechanism, interaction with the transmembrane domain of the receptor, an interaction crucially dependent on the presence of a histidine residue, His499. We present the first comprehensive QSAR study of several hundred diverse atypical TPO agonists.

MEDI 279

“Plinabulin” a diketopiperazine-type vascular targeting anti-cancer agent based on microtubule depolymerization activity

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Our efforts to develop novel microtubule depolymerization agents, which was focused on a natural diketopiperazine, phenylahistin (Halimide), have succeeded in creating a highly potent anticancer drug candidate “Plinabulin (NPI-2358)” that has been in Phase II clinical trials as a “vascular disrupting agent”, which induces tumor-selective vascular collapse. SAR study from plinabulin has been conducted to develop more potent derivatives. A benzophenone derivative **3** exhibited one of the potent IC₅₀ values of 1.4 nM. By further modification of the benzophenone moiety in **3** we developed more potent derivative **4**, which exhibited 30-times higher cytotoxicity than plinabulin. This would be promising candidate for further drug development. Additionally, we have been investigating the tubulin-binding site of this type of compounds using KPU-244-biotin conjugates **5** as photoreactive chemical probes in order to understand the precise mechanism of their microtubule depolymerization and vascular disrupting activity. A new method for the convenient synthesis of DKP derivatives via acid-catalyzed cyclization of *N*- α -ketoacylamino acid amides has already been developed.



MEDI 280

NPC1L1 as the target of Ezetimibe

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Ezetimibe is the first member of a class of cholesterol absorption inhibitors to treat Hypercholesterolemia. *In vivo* studies with Npc1l1 null mice established a central role of Niemann-Pick C1 Like 1 (NPC1L1) in the Ezetimibe-sensitive cholesterol uptake into enterocytes. To determine whether NPC1L1 is the direct molecular target of Ezetimibe, we have established a binding assay for Ezetimibe using enterocyte brush border membranes (BBMs) from several species and membranes from HEK293 cells expressing recombinant NPC1L1. These studies demonstrate that Ezetimibe binds specifically to a single class of binding sites with saturable binding profile. Moreover, the binding affinities of Ezetimibe and several key analogs to recombinant NPC1L1 are virtually identical to those observed for native BBMs, and Ezetimibe no longer binds to intestinal BBMs from Npc1l1 null mice. Solubilization and Purification of NPC1L1 to homogeneity in an active state is the unequivocally biochemical evidence that the target of Ezetimibe is NPC1L1.

MEDI 281

Development of KT6-971: A C-glycoside of NPC1L1 transporter inhibitor

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After the successful introduction of ezetimibe into clinical settings, there has been considerable interest generated regarding the medical advantages of inhibiting cholesterol absorption through NPC1L1 on the intestinal surface. The importance of intestinal cholesterol absorption inhibition is two-fold. The first is to achieve the

more restricted goals recommended by NCEP with concomitant use of statins and the second is to prevent oxidative cholesterol intake from daily cooked foods, which seems to render atherosclerotic plaques unstable. We initiated our project to synthesize, C-glycoside analogs of the ezetimibe glucuronide conjugate because, this conjugate is believed to be an active metabolite and its potency is a few orders of magnitude greater than ezetimibe. Among C-glycosides synthesized, KT6-971 was selected for further development because of its potency and stability in biological fluids. KT6-971 inhibited cholesterol absorption via NPC1L1 transporter both *in vitro* and *in vivo* and prevented cholesterol blood level elevation in animal models by once-daily oral administration. Furthermore, the systemic exposure of KT6-971 is minimal, which might predict safer adverse effect profiles for this compound. Steady state feces concentration in animals can be obtained within a few days after once-daily administrations in animals. Selected clinical results will be presented and discussed in this presentation.

MEDI 282

Novel potent dipeptide substituted azetidinones as cholesterol absorption inhibitors with low systemic uptake

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Increased levels of LDL are associated with higher risk for cardiovascular diseases. Treatment with statins is well established and in recent years also cholesterol absorption (CA) inhibitors i.e. Ezetimibe has been introduced. The target, later identified to be NPC1L1 is expressed in the intestine and the hypothesis was that a systemic exposure would not be required for inhibiting the cholesterol absorption. The objective for our project was to identify potent CA inhibitors with low permeability. By avoiding systemic uptake we saw an opportunity to develop drug candidates with potential less side effects. Our approach was to search for positions in otherwise absorbable inhibitors that could be substituted with moieties that decrease the permeability and absorption for the compounds. This presentation will discuss the efforts to find novel CA inhibitors that are potent *in vivo* and active on the target NPC1L1. Dipeptides were found to be appropriate moieties to substantially reduce the permeability of the molecules. These peptides also gave the possibility to increase the potency of the molecules. A clinical candidate and additional backups were identified. The chemistry development with some challenging synthetic chemistry, results from screen *in vivo* and the correlation with *in vitro* data will be discussed as well as pharmacokinetic data.

MEDI 283

Canosimibe: Design, synthesis, and in vivo activity of a nonsystemic inhibitor of cholesterol absorption

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Elevated plasma LDL-C is a major risk factor for cardiovascular disease. Combination therapy with e.g. a statin (inhibiting the endogenous synthesis of cholesterol by inhibiting HMG-CoA reductase) and a compound which inhibits the intestinal absorption of dietary and endogenous cholesterol (e.g. ezetimibe) was found to effectively reduce elevated LDL-C to levels recommended in treatment guidelines. The aim of a novel approach was to test the hypothesis that the target(s) of cholesterol absorption inhibitors might be accessible at the luminal side of the intestine, thus limiting systemic drug load and systemic side effects as well as minimizing drug-drug-interaction potential. By retaining the pharmacophore of ezetimibe and by introducing linker-spacer groups as well as low absorption groups (LAGs) to different parts of the molecule we probed the spatial acceptability of those modifications. As LAGs polar residues such as polyols, permanent cations or permanent anions were coupled to the pharmacophore *via* various linkers (e.g. of the amido-, ureido- or sulfonamido-type) and spacers of various lengths and structural types. The compounds were tested *in vivo* in a mouse model for their ability to inhibit cholesterol absorption after oral application of the drug. Active compounds underwent a PK study in the rat. Compounds which met the “low absorption - non-systemic” criteria were further tested in other small animal models for their ability to inhibit cholesterol absorption and lower LDL-C in models of hypercholesterolemia. The design, synthesis, SAR, and *in vivo* activity of non-systemic inhibitors of cholesterol absorption, which culminated in the invention of the clinical candidate Canosimibe (AVE5530), will be presented.

MEDI 284

Non-systemic cholesterol absorption inhibitors

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High LDL-cholesterol levels are associated with increased risk of cardiovascular diseases and health authorities guidelines are encouraging aggressive treatment with target levels as low as 70 mg/dl for patients at risk. Cholesterol absorption inhibitors (CAI), with ezetimibe as the first-in-class and only marketed drug, have shown to be effective at reducing LDL-C levels alone (Zetia®) or in combination with a statin (Vytorin®). Lipideon Biotechnology AG are developing a second-generation CAI with local mode of action in the small intestine and minimal systemic exposure. Indeed, a non-absorbable GI-tract topical drug would have

reduced risks of drug-drug interactions and systemic toxicity and would thus be beneficial for patients as an alternative to ezetimibe. We have identified a number of classes of molecules that meet this criteria. Structure-activity relationship studies towards an active and minimally absorbed CAI will be presented.

MEDI 285

Discovery of second generation cholesterol absorption inhibitors

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Zetia® (ezetimibe) is the first approved cholesterol absorption inhibitor (CAI) for use in treating hypercholesterolemia. Ezetimibe undergoes hepatic recirculation *in vivo* and is rapidly metabolized to a more active glucuronide metabolite, which leads to excellent efficacy at a low dose (10 mg once daily). In addition, when ezetimibe is combined with a statin, superior LDL-C lowering is observed in patients as compared to either a statin or a cholesterol inhibitor alone. Recently, based on Merck and Schering-Plough's collaborative efforts, the Niemann-Pick C1 Like-1 (NPC1L-1) protein was identified as the putative target of ezetimibe. NPC1L-1 is located mainly in the jejunum of the small intestine consistent with its proposed function of cholesterol absorption. This presentation will describe the results from the NPC1L-1 team which explored structurally novel CAI's in order to identify second generation compounds that are minimally absorbed and do not depend on excretion of an active metabolite for efficacy.

MEDI 286

Clinical studies with ezetimibe

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The cholesterol absorption inhibitor ezetimibe was approved for the treatment of hypercholesterolemia (and phytosterolemia) in 2002, both as monotherapy and for co-administration with statins. While the direct action of ezetimibe is the inhibition of the cholesterol transporter NPC1L1, evidence indicates that it is increased plasma clearance of LDL that produces the drug's LDL-lowering effect, presumably via upregulation of hepatic LDL-receptors. A large amount of additional clinical trial data relevant to ezetimibe's efficacy and safety in various

contexts has accumulated since its approval. These data will be reviewed, with a focus on completed and ongoing studies addressing the effects of LDL-C lowering with ezetimibe on atherosclerosis and cardiovascular events.

MEDI 287

Approaches and status of methods to inhibit Abeta production for Alzheimer's Disease

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Alzheimer's Disease (AD) is the leading cause of dementia and is estimated to affect more than 35 million people worldwide. Due the aging population, the incidence of AD is expected to triple by 2050. Pathology data, analysis of familial AD mutations, and preclinical studies support the hypothesis that Abeta peptides cause the initiation and progression of AD. Abeta peptides are a series of peptides formed by the sequential cleavage of the amyloid precursor protein first by BACE and then by gamma-Secretase. Based on the amyloid hypothesis, several approaches to inhibit Abeta production, including BACE inhibitors, gamma-Secretase inhibitors, gamma-Secretase modulators, and glutamyl cyclase inhibitors, are being pursued. In this presentation, the rationale and issues with the discovery and development of molecules for each of these targets will be reviewed. In addition, the clinical status of molecules directed toward these targets will be summarized.

MEDI 288

Gamma secretase modulators that acutely reduce soluble A β 42 levels in non-transgenic rodents

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The lowering of neurotoxic A β peptide production from APP (Amyloid Precursor Protein) has been the focus of multiple drug discovery efforts over the last decade for the treatment of Alzheimer's disease (AD). The APP processing enzyme, gamma secretase (GS) is an attractive target that is particularly amenable to brain penetrant small molecule drug discovery. Direct gamma

secretase inhibitors (GSIs) decrease A β production in animal models and humans. However, the clinical development of GSIs has been hampered by limiting side effects associated with this mechanism of action. In particular, GSIs also inhibit GS-mediated Notch processing, which results in gastrointestinal toxicity. These safety concerns have led to the discovery of gamma secretase modulators which selectively inhibit the production of the toxic A β 42 peptide while maintaining total A β peptide levels and sparing Notch. A review of the SAR of a compound series which led to the discovery of EVP-14936, an orally bioavailable, CNS-penetrant GSM will be presented.

MEDI 289

Testing the amyloid hypothesis: Optimization of a series of sulfonamide γ -secretase inhibitors and the discovery of BMS-708163

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Amyloid- β (A β) peptides are implicated in the development of Alzheimer's Disease (AD) by pathology, genetics and numerous preclinical studies. Cleavage of APP by γ -secretase is necessary for the production of A β peptides, and the development of γ -secretase inhibitors (GSI) represents an attractive therapeutic approach for treating and/or preventing AD. However, γ -secretase also cleaves Notch proteins, which are essential to various cell fate decisions. In addition, γ -secretase pharmacology is complicated by inhibitor potency shifts and A β rises under certain conditions. The challenges encountered in optimizing a series of sulfonamide GSIs for potency, selectivity towards inhibition of APP processing, and brain penetrance will be described. Advanced leads required modification to address metabolism and other pharmacokinetic issues. These efforts resulted in the discovery of BMS-708163, a potent, Notch-sparing GSI which reduces A β in rats, dogs and humans. BMS-708163 is currently being tested in Phase II clinical trials for AD.

MEDI 290

Discovery of small molecule, orally active and brain penetrant BACE1 inhibitors

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Alzheimer's disease (AD) is a progressive neurodegenerative disease that is a leading cause of death in the elderly. It is believed that abnormal proteolytic processing of the amyloid precursor protein (APP) and resultant accumulation of the toxic amyloid peptides A β 40 and A β 42 in the brains of AD patients is central to disease pathogenesis. The initial step in the proteolysis of APP to produce A β 40 and A β 42 is mediated by BACE1, a membrane-anchored aspartyl protease expressed in neurons. Because accumulation of A β 40 and A β 42 is implicated in AD pathogenesis, substantial efforts have been directed towards development of BACE1 inhibitors as potential disease-modifying therapeutic agents. However the development of selective, brain penetrant BACE1 inhibitors has proven to be a difficult challenge. We have designed a novel series of iminohydantoin BACE1 inhibitors originating from a fragment-based screening hit and application of structure-based design guided by X-ray crystallography. Modification of the iminohydantoin core, optimization of the aromatic substituent residing in S1 and extension into the S3 pocket of BACE1 resulted in identification of potent, orally bioavailable and brain penetrant BACE1 inhibitors. The SAR and in vivo characterization in rodents of lead inhibitors that resulted from this work will be described.

MEDI 291

Beta-secretase inhibitors for treatment of Alzheimer's disease

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michael.a.brodney@pfizer.com, Pfizer Global Research and Development, Eastern Point Road, PO Box 8220-4310, Groton, CT 06340 A major pathophysiology of Alzheimer's disease (AD) is the presence of amyloid plaques

which are primarily composed of the A-beta peptide. The formation of the A-beta peptide is the result of sequential enzymatic cleavage of the Amyloid Precursor Protein (APP) by beta-secretase (BACE) and subsequently by gamma secretase. BACE is a membrane bound aspartyl protease which is characterized by a large binding pocket designed to recognize 6-8 amino acid residues of APP. Identification of small molecule development candidates that inhibit BACE remains a major hurdle due to challenges in identifying compounds with the appropriate balance of potency, clearance and CNS penetration. A strategy to align a set of physicochemical properties in one molecule led to the discovery of a novel class of inhibitors. Optimization of the lead compounds using structure based drug design has resulted in a series of BACE inhibitors that adequately penetrate the CNS and acutely lower brain A-beta levels in APP transgenic mice.

MEDI 292

Identification of selective BACE1 inhibitors as potential disease modifying treatments for Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by gradual and increasing loss of cognitive function and behavioral abnormalities. The formation of b-amyloid plaques and neurofibrillary tangles are recognized as the key pathologies of the disease. Amyloid b-peptide (Ab) is produced in vivo through proteolytic cleavage of the membrane-bound b-amyloid precursor protein (APP) by b- and g-secretases sequentially. The accumulation and aggregation of these monomers to form plaque residues is seen as a key event in the progression of the disease. Increasing evidence implicates Ab (39–43 residues) in the pathology of neurodegeneration, and it follows that inhibition of enzymes responsible for Ab formation may stop or slow the progression of AD. The design and synthesis of potent and selective inhibitors of b-secretase (BACE1) has been a daunting challenge for the pharmaceutical industry. Nearly a decade of research has focused on this elusive target through a myriad of medicinal chemistry based approaches. Through the use of molecular modeling and x-ray techniques the active site of BACE1 has been mapped and thoroughly explored. However, the complexity of the topological surface of the enzyme coupled with the challenges associated with an intracellular, central nervous system target have made the design of drug-like ligands extremely difficult. Through a combination of structure based design strategies, medicinal chemistry SAR and complex pharmacokinetic SPR, we have identified potent orally bioavailable ligands for the BACE1 enzyme. This presentation will highlight our results towards the potential development of disease modifying treatments for AD.

MEDI 293

Scanning and phage display technologies for global identification of small molecule targets

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Phage display cloning using a small molecule bait is an excellent method to empirically determine all of its cytoplasmic protein targets. Key to the method is attachment of an affinity linker at a site unimportant for biological activity of the molecule. Preparation of a family of systematically substituted derivatives of a compound and their testing in a functional, cell-based assay (“scanning”) enables their interactions with all proteins to be evaluated. This method identifies regions of a molecule important for activity even with unknown targets and enables preparation of an effective affinity ligand. Methyl scanning was applied to demethylasterriquinone B1, an insulin mimic; the results were used to design a biotinylated conjugate with which phage display identified several previously unknown binding partners. Iodine scanning was applied to ChemBridge 5271050, an inhibitor of endomembrane trafficking. This method enables a simpler preparation of an affinity ligand from molecules proven to be active.

MEDI 294

Rapid and efficient method for identifying photoaffinity labeled sites within proteins

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The method of photoaffinity labeling is a direct approach for mapping the ligand binding site of proteins that are hard to elucidate with crystallography or nmr. However, experimental routines required for identifying photoaffinity labeled sites within proteins still remain as a laborious task, which significantly hampered the wide application of this powerful method in the field of functional proteomics. The talk focuses the recent development of our diazirine-based multifunctional photoaffinity probes designed for rapid identification of labeled sites and an efficient approach for improving the arduous steps of photoaffinity labeling experiment by manipulating labeled proteins and peptides on matrices. The use of multifunctional photoprobes together with solid phase technology significantly accelerated the identification of binding cavity peptide fragments. Makoto Hahimoto and Yasumaru Hatanaka, Recent Progress in Diazirine-based photoaffinity labeling, *Eur. J. Org. Chem.*, **2008**, 2513 – 2523 (2008); Nlandu B. Bongo, Takerori Tomohiro, and Yasumaru Hatanaka, Synthesis and evaluation of novel photoreactive α -amino acid analog carrying acidic and cleavable functions, *Bioorg. Med. Chem. Lett.*, 19, 80-82 (2009).

MEDI 295

Photoaffinity labeling studies to better define the mechanism of action for Phase II oncology drug KX2-391

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KX2-391 is an orally administered small molecule oncology drug that has successfully completed Phase I clinical trials in cancer patients and is entering Phase II trials. A series of photoaffinity analogs of KX2-391 were synthesized and one of these was found to be equipotent (low nM level activity) in blocking the growth of various tumor cell lines. Photoactivated crosslinking of this analog to the target proteins in tumor cells, followed by their isolation and MS identification with the aid of “click” chemistry led to a more complete understanding of the mechanism of action for this drug. The photoaffinity studies also allowed the identification of the target protein binding site. This case study illustrates the potential power of photoaffinity labeling for defining the mechanism of action of a compound in a whole cell environment.

MEDI 296

Photoreactive activity-based probes for mapping small molecule-protein interactions

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Genome sequencing projects have revealed that eukaryotic and prokaryotic organisms universally possess a huge number of uncharacterized proteins. Chemical probes that can bind and perturb the function of proteins are needed to assist in their functional analysis. Here I will present research from our laboratory aimed at developing and applying “clickable”, photoreactive activity-based probes for the characterization of small-molecule-protein interactions in proteomes and living systems.

MEDI 297

Identification and characterization of gamma-secretase using photoactivable inhibitors

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Gamma-secretase, a catalyst of Alzheimer disease and signal transduction, cleaves substrates within the transmembrane domain. Gamma-secretase is a large multi-protein complex composed of at least four proteins possessing 19 putative transmembrane domains. Elucidating the structure and function of

gamma-secretase has been a formidable challenge that requires novel chemical insights. We have developed a series of active site-directed and photoactivable inhibitors and applied them in identification and localization of gamma-secretase. We have provided compelling evidence that presenilin is the catalytic subunit of gamma-secretase and that active gamma-secretase is present in the plasma membrane. Recently, we have developed a multiple photo-affinity probe approach that allows to detect changes in the conformation of the gamma-secretase active site. We will discuss the application of this approach in determining the mode of action of allosteric gamma-secretase inhibitors and elucidating the molecular mechanism of presenilin mutations that are linked with Alzheimer disease.

MEDI 298

Molecular mechanism of cotransins: Selective inhibitors of secretory and membrane protein expression

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Target identification is often the rate-limiting step in deciphering the molecular mechanism of biologically active small molecules. We have combined diazirine photochemistry and copper catalyzed Huisgen cyclization (“click”) chemistry to identify the target of cotransins. Cotransins comprise a family of cyclic heptadepsipeptides which inhibit the cotranslational translocation of nascent secretory proteins into the endoplasmic reticulum (ER). Inhibition occurs at the level of insertion of the nascent protein into a membrane-embedded multiprotein complex, termed the translocon, which recognizes signal sequences and transmembrane domains and forms a channel through which substrate proteins traverse. We designed and synthesized an alkyldiazirine-based photo-affinity probe that is isosteric with the parent cyclodepsipeptide. Using this probe, we identified an integral membrane protein subunit of the translocon complex, Sec61 α , as the direct molecular target. Our current goal is to unravel the mechanism by which cotransins block the expression of a subset of human secretory and membrane proteins.

MEDI 299

Lean transformation of lead optimization

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All of the properties of a new drug are determined by its chemical structure. Lead optimization, wherein the structure/activity profile of each chemotype guides the synthesis of new molecules with improved properties, represents the best opportunity for creating a safe and effective candidate. When analyzed by

principles of lean thinking, customary practices for lead optimization reveal multiple opportunities for increasing knowledge gained and, therefore, eventual clinical success. The ideal state sought in lead optimization requires that three performance measures be maximized: **timeliness** (shortest possible time from synthesis to assay result); **completeness** (widest possible characterization of novel compounds); and **efficiency** (lowest resource cost per result). Our experience suggests that aggressively targeting efficiency provides the shortest path to meaningful improvements in timeliness and completeness. The effectiveness of this approach is further enhanced by empowerment of individual scientists to apply the scientific creativity that is the driving force for success in drug discovery.

MEDI 300

Lean thinking, creativity and innovation: Concordant or conflicting?

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Faced with the well-documented challenges of increasing competition, rising costs and high attrition in our field we, and others, have embarked on a journey to try to apply lean sigma principles to drug discovery to improve the speed and quality of drug hunting. However, lean sigma's manufacturing roots have caused some people to question its suitability as a vehicle for improvement in the creative and innovative environment of drug discovery. During this presentation, changes that have been made to increase speed and quality of drug discovery will be presented, and the benefits will also be considered in the context of whether creativity and/or innovation have been hampered by the changes. Additionally, some ideas for how creativity, innovation and lean sigma might comfortably co-exist and perhaps even co-operate to mutual benefit will be offered.

MEDI 301

Lean-6 Sigma and the improvement of processes in early Lead generation drug discovery efforts

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Lean 6-Sigma has been used to improve various aspects of the pharmaceutical industry. This presentation describes our attempts to improve early Lead Generation efforts through the application of Lean tools and philosophy and the impact it has had on our Drug Discovery process.

MEDI 302

Application of lean tools to eliminate waste in drug discovery

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Currently, pharma faces huge pressures to increase productivity and move new drugs to market faster. While the drug development phase typically has been the focus of cycle time improvements, process improvement methodologies, such as Lean and Six Sigma, have only recently been applied in the Drug Discovery arena. The reluctance of Discovery to embrace these proven improvement platforms may stem from the misconception that implementing standardized processes and controlling variation is contrary to the creativity and innovation that drives successful drug discovery. In the Medicinal Chemistry department at Boehringer Ingelheim, we have taken the view that standardization does not stifle creativity, but frees up time to do more and better science. As such, we applied Lean thinking to eliminate waste and non-value added activity from our daily work, with the goal of liberating more time to spend on creative and innovative problem-solving. With this, we have employed the Lean tools of “value stream mapping” and “baselining” to highlight wasteful activities within our department. Subsequently, the DMAIC (Define, Measure, Analyze, Improve and Control) process was employed to identify root cause, propose solutions, and gain management support for improvement efforts. Two case studies, one operational and one transactional, will be discussed.

MEDI 303

Accelerating research through continuous improvement

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In most pharmaceutical R&D operations it is difficult to accurately measure quality of compound design, speed of project progression, integrity of biological data, relevance of biological testing, quality of project decision making, decision outcomes, etc. In the absence of such data, project teams make decisions based on past experience, rules of thumb, qualitative data or any combination of the above. Our objective was to quantitatively and continuously improve the performance of project teams throughout the research and development processes and therefore it was essential that we identify methods to baseline current activities. How and why do research teams make decisions? How successful are those decisions in reality? What data is used to inform those decisions? This presentation will highlight our efforts to accelerate the research process by working with teams to understand the obstacles they face and to provide Continuous Improvement tools, expertise, and support to enable them to go beyond the routine and strive to be extraordinary. By facilitating decision making, expanding data analysis and interpretation, and improving accountability and team learning we have been able to improve dramatically both efficiency and

effectiveness of project execution within Pfizer Global Research and Development.

MEDI 304

Merck experience with application of lean-sigma principles to DMPK workflows in support of drug discovery

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Support of drug discovery includes a substantial investment in resources to address DMPK properties of potential drug candidates. Many DMPK assays have become relatively commoditized, including in vitro assays such as plasma protein binding and metabolic stability, as well as more resource intensive work such as in vivo PK screening. When supporting numerous projects at a given site, there will always be routine, typically weekly demand for commoditized assays, even if a “right assay at the right time” or issue-driven approach is used to address DMPK properties. Effective and efficient use of the resources needed to support these routine assays can be realized by applying Lean-Sigma principles to optimizing and controlling the processes. Examples of significant improvements in productivity, including reduced and less variable turnaround time and improved data reliability will be illustrated for several DMPK workflows.

MEDI 305

Importance of the glutamate moiety for folate receptor targeting and GARFTase inhibitory activity in classical thieno[2,3-d]pyrimidine antifolates

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We have recently reported a series of thieno[2,3-d]pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC₅₀ values. In addition, these analogs are not transported via the reduced folate carrier (RFC) into normal cells. Glycinamide ribonucleotide formyl transferase (GARFTase) was confirmed as the target. To further investigate the structural requirements of antifolates with respect to FR substrate activity and antitumor activity, a series of analogs with variations in the glutamate moiety were designed and synthesized.

The synthesis and FR substrate and antitumor activity of these analogs will be presented.

MEDI 306

Thyroid hormone action and selective thyromimetics

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Thyroid hormones play important roles in both development and maintenance of homeostasis in adults. Thyroxine (T_4) is the primary thyroid hormone secreted from the thyroid gland, but its deiodination product 3,5,3'-triiodothyronine (T_3) is responsible for a most of thyroid hormone action in target tissue. T_3 binds with high affinity to thyroid hormone receptors (TRs) that belong to the nuclear receptor superfamily of ligand activated transcription regulators. There are two thyroid hormone receptors, $TR\alpha$ and $TR\beta$, the distribution of which varies from tissue to tissue. The development of selective thyromimetics—or thyroid hormone agonists that show tissue selective thyroid hormone action—has recently emerged as a potential new therapeutic mechanism for the treatment of metabolic disorders including hyperlipidemia, diabetes, and obesity. This symposium will focus on the latest developments in this field, and this presentation will provide an introduction to the chemistry, biology and medical physiology of thyroid hormone action.

MEDI 307

Design strategies for achieving $TR\beta$ -selectivity

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Thyroid hormone receptor subtypes ($TR\alpha$ and $TR\beta$) mediate differential functions, suggesting the possibility of developing selective thyromimetics that cause therapeutic increases in metabolic rate, and lipid lowering and modulation without deleterious effects on eg. the heart. The predominant hypothesis is that selective $TR\beta$ activation can give such a profile. Based on the examination of several x-ray crystallographic structures of $TR\alpha$ and $TR\beta$ LBD in complex with various thyromimetics, $TR\beta$ selective ligands have been designed. In this talk, several structurally different thyromimetics will be discussed in detail in the context of the structural requirements required for achieving $TR\beta$ selectivity.

MEDI 308

Mechanisms of STRM action

P. Webb, pwebb@tmhs.org. Department of Medicine, The Methodist Hospital Research Institute, Houston, TX, United States

We used X-ray structural biology, molecular biology and genomics to characterize selective thyroid receptor (TR) modulators (STRMs). X-ray structures of TRs with the TR β selective ligand GC-1 reveal the mechanism of isoform-selective binding. However, there are no differences in TR fold, relative to each other or similar complexes with triiodothyronine (T₃) and gene profiling reveals no major differences between T₃ and GC-1 in mouse liver, or human liver cells (HepG2) that express endogenous TR β . There are minor variations in GC-1 action at genes with unusual promoter architecture and differential effects of exogenous TR α and TR β at 1% of TR-regulated genes in two types of stable cell lines. We conclude that differential effects of GC-1 are due to TR β and tissue selectivity and that gene-specific action is rare. We predict that gene-specific actions will be common with ligands that perturb TR fold, such as the highly TR β selective agonist GC-24.

MEDI 309

Anti-obesity, anti-diabetic, and lipid lowering effects of the thyroid receptor b subtype selective agonists KB-141 and GC-1

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Selective thyroid hormone receptor subtype-b (TRb) agonists have received attention as potential treatments for hypercholesterolemia, diabetes and obesity. The TRb selective agonist KB-141 induces 5-10% increases in metabolic rate and lowering of plasma cholesterol levels without tachycardia in lean rats, unlike T₃. Body weight, adiposity (DEXA), and lipid levels were examined following P.O. administration of KB-141 to obese Zucker *fa/fa* rats at 0.00547-0.547 mg/kg/day for 21 days, and in *ob/ob* mice at 0.5 mg/kg/day KB141 for 7 days. In rats, KB-141 reduced body weight in a dose-dependent manner without tachycardia. In *ob/ob* mice, KB-141 lowered serum cholesterol (35%), triacylglycerols (35%) and both serum and hepatic free fatty acids (18-20%) without tachycardia. Treatment of *ob/ob* mice with KB-141 (0.0547 or 0.328 mg/kg/day, 2 weeks) improved glucose tolerance and insulin sensitivity. Results with GC-1 were similar showing some degree of weight loss without tachycardia.

MEDI 310

Design and characterization of thyroid hormone receptor- β agonists that selectively target the liver

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Thyroid hormone receptor (TR) agonists produce a unique lipid lowering profile largely through modulation of hepatic gene expression. However, concomitant effects on genes expressed in extra-hepatic tissues such as the heart, skeletal muscle, bone and pituitary lead to dose-limiting side effects that greatly impede the clinical development of this drug class for the treatment of hyperlipidemia. Efforts to discover strategies that confine TR activation to the liver resulted in a series of phosphonate-containing TR agonists that distribute poorly into most tissues other than the liver due to their high negative charge and transporter specificity. Liver targeting was further enhanced by using HepDirect prodrugs which cleave selectively in the liver via a cytochrome P450-catalyzed oxidation. Pre-clinical studies evaluating the ability of the lead drug candidate, MB07811, to target the liver and lower lipids with an improved therapeutic index will be presented as well as results from a 14-day human clinical trial.

MEDI 311

Preclinical and clinical studies of thyromimetics

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Current therapies for dyslipidemia have not adequately decreased the incidence of heart attack and stroke and newer therapies are needed. Likewise, new therapies for obesity and Type 2 Diabetes need to be developed. We obtained thyroid hormone receptor selective modulators (STRMs) which can be used to address all of these medical concerns. We have shown safety and efficacy for cholesterol-lowering and have obtained promising results for other aspects of metabolic syndrome. Here, we discuss recent findings about mechanisms of action of STRMs in preclinical animal models and review results of early clinical studies of STRMs in humans.

MEDI 312

Bariatric surgery: Clues for type II diabetes

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Bariatric Surgery is an effective treatment for severe obesity, and can also have profound effects on glucose control. Greater than 80% of obese Type II diabetics who undergo Roux-en-Y gastric bypass see rapid resolution of their diabetes. The hypotheses that have been suggested to account for this phenomenon will be introduced. This presentation will then focus on how these hypotheses lead to consideration of what molecular targets and signaling pathways could be

involved in the diabetes remission, and how drug discovery scientists might develop pharmacological agents that could mimic the efficacy seen with Roux-en-Y gastric bypass surgery.

MEDI 313

Discovery of selective small molecule GPR40 agonists as antidiabetic compounds

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Type 2 *diabetes mellitus* (T2DM) is becoming a global epidemic that is strongly related to life style and economic changes. The disease is characterized by high blood glucose, insulin resistance and relative insulin deficiency. Sulfonylureas have been used clinically for decades as insulin secretagogues to control blood glucose levels in diabetic patients. However, they stimulate the secretion of insulin continuously, regardless of prevailing glucose levels, thereby may cause hypoglycemia and b-cell exhaustion. Agents that promote glucose-stimulated insulin secretion (GSIS) are highly desirable, as evidenced by the recent introduction of GLP-1 analogs and DPP4 inhibitors as antidiabetic agents in the clinic. The G-protein coupled receptor GPR40 is highly expressed in pancreatic islets and is activated by long-chain free fatty acids (FFAs). Activation of GPR40 potentiates GSIS *in vitro* and *in vivo*. We have developed a series of biaryl ether analogs that demonstrated mechanism based efficacy in animal models. The evolution of the series and recent progress will be discussed.

MEDI 314

Targeting TGR5 in diabetes: Focus on S-EMCA (INT-777) a potent and selective bile acid mimetic agonist

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TGR5 has emerged in recent years as an attractive target for obesity and type-2-diabetes in view of its roles in the regulation of glucose metabolism and energy homeostasis. These effects are linked to the ability of TGR5 to stimulate the type 2 iodothyronine deiodinase (D2) that, in turn, induces the production of glucagon-like protein 1 (GLP-1) in enteroendocrine cells and the activation of thyroid hormone in the most important thermogenically regulated tissues such as brown adipose tissue (BAT) and muscle. In this scenario, we have been committed

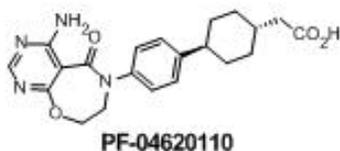
toward the identification of novel bile acids (BAs) derivatives as potent and selective agonists for TGR5. Our efforts have hitherto resulted in the disclosure of S-EMCA (INT-777), a compound that incorporates a 23(S)-Methyl and a 6 α -Ethyl moiety into the cholic acid structure. Being endowed with remarkable properties of potency, selectivity and metabolic stability, S-EMCA (INT-777) was chosen for preclinical characterization and submitted to a combination of pharmacological and genetic gain- and loss- of function studies *in vivo*. It was shown, in particular, that S-EMCA (INT-777) increases the intracellular levels of cAMP, GLP-1 release, oxygen consumption, cytochrome-c oxidase activity, and the ATP:ADP ratio in enteroendocrine L cells. Remarkably, oral administration of S-EMCA (INT-777) was shown to prevent obesity, insulin resistance and glucose intolerance in mice during high fat feeding. In this presentation, the chemistry and salient biological results related to S-EMCA (INT-777) will be reported. Also, the possible analogies between increased serum bile acid levels, weight loss and improved metabolism following Roux-en-Y gastric bypass surgery (GB) and the results of S-EMCA (INT-777) induced TGR5 activation will be discussed.

MEDI 315

Discovery and preclinical pharmacology of PF-04620110: A selective inhibitor of DGAT-1 for the treatment of type-2 diabetes

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Inhibition of acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1), an enzyme that catalyzes the final committed step of triglyceride synthesis, represents a potential therapeutic entry point for the treatment of diabetes and obesity. This talk will detail the discovery, safety derisking strategies and preclinical pharmacology profile of PF-04620110, which has entered Phase I studies for the treatment of Type-2 diabetes.]



MEDI 316

Discovery of JNJ-28630355, a potent and selective trisubstituted pyrimidine GPR119 agonist

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Pancreatic b-cell dysfunction is a hallmark event in the pathogenesis of type 2 diabetes. Injectable peptide agonists of the GLP-1 receptor have shown significant promise as anti-diabetic agents by virtue of their ability to amplify glucose-dependent insulin release and preserve pancreatic b-cell mass. These effects are mediated via stimulation of cyclic AMP through b-cell GLP-1 receptors. The G_{α_s} -coupled receptor GPR119 is largely restricted to insulin-producing b-cells of pancreatic islets and incretin producing K- and L-cells of the GI tract. Unlike receptors for GLP-1 and other peptides that mediate enhanced glucose-dependent insulin release, GPR119 appears to be a small-molecule receptor, responding to several fatty acid amides distinct from endocannabinoids selective for CB1 and CB2 receptors. Potent GPR119-specific agonists described herein significantly increased cyclic AMP accumulation in b-cells *in vitro* and also enhanced glucose-dependent insulin release *in vitro* and *in vivo*, and improved oral glucose tolerance in wild-type mice, but not in GPR119-deficient mice. Dosing in diabetic rodents led to markedly improved glucose tolerance. Orally active GPR119 agonists may offer significant promise as novel anti-diabetics acting in a glucose-dependent fashion.

MEDI 317

Small molecule inhibitors of lysine-specific demethylase 1 as epigenetic modulators for the treatment of cancer

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The enzyme lysine-specific demethylase 1 (LSD1) mediates an important cellular mechanism for epigenetic control of gene expression. In particular, dimethyl lysine 4, histone H3 (H3K4me2) is a transcription activating chromatin mark at gene promoters, and aberrant demethylation of this mark by LSD1 may broadly repress the expression of tumor suppressor genes that are important in human cancer. We and others have conducted studies verifying that LSD1 is an exciting new therapeutic target. We reported a series of (bis)guanidines and (bis)biguanides that are potent inhibitors of recombinant human LSD1. These inhibitors significantly increase H3K4me2 levels, initiate chromatin remodeling and induce the re-expression of tumor suppressor genes, making them suitable leads for analogue development. We were the first to demonstrate antitumor effects of LSD1 inhibitors *in vitro* and have recently demonstrated their significant antitumor effects *in vivo*. These studies provide proof of principle that inhibition of LSD1 can lead to significant antitumor effects. We now report an extended series of (bis)guanidines, (bis)biguanides and their isosteres that are potent LSD1 inhibitors, and that produce significant re-expression of aberrantly silenced genes

in multiple tumor cell lines. The synthesis and in vitro evaluation of these agents will be discussed in this presentation.

MEDI 318

GS-9350: A novel and selective pharmacoenhancer without anti-HIV activity

L. Xu, lianhong.xu@gilead.com. Department of Medicinal Chemistry, Gilead Sciences, Foster City, CA, United States

The HIV protease inhibitor (PI) ritonavir (RTV) is a potent, mechanism-based inhibitor of cytochrome P450 3A (CYP3A), an enzyme responsible for metabolizing most HIV PIs. Low, subtherapeutic doses of RTV improve the pharmacokinetic (PK) profiles of concomitant PIs, and RTV boosting has become the standard-of-care in PI-containing HAART regimens. Coadministration of RTV with the investigational integrase inhibitor elvitegravir (EVG) enhances the PK profile of EVG, and EVG boosted with RTV is currently in Phase 3 studies administered once-daily. However chronic use of RTV has been associated with gastrointestinal and metabolic side effects, and its use as a pharmacoenhancer at a subtherapeutic dose could potentially induce PI resistance mutations if administered in the absence of a fully active PI. A series of novel 1,4-diamine carbamates was synthesized, their SARs with respect to antiviral activity, human CYP3A inhibition and pregnane X receptor (PXR) activation were assessed. Extensive optimization led to the discovery of GS-9350, which is a potent mechanism-based CYP3A inhibitor. Compared to RTV, GS-9350 has no antiviral activity at concentrations up to 90 μ M and has reduced in vitro effects on adipocytes. In addition, GS-9350 has a lower potential for off-target effects including inhibition of CYP2D6 and activation of PXR. GS-9350 has high aqueous solubility and has been co-formulated with EVG and the NRTI backbone emtricitabine/tenofovir DF. Clinical studies have shown that GS-9350 enhances the PK of several CYP3A substrates (midazolam, EVG and atazanavir). GS-9350 is currently being evaluated in Phase 2 studies as a pharmacoenhancer in HIV-infected patients.

MEDI 319

Discovery of VA111913, a selective and orally available V_{1a} antagonist undergoing clinical development for the treatment of dysmenorrhea

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Dysmenorrhea (painful menstrual cramps) is a common gynecological condition occurring in more than 50% of menstruating women. These women have increased uterine muscle tone and contractions and decreased blood flow to the uterus. This leads to the pain experienced in dysmenorrhea. The hormone

vasopressin, via the V_{1a} receptor, is able to induce contractions in both uterine smooth muscle and uterine blood vessels. A V_{1a} receptor antagonist will potentially inhibit these contractions and in turn reduce the pain experienced in dysmenorrhea. VA111913 originated from screening of Vantia's vasopressin library of molecules. The hit compounds were modified to optimize the ADME properties and to provide orally available compounds. SAR advancements led to potent and selective antagonist activity at the V_{1a} receptor. This work led to the compound VA111913, whose structure will be disclosed for the first time and is in Phase II clinical trials.

MEDI 320

Discovery of BI 201335: A potent and specific inhibitor of the Hepatitis C Virus NS3/4A protease with proven antiviral effect in humans

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The quest to develop direct acting antiviral agents to treat hepatitis C virus (HCV) infections has continued for 20 years. One of the first targets to be exploited for drug discovery was the serine protease of the NS3 protein. The impressive reduction of HCV RNA plasma levels observed for HCV NS3 protease inhibitors in clinical trials illustrates the potential of the viral enzyme-targeted drug discovery approach for the development of new HCV therapeutics. BI 201335 is a potent, specific and reversible peptidomimetic inhibitor of the HCV serine protease NS3/4A with low-nanomolar activity against HCV replication. Its binding affinity is derived from highly optimized non-covalent interactions with the enzyme. BI 201335 is being studied in chronic HCV genotype-1 infection in combination with pegylated interferon + ribavirin in large phase II trials. Details of the SAR leading to the discovery of BI 201335 will be described.

MEDI 321

Structure based design and biological evaluation of benzimidazole HIF prolyl hydroxylase inhibitors for the treatment of anemia

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Using structure based design for specific compounds employing both literature crystal structures and ligand docking, we have identified certain glycine amide heterocyclic analogs of 2-oxoglutarate that competitively and potently inhibit prolyl hydroxylases ($IC_{50} < 100$ nM) in vitro and stabilize HIF protein and stimulate EPO production in whole cell cultures. We also have shown that simple divalent metal chelators (such as certain 8-hydroxyquinolines and 1,10-phenanthrolines) functionally inhibit PHD enzymes, but via a non-competitive process that likely involves general iron chelation. By setting up primary functional assays for both PHD inhibition as well as iron chelation, we created a compound analysis and progression path that rapidly separated mechanism-based inhibitors from general iron chelators allowing us to pursue only the former. In this talk, the above x-ray structure analysis program, including new x-ray co-crystal structures, resulting compounds, and associated data will be presented as a new approach in the treatment of anemia.

MEDI 322

Second generation HCV NS3 serine protease inhibitor: Discovery and advancement of SCH 900518 for human clinical studies

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Hepatitis C virus (HCV) is the etiologic agent of non-A, non-B hepatitis leading to liver cirrhosis, hepatocellular carcinoma and liver failure in humans. An estimated 3% of the human population, including 4 million in the USA, is infected with HCV. Therapeutic potential of inhibiting HCV NS3 protease, vital for viral replication, is being validated in the clinic. Boceprevir, discovered in our laboratories, and Telaprevir are the most advanced HCV NS3 protease inhibitors that are currently undergoing studies in human. Since discovery of Boceprevir, the major goal of our research program was to identify an improved (invitro potency and pharmacokinetic properties), specifically-targeted, orally active compound that could be developed as a second generation HCV NS3 protease inhibitor to further enhance the virologic response. Comprehensive SAR studies, along with collaborative efforts between medicinal and structural chemistry, virology, and drug metabolism groups at SPRI culminated in the discovery of **SCH 900518**, a novel, selective, potent, and orally bioavailable second generation NS3 serine protease inhibitor currently undergoing phase II human clinical trials for the treatment of hepatitis C viral infections.

MEDI 323

Discovery of Chantix™ (varenicline tartrate): An aid to smoking cessation

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Tobacco related illness is the leading cause of preventable death. In 1993, Pfizer scientists initiated a project in its Groton Labs specifically to discover a new smoking cessation treatment. Key aspects of nicotine dependence and addiction that make quitting smoking difficult for smokers were considered. The phasic nature of smoking creates neurochemical imbalances such that when not smoking the neurochemical deficit (of dopamine) causes serious discomfort, irritability, preoccupation and nervousness. Smoking almost immediately resolves these sensations by quenching them with a sense of relief, calm and clarity. To break this "cycle of addiction" we set out to discover a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor, a compound to theoretically relieve craving and withdrawal in the absence of smoking while simultaneously blocking the reinforcing neurochemical response to inhaled nicotine from smoking. The discussion will describe the discovery of varenicline and the science behind it.

MEDI 324

Discovery of the cholesteryl ester transfer protein inhibitor Anacetrapib

P. J. Sinclair, Peter_sinclair@merck.com. Merck Research Laboratories, Rahway, NJ, United States

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

MEDI 325

**Award Address (Earle B. Barnes Award for Leadership in Chemical Research Management Sponsored by The Dow Chemical Company).
Dispelling the myths of pharmaceutical R&D**

J. L. LaMattina, john.lamattina@comcast.net. Chemistry, Pfizer (retired), Stonington, CT, United States

Pharmaceutical companies play an essential role in maintaining our health. Without their contributions, people around the world would be plagued by pain, infectious diseases like AIDS, and mental disorders such as depression and schizophrenia. Yet, these contributions are largely unrecognized by the majority of people in the world. This presentation will focus on the myths that surround the pharmaceutical industry, such as “the industry invents diseases”, “the industry is not innovative” and “the industry doesn’t care about diseases of the developing world”. In each case, facts will be presented along with specific examples of work done in the pharmaceutical industry in the discovery and development of new medicines. Each of these examples will serve to dispell each myth. The lecture will conclude by showing the future exciting therapies that the industry will bring forward over the coming years to benefit patients around the globe.

MEDI 326

Complex cascade reactivity on the path to architecturally diverse natural products

E. J. Sorensen, ejs@princeton.edu. Frick Chemical Laboratory, Princeton University, Princeton, New Jersey, United States

In 180 years of research in the field of organic chemistry, the vast majority of the chemical reactions that have been developed to do synthesis produce only one to two bonds at a time. This circumstance reflects the intrinsic challenge of controlling the outcomes of reaction sequences that generate multiple bonds by one-flask processes. That said, there are several achievements in the field of organic natural product synthesis that offer powerful lessons about how molecular complexity may be created by the purposeful execution of cascades of bond forming events. This lecture will address some of these examples in the context of our ongoing efforts to design and execute chemical reactions that quickly produce the complex structural elements of several biologically active natural products.

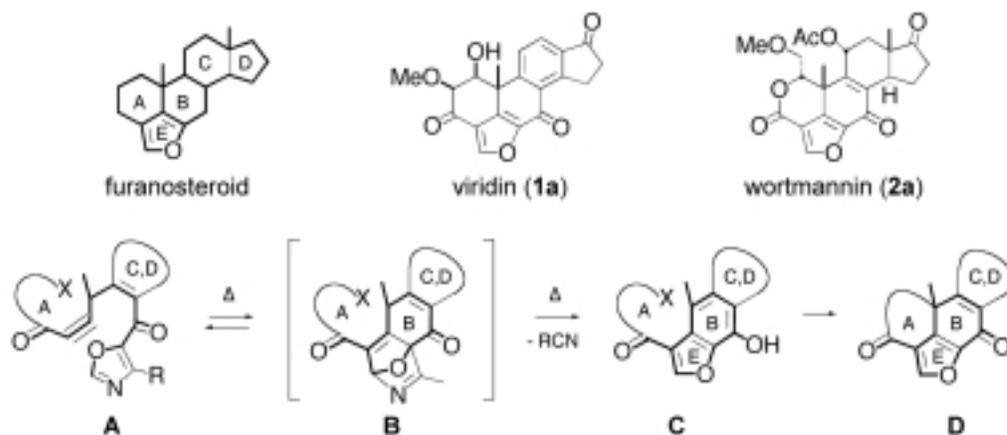
MEDI 327

Synthetic studies on selective phosphatidylinositol 3-kinase inhibitors

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In this paper we describe new synthetic approaches to the furanosteroid class of PI3-K inhibitors, exemplified by members of the viridin (**1a**) and wortmannin (**2a**) families. Our strategy consists of three parts: (1) Synthesis of highly substituted alkyne oxazoles of type **A**; (2) intramolecular DA/*retro*-DA reaction of **A** with

concomitant tautomerization to give phenols **C**; and (3) elaboration of **C** to the funanosteroid skeleton **D** by intra- or intermolecular vinylogous aldol-like condensation.



MEDI 328

Award Address (Alfred Burger Award in Medicinal Chemistry Sponsored by GlaxoSmithKline). Discovery of Alimta, a broadly effective new antitumor drug

E. C. Taylor, Etaylor@princeton.edu. Chemistry, Princeton University, Princeton, NJ, United States

The pteridine ring system was first identified in a study of the constituents of butterfly wing pigments. We now know that several pteridine derivatives, such as the molybdenum cofactor and folic acid, are required for all forms of life. Cofactors derived from folic acid are essential, inter alia, for the biosynthesis of DNA, RNA, and ATP. Our long-time fascination with pteridines and heterocyclic chemistry, starting in 1946, developed in the '70s into a search for inhibitors of folate-dependent enzymes. This lecture will describe the tortuous explorations that eventually led to the discovery of Alimta. The success of this research effort critically depended, in its latter stages, on a remarkably successful and harmonious collaboration between Princeton and Lilly. This project provides a vivid example of the potential of purely academic basic research motivated entirely by curiosity, and the effectiveness of true collaboration between academia and industry.

MEDI 329

History and outlook: The state-of-the-art in chemical manufacturing of complex peptide APIs

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The complexity of peptide-based active pharmaceutical ingredients (APIs) has increased exponentially in recent years. Whereas classical peptide APIs were marked by small size and exclusively proteinogenic amino acids, the latest generation of peptides in the clinic are far more complex. These molecules are marked by backbone modifications, heterocyclic building blocks, and complex side-chain modifications. In this presentation, advances in synthetic and purification capabilities for this next generation of complex peptide APIs are outlined. The overall message is that manufacturing capabilities have evolved hand-in-hand with chemical complexity, and are well equipped for the next generation of peptide APIs.

MEDI 330

Synthesis and development of peptide-antibody conjugates

D. Tumelty, david.tumelty@pfizer.com. Chemistry, CovX Research LLC, San Diego, CA, United States

Over the past five years, CovX Research LLC (wholly-owned by Pfizer) has been developing defined peptide-antibody conjugates (termed CovX-Bodies) as drug candidates for oncology and metabolic diseases. Our first three clinical candidates, CVX-045, CVX-060 and CVX-096 have presented various synthesis and development challenges, largely due to the increased complexity of each successive peptide. The presentation will detail some of the peptide development activities in bringing these CovX-Bodies from Preclinical candidates to Phase 1 Clinical trials.

MEDI 331

Peptide antagonists of FcRn for the treatment of IgG-mediated autoimmune diseases

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The neonatal Fc receptor, FcRn, is responsible for the long half-lives of IgG molecules in vivo and thus represents a possible drug target for the treatment of autoimmune diseases. A family of peptides that inhibits the FcRn:IgG protein-protein interaction was discovered using phage display screening. Data will be presented on the chemical optimization of this peptide family and their effects on IgG catabolism in mice and non-human primates.

MEDI 332

Oligopeptide-based quorum sensing in *S. aureus* as target for immunotherapy

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Cell-to-cell communication via the exchange of small molecules, termed “autoinducers”, is a widespread phenomenon among Gram-negative and -positive bacteria. This microbial intercellular signaling that synchronizes population-wide gene expression in a cell density-dependent manner has been coined “quorum sensing” (QS). Specifically, the initial discovery that Gram-negative bacteria employ non-peptide structures, namely N-acyl homoserine lactones, to globally regulate the production of secondary metabolites and proteins, initiated a new area in microbiological research. Subsequently, other quorum sensing systems and small signaling molecules have been identified. With the emergence of antibiotic-resistant bacterial strains, most prominently methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, new approaches for combating bacterial infections are urgently needed. Inhibition of QS results in attenuation of bacterial virulence rather than direct killing of the microbe. In my presentation, I will highlight our current approaches to control bacterial virulence using an immunotherapeutic strategy that effectively quenches bacterial QS signaling.

MEDI 333

Synthetic lung surfactants enhanced by helical peptoid mimics of lung surfactant proteins B and C

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We are developing a new family of amphipathic peptide mimics for a synthetic lung surfactant (LS) replacement. Presently used exogenous LS replacements are extracted from animal lungs to treat respiratory distress syndrome in premature infants. The hydrophobic lung surfactant proteins SP-B and SP-C are necessary constituents of an effective surfactant replacement for the treatment of respiratory distress. As there are cost concerns and other limitations associated with animal-derived surfactants, much recent work has focused on synthetic peptide analogues of SP-B and SP-C. One approach that overcomes these difficulties is the use of helical poly-N-substituted glycines, or “peptoids,” to mimic SP-C. We discuss advances in the design and characterization of peptoid-based SP-C mimics, which recently have led to the creation of our most biomimetic surfactant replacements to date. There are several other potential applications for a safe, low-cost, and non-immunogenic replacement for animal surfactant other than treating respiratory distress, including the treatment of ARDS in adults

and children. We present the first in vivo results for the testing of peptoid-based surfactants in an animal model of respiratory distress.

MEDI 334

Studies toward the discovery of dual-acting SSRI-5-HT_{1A} receptor antagonists for the treatment of depression

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More than 15 million adults in the US suffer from major depressive disorder (MDD) each year. Currently available antidepressants suffer the drawback of having a delayed onset of full efficacy. Also, they are often accompanied by sexual side effects, and may not work in patients with refractory depression. Clinical and/or preclinical studies suggest that combination of an SSRI with a serotonin 5-HT_{1A} receptor antagonist reduces the time of onset of efficacy and also reduces sexual side effects, relative to the SSRI alone. Studies toward the discovery and development of a single molecular entity that incorporates both serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism have been undertaken in our laboratories. SAR efforts leading to the discovery of WAY-253752 will be presented. The inherent difficulty of attaining the desired level of receptor selectivity with these dual-target compounds will be discussed.

MEDI 335

Challenges and strategies in the design of multi-targeted ligands

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It has been widely recognised over the recent years that effective therapies for diseases with complex aetiologies such as cancer and psychiatric disorders require simultaneous modulation of multiple biological targets. Consequently, there is an increasing interest in developing therapeutic agents with specifically targeted polypharmacology. However, designing such ligands is frequently a challenging endeavour for medicinal chemists, with the need to appropriately balance affinity for two or more targets whilst obtaining physicochemical and pharmacokinetic properties that are consistent with oral administration. In this talk we will discuss the challenges, current strategies and potential future

directions for the generation and optimisation of ligands with a specific multi-target profile (designed multiple ligands, or DMLs).

MEDI 336

Survey of multipharmacology: General features of promiscuous drugs and targets

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Following absorption, drugs face a huge array of potential binding sites within the body. It is now established that many safe drugs interact with a large array of targets at clinically relevant concentrations, and that this spectrum of activity is sometimes important to the therapeutic effect of the drug. Analysis of large-scale SAR data can reveal some of the general features of this multi-targeted nature of drugs, and also provide the basis for prediction of activities outside of those established via experiment. Additionally, some targets/pharmacology are consistently clustered or correlated, and again this can be identified by data-mining approaches. Finally, the architecture and properties of binding sites (where known or reasonably modelled) can be used to identify common recognition motifs and potentially shared pharmacology.

MEDI 337

Combating bacterial resistance by design: The discovery of dual acting gyrase/topoIV inhibitors

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The discovery of new antibacterial agents with novel mechanisms of action is necessary to overcome the problem of bacterial resistance that affects all currently used classes of antibiotics. Bacterial DNA gyrase and topoisomerase IV are well-characterized, clinically validated targets of the fluoroquinolone antibiotics which exert their antibacterial activity through inhibition of the catalytic subunits. Inhibition of these targets through interaction with their ATP sites has been less clinically successful. Using structural information for both gyrase and topoisomerase IV to guide medicinal chemistry efforts the benzimidazole ureas emerged as potent inhibitors of both enzymes. The benefits of dual inhibition by this class are realized through potent antimicrobial efficacy against wild type and resistant pathogens.

MEDI 338

Targeting Janus kinases

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Protein kinases, which serve many critical functions in cellular signal transduction, are popular therapeutic targets. Multiple kinase inhibitors have been FDA approved, each of which shows nanomolar potency. Initially, it was argued that a high degree of selectivity was essential for the generation of clinically useful drugs. However, recent work has revealed that many of these approved compounds target more than one kinase and this is apparently acceptable; indeed, it may be therapeutically advantageous. Janus kinases are essential elements in signaling by Type I and II cytokine receptors, which bind many cytokines, interferons, colony stimulating factors and hormones. The rationale for generating Janus kinase and their present status will be discussed, along with the advantages and disadvantages of selectively inhibiting this class of kinases.

MEDI 339

Estrogen Receptor: Structure, ligand design, activities, and in vivo imaging

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Guided by X-ray structures, we have developed modular methods to synthesize non-steroidal estrogens, adaptable to combinatorial approaches, and have prepared novel estrogens that are highly selective for only one of the two estrogen receptor subtypes, ER α or ER β ; these are proving to be useful as pharmacological probes of the functions of the two different ERs. We have diversified the structure and elemental composition of ER ligands, introducing three-dimensional core elements and replacing a carbon-carbon double bond with a boron-nitrogen bond, giving compounds that have unexpected biological selectivities that could be medically important. We have also prepared dendrimer-bound estrogens that can be used to activate selectively rapid non-genomic estrogen signaling. We have prepared high affinity receptor ligands, labeled with the positron-emitting radionuclide fluorine-18, for positron emission tomographic imaging of these tumor receptors which provides valuable information in selecting both breast cancer patients most likely to benefit from endocrine therapy.

MEDI 340

Discovery of a novel class of 3,3-diarylpropionamide-based selective glucocorticoid receptor modulators

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There is strong interest in the identification of glucocorticoid receptor (GR) ligands which modulate the activity of the receptor in a pathway-selective manner, ultimately maintaining the anti-inflammatory and immunosuppressive activity of steroidal glucocorticoids while minimizing the extent of side effects associated with their administration. A series of dihydro-9,10-ethano-anthracene carboxamides served as the starting point for our efforts to identify such modulators (“dissociated agonists”), which led to the identification of several more advanced series of selective GR agonists based on the 3,3-diarylpropionamide sub-structural motif. The synthesis, SAR and pharmacologic profiles of these modulators will be described in detail.

MEDI 341

Discovery of a novel class of glucocorticoid receptor modulators

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Glucocorticoids (GC) such as dexamethasone and prednisolone are among the most potent anti-inflammatory agents in clinical use. However, chronic use of GC's may be limited due to side effects such as osteoporosis, glucose intolerance, lipid redistribution and acute psychosis. Identification of novel glucocorticoid receptor (GR) ligands that maintain the anti-inflammatory efficacy of currently marketed steroids whilst exhibiting the potential for an improved side effect profile is highly desirable. We have identified a series of non-steroidal molecules that display specific high affinity binding for the GR and function as partial agonists in cell-based models of GR-mediated transrepression and transactivation. Moreover, a set of molecules have been identified that are orally bio-available and display potent anti-inflammatory activity following chronic administration to mice with collagen induced arthritis. When compared to standard glucocorticoids, animals treated with these novel dissociated ligands displayed a significant reduction in side effects of clinical importance. The profile of this class of dissociated GR ligands will be reviewed.

MEDI 342

Chemical probes for orphan nuclear receptors

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Well-characterized, potent and selective chemical probes enable research around the biological function and the therapeutic potential of orphan nuclear receptors. Previous efforts identified chemical probes for orphan nuclear receptors and resulted in functional validation and drug development for disorders of lipid, sterol, and bile acid metabolism. In this presentation, we will describe several new chemical probes for additional orphan nuclear receptors, including their discovery and functional characterization

MEDI 343

Hydrogen-deuterium exchange (HDX) reveals unique interactions between nuclear receptors and ligands

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Hydrogen/deuterium exchange coupled with mass spectrometry (HDX-MS) has emerged as a powerful technology for analysis of protein dynamics and ligand interactions. Here we present conformational dynamics of three members of the nuclear receptor super family of ligand dependent transcription factors: the estrogen receptors (ER) alpha and beta, and the vitamin D receptor (VDR). Differential HDX analysis of the ligand binding domain (LBD) of ER in complex with known ER ligands reveals that alterations in structural dynamics can be related to the pharmacological properties of a given ligand thereby providing a novel approach to probe selective estrogen receptor modulators (SERMs). In contrast, perturbations in HDX dynamics of ERbLBD upon binding of a ligand suggest that ERb has a different degree of plasticity in its LBD cavity compared with ERa. For human VDR, HDX-MS reveal conformational dynamics of the LBD of VDR upon binding the natural ligand VD3, and two structurally similar analogs ED-71 and alfacalcidol. Moreover, conformational dynamics of the intact heterodimer complex of VDR and retinoid X receptor (RXR) alpha upon interaction with DNA, VDR/RXR agonists and the co-factor SRC1 indicates that DNA binding alters dynamics of the VDR/RXR heterodimers in regions remote of the DBD that appear to regulate SRC1 binding. In summary, differential HDX analysis provides insight into the molecular mechanism of nuclear receptor modulators thus providing insights towards the development of novel therapeutic ligands.

MEDI 344

Discovery of novel small molecule modulators for nuclear hormone receptors

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In recent years Wyeth Research has been involved in the discovery of novel small molecule modulators for various nuclear hormone receptors, including estrogen, progesterone, liver X (LXR) and farnesoid X (FXR) receptors. Successful fruition of these endeavors could lead to innovative therapies in the areas of osteoporosis, contraception, fibroids, endometriosis, dyslipidemia and atherosclerosis, to name but a few of the possible disease areas. In this presentation, we will outline our medicinal chemistry research goals, strategies and results in one or more of these areas.

MEDI 345

Prodrugs in drug design: A rich past and an even richer future

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Despite the best efforts of medicinal and pharmaceutical scientists, an advanced lead or clinical candidate may exhibit a characteristic, such as poor oral bioavailability or toxicity, that hinders its further development. Instead of retreating to other candidates, one can consider the design of prodrugs to overcome the drug lead's deficiency. Over the last 50 years, the field of prodrug design has expanded from rather simple hydrolytic bioactivation approaches, to the use of selective transporters, tissue specific bioactivation, ligand and antibody directed tissue targeting and bioinformatics. The lecture will cover highlights of recent advances and concepts in prodrug design, with some examples from our current research.

MEDI 346

Use of a phosphonoxymethyl prodrug approach to successfully improve the oral delivery of HIV-1 attachment inhibitors: Design, preclinical profile, and human exposure

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Proof of concept for the antiviral efficacy of a small molecule inhibitor that targets HIV-1 gp120 and prevents interaction with host CD4 antiviral efficacy was previously provided in a Phase IIa clinical study using the compound 1-(4-Benzoylpiperazin-1-yl)-2-(4,7-dimethoxy-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)ethane-1,2-dione (BMS-488043). However, in order to achieve this result, concomitant co-administration of a high fat meal was necessary to ameliorate the solubility/dissolution limited absorption of this compound. Subsequently, a phosphonoxymethyl prodrug strategy was explored as an alternate means of increasing solubility in the gastrointestinal tract and improving plasma exposure while avoiding the necessity of the high fat meal. In pre-clinical studies, the prodrug improved the solubility and *in vivo* exposure of BMS-488043 while clinical evaluation revealed that this approach successfully improved exposure in the absence of high fat meal. Details and results of the discovery and clinical program for the phosphate prodrug of BMS-488043 will be described.

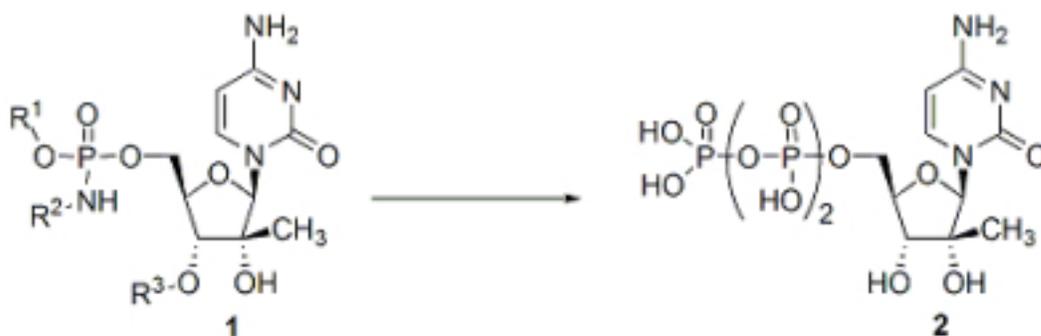
MEDI 347

Kinase bypass approach for the treatment of Hepatitis C virus infection

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Infections caused by Hepatitis C Virus (HCV) are a significant world health problem for which novel therapies are in urgent demand. The NS5B RNA dependent RNA polymerase of HCV is responsible for the replication of viral RNA and has been a prime target in the search for novel HCV therapeutics. The application of a kinase bypass approach to the nucleoside inhibitor 2'-C-Methylcytidine will be presented. SAR around the 5'-phosphoramidate class of prodrugs **1** led to the identification of novel classes of compounds, which formed efficiently nucleotide triphosphate **2** in HCV subgenomic replicon cells and in hepatocytes of different species. The *in vivo* profile of selected compounds in preclinical species will be presented.



MEDI 348

Strategies and issues in the design of nucleoside prodrugs

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Nucleosides and their analogues are an important class of anticancer and antiviral agents. However, poor biopharmaceutical properties and an unfavorable therapeutic index often limit their use as therapeutic agents. One potential method to circumvent this problem is to design viable prodrugs that improve the pharmacological properties and reduce undesirable side effects of the parent drug. We will present the utility of esters of cyclopropanecarboxylic acid as prodrugs to substantially increase stability under both acid- and base-catalyzed hydrolytic conditions by comparing the prodrug valacyclovir with the corresponding cyclopropane amino acid ester and with several other examples. The rationale for this increased stability will be presented. In contrast, issues with utilizing aminoacyl amide nucleosides as prodrugs will be illustrated with an unexpected facile rearrangement. In addition, the prodrug of gemcitabine, currently undergoing clinical trials, will be presented.

MEDI 349

Prodrugs improve solubility and oral bioavailability: Prodrugs of CVT-6883, an A_{2B} adenosine receptor antagonist

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In our recent publications, we have disclosed the synthesis of several high affinity and selective A_{2B} adenosine receptor antagonists. One of these analogs CVT-6883 (I) has successfully completed two Phase I clinical studies as a candidate for chronic airway inflammatory diseases. While in the discovery approach we

synthesized several prodrugs containing groups like alkyl, oxymethyl carbamates, oxymethyl esters (II) and oxymethyl phosphonates (III) at the N-7 position of the xanthine core, as xanthine analogs are generally known to display low solubility and oral absorption. The oxymethyl ester (II) and oxymethyl phosphonate (III) groups exhibited substantially high levels of drug substance in the plasma of rats and dogs compared to the parent compound and no prodrug was observed in the plasma. The phosphonate prodrug (III) has excellent solubility and displayed higher oral bioavailability compared to the parent compound. The details of the synthesis and pharmacokinetic data of these compounds will be presented.

MEDI 350

Liver-targeted drug delivery using HepDirect™ prodrugs

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Organ-selective drug delivery remains an important goal for improving drug efficacy and/or safety. One strategy capable of achieving this goal is to use prodrugs that cleave to the active drug via an intracellular enzyme expressed predominantly in the target organ. Efforts to target drugs to the liver led to the discovery of HepDirect prodrugs, which are aryl-substituted cyclic 1,3-propanyl esters of phosphates or phosphonates that cleave following an oxidation catalyzed by a cytochrome P450 (CYP3A) expressed principally in the liver. Pre-clinical and clinical results for three HepDirect prodrugs, namely pradefovir (hepatitis B), MB07133 (hepatocellular carcinoma) and MB07811 (hyperlipidemia) will be presented, including results from studies evaluating their liver targeting potential and the corresponding effect of liver targeting on drug efficacy and safety. In addition, studies that address inter-patient drug variability and the impact of hepatic disease, drug-drug interaction potential and byproduct safety will be presented.

MEDI 351

Prasugrel, a third generation thienopyridyl oral antiplatelet prodrug

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Thienopyridyl oral antiplatelet agents, including ticlopidine and clopidogrel, require metabolism *in vivo* to active metabolites that irreversibly inhibit the platelet P2Y₁₂ ADP receptor. Clopidogrel's platelet inhibitory effects exhibit a relatively slow onset and are highly variable. In contrast prasugrel, a more recent thienopyridyl prodrug, has a relatively faster onset of action and less variability in antiplatelet effects. Furthermore these activities of prasugrel are achieved at a dose approximately 1/10th that of clopidogrel. The prasugrel pro-drug is: a) is

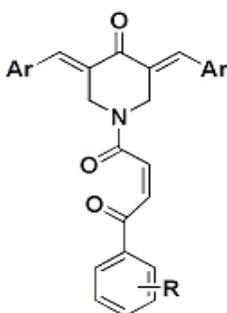
more resistant to metabolism to inactive metabolites, b) is more rapidly converted to an obligate intermediate metabolite, and c) requires only a single CYP-450 mediated oxidation step. Pharmacokinetic studies support the more rapid and efficient activation of prasugrel.

MEDI 352

3,5-Bis-Arylidene-4-piperidone derivatives: A novel class of potent anticancer agents

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Efficacy of an anticancer drug relies on its ability to select between malignant and normal cells. A number of α,β -unsaturated ketones were designed as alkylators of cellular thiols with little or no affinity for hydroxy and amino groups found in nucleic acids. Inhibition of tumor growth is the result of the enone pharmacophore alkylating sulfhydryl-rich key enzymes like topoisomerase II in cancer cells by rapid and selective Michael addition. Development of unsaturated ketones as candidate cytostatic agents may lead to drugs which are devoid of genotoxic properties unlike other alkylating agents used in cancer chemotherapy. We have synthesized a series of 3,5-bisarylidene-4-piperidone derivatives with heteroaromatic rings to study change in cytostatic activity compared to aromatic phenyl rings. *N*-Acryloyl derivatives of bisarylidene-4-piperidones displayed greater cytostatic properties than their *N*-unsubstituted counterparts. Therefore, in synthesized analogs, one of the methylene protons of *N*-acryloyl group was replaced by *N*-arylcabamoyl substituents to introduce additional sites for protein thiolation. *Bis*heteroarylmethylidene-4-piperidones were prepared under base-catalyzed Claisen-Schmidt condensation. *N*-Arylmaleamic acids were synthesized following procedures reported in literature. Final step of synthesis involved condensation of 3,5-bisarylidene-4-piperidones with *N*-arylmaleamic acids using methyl chloroformate under anhydrous basic conditions. All compounds synthesized were screened against three cancer cell lines using melphalan as standard reference drug. Synthesis and biological activity will be presented.

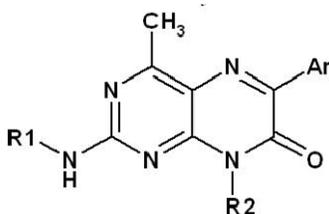


MEDI 353

4-Methylpteridinone as orally-active and selective PI3Ka/mTOR dual inhibitors

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Based on our original 4-methyl-pyrimidine-pyridinone lead in PI3K α program, 4-methylpteridinones were designed and developed to be potent and highly selective PI3K α /mTOR dual inhibitors. SAR analysis and structure-based drug design on co-crystal structures led us to compounds with good ADME and excellent cellular inhibition of phosphorylation of AKT T308, AKT S473 and pS6RP S235/236. In addition, robust anti-tumor activity was also observed in xenograft models.



4-methylpteridinone

MEDI 354

Design, synthesis, and biological studies of novel derivatives of indolin-2-one for acute myeloid leukemia

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Leukemia is a malignant proliferation of white blood cells in the human body and the prevalence of this disease is approximately 0.01 % in USA. FMS-like tyrosine kinase-3 (flt-3) gene is the most common mutation in acute myelogenous leukemia (AML) and is resulted in a constitutively active tyrosine kinase. The pivotal role of flt-3 in AML promotes us to design inhibitors targeted to this

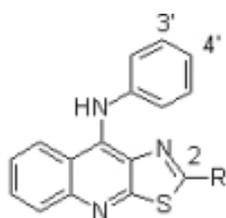
aberrant kinase. The indolin-2-one core structure was modified at its different positions with various linkers, and a series of compounds were synthesized. The enzymatical and cellular activities of these compounds were evaluated. 3-Substituted indolin-2-one compounds with 6-uriedo derivatives demonstrated nanomolar range activity against multiple receptor tyrosine kinases including mutated flt-3. *In vivo* efficacy of selected compound was also investigated by a MV4-11 xenograft model.

MEDI 355

Synthesis and cytotoxic evaluation of novel derivatives of 9-anilinothiazolo[5,4-*b*]quinoline

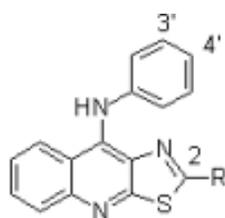
A. Lira-Rocha, lira@servidor.unam.mx, F. Reyes-Rangel, A. K. López-Rodríguez, M. Loza -Mejía, and J. D. Solano. Departamento de Farmacia, Facultad de Química, UNAM, Mexico, D.F., Mexico

In previous studies, we found increased cytotoxicity in the 9-anilinothiazolo[5,4-*b*]quinoline derivatives against human cancer cell lines, when a dialkylaminoalkylamino (**1a,1b**) chain was incorporated at the 2-position, whereas the opposite effect was observed when a saturated heterocyclic was introduced (**1c**). The last finding prompted us to analyze the importance of the substituent at the 2-position. Here, we present the synthesis and *in vitro* cytotoxic activity of several compounds lacking substituents, or with a cycloalkylaminoalkylamino group, at the 2-position (**2a, 2b**). The removal of the substituent decreased or abolished the cytotoxic activity (**2c**). So, the presence of a bulky group is a requirement for cytotoxicity, for instance, a –SCH₃ group. On the other side, the replacement of the *N,N*-dialkyl group of the side chain with a pyrrolidin-1-yl or piperidin-1-yl moiety had little influence on cytotoxicity.



1a R = NH-CH₂CH₂N(CH₂CH₃)₂
1b R = NH-CH₂CH₂CH₂N(CH₂CH₃)₂
1c R = N(CH₂CH₂)₂NCH₃

3' or 4' = Cl, CN, OMe



2a R = NH-CH₂CH₂N(CH₂CH₂)₂
2b R = NH-CH₂CH₂N(CH₂CH₂)₂CH₂
2c R = H

3' or 4' = Cl, CN

MEDI 356

Targeted virus nanoparticles for localized chemotherapy of breast cancer treatment

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In this work, we aim to develop a unique and innovative drug delivery technology to deliver chemotherapeutic agents specifically to breast cells and limit the exposure of drugs to normal non-breast tissues. Our drug delivery system is based on adeno-associated virus (AAV), a 25nm virus that is currently in clinical trials for a variety of gene therapy applications. A critical difficulty in designing nanotherapeutics is in developing highly targeted platforms that can reach target sites with high efficiency. Purely rational improvements to nanoparticle design can be extremely difficult. In addition, currently, there is no biomarker available that specifically identifies breast cancer cells due to the high degree of heterogeneity in breast tumors within patient as well as between patients. The AAV capsid is a supramolecular assembly of 60 protein subunits, lending itself well to multivalent conjugation of drug molecules. More importantly, the link between virus capsid phenotype and genotype allows the application of laboratory directed evolution approaches to create virus nanoparticles that can specifically bind breast tissue. We will investigate methods to conjugate paclitaxel (as a model drug) onto the virus scaffold. Drugs will be covalently attached to surface-exposed residues on the virus capsid at various molar ratios. Drug-virus nanoparticles will be assayed for degree of conjugation with HPLC, MALDI-MS, proper capsid assembly with ELISA for intact capsid and TEM, proper genome packaging with Q-PCR, maintenance of tropism with an affinity column assay, and cytotoxicity with cell viability assays.

MEDI 357

Design, synthesis and biological evaluation of classical two carbon chain 6-substituted pyrrolo[2,3-*d*]pyrimidine for folate receptor targeting antifolate agents

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One of the major hurdles in cancer chemotherapy is the inability of the chemotherapeutic agent to selectively target tumor cells. The clinical anti-cancer drug pemetrexed(PMX) suffers from dose-limiting toxicity due to its transport by reduced folate carrier(RFC) which is ubiquitously expressed in normal cells. We recently reported a series of 6-substituted pyrrolo[2,3-*d*]pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC₅₀ values. In an attempt to determine if transposing the side chain from the 5-position in PMX to the 6-position would maintain the multitarget attributes of PMX and provide selectivity of FR over RFC, we synthesized the 6-regioisomer of PMX. The synthesis and

evaluation of the 6-regioisomer of PMX as a substrate for folate transporters RFC, FR α , FR β and PCFT (proton coupled folate transporter) and as an inhibitor of thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFTase) will be presented.

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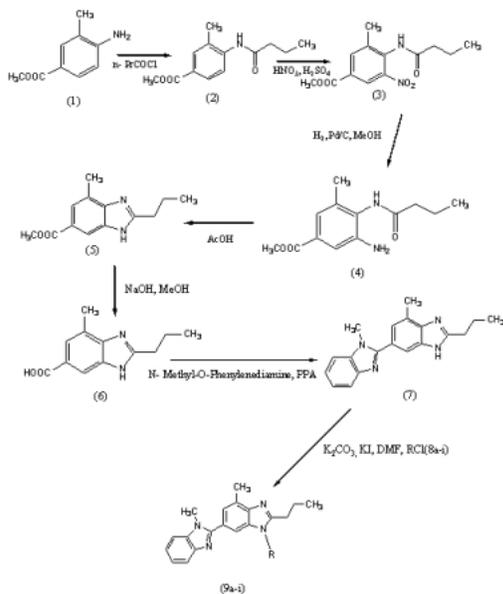
Design, synthesis and screening of novel bis-benzimidazole derivatives as cytotoxic agents based on selective optimization of side activity, a novel tool for drug discovery

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Bis-benzimidazole, heterocyclic dimers, with acyclic and cyclic spacers, targets the DNA to exhibit their anticancer activity by intercalation and alkylation mechanism. Moreover telmisartan also bears a bis-benzimidazole dimer and telmisartan reported as cytotoxic agent in prostate cancer cell line. So, using bis-benzimidazole of telmisartan as “lead” and optimize side effect to produce novel cytotoxic agents. The present study deals with the synthesis of novel bis-benzimidazole derivatives (**9a-i**) from methyl 4-amino-3-methylbenzoate (**1**).

Scheme - 1
Schematic representation for the synthesis of novel bisbenzimidazole derivatives



Where

Com. no.	R ⁻	Com. no.	R ⁻	Com. no.	R ⁻
9a		9d		9g	
9b		9e		9h	
9c		9i		9l	

All the compounds were characterized using IR, ¹H NMR, MS and elemental analysis and screened for their cytotoxic activity by XTT assay. Results of *in vitro* assay indicates that electron withdrawing substitutions at para position of phenyl ring and increasing lipophilicity of the compound increased the cytotoxic activity. Most active compound in the synthetic series was 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)-N-(4-nitrophenyl)acetamide (**9e**) and demonstrated higher selectivity toward MCF-7 cell line. The LogIC₅₀ values were 0.022 nM and 0.036 nM for test compound (**9e**) and vinblastin (reference drug), respectively.

MEDI 359

Platinum(II) complexes as a new class of topoisomerase I poisons

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A new class of highly cytotoxic luminescent platinum(II) complexes containing C^NN moiety were prepared. These complexes are stable in physiological conditions, and have unexpected high anti-proliferation activities towards cancers with IC₅₀ values down to nanomolar range, and are much more potent than the clinically used Topoisomerase I (TopoI) poison camptothecin (CPT) in killing cancer cells. Importantly, these complexes show relatively low potency toward normal human cell. [Pt^{II}(C^NN)(C≡NR)](ClO₄) **1c** (HC^NN = 6-aryl-2,2'-bipyridine; R = *tert*-butyl) binds DNA through intercalative mode with a binding constant 1.0×10⁶ mol⁻¹ dm³, accompanied by up to 175-fold increase in the intensity of photoluminescence at I_{max} = 620 nm. The strong and selective binding of **1c** toward DNA may account for its highly cytotoxic in killing human cancer cells. The cell death pathway is, at least in part, by stabilizing the TopoI-linked DNA via intercalation resulting in topoisomerase poisoning, which triggers DNA damage leading to apoptosis.

MEDI 360

Small molecule inhibitors of Rac1 as anti-invasive breast cancer compounds

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Rac1 plays a critical role in several aspects of cancer progression, and has been associated with the proliferation and invasion of several breast cancer cell lines. The crystal structure (Sondek, J., *et al.*, 2000) of Rac1 in complex with its GEF Tiam1 revealed a key groove on Rac1 that is responsible for the specificity of binding with its GEF. Based on these findings, Gao *et al.*, 2004 identified NSC23766 from a virtual screening from the NCI database, as a specific inhibitor of the Rac1-Tiam1 interaction. In our research, new derivatives of NSC23766 were synthesized to improve the inhibitory action of NSC23766. Several of these new derivatives are more potent inhibitors of Rac activity in MDA-MB-435 metastatic breast cancer cells without affecting cell viability of mammary epithelial cells (MCF-10A). The new compounds demonstrate to be more efficient than NSC23766 in inhibiting cell migration and reducing cell spreading and extension of lamellipodia.

MEDI 361

Developing a novel class of cationic, amphipathic peptoids for anti-cancer applications

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Many current chemotherapeutic drugs have difficult-to-endure side effects, and become ineffective in a given patient as resistance develops. There is a need for more selective anti-cancer drugs that are unaffected by the common mechanisms by which chemo-resistance develops. We have been developing peptidomimetic peptoids (sequence-specific, chain-length specific poly-*N*-substituted glycines) for anti-cancer applications. Peptoids are advantageous as drug candidates, in comparison to peptides, because of their protease resistance, enhanced bioavailability, and reduced specific recognitions by the immune system. Inspired by the findings that some cancer cells have slightly higher transmembrane potentials and more negative membrane charges than healthy tissue cells, and that at certain concentrations, some cationic, amphipathic peptides can kill cancer cells while causing no detectable harms to normal human cells, we constructed a cationic, amphipathic peptoid library with various sequences, chain lengths, charges, hydrophobicities and

amphipathicities, and screened them *in vitro* for compounds with potent cytotoxicities towards cancer cell lines while being relatively safe to freshly isolated red blood cells and primary dermal fibroblasts. We found several hits and they can kill multidrug resistant cancer cells as effectively as non-resistant cells. The *in vivo* testings of these peptoids in mouse ovarian cancer models (s.c. implanted or i.p. implanted xenografts) are ongoing.

MEDI 362

PAMAM G3.5-SN38 conjugates: Effect of spacer on drug loading, stability and activity in human colorectal cancer cells

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7-Ethyl-10-hydroxy-camptothecin (SN38) is a highly potent topoisomerase I inhibitor. Low water solubility and high toxicity, limit the clinical utility of this drug. Irinotecan (CPT-11) is the water soluble, prodrug of SN38 which is currently approved for colorectal cancer treatment. However, it causes gastrointestinal toxicity, has poor oral bioavailability and is 100-1000 times less active than SN38. Conjugation of SN38 to poly(amido amine) (PAMAM) dendrimers can increase the drug's solubility, potentially improve bioavailability and facilitate accumulation in cancer cells. In this work, carboxyl terminated PAMAM G-3.5 was covalently attached to SN38 via different spacers. The conjugates were stable at pH 7.4 and moderately hydrolyzed in cell culture media and plasma. Similar to SN38 but to a lesser extent, both conjugates inhibited proliferation of human colorectal cancer HCT-116 cells, arrested the cell cycle in the G2/M phase and led to nuclear fragmentation. However activity of the conjugates varied with the type of spacer. These PAMAM-SN38 conjugates have potential for targeted therapy of colorectal carcinoma. Financial Support was provided by the NIH (R01 EB007470) and Utah Science Technology and Research (USTAR).

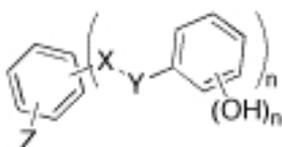
MEDI 363

Inhibitors of basal glucose transport as anticancer agents

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Glucose transport inhibitors are known to sensitize cancer cells to undergo apoptosis induced by drugs such as cisplatin and paclitaxel. In addition glucose

transport inhibitors may exert anticancer activity on their own. We have prepared a series of polyphenolic compounds based on the antidiabetic compound α -PGG. We have examined the structure activity relationship of these compounds with respect to the linkage between the core aromatic ring and the phenols, the number and position of phenolic substitution, and the substitution on the core aromatic ring. We have identified stable, lower molecular weight analogs that show good anticancer activity and good glucose uptake inhibition. We will present the structure, synthesis and pharmacological activity of these novel anticancer agents.



MEDI 364

Design, synthesis, and evaluation of novel RhoB modulating agents for anticancer chemotherapy

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Rho GTPase B (RhoB), a member of RhoA-like isoforms is a family of Ras-homologous GTPase which is considered as a potent target of anticancer therapy. Modulating RhoB is an important role for inhibiting certain tumor survival pathways, because only one isoform, RhoB is related in tumor suppression, whereas other Rho isoforms are related in tumor proliferation. Even though RhoB can be a good target for anticancer therapy, only few chemical entities are used for regulating RhoB protein. G02, found as a good lead compound, has good anti-proliferative activity for NUGC-3 cell lines. Based on the structure of G02, we designed and synthesized numerous derivatives which have a good tumor inhibitory activity. Among these analogs, A665 has been selected as a potent candidate for anticancer therapy, especially in PC-3 and NUGC-3 cell lines. Even though the acute binding mechanism between RhoB protein and our derivatives is not clear yet, experimental data and biological evaluation of derivatives showed that A665 could be an excellent candidate for anti-cancer therapy.

MEDI 365

Biological activity: The importance of functional groups on (E)-4,4'-disubstituted stilbenes toward cell protection

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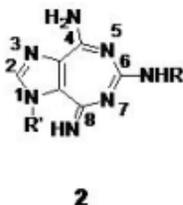
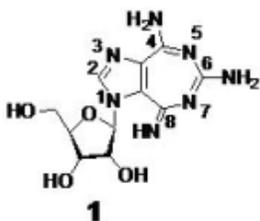
Disubstituted (*E*)-stilbene derivatives are of potential therapeutic value due to their structural similarity to resveratrol. This work probes the relationship between functional group and biological activity. The biological activity of (*E*)-4,4'-dicyanostilbene, (*E*)-4,4'-diacetylstilbene, and the non-substituted *trans*-stilbene was assessed using the MTS cell viability assay in differentiated PC12 cells. These stilbenes were found to be non-toxic to cells at micromolar concentrations. The activity of these stilbenes in the presence of 0.1% H₂O₂, a byproduct of mitochondrial activity, was investigated. It was found that stilbene-H₂O₂ mixtures were 2-3 times more toxic than the H₂O₂ control indicating that they may intensify cellular sensitivity to H₂O₂. It was concluded that stilbenes with electron withdrawing functional groups may be prone to attack by H₂O₂, resulting in the formation of a cytotoxic compound. The results from disubstituted (*E*)-stilbene derivatives with electron-donating groups (hydroxy and methyl) will also be discussed.

MEDI 366

Synthesis of a series of ring-expanded heterocyclic bases containing the 5:7-fused imidazo[4,5-*e*][1,3]diazepine ring system as potent anti-cancer agents

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The ring-expanded nucleoside 4,6-diamino-8-imino-8*H*-1-β-D-ribofuranosyl imidazo[4,5-*e*][1,3]diazepine (**1**) exhibited potent broad spectrum anticancer activities *in vitro* against a wide variety of human tumor cell lines. The heterocyclic aglycon of this nucleoside with a long C₁₈ alkyl attached to 6-amino position (**2**; R=C₁₈ alkyl, R'=H) was also found to exhibit potent *in vitro* anti-cancer activity against prostate, breast, ovarian and lung cancers. Based on this prototype structure, and as part of the SAR studies, a series of heterocyclic bases containing 5:7 fused imidazo[4,5-*e*][1,3] diazepine ring system were synthesized with various alkyl and aralkyl functionalities at the 6-amino position and with a benzyl or substituted benzyl group at the imidazole N-1 position. Synthesis and anticancer activities of the title compounds will be presented.



R=C₁-C₁₈ alkyl, C₃-C₄ phenyl
R'=H, PhCH₂, p-OMe-PhCH₂, p-NO₂PhCH₂

MEDI 367

Identification of novel macrocycles as potent inhibitors of the hedgehog signaling pathway

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Sonic hedgehog (Shh) is an extracellular protein that is part of a signaling pathway important for embryonic development and tissue differentiation. Aberrant activation of the Shh pathway is observed in many cancers, and the inhibition of this pathway could lead to the development of effective cancer therapeutics. A screening program utilizing small-molecule microarrays of diversity-oriented synthesis libraries led to the identification of a macrocycle which binds to Shh and blocks its function. Results of medicinal chemistry efforts leading to analogs with improved potency and physical properties are presented here.

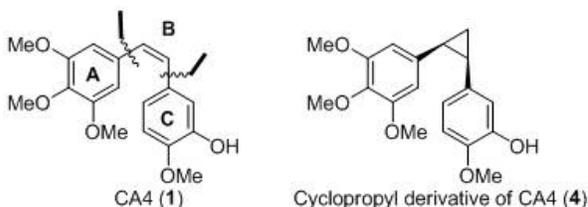
MEDI 368

Synthesis, anti-tumor activity, and docking studies of novel combretastatin analogs

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Combretastatin (**1**), a highly oxygenated stilbene derivative isolated from the African willow tree *Combretum caffrum* by Pettit and coworkers, was identified as biologically highly potent anti-tumor drug. The natural product selectively binds to

the colchicine site at tubulin resulting in disruption of the formation of microtubules and cell cycle arrest at the transition of meta- to ana-phase. Although *in vitro* activity of combretastatin is extremely promising, *in vivo* activity is limited because of the high tendency of the system to undergo cis/trans isomerization under physiological conditions. Several derivatives of the natural product were synthesized (**4**) with carbocyclic ring motifs instead of the stilbene double bond locking the system in the biologically active conformation by preventing cis/trans isomerization.



These novel combretastatin derivatives show promising antitumor activity with IC_{50} values in the sub-micromolar range. Molecular modeling and docking studies at the colchicine binding site reveal the importance of an H-bond donor present at one of the aromatic rings.

MEDI 369

Highly potent caspase-1 inhibitor that utilizes a key 3-cyanopropanoic acid moiety

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There is tremendous need for small molecule inhibitors of caspase-1 given its role as a regulator of inflammation and immune response. Inhibitors of caspase-1 are sought for intervention strategies within ischemic disorders, Huntington's disease, amyotrophic lateral sclerosis (ALS), rheumatoid arthritis, osteoarthritis, and inflammatory bowel disease. The design of small molecule inhibitors of cysteine proteases often rely heavily on covalent modification of the active site thiol. In this study, we explored the use of nitriles as reversible covalent modifiers. To this end, two molecules based on an established caspase-1 peptide inhibitor were synthesized to insert a 3-cyanopropanoic acid 'warhead' and were found to be extremely potent sub nM) caspase-1 inhibitors. These molecules additionally possessed very high selectivity among the human caspases class (>100-fold selectivity for caspase-1 in all cases), and validate the utility of 3-cyanopropanoic acid as a 'warhead' for small molecule inhibitors of caspases.

MEDI 370

Efficient synthesis of α -fluoromethylhistidine di-hydrochloride, its interaction with HDC, and the structure-based identification of novel HDC inhibitors

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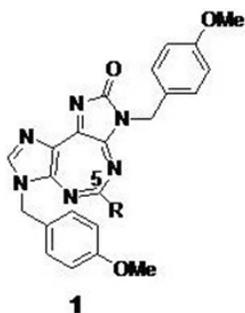
Histidine decarboxylase (HDC) is an enzyme that converts histidine to histamine. Inhibition of HDC has many medical applications including tumor suppression, ulcer therapy, circadian rhythm modulation, and allergy relief. Moreover, HDC inhibitors are needed to study histidine metabolism. α -fluoromethylhistidine di-hydrochloride (α -FMH) is an extremely potent HDC inhibitor. Unfortunately, α -FMH is commercially unavailable. Here we report on the novel, inexpensive, and efficient synthesis of α -FMH, opening the door to commercially available α -FMH. To study the irreversible binding of α -FMH, we carried out covalent docking studies on an HDC homology model. In an effort to identify novel inhibitors of HDC, we performed virtual screening using the same homology model. To the best of our knowledge, this is the first virtual screen applied to HDC. The present study makes an important contribution to the science of HDC inhibition and suggests new avenues for studying and therapeutically modulating HDC.

MEDI 371

Tricyclic 5:7:5-fused-diimidazo[4,5-*d*:4',5'-*f*][1,3]diazepines as potent anticancer agents

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We have recently reported the first synthesis of a tricyclic heterocycle, 3,7-Dihydro-3,7-bis[(4-methoxyphenyl) methyl]-2*H*-diimidazo[4,5-*d*:4',5'-*f*][1,3]diazepin-2-one (**1**; R=H)). We have subsequently discovered that **1** possesses potent antineoplastic activity in cancers of lung, breast, colon and prostates. Mechanistic studies of anticancer activity further revealed that one of the most likely targets is a DEAD-box enzyme human RNA helicase, called DDX3. We, report herein our structure-activity relationship (SAR) efforts to increase the efficacy, aqueous solubility, and bioavailability of **1** by various substitutions at the 5-position of the heterocycle.



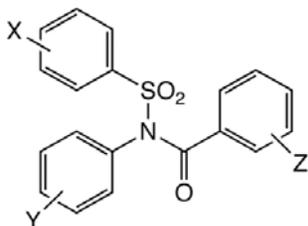
R=H, Ph, *p*-Me-Ph, *p*-NO₂-Ph, *p*-CO₂H-Ph, 2,4,5-tri-CO₂H-Ph

MEDI 372

N-Aryl-N-(arylsulfonyl)benzamides: Potent mitotic cell cycle inhibitors

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Microtubules are linear polymers of α - and β - tubulin dimers. The tubulin dimers polymerize end to end in protofilaments. Microtubules are a part of the cell's cytoskeleton and are involved in the formation of mitotic spindles in eukaryotic cells to segregate their chromosomes correctly during cell division. They connect the chromosomes, help them with their first split and then move to each new daughter cell. There are some toxins and drugs like taxol, colchicines, vinblastine and Nocodazole that can bind to tubulin to either polymerize or depolymerize it. For example, Taxol blocks dynamic instability of GDP bound β - tubulin by stabilizing it and thus inhibiting the shrinkage. Development of microtubule inhibitors, which interfere with microtubule assembly and disassembly specific in M phase is useful for the investigation of the biological function of microtubules-associated proteins (MAPs) as well as for cancer therapy. Here, we describe the synthesis of a new class of small molecules containing keto-sulfonamides, which we suspect to be a tubulin inhibitor thus effecting the mitotic cell cycle. We also report the structure-activity relationships and biological activity of these compounds tested against two cancer cell lines.

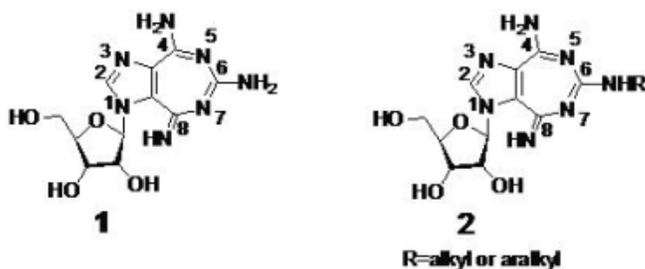


MEDI 373

Structure-activity relationship studies of a ring-expanded nucleoside containing the 5:7-fused imidazo[4,5-e][1,3]diazepine ring system with a broad-spectrum anticancer activity

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The ring-expanded nucleoside 6-diamino-8-imino-8*H*-1- β -D-ribofuranosylimidazo[4,5-*e*][1,3]diazepine (**1**) showed potent broad spectrum anticancer activities *in vitro* against a wide variety of human tumor cell lines. A related nucleoside with carbonyl functionalities at the 4- and 8-positions and with an extended alkyl chain attached to the amino group at the 6-position was also found to possess potent anticancer activity against breast, prostate and lung tumor cell lines *in vitro*. As part of the structure-activity relationship (SAR) studies, we report here the synthesis and biological screening studies of analogues of **1** (*i.e.* **2**) with extended alkyl or aralkyl chains attached to the amino group at position-6.



MEDI 374

Synthetic antitumor compounds as mRNA spliceosome modulators

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We have recently reported the design and the highly enantioselective synthesis of a potent analog of the spliceosome inhibitor FR901464, using a non-natural product scaffold.^{1,2} The design of this compound was facilitated by a pharmacophore hypothesis that assumed key interaction types that are common to FR901464 and to an otherwise unrelated natural product (pladienolide). Here we discuss our progress on the development of new synthetic anti-cancer lead

compounds that modulate the splicing of mRNA. We present data that demonstrate these synthetically analogs to be substantially more chemically stable than the natural products. We have developed active ester and carbamate analogs of our initial compound, including the equipotent hindered ester that has new diverse steric and physical properties, that present a range of cytotoxic activity in sensitive tumor lines. We have explored the scope of the selective anti-tumor cytotoxic activity of the initial lead compounds. These findings have led to the initial *in vivo* anti-tumor efficacy studies using our compound that clearly demonstrate significant *in vivo* inhibition of JeKo-1 tumor growth in SCID mice with only five single daily IV doses. We discuss here the enantioselective and diastereospecific synthesis of a new next generation template using an improved synthetic scheme that leads to new analogs with significant improvements in measured solubility, which dramatically facilitates the formulation of these compounds for intravenous dosing. We will present details on the initial SAR, MTD and efficacy studies of our new potent analogs.

References:

1. Lagisetti, C.; Pourpak, A.; Jiang, Q.; Cui, X.; Goronga, T.; Morris, S. W.; Webb, T. R., *J. Med. Chem.* **2008**, 51, (19), 6220-6224.
2. Lagisetti C., Pourpak A, Goronga T, Jiang Q, Cui X, Hyle J, Lahti J, Morris SW, Webb TR. *J. Med. Chem.* 2009 (*in press*)

MEDI 375

Structure based drug design and synthesis of potential anti angiogenic drug leads

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De novo drug design is a powerful strategy for drug discovery complementary to classical virtual high throughput screening (VHTS) method. We have recently applied the de novo design program SPROUT, developed at Leeds, to the discovery of potential anti angiogenic inhibitors. Novel scaffolds were designed, synthesized and screened against the VEGFR2 and FGFR kinases using a FRET based Z-lyte assay. A series of inhibitors was rapidly identified showing good activity at < 10 μ M in both the enzyme and cellular assay. A hit-to-lead optimization strategy including x-ray crystallography trials progress and it is anticipated that this approach will result in the creation of novel anti angiogenic drug leads.

MEDI 376

New family of proteomimetics: Disruption of p53/MDM2 binding interactions through the antagonistic actions of functionalized piperazine based α -helix mimics

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The p53 protein directly effects tumor suppression by acting as a checkpoint in the cell cycle, inducing cell cycle arrest or apoptosis to irreparable cells. Levels of p53 must be strictly regulated for proper cell function, and the major regulator of p53 is the cellular MDM2 oncoprotein. (1) Over-expression of MDM2 and subsequent p53/MDM2 binding interactions, inhibits the p53 protein's ability to induce cell cycle arrest and/or apoptosis, allowing tumor formation by continued growth and division of damaged cells. Previously reported crystallographic analysis of the p53/MDM2 complex infers that the p53 protein forms an amphipathic α -helix whose hydrophobic face interacts within a hydrophobic cleft in the NH₂-terminal domain of the globular MDM2. (2) This suggests that the synthesis of small molecular derivatives that directly mimic the α -helical region of the p53 peptide, capable of disrupting the p53/MDM2 binding interactions, could represent a great potential for medicinal chemistry studies. (2) Successful syntheses of molecules that mimic the α -helix region of p53, containing key residues in the *ith*, *ith+3* or 4, and *ith+7* positions, have been amply documented in the literature. (3) However, these scaffolds possess poor solubility properties and their synthesis proved to be difficult and inefficient, limiting their usefulness as potential drug candidates. Presented is the design and proposed synthesis of a new family of proteomimetics based on an α -helix mimetic scaffold derived from a functionalized piperazine unit. These mimetics are designed to have a higher degree of solubility and notably facile synthesis yet still maintain the desired spacial arrangements of hydrophobic side chains in the *ith*, *ith+3* or 4, and *ith+7* positions.

1. D. Alarcon-Vargas, Z. e. Ronai, *Carcinogenesis* **23**, 541 (2002).
2. P. H. Kussie *et al.*, *Science (Washington, D. C.)* **274**, 948 (1996).
3. P. Restorp, J. Rebek, *Bioorganic & Medicinal Chemistry Letters* **18**, 5909 (2008).

MEDI 377

Design and synthesis of non-peptidic α -helix mimics targeting for MDM2-p53 protein-protein interaction

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The p53 tumor suppressor protein plays a paramount role as the activator of the apoptosis (programmed cell death) in damaged cells. MDM2 is the major regulator of p53. MDM2 can directly bind to the wild-type p53 thereby inhibiting the activities of p53. The binding interactions between the two proteins, shown by crystallographic study, are formed between one α -helical structure from p53 and the deep hydrophobic pocket at the NH₂-terminal of MDM2. Therefore, the design and synthesis of the small molecules capable of binding to the MDM2 pocket could prevent the binding between MDM2 and p53, thus activate apoptosis. Protein p53 forms an α -helical structure that binds to MDM2, so it is reasonable to expect the α -helical peptides to be potent inhibitors of MDM2. However, peptides are usually unsuitable for intracellular targets. Following the previously reported non-peptidic α -helix mimics, we present the design and synthesis of non-peptidic molecules, containing the mixed structures of amino acids, pyrimidines, and triazoles.

MEDI 378

Cytotoxic, non-mutagenic DNA damage targeted to estrogen receptor-positive cells

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This paper describes the design, synthesis and testing of compounds capable of producing cytotoxic, non-mutagenic DNA adducts in cells that over-express the estrogen receptor. These compounds are designed to exclusively produce the cytotoxic N3-methyladenine DNA adduct. Through the use of the ligand estradiol, these compounds will be targeted to estrogen receptor-positive cells. The DNA binding characteristics, DNA methylating ability, and estrogen receptor targeting ability of these compounds will be presented.

MEDI 379

Designing small molecule inhibitors of transcription: Modulating expression of the erbB2 oncogene

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Aberrant transcription is associated with a wide variety of human diseases. External agents that modulate the transcription of genes associated with the development of diseased states offer a novel and potentially powerful approach to treatment. Because of the complexity of the protein-protein interactions involved, it has proven difficult to develop small molecules that act in this manner. We show that small molecules which mimic the activation domains of transcriptional activator proteins have the potential to inhibit transcription of misregulated genes. Starting from a scaffold known to function as a generic mimic of transcriptional activation domains, we design molecules which more closely resemble the activation domain of the transcription factor ESX. Our results show that these molecules curb overexpression of the ESX-regulated oncogene *erbB2* and inhibit the proliferation of *erbB2*+ cancer cells. This indicates that mimicking specific activation domains is a powerful approach to the design of small molecule transcriptional inhibitors.

MEDI 380

Comparisons between parthenolide and other related sesquiterpene lactones triggering apoptosis in leukemia cells

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Parthenolide is a sesquiterpene lactone (SQL) and the primary anti-inflammatory agent in the herbal remedy feverfew (*Tanacetum parthenium*). Parthenolide contains an α -methylene- γ -lactone functional group that is believed to give rise to its cytotoxic effect. Various SQLs possessing the same reactive moiety have been shown to be cytotoxic against many types of cancer. In our study, we assessed the anti-cancer functions of parthenolide and four related SQLs (DMAPT, alantolactone, helenalin and costunolide) against acute myelogenous and chronic myelogenous leukemia cells. All five compounds were shown to deplete intracellular thiols, promote ROS generation, and induce apoptosis. However, they exert their effects through apparently different molecular mechanisms. These observations lead us to conclude that although the α -methylene- γ -lactone functional group might be involved in the various activities ascribed to this class of SQLs, it is insufficient to explain their full cytotoxic effects against leukemia cells or their exact mechanisms of action.

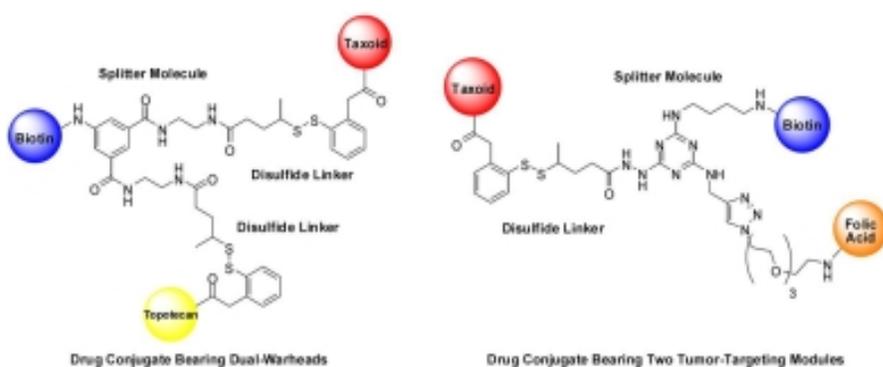
MEDI 381

Towards novel tumor-targeting anticancer drug conjugates

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Two novel drug conjugates for tumor-targeted chemotherapy were designed and synthesized utilizing a small aromatic molecule as a splitter. The first drug conjugate includes two anticancer drugs possessing different mechanisms of action, i.e. a taxoid and topotecan. We believe that this dual mechanism of action makes the drug conjugate highly efficacious. The second drug conjugate is a taxoid-based drug conjugate that includes two tumor-targeting modules, i.e. biotin and folic acid. We believe that two targeting modules will increase the chance of drug conjugate-internalization into various cancer cells at the tumor site. Cancer cells overexpress vitamin receptors. Thus, vitamin bearing drug conjugates will be specifically delivered to cancer cells and internalized *via* receptor-mediated endocytosis. After internalization, the drug moieties are released in their active form through the self-immolation of disulfide linkers triggered by the presence of a cellular thiol. The synthesis and biological evaluation of both drug conjugates will be presented.



MEDI 382

Structural modifications of the amino steroid PC-37: Effect on cancerous cell growth and rat plasma concentration

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PC-37 is a new N-derivative of 2 β -piperazino-5 α -androstane-3 α ,17 β -diol synthesized from epiandrosterone. This aminosteroid showed a large spectrum of cell growth inhibition on different cancer cell lines (Shionogi: IC₅₀ = 0.2 μ M, MCF-7: IC₅₀ = 0.5 μ M, OVCAR-3: IC₅₀ = 1.4 μ M, LNCaP: IC₅₀ = 1.5 μ M and HL-60: IC₅₀ = 2.3 μ M) and a good selectivity factor on normal WI-38 cells and lymphocytes (> 10 and 14, respectively). When injected subcutaneously in rat (2.3 mg/Kg), the plasma concentration of PC-37 increased rapidly to 85ng/mL at 3h, but dropped to 1ng/mL at 12h suggesting an important in vivo metabolism. Structural modifications of PC-37, such as 17 β -O-methylation (**I**), 17 α -methylation

(II), 17 α -ethinylation (III), 3 α ,17 β -disulfamoylation (IV) and 3 α ,17 β -diesterification (V), were achieved to determine their effect on cell growth inhibition and on plasma concentration. The cytotoxicity of PC-37 reported as IC₅₀ value in μ M (2.3) was reduced to 4.5 (I), 4.7 (II), 4.9 (IV) and >10 (V) but, interestingly, not affected with ethinyl compound III (1.9) when tested on HL-60 cells. In addition to the determination of plasma concentration of I-V, which is under progress, the details of chemical synthesis and cell proliferative assay will be presented.

MEDI 383

Design, synthesis and biological evaluation of tyrosine-chlorambucil hybrids showing activity against breast and ovarian cancers

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In our search for anticancer agents with better therapeutic index and selectivity towards breast and ovarian cancers, we have designed and synthesized a new class of amino acid-linked nitrogen mustard hybrids. The new hybrids are designed to imitate estradiol, the female sex hormone, in order to bind to the estrogen receptor. For this purpose, tyrosine was used as the starting material to which chlorambucil was added to construct several tyrosine-chlorambucil hybrids. The phenol group of the tyrosine moiety is used as a bioisosteric function imitating the phenol group of estradiol. Thus, the new hybrids are designed to target the estrogen receptor directing the cytotoxic moiety to hormone-dependent breast and ovarian cancers. Our goal is to extend the use of chlorambucil to female cancers. Chlorambucil is a slow acting nitrogen mustard which can be administered orally. It is mainly used in chronic lymphocytic leukemia and primary macroglobulinemia. It is also useful in treating lymphosarcoma and Hodgkin's disease. The novel hybrids were made using two distinct synthetic methodologies, linear and convergent, which will be described and compared in terms of their efficiency. Two different families of hybrids were made. Molecular modeling shows the possible interactions of the two families of hybrids with the estrogen receptor. MTT assays on several breast and ovarian cancer cell lines show that the novel compounds generally possess higher biological activities when compared to chlorambucil. They are from 2 to 10 times more powerful than the parent drug. The cytotoxic activity of these tyrosine-chlorambucil hybrids could advantageously be used to provide compounds with anticancer activity against hormone-dependent female cancers.

MEDI 384

Synthesis and biological evaluation of anibamine and analogs for anti-cancer activity

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Prostate cancer (PCa) is a leading cause of death in males in the United States. Its epidemiology has been linked to inflammation. CCR5, a critical chemokine receptor in inflammation, has been found to be overexpressed in many types of PCa. A CCR5 antagonist, TAK-779, has been shown to inhibit the proliferation of PCa cell lines. Anibamine, a natural product CCR5 antagonist, binds to CCR5 at micromolar levels. Its total synthesis has been accomplished recently in our lab. Anibamine provides a unique molecular scaffold to design novel CCR5 antagonists. Analogs of anibamine have been designed following the "Deconstruction-Reconstruction-Elaboration" concept. Synthesized molecules were evaluated for anti-proliferative effect in three PCa cell lines. A number of analogs have shown anti cancer activity at submicromolar levels. Results of the biological screening will be discussed in terms of the structure-activity relationship of anibamine.

MEDI 385

Strategies for anticancer chemotherapy: Design, synthesis and biological evaluation of tubulysin derivatives and usage of dendritic carriers for their selective delivery to cancerous tissues

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Current methods of cancer chemotherapy suffer from several limitations. The drugs used typically have poor water solubility, which limits their administration to the patient. Once the drug is injected into the body, a large portion is filtered from the bloodstream by the kidneys, and so multiple doses are required to maintain an effective drug concentration. From the circulatory system, the drug can travel anywhere within the body, leading to side effects like fatigue, nausea, and hair loss. One possible way to address these limitations is to attach a drug to a suitable macromolecular carrier, which would add water solubility, reduce the toxicity of the drug towards healthy tissue, cause the drug to accumulate at higher levels in the area surrounding the tumor, and release the drug in its native form at the tumor site. Currently dendritic polymers as vehicles for anticancer drug delivery are under investigation. It is known that in general large molecules (> 40 kDa) will accumulate selectively in tumor tissue due to the Enhanced Permeation and Retention (EPR) effect. Dendrimers, however, can carry multiple copies of a drug and thus increase the effective dose per carrier and can

selectively release the drug under acidic conditions. Tubulysin D has been reported to be one of the most potent cytotoxic natural products yet identified. Thus a suitably substituted tubulysin derivative has been synthesized and attached to a dendritic carrier with an acid labile acyl hydrazone linkage. The drug-dendrimer conjugate is under biological evaluation for further chemotherapeutic studies.

MEDI 386

Utilizing DNA abasic site to design DNA alkylating agents for potential drug resistance suppression

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Many anticancer drugs exert their functions by producing DNA damage in cancer cells and subsequently inducing their apoptosis. However, the efficiency of anticancer drugs is reduced with the emergence of DNA repair in cancer cells, also known as drug resistance. One of the major repair pathways is the base excision repair (BER), in which the damaged nucleobases are removed by DNA glycosylases to produce a key intermediate (abasic site) followed by incorporating the correct nucleotides by AP endonucleases and DNA polymerases. We plan to design molecules that can specifically recognize DNA abasic sites and form covalent bonds with the nucleobase opposite to the abasic site. The resulting adducts are expected to block the enzyme binding sites in the BER pathway and could be used for drug resistance suppression. The molecules' synthesis and characterization and their ability to form adducts with DNA oligonucleotides containing abasic site will be presented.

MEDI 387

Total synthesis of Berkeleyamide-A: A potent caspase-1 inhibitor

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Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system characterized by inflammatory demyelination and currently has no cure.

Caspase-1, also known as interleukin-1 β converting enzyme (ICE), is recognized to play an important role in regulation of the inflammatory processes leading to demyelination. Studies over the years, using ICE deficient mice, have indicated prominent role of ICE in inflammatory processes. Inhibitors of ICE, therefore, have the potential to culminate in a possible treatment option for MS. Stierle and coworkers isolated Berkeleyamide A (BerKA) from the fungus *Penicillium rubrum* in 2008, which exhibited low micromolar ICE inhibitory activity. BerKA has a

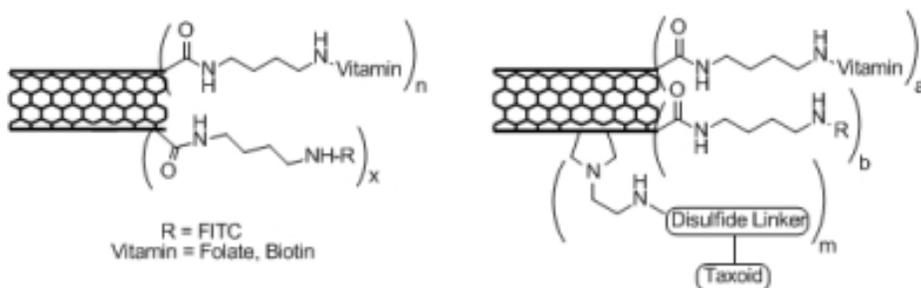
pyrrolidone scaffold containing three stereogenic centers with ambiguous absolute configuration. The total synthesis was achieved by constructing the target molecule from commercially available amino acids. Key reactions, such as asymmetric aldol reaction, Horner-Wadsworth-Emmons reaction, azide transfer reaction and palladium catalyst mediated cyclization will be discussed. This study will aid in identification of bioactive isomer of the natural product, which then will be subjected to further structure activity relationship studies.

MEDI 388

Functionalized SWNT as a versatile platform for tumor-targeted therapy

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Vitamin receptors are overexpressed in various tumor cells, which serve as tumor-specific targets for drug delivery. We have demonstrated the highly cancer cell-specific receptor-mediated endocytosis of SWNT-based vitamin-taxoid conjugates and efficient drug release inside cancer cells. In the present study, we have exploited a characteristic property of SWNTs in addition to cytotoxic drug delivery. SWNTs emit heat when they absorb energy from near-IR light. Thus, cancer cell-specific thermal ablation is possible with vitamin-SWNT conjugates. Moreover, a combination of tumor-specific drug delivery and near-IR induced thermal ablation is possible with the use of SWNT-based vitamin-taxoid conjugates. Suitable functionalization of the SWNT provides a versatile platform for conjugating multiple drugs and multiple targeting modules. With incorporation of fluorescent probe moieties, these SWNT conjugates enable us to monitor the fate of the SWNT, as well. The synthesis, characterization and biological evaluation of these novel tumor-targeting SWNT conjugates will be presented.



MEDI 389

Discovery of quinazolin-4-ones as hypoxia-inducible factor-1a inhibitors

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HIF-1 α plays a pivotal role in regulating cellular responses to hypoxia conditions. It is considered an attractive molecular target for the development of novel anticancer drugs. We recently identified a quinazolin-4-one inhibitor of HIF-1 α from a high-throughput screen. In this presentation, we will describe the synthesis and SAR studies.

MEDI 390

Cytotoxic activities of a twelve-member library of emetine dithiocarbamate ester analogs on androgen-independent PC3 and DU145 prostate cancer cell lines

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We have previously reported the synthesis and characterization of a 12-member library of dithiocarbamate ester analogs of emetine. In the present study, these compounds are screened against two androgen-independent (PC3 and DU145) prostate cancer cell lines. The anticancer activities with structure-activity relationship studies of these compounds on PC3 and DU145 prostate cancer cell lines are presented.

MEDI 391

Cell-permeable, phosphatase-stable phosphopeptide mimetic prodrugs targeted to the SH2 domain of Stat3 inhibit invasion, growth and vasculogenic mimicry of tumor cells

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Signal transducer and activator of transcription 3 (Stat3) transmits signals from IL-6 family cytokines, EGF, VEGF, etc., is constitutively activated in lung, head and neck, breast, prostate, AML and other cancers, and is a target for cancer drug design. To uncouple Stat3 from its roles in proliferation, survival, angiogenesis, and invasion, we are targeting its SH2 domain with phosphopeptide mimetics derived from the recognition sequence, pTyr-Leu-Pro-Gln. We present a convergent synthesis in which a bis-POM β -methyl phosphonodifluoromethylcinnamate active ester is coupled to amino acid

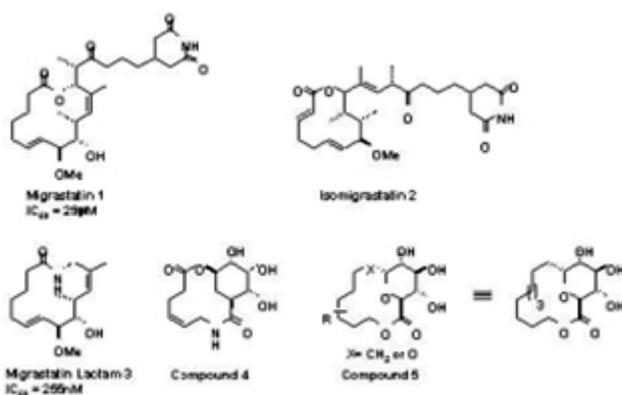
sequences containing novel glutamine surrogates to prepare cell-permeable prodrugs. We report that a series of prodrugs inhibits constitutive phosphorylation of Stat3 at 50 – 1000 nM in cells. The inhibitors do not bind to the SH2 domains of Src, the p85 regulatory unit of PI3K, or Stat5. One inhibitor, PM-73G, at 5 μ M, inhibits tumor cell invasion, anchorage independent growth, and vasculogenic mimicry 70-90%.

MEDI 392

Synthesis of macrocyclic compounds as potential anti-tumour agents

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Migrastatin **1** is a macrolactone containing compound that occurs naturally in streptomyces plantensis bacteria. Migrastatin and its analogues are inhibitors of tumor cell migration. The migration of tumor cells is the leading cause of death in cancer patients. Therefore, migrastatin and analogs hold great potential as therapeutic agents for the treatment of cancer. Danishefsky has synthesized analogues of the macrolide core of migrastatin and showed they are more potent than migrastatin itself (**3**). Bewley et al. have prepared the new synthetic macrolides such as compound **4** which has structural similarity to **2**. These compounds are derived from a pentenoic or heptenoic acid and quinic acid. The most potent compound identified from the quinic acid analogue series is compound **4**. This has initiated our interest in the synthesis of a series of analogues of macrolactones based on glucuronic acid **5** with similar features that may have improved biological activities.



MEDI 393

Perylene derivatives induce G-quadruplex formation of the proximal promoter region of the human VEGF gene and down-regulate its expression in A549 lung cancer cells

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The proximal promoter region of the human vascular endothelial growth factor (VEGF) gene contains a guanine-rich motif that can form an intramolecular G-quadruplex and act as a transcriptional repressor. In this study, we demonstrate that some perylene derivatives can preferentially induce intramolecular G-quadruplex formation from a duplex containing this guanine-rich motif *in vitro* by using the electrophoretic mobility shift assay, DNA polymerase stop assay, and computer-aided molecular modeling. Reverse transcription-polymerase chain reaction (RT-PCR) analysis and Western blot analysis show that these compounds can suppress VEGF gene expression in A549 lung cancer cells. This study might provide a basis for developing these perylene derivatives into a novel anti-angiogenesis agent.

MEDI 394

2-Thienyl-4-furyl-6-aryl pyridine derivatives: Synthesis, topoisomerase I and II inhibitory activity, cytotoxicity, and structure activity relationship study

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Designed and synthesized sixty 2-thienyl-4-furyl-6-aryl pyridine derivatives were evaluated for their topoisomerase I and II inhibitory activities at 20 μ M and 100 μ M and cytotoxicity against several human cancer cell lines. Compounds **8**, **9**, **11** - **29** showed significant topoisomerase II inhibitory activity and compounds **10** and **11** showed the significant topoisomerase I inhibitory activity. Some of the compounds **7** - **9**, **19** and **21** showed higher cytotoxicity against HCT15 cell line whereas weaker cytotoxicity against MCF-7, HeLa, DU145 and K562 cell lines as compared to positive controls. Structure-activity relationship study revealed that 2-(5-chlorothiophen-2-yl)-4-(furan-3-yl) moiety has an important role in displaying biological activities.

MEDI 395

Synthesis, topoisomerase I and II inhibitory activities and cytotoxicity of hydroxylated terpyridine bioisosteres

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Several terpyridine bioisosteres, substituted with hydroxylated phenyl at 2 or 4 position and various 5- or 6- membered heteroaromatics at 6 position of central pyridine, were synthesized. Hydroxyl group was placed either at ortho, meta or para position. Compounds were evaluated for their potential to inhibit topoisomerase I and II and relative cytotoxic activity. Some of the compounds possessed considerable topoisomerase II inhibitory activity and significant cytotoxicity against several human cancer cell lines. The structure-activity relationship was also studied.

MEDI 396

Discovery of novel EGFR tyrosine kinase inhibitors as anti-cancer agents

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Non-small-cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancers, and EGFR overexpresses in 62% of all NSCLC patients. gefitinib (Iressa[®]) and erlotinib (Tarceva[®]) are drugs of EGFR tyrosine kinases inhibitors (EGFR-TKIs) in the treatment of NSCLC. However, cancer cells have resistance to TKIs with the mutation (T790M) on EGFR tyrosine kinase. We designed and synthesized novel compounds as EGFR-TKIs, and expect to overcome the resistance issues for potential NSCLC therapy. BPR1Q-A was synthesized with hybrid design and enhanced activity in EGFR kinase (IC₅₀ = 677 nM). By utilizing knowledge-base design, we introduced Michael acceptor group to BPR1Q-A leading to the identification of BPR1Q-B with activity towards EGFR kinase (IC₅₀ = 2.9 nM) and L858R/T790M mutant kinase (IC₅₀ = 79 nM). After chemical modification and lead optimization, several drug leads will be subjected to pharmacokinetic experiments and animal model studies in order to choose the potential drug candidates for further development.

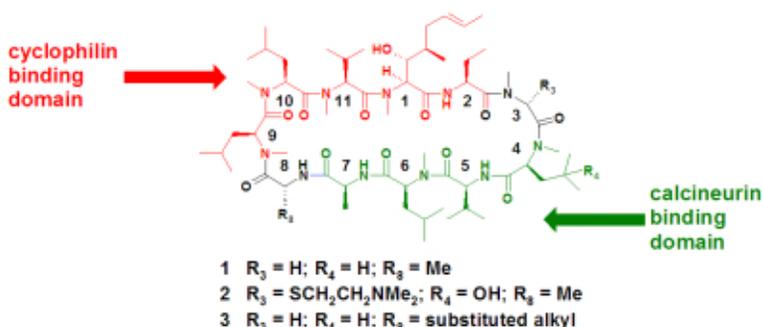
	EGFR kinase	HCC827 cell	L858R/T790M EGFR
BPR1Q-A	677 nM	137 nM	0 % inhibition@10μM
BPR1Q-B	2.9 nM	2.5 nM	79 nM
BPR1Q-C	5.0 nM	1.6 nM	211 nM
Iressa	38.4 nM	14.0 nM	2900 nM

MEDI 397

Synthesis and biological evaluation of [D-lysine]⁸cyclosporin A analogs as potential anti-HCV agents

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Current interferon-based therapeutics for hepatitis C virus (HCV) are successful in only 40-50% of patients treated, and while there are candidates in development that inhibit key HCV proteins such as NS3-4A protease and NS5B polymerase, there remains a need to find new agents with novel targets. Cyclosporin A (CsA, **1**) is a cyclic undecapeptide isolated from the fungus *Tolypocladium inflatum* that exhibits anti-HCV activity by binding cyclophilin using residues 9-11 and 1-2, but also causes immunosuppression by binding calcineurin using residues 4-7. The clinical candidate SCY-635 (**2**) possesses a thioalkylamine sidechain at residue 3 that serves to enhance anti-HCV activity and water solubility, and a γ -hydroxyl at residue 4 to attenuate immunosuppression. Herein, we report the synthesis and SAR of CsA analogs (**3**) modified at residue 8 as an alternative site to improve anti-HCV activity and water solubility while also minimizing immunosuppression. Within this series we have observed anti-HCV activity <200 nM, and weak immunosuppressive potential.



MEDI 398

Macrocyclization studies of simple tripeptide acylsulfonamides: Identification of potent and selective macrocyclic inhibitors of HCV NS3 protease

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It has been estimated that there are more people worldwide who are infected with HCV than HIV. HCV virus has infected about 3% of the world's population. While primary infection with HCV is often asymptomatic, most HCV infections progress to a chronic state that can persist for decades ultimately causing liver cirrhosis, liver failure or liver cancer. Consequently, the prevalence of these

serious liver problems is expected to increase dramatically over the next 20 years. The current standard of care for HCV infection is a combination of non-specific antiviral agents: pegylated alpha-interferon combined with ribavirin. Patients infected with HCV genotypes 1a and 1b respond poorly to this therapy (40-60% sustained response rate after 48 weeks of therapy). Moreover, interferon-based therapies are often poorly tolerated. Therefore, there is a clear medical need to develop more effective antiviral agents for HCV. The HCV NS3 protease is essential for viral replication and has been validated as a therapeutic target in clinical trials. We describe herein the design, synthesis, and SAR of novel macrocyclic and azamacrocyclic isoquinoline tripeptides as HCV NS3 protease inhibitors. These 15-membered P1-P3 macrocycles are substituted with an acylsulfonamide moiety at the P1-P1 prime region. Many of these compounds have demonstrated sub-10 nM potencies in biochemical and whole cell replicon screens.

MEDI 399

Discovery of novel acylsulfonamide tripeptide analogs as potent, selective, and orally bioavailable inhibitors of HCV NS3 protease

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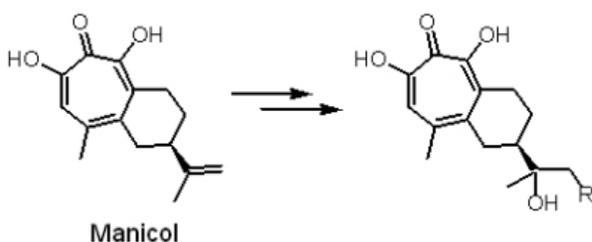
Hepatitis C virus (HCV) infection has emerged as a pressing global health concern due to its progression to cirrhosis and eventual development of end stage liver disease. The current standard of care consists of treatment with pegylated interferon and ribavirin (Peg-IFN/RBV). This regimen provides only modest sustained viral response rates of approximately 50% in patients infected with HCV genotype 1 and moreover has a pronounced side effect profile that includes depression and persistent flu-like symptoms. A clear medical need therefore exists for the discovery of novel anti-HCV therapies that demonstrate enhanced efficacy and an improved side effect profile. The HCV NS3/4A protease is an essential enzyme for viral replication and, as such, has been validated as a target for anti-HCV therapy in clinical trials. Herein, we describe a rational structure-based drug design approach leading to the discovery of a series of acylsulfonamide tripeptides as potent inhibitors of the HCV NS3 protease enzyme. Program optimization of potency, selectivity and ADME properties identified BMS-339 as clinical lead. Details as to the preclinical profile of BMS-339, as well as early clinical data will be provided.

MEDI 400

Syntheses and evaluations of manicol derivatives as inhibitors of HIV-1 RT RNase H activity

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RNase H activity of HIV has been recognized as a potential target for antiviral therapy. However the discovery of potent inhibitors specifically blocking its activity has been slow, and so far no RNase H inhibitor has yet to reach the clinical trial. A high throughput screening of a pure natural product library led us to the identification of a new class of RNase H inhibitor, β -thujaplicinol and manicol which have an α -hydroxy-tropolone scaffold. Our investigation focused on derivatization of these inhibitors in order to increase potency and selectivity. Fifteen manicol derivatives were initially synthesized and their inhibitory activities were evaluated. The IC₅₀s of these compounds have a range of sub to low micro molar. This study demonstrates that manicol derivatives represent a novel family of HIV-1 reverse transcriptase inhibitor, targeting RNase H activity that may lead to the development of therapeutically relevant compounds to treat AIDS.



MEDI 401

Developing HIV-1 microbicides presented on carbonano scaffolds

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Currently, much effort has been made in the science community to provide preventive methods for reducing the number of new HIV-1 infections. Although a few preventive gels have made it through several clinical trial stages, currently there are no FDA-approved HIV microbicides. Most of the microbicides in clinical trials are known to be abrasive and compromise vaginal integrity due to the use of detergent-like materials as active components in the gel formulation. Hence, the current art in preventing HIV infection is begging for better drug candidates. Our laboratory synthesized and established that DCM205 completely deactivates the HIV-1 virus by irreversibly binding near the V3 loop of the glycoprotein gp120. We are proposing to evolve the small molecule DCM205 as a topical therapeutic for HIV-1 prevention. We thus hope to achieve better interaction through

multivalency, by presenting the active compound DCM205 on a sugar backbone termed carbonano scaffolds. The concept of polyvalent or multivalent presentation of these compounds via nanosize dendrimeric or oligomeric backbones and also gold or silicon nanoparticles has been greatly explored. Based on our previous reports for the synthesis and characterization of various carbohydrate scaffolds, we propose to use these scaffolds as a nanosize sugar backbone for presenting DCM205 as a topical treatment for HIV-1. The structured carbohydrate backbone will not only enhance recognition of DCM205 by the viral particle, but it may also serve to localize the active compound in the area of application.

MEDI 402

Self-assemblies of amphiphilic lipid prodrug of zidovudine: Potent anti-HIV activity in vitro and macrophage targeting in vivo

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The self-assemblies of cholesteryl-phosphoryl zidovudine (CPZ), an amphiphilic lipid prodrug, were prepared as self-assembled drug delivery systems (SADDS). The assemblies of CPZ and cholesteryl succinyl poly(ethylene glycol) 1500 (CHS-PEG) (20:1, mol/mol), were prepared through injecting CPZ/CHS-PEG solution in tetrahydrofuran into water followed by removal of solvent. The stable vesicular assemblies were 123 nm in size, and the zeta potential was -34 mV. They showed the potent anti-HIV activity on MT4 cell model with the lower 50% effective concentrations (EC_{50}) compared with AZT (5 nM, EC_{50}). When drugs were applied together with virus or one hour previously, the EC_{50} of assemblies were 0.5 and 0.1 nM, respectively. CPZ showed a rapid elimination from circulation and targeted to the mononuclear macrophage system (liver and spleen as reservoir of HIV with weak phosphorylation) after intravenous administration followed by slow degradation. CPZ self-assemblies are a promising anti-HIV medicine with macrophage targeting.

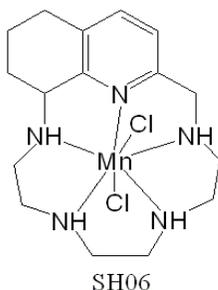
MEDI 403

Synthesis of Cu, Fe, Mn and Zn complexes of macrocyclic polyamines to evaluate their chemokine receptor interactions and anti-HIV activity profile

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Macrocyclic polyamines and their metal complexes are of significant medicinal interest. Recently, a number of macrocyclic polyamines and their manganese complexes were synthesized and tested for inhibition of HIV replication. Among

the compounds tested, 3,4,5,6,7,8,9,10,11,12,13,13a,14,15,16-pentdecahydro-2,17-etheno-1,4,7,10,13-benzopentaaza-cyclopentadecine dichloromanganese(II) (SH06) interacts with both of the cellular HIV co-receptors, CXCR4 and CCR5. These compounds also inhibit HIV entry into CD4⁺ T cells and consequently inhibit viral replication. Several other analogs have been synthesized to decipher in more detail the mechanisms of chemokine receptor interaction and antiviral activity. In addition to manganese complexes, copper, iron and zinc complexes are also considered for testing and are being synthesized. SH06 was tested as a racemic mixture and efforts are also under way to prepare the pure enantiomers for further anti-HIV-1 activity assays.

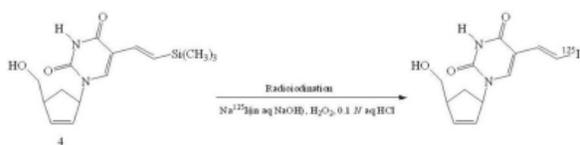


MEDI 404

Synthesis of the stable radioiodovinyldeoxyuridine(IVDU) derivative for imaging HSV-1 TK expression and biological evaluation

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We synthesized carbocyclic radioiododeoxyuridineanalogue (ddIVDU) and carbocyclic intermediate as efficient carbocyclic radiopharmaceuticals. MCA-RH7777 (MCA) and MCA-tk (HSV1-tk positive) cells were treated with various concentration of carbocyclic ddIVDU, and GCV. Cytotoxicity was measured by the MTS methods. For in vitro uptake study, MCA and MCA-tk cells were incubated with 1uCi of [¹²⁵I]carbocyclic ddIVDU. The radioiododemallation for radiolabeling gave more than 80% yield with >95% radiochemical purity. GCV was more toxic than carbocyclic ddIVDU in MCA-tk cells. Accumulation of [¹²⁵I]carbocyclic ddIVDU was higher in MCA-tk cells than MCA cells.



Cell Lines	Nucleoside Analogues Concentration (M)	
	GCV ⁴⁰	Carbocyclic ddIVDU
MCA ⁴⁰	7.00×10^{-5}	6.97×10^{-5}
MCA-tk ⁴⁰	1.17×10^{-7}	5.14×10^{-5}

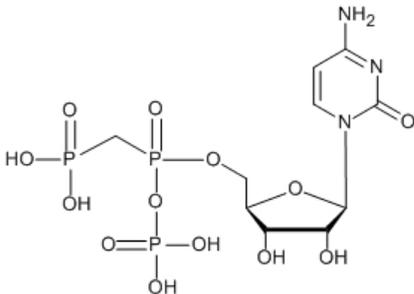
Biological data reveal that ddIVDU is stable in vitro, less toxic than ganciclovir (GCV), and selective in HSV1-tk expressed cells. Thus, this new carbocyclic nucleoside, referred to in this paper as carbocyclic 2',3'-didehydro-2',3'-dideoxy-5-iodovinyluridine (carbocyclic ddIVDU), is a potential imaging probe for HSV1-tk.

MEDI 405

Structure-activity relationship studies of modified nucleoside β -triphosphates for polymerase and RNase H of HIV-1 reverse transcriptase

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Modified nucleoside triphosphates are subjects of major interest as mechanistic probes since they can mimic naturally occurring deoxyribo- and ribonucleoside triphosphates in many biochemical pathways involving nucleotides. Nucleotides with modified triphosphate moieties may have applications in studying the activity of enzymes involved in oligonucleotide synthesis. The inhibitory activities of a number of nucleoside 5'-O- α,β -methylene- β -triphosphates were compared towards polymerase and RNase H of HIV-1 reverse transcriptase (RT). The compounds did not show any significant inhibition against the polymerase activity of RT at a fixed concentration of 1 mM, however a number of compounds exhibited inhibitory potency against RNase H function. Among all the compounds, cytidine 5'-O- α,β -methylene- β -triphosphate inhibited RNase H activity of HIV-1 reverse transcriptase with an IC₅₀ value of 585 μ M as determined by Cheng-Prusoff equation. Further Dixon kinetic analysis of the cytidine analogue demonstrated the competitive nature of inhibition and a K_i value of 225 μ M. This compound may have application as a mechanistic probe in studying RNase H activity of RT with further optimization.

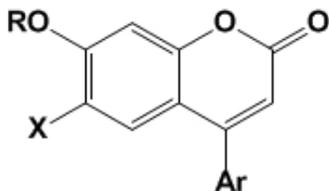


MEDI 406

Progress towards the synthesis of potent neuraminidase inhibitors

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Bacterial pneumonia is a burgeoning threat for an aging populace. The neuraminidases of *P. aeruginosa*, frequently linked with ventilator-associated pneumonia, and *S. pneumoniae*, the most common cause of community-acquired pneumonia, are both important for the formation of bacterial biofilms and in animal models of infection. While inhibitors of viral neuraminidases are commercially available, inhibitors of bacterial neuraminidases are not, and antibiotic resistance is becoming an increasing problem in the treatment of both organisms. We screened a library of compounds *in silico*. 40 compounds were selected and tested in an *in vitro* neuraminidase assay. Two hits were investigated and SAR profiles were established. Of the compounds prepared two compounds showed low micromolar potency with IC₅₀'s of 4.5 μM and 8 μM against *S. pneumoniae*. The IC₅₀ for oseltamivir in the same assay is 2mM. Our compounds are currently being optimized and further studies are being done.



MEDI 407

Fullerene C60-based HIV-1 PR inhibitors: Applying the QSAR based balance of correlation for activity prediction

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A set of fullerene C60 derivatives were subjected to the QSAR studies by two approaches to find structural and physico-chemical features that responsible for the HIV-1 PR enzyme activity. The HIV-1 PR inhibition activity of 20 fullerene C60 derivatives has been modeled by means of balance of correlations for training and calibration sets. The obtained models were evaluated with the external test set. Two approaches were utilized - optimal descriptors approach based on the simplified molecular input line entry system (SMILES) and multiple linear regression analysis combined with genetic algorithm (GA-MLRA) approach to compare performance for the studied systems. For GA-MLRA approach were used a set of fragment, physico-chemical, constitutional and quantum-chemically calculated descriptors. In this study the models based on the balance of correlations and models which were obtained on basis of the total training (i.e., in case of utilization both training and calibration sets as the one combined training set) have been compared and discussed. The best descriptors that responsible for HIV-1 PR inhibition activity and best approach that suitable for good prediction of studied activity are determined.

MEDI 408

Microsecond timescale MD simulation suggests that partial dimer dissociation is the flap opening mechanism of HIV-PR

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We present a working model of the flap-opening mechanism captured in a microsecond timescale MD simulation on an apo wild-type HIV-1 protease with TIP3P explicit solvent. Based on detailed structural analysis, we propose that the *inter-subunit* interactions are critical for the dimer stability associated with protein dynamics; the binding strengths of different parts of the dimer interfaces vary, where weakness in certain areas may be a requirement for protein function, i.e., allowing partial dissociation to render an open form. This novel opening mechanism is supported by the natural tendency of dimers to dissociate and provides insights into mechanisms of drug resistance for mutations outside the binding cavity. In addition, this working model provides a potential target for allosteric inhibition of the viral protease, targeting a weaker part of the dimer interface would interfere with the dimer stability, and thus its dynamics.

MEDI 409

Development and optimization of fluorescence polarization and time-resolved fluorescence resonance energy transfer assays for B-Cell Lymphocyte/Leukemia-2 family proteins

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The anti-apoptotic B-cell lymphocyte/leukemia-2 (Bcl-2) family proteins, such as Bcl-2, Bcl-xL, and Mcl-1, are potent apoptosis inhibitors, which can inhibit pro-apoptotic proteins such Bid, Bak, Bad, and Bax by forming complexes via a conserved Bcl-2 homology 3 (BH3) domain. Designing small-molecule inhibitors that target the BH3 domains, is a promising strategy for inhibiting the anti-apoptotic activity of these proteins and for novel drug discovery for cancers. Here, we report the development and optimization of two novel homogeneous assays based on Fluorescence Polarization (FP) and Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) to determine the binding affinities of small-molecule inhibitors to Bcl-2, Bcl-xL, and Mcl-1. Tracers generating large dynamic ranges and low assay limits were selected for FP assays. Assay stability over time, DMSO tolerance and reproducibility (Z') were evaluated. Results indicated that both FP and FRET assays are suitable for high throughput screening of inhibitors binding to Bcl-2, Bcl-xL, and Mcl-1.

MEDI 410

Combinatorial QSAR analysis of RecA inhibitors and QSAR-based virtual screening

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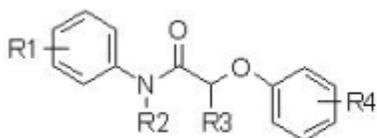
Antibiotic resistance is an escalating problem requiring the discovery of novel antibiotic classes acting on nonclassical cellular targets. Targeting the nonessential genes, for example RecA, offers possible attractive solution. We have developed combinatorial Quantitative Structure-Activity Relationship (QSAR) models for 145 RecA inhibitors and 185 structurally similar inactive compounds resulting from high-throughput screening and the subsequent confirmatory binding assays. The dataset was clustered into three groups according to structure similarity, and three methods, k -Nearest Neighbor (k NN), Random Forest (RF) and Support Vector Machines (SVM), were employed for model building within each group. Models were further validated via external validation set with the Correct Correlation Rate (CCR) as high as 0.91, which is greatly improved compared to the CCR of 0.79 for model building without cluster. With two differently defined applicability domain thresholds, the robust QSAR models were used to mine the ZINC7 library to discover novel structural compounds and the Word Drug Index (WDI) database in an effort for drug repurposing. To identify RecA inhibitors with both high potency and tolerate solubility character, solubility models were also be applied to hits filtered by virtual screening. The identified computational hits will be further tested experimentally.

MEDI 411

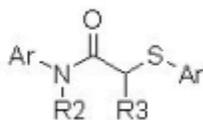
Design, parallel synthesis and high-throughput screening of N-aryloxy- and N-arylsulfanyl-acetamide library as potential EthR ligands and boosters of ethionamide activity

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Tuberculosis remains a major cause of mortality killing each year more than two million people. Current tuberculosis therapies include a large number of prodrugs that are activated inside of the mycobacteria. The protein EthA is responsible for the activation of Ethionamide, a second-line antibiotic. The regulation of *ethA*, exerted by the bacterial transcriptional repressor EthR, limits the effectiveness of the prodrug.[1] Thus, EthR contributes to the innate resistance of mycobacteria to this antibiotic. We recently reported that drug-like EthR inhibitors were able to boost the antimycobacterial efficacy of Ethionamide both *in vitro* and *in vivo*. [2] In the course of identification of new chemical entities, compound BDM5683, a N-aryl-phenoxyacetamide derivative, was identified as a potent ligand of EthR. The co-crystallization of BDM5683 with the protein showed that N-aryloxyacetamide motif is the key pharmacophore for binding. In this context, we designed and synthesized a library of 1440 N-aryloxy- and N-arylsulfanyl-acetamide derivatives using diverse anilines, phenols and thiols. The drug-like properties of the library members were evaluated computationally on the basis of Lipinski and Veber rules. The library was screened using a fluorescent thermal shift assay in order to identify potent ligands of EthR. Best compounds were evaluated as booster of the antimycobacterial efficacy of Ethionamide.



960 members



480 members

[1] Engohang-Ndong, J. *et al. Mol Microbiol* **2004**, 51, (1), 175.

[2] Willand, N. *et al. Nat Med* **2009**, 15, (5), 537.

MEDI 412

Withdrawn

MEDI 413

Squaramides: Novel chemical probes for cell adhesion

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Cell adhesion is a spatial-temporal process that is dependent on the binding of Arg-Gly-Asp (RGD) peptide motif to the integrins on the cell surface. Numerous efforts have been made to develop potent RGD mimics that can prevent adhesion of cells but most drugs have been clinically ineffective. Here, we describe a class of Arg-Gly-Asp (RGD) mimics that inhibit mammalian cell adhesion in solution, but induce enhanced cell signaling when immobilized on surfaces and thus lead to mature cell adhesion. This class of RGD mimics is based on a squaramide moiety that can be synthesized in 2 steps. We observe that squaramide ligands when presented on a bio-inert surface mediate cell adhesion more effectively than the linear RGD ligands. Compared to RGD ligands squaramide ligands promote an increased rate of cell attachment, increased number of focal adhesions and demonstrate lower focal adhesion size validating its high binding nature. Cells adhered to the squaramide surface also display enhanced actin fiber development and greater area of focal adhesion indicating over-expression of adhesion cell surface receptors through stimulation by squaramides. We believe that our results will encourage new approaches towards the design of RGD mimics, and provide strong adhesion ligands for tissue engineering.

MEDI 414

Development of amide isosteres as AFC mimics for isoprenylcysteine carboxymethyl transferase (Icmt) inhibition

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Isoprenylcysteine Carboxymethyl Transferase (Icmt) is a membrane-bound methyl transferase that esterifies the prenylated cysteine residue of post-translationally modified proteins, such as Ras. Ras is an oncogenic protein implicated in 30% of all human cancers. Icmt inhibition mislocalizes Ras and disrupts oncogenic signaling. *N*-Acetyl-*S*-Farnesylcysteine (AFC) is the minimal substrate for Icmt. AFC analogs are modest Icmt inhibitors, but possess peptidic characteristics. Our primary goal is to enhance Icmt inhibition by investigating suitable isosteres. We have successfully synthesized and evaluated over 60 analogs from five diverse structural classes as Icmt inhibitors. All amide mimetic classes have exhibited low micromolar Icmt inhibition *in vitro*. In the absence of structural information on Icmt, the valuable inhibition data from these structurally diverse motifs have helped garner information on the structural requirements for Icmt inhibition. These data fuel our efforts in the rational design of potent, drug-like Icmt inhibitors.

MEDI 415

Synthesis and structure-activity relationships of 4-oxo-3-carboxyl quinolones as antimalarial agents

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Malaria is one of the most important infectious diseases in the world. Approximately over 500 million cases of malaria are reported annually. Because of the worldwide spread of resistance to the most important and least expensive antimalarial drug, Chloroquine, the development of new antimalarial agent is always welcome. WHO/TDR selected, from commercially available screening compounds, an initial series for evaluation and found two lead compounds (TDR17516 and TDR42098) that showed better *in vitro* antimalarial activity than chloroquine and were active *in vivo* in rodent models. We performed comprehensive studies of the structural elements governing the structure-activity of a series of quinolone antimarials. The preliminary structure activity relationship (SAR) suggested the antimalarial potency was clearly associated with 3-carboxylate, 4-keto, 7-methoxy functionalities, and substituents at the *meta*-position of 2-aromatic ring.

MEDI 416

Discovery and mechanistic study of a type of potent protein arginine methyltransferase inhibitors

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Protein arginine methyltransferases (PRMTs) are relatively new enzymes discovered in recent years that play key regulatory roles in epigenetic remodeling. Increasing evidence shows that functions of PRMTs go beyond the realm of chromatin biology. Various cellular processes can be greatly affected by protein arginine methylation including signal transduction and RNA metabolism. Deregulation of PRMT activity has been linked to several pathological states such as cancer and cardiovascular disorder. Thus, development of effective PRMT inhibitors will facilitate the functional study of PRMTs in normal physiology and diseases, and may also provide new avenues for therapy discovery. In this work, we disclosed ten new compounds that share a sulphonyl-naphthalene pharmacore and inhibit PRMT1 activity with micromolar potency. Although these compounds bear no structural similarity to the known peptide substrates of PRMT1, our data from steady-state kinetic assays as well as fluorescence binding assays clearly showed that they are competitive inhibitors versus peptide substrates and noncompetitive versus the methyl donor. To investigate the inhibition mechanism, we conducted a diversity of biophysical measurement including spectrophotometry, fluorescence, MALDI-MS and ITC assays, and

concluded that this type of inhibitors does not target the PRMT enzyme; instead, they bind to the substrate directly and the binding prevents the substrate from being methylated by PRMTs. Therefore, these sulphonyl-naphthalene derivatives are substrate-targeted inhibitors. These new organic inhibitors should be of wide use for chemical biology study of PRMTs. The elucidation of the inhibitory mechanism has important implications for their biological application and for the understanding of the cellular effect caused by these small molecule PRMT inhibitors.

MEDI 417

Synthesis and biological evaluation of lycorine analogs

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The derivatization of alkaloid lycorine at various positions is presented. Generation of analogues of natural products has been recognized as a useful tool in identification of potential drugs or compounds with even higher activity than that of the parent compound. Although lycorine was isolated near 100 years ago and many of its medicinally useful activities have been discovered over the years, none of its analogues has advanced into human clinical trials so far. In continuation of these efforts, we have accomplished different types of reactions on the lycorine scaffold. Dihydroxylation of the double bond, hydroxyl group discrimination, oxidations of the benzylic position and of the allylic hydroxyl, acylation with various acids, [3,3]-sigmatropic rearrangement, among others, were carried out successfully in good yields. Biological testing of the synthesized analogues revealed that lycorine skeleton is critical for activity, and conversion of amine to lactam failed to result in more potent compounds. On the other hand lycorine with lipophilic groups attached to C1 or C2 hydroxyls proved to be a good alternative with similar or better activity as the parent compound. The details of this investigation will be reported at the meeting.

MEDI 418

Withdrawn

MEDI 419

Synthesis, characterization and TLR-7 antagonism in a library of 3*H*-Imidazoquinolines

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Toll-like receptor-7 (TLR7) and -9 are activated by HIV viral RNA, causing activation of innate immune responses which is thought to contribute to immune exhaustion seen in end-stage HIV/AIDS. The only known class of TLR-7 antagonists is single-stranded phosphorothioate oligonucleotides, and the availability of selective and potent small-molecule TLR7 antagonists should allow the formal testing of potential benefits of suppression of TLR7-mediated immune activation in HIV/AIDS. We had recently reported an *N*³-substituted 3*H*-imidazoquinoline TLR-7 antagonist. We have now explored structure activity relationships (SAR) in a test library of 3*H*-imidazoquinolines. The synthetic schemes we have developed allows access to chemoselective derivatization of the imidazole and the quinoline nitrogens. The resulting regioisomers can be characterized unequivocally by 2D-NOESY experiments. Preliminary SAR studies have led to the identification of a novel TLR-7 antagonist with an IC₅₀ value of 2 μM in reporter gene assay.

MEDI 420

Withdrawn

MEDI 421

Computational docking of *R*- and *S*-Thalidomide to DNA

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Although thalidomide has been shown to have anti-angiogenesis effects, the biological pathway affected by thalidomide is uncertain. Several pathways have been shown to promote angiogenesis, including intercellular cascades stemming from the VEGF pathway. Previous studies have found that *R*-thalidomide can bind favorably with GC rich regions of a modified DNA aptamer. Computational docking analyses of *R*-thalidomide, *S*-thalidomide and ethidium bromide were performed on 26 DNA crystal structures using Autodock Vina® and Hex® with ethidium bromide used as an intercalation standard. Trends with both HEX and Vina found ethidium bromide had the best docking energies of all three with an overall average difference of -41.2 kJ/mol between ethidium bromide and *R/S*-thalidomide (HEX) and -0.25 kcal/mol (Vina) respectively. Additionally, there

seems to be only a slight difference of docking energies between AT and GC rich regions of DNA for all three ligands.

MEDI 422

Synthesis of novel azo-linked thalidomide derivatives

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Thalidomide has reemerged as a novel therapy that is both anti-angiogenic and immunomodulative. Although thoroughly researched under clinical conditions, its mechanism of action is still unknown. The coupling of thalidomide and its derivatives with dyes, specifically spiropyran, would help elucidate a possible mechanism. This research uses two microwave syntheses of thalidomide derivatives (32-52%) and spiropyran (48 – 88%). These products are then paired using a reduction reaction with a palladium catalyst to produce novel nitro-spiropyran linked thalidomide derivatives. A biotinylation of the thalidomide derivatives will also assist the understanding of the molecule's binding capabilities to specific proteins. Future work will test these spiropyran linked thalidomide derivatives under biological conditions to assist in the elucidation of a mechanism.

MEDI 423

Withdrawn

MEDI 424

Fluorescence anisotropy screening for inhibitors of tRNA-T Box antiterminator RNA riboswitch interaction

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The T box transcription antitermination riboswitch regulates gene expression by the interaction of uncharged cognate tRNA with the 5' untranslated region of the mRNA during transcription. This interaction involves, in part, the base pairing of the tRNA acceptor end with four bases in the bulge region of the T box antiterminator RNA element. This interaction prevents the formation of an alternative terminator element and results in complete transcription of the gene. We developed a fluorescence anisotropy assay using fluorescently labeled RNA model AM1A to monitor tRNA binding to the T box antiterminator. The choice of

fluorophor was optimized and the assay was used to identify ligands that disrupt the tRNA-T Box antiterminator RNA interaction. Two sets of small molecules were screened in a multi-well plate array and several compounds were identified with greater than 60% inhibition efficiencies. The interaction between the lead compounds and T Box antiterminator model RNA was studied in more detail using Fluorescence Resonance Energy Transfer (FRET) and enzymatic probing.

MEDI 425

Withdrawn

MEDI 426

Squarylated homoserine lactone: New unnatural modulator for quorum sensing and biofilm formation

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Quorum sensing (QS) is a process by which microbials secrete and sense small chemicals (called auto inducers) to monitor their local population densities and to carry out large physiological and communal response. In Gram-negative bacteria, as the threshold cell density is reached, chemical signals or N-acyl-L-homoserine lactones (AHLs) bind to their cognate receptor proteins and trigger the expression of target genes that cause biofilm formation or lead to an expression of virulence factors. Hence, manipulation of quorum sensing is key to controlling bacterial populations and for preventing infectious diseases. Here, we report an efficient synthesis of a library of unnatural autoinducers for Gram-negative bacteria based on a squarate moiety. Evaluation of these squarate ligands on biofilm formation has revealed a potent set of quorum sensing inhibitors. These squarate derivatized compounds offer new structures to tackle infectious bacterial diseases and will provide insights to understand bacterial pathogenesis.

MEDI 427

PK/DB: Database for pharmacokinetic properties and predictive *in silico* ADME models

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In an effort to create high quality pharmacokinetic property (PK) data and predictive models available to a worldwide scientific community, PK/DB (a freely available database for PK) was designed by our research group incorporating robust databases of structurally diverse drug, drug-like and lead-like molecules

for a variety of PK. The chemical and pharmacokinetic data were collected both from public databases and from the literature, resulting in approximately 1400 compounds with more than 3000 property values grouped and organized. In PK/DB, a web-based query tool incorporating a molecular drawing interface enables the database to be searched by chemical structure or standard name, substructure or molecular fragment, molecular formula or by an exact or range of a specific pharmacokinetic property. Also available for searching is the information on human CYP-mediated drug metabolism for a number of compounds. The user can also employ a combination of criteria as a useful way for database searching. PK/DB presents five *in silico* predictive models for the evaluation of ADME properties, including human oral bioavailability, plasma protein binding, human intestinal absorption, blood–brain barrier permeation and water solubility. These predictive models are statistically robust and have both good internal and external consistency. PK/DB is a database that provides useful information on a variety of important PK, as well as access to predictive *in silico* ADME models. The PK/DB suite is designed to be utilized by all researchers in the drug discovery field, and can be freely accessed using a web browser at <http://www.pkdb.ifsc.usp.br>

MEDI 428

Selective recognition of Rifampicin using molecularly imprinted polymer beads within a microchannel

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A novel method of fast and selective recognition for rifampicin using MIP beads within a microchannel by online CL detection was developed. Uniform-size molecularly imprinted polymer beads were prepared by controlled suspension polymerization in a “T”-shaped microchannel, in which rifampicin were used as template molecules, and methacrylic acid used as functional monomers. Resulted MIP beads were introduced into a microchannel fabricated with glass slide. Imprinted effects were measured by CL detection, which results suggested that good selective adsorption for rifampicin was achieved on molecularly imprinted polymer beads, and adsorption percentage of rifampicin was up to 76%, and overall analysis time was only 5 min.

MEDI 429

Gold-silver alloy nanoshells: A new candidate for nanotherapeutics and diagnostics

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Gold-silver alloy on Gd-doped iron oxide nanoparticles were successfully prepared via solution-phase reduction of a mixture of Au(III) and Ag(I) salts. The morphology, size, elemental composition and optical properties of the nanoshells were characterized with XRD, TEM, DLS, ICP-AES, SEM/EDX, UV-Vis and FT-IR spectroscopy. The experimental results demonstrated the successful growth of the alloy shells on the magnetic nanocores. The UV-Vis spectroscopy indicated that this unique nanosystem exhibits strong absorption in the range of 600-800 nm. Thus, these nanoshells have great diagnostic and treatment potentials in the medical field, namely for MRI and laser ablation of tumor cells.

MEDI 430

Isolation and identification of immunostimulatory compounds from Juzen-taiho-to

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Juzen-taiho-to (JTT) is an herbal medicine known to exhibit immunostimulatory activity, and it is often prescribed for patients undergoing chemotherapy and radiation therapy. Although JTT is recognized as a potential source of immunostimulatory compounds, the chemical constituents responsible for its therapeutic effects are poorly characterized due to the heterogeneity of the formulation. Our group has utilized “biomarker-guided screening” protocol to uncover the previously overlooked bioactive compounds from oriental herbal medicines. In this screening, mRNA markers of its therapeutic effects are first identified through GeneChip profiling and then used for purification guided by quantitative real-time PCR. Using this screening method, our group has identified diacylglycerol glycosides (DGGs) as the potent immunostimulatory compounds in JTT. This finding and further structural and mechanistic characterization of these DGGs enable us to better understand the biological property of JTT.

MEDI 431

Design, synthesis, and SAR of small molecule inhibitors of the metalloprotease gp63 as novel antileishmanial agents

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Leishmaniasis is a tropical/sub-tropical parasitic disease, infecting approximately 2 million people annually. The limited chemotherapeutic approach for the treatment of leishmanial infections is based on amphotericin B, miltefosine, paromomycin, and antimony agents like sodium stibogluconate and meglumine antimoniate. These are unsatisfactory therapeutics characterized by high toxicities causing serious side effects that often result in patients deserting the treatment. Also, these drugs are cost prohibitive, restraining their availability in developing countries where most of the infection occurs. Therefore, there exists an urgent need for affordable alternatives to curtail leishmaniasis. GP63, a zinc metalloprotease, is a vital virulence factor which has been implicated in leishmania pathogenesis and it is an attractive target for the development of new chemotherapeutics. Despite the attractiveness of gp63 as anti-leishmanial target, currently there are no efficient, non-toxic inhibitors of gp63. We report here the design, synthesis and SAR of potent 3-hydroxypyridin-2-ones and their thiol analogs that inhibit the zinc metalloprotease activities of gp63. We are following a traditional SAR approach backed by molecular modeling studies on gp63. Several compounds show high potency with limited cytotoxicity to normal mammalian cells. This study provides a basis for further structural optimization of 3-hydroxypyridin-2-thiones to yield more potent drugs.

MEDI 432

GALAS modeling methodology applications in the prediction of the drug safety related properties

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Early computational evaluation of drug candidate properties related to its pharmaceutical safety is becoming increasingly important in the drug discovery process. Yet the effective use of any available third-party predictive algorithms for these properties in the pharmaceutical industry is severely hindered by a number of problems. E.g. the training set rarely covers the specific part of the chemical space occupied by the compounds that a certain company is working with or a specific experimental protocol is used to measure the corresponding properties or activities 'in house'. Therefore the need arises for a method that would allow any company to tailor a third-party predictive algorithm to its specific needs using proprietary 'in house' data. Here we present a novel GALAS (Global, Adjusted Locally According to Similarity) modeling methodology that provides a possibility for a researcher to expand the Applicability Domain of the resulting models with the help of a custom database of experimental values for the

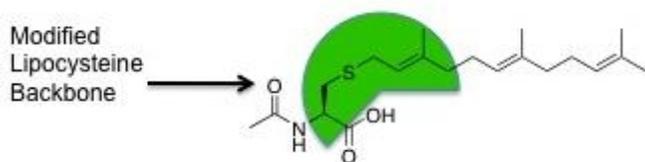
property of interest. A Reliability Index (RI) is also calculated as a measure of the quality of the particular prediction. The use of the method is illustrated with examples of its application in predicting CYP3A4 and hERG inhibition which figure among the major factors attributing to the rising attrition rate, being responsible for the various unwanted drug-drug interactions and cardiotoxicity respectively. 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. Similarly the models are shown to be able to utilize 'in house' data obtained using different protocol compared the experimental training set data. Most importantly all of the above benefits are obtained without time consuming statistical retraining of the initial GALAS models.

MEDI 433

Non-lipocysteine based inhibitors of isoprenylcysteine carboxymethyltransferase

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Post-translational modifications are essential to oncogenic Ras proteins, which are found mutated in approximately 30% of all cancers. Ras is a GTPase that is essential for cellular signaling and is implicated in a wide variety of cellular processes. There are three necessary steps for the complete processing of Ras. Prenylation and proteolytic events initiate the necessary modifications of Ras, followed by the methylation of the newly generated lipidated cysteine by Isoprenylcysteine carboxymethyltransferase (Icmt). Icmt is the only known enzyme capable of this activity and thus Icmt emerges as a potential therapeutic target of Ras driven tumors. Analogs of the minimal substrate, *N*-Ac-S-Farnesyl-Cysteine (AFC), that entail minute modifications about the lipocysteine backbone are the engine that fuels our current investigation into Icmt inhibitors. We are currently investigating non-lipopeptidic prenyl cysteine analogs to this effect and low micromolar inhibitors of Icmt have been realized.



MEDI 434

Sappyrins and heterosappyrins: Potential inhibitors of *Leishmania*

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Sapphyrins and a series of related expanded porphyrins have been investigated as potential therapy agents against *Leishmania*, obligate intracellular parasites that lead to leishmaniasis, which affects more than 12 million people worldwide; current treatments are unsatisfactory. The expanded porphyrins were incubated at different concentrations as a single dose *in vitro* with *Leishmania tarentolae* in the presence and absence of light. *Leishmania* were also incubated with daily additions of expanded porphyrins. The effects of the compounds were assessed by light microscopy, confocal microscopy, and the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) viability assay. Sapphyrin and two related heterosapphyrins were shown to be active as inhibitors to *L. tarentolae* growth using either a single or a daily dose. Confocal microscopy demonstrated these were taken up by the parasites and induced production of superoxides monitored by using a fluorescent probe. Sapphyrins have been previously investigated as anticancer agents and show inhibitory effects against *Leishmania*, suggesting therapeutic potential.

MEDI 435

Synthesis, functionalization and photo-Bergman chemistry of enediyne bioconjugates

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One of the most promising means to address the problem of tumor targeting is through the use of monoclonal antibody (Mab) conjugates, where the antibody specifically and selectively targets a tumor cell surface antigen. The first FDA approved Mab conjugate was Wyeth's Mylotarg®, which is composed of an enediyne cytotoxin coupled through a linker group to an anti CD33 antibody [hP67.6]. Mylotarg® is clinically effective in the management of acute myeloid leukemia (AML) and its approval by the FDA was a watershed event in the development of targeted therapeutics. A goal of this program is to apply nanoparticle targeting techniques in the synthesis and delivery of locally activated enediyne-conjugates of a variety of monoclonal antibodies. In pursuit of this goal we have coupled a number of enediyne prodrugs to select antibodies using heterobifunctional PEG linkers and applied to the technology to development of surface modified Au nanoparticles. The target of the enediyne toxin is nuclear DNA and it is expected that affinity for this target, hence effectiveness of the agents, can be enhanced using nanoparticle affinity ligands. Applications of the technology in cellular imaging will also be presented.

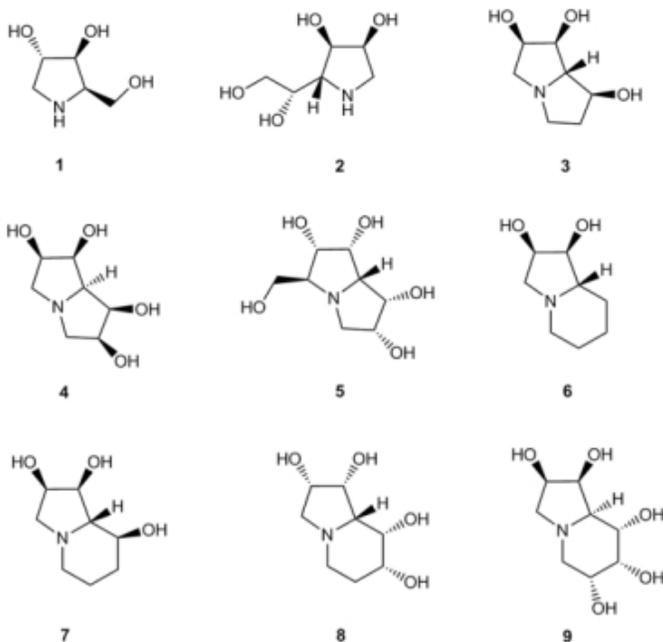
MEDI 436

Virtual screening of carbohydrate processing enzymes against polyhydroxylated pyrrolidines, pyrrolizidines, and indolizidines I: Golgi α -mannosidase II

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Golgi α -mannosidase II, a key enzyme in *N*-glycan processing, is a target in the development of anticancer therapies. In conjunction with a project aimed at developing general, efficient asymmetric syntheses starting from commercially-available sugars, AutoDock screening of libraries of polyhydroxylated pyrrolidines, pyrrolizidines, and indolizidines has identified potential inhibitors **1-9**. Screening of several known inhibitors demonstrates excellent agreement between experimental and computed binding modes. Inclusion of protonated forms and viable conformers in the libraries allows for the assessment of the effect of pH and changes in ring conformation. Analysis of the docked structures allows for determination of the different binding motifs of potential inhibitors.



MEDI 437

Probabilistic model of regioselectivity of metabolism in human liver microsomes

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Here we present a model for in silico prediction of the most probable sites of human liver microsomal metabolism in a molecule. The developed models calculate the probabilities of being a target of human cytochrome P450 enzymes (CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2) for any atom in a molecule and allow forecasting of the most probable phase I metabolites. The novel GALAS (Global, Adjusted Locally According to Similarity) modeling methodology was used for development of probabilistic models. It provides a possibility to estimate the reliability of prediction. Moreover, the Applicability Domain of the models can be easily expanded to cover compound classes of user interest by incorporating 'in house' databases containing experimental metabolism data. Experimental data for >600 compounds with >6000 different carbon atoms were used for modeling. Four baseline models were developed for four types of atoms (aromatic carbon, aliphatic carbon, carbon near nitrogen, carbon near oxygen). GALAS modeling methodology finds most similar metabolism sites in the training set, according to which corrections to the baseline predictions are made and final prediction quality is estimated in the form of Reliability Index (RI). The numbers of mispredictions and inconclusive results reduce significantly when only results of high quality (RI>0.5) are taken into account, demonstrating that RI reflects accuracy of prediction. The regioselectivity models are shown to be trainable using experimental data for compounds not present in the training set.

MEDI 438

Design and synthesis of novel cyclic HYD1 peptide as β 1 integrin inhibitor

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Standard chemotherapy treatments have been unsuccessful to eliminate Minimal Residual Disease (MRD) while treating leukemia and multiple myeloma patients. This relapse in cancer and leukemia arises due to emergence of drug resistance that decreases chemotherapy sensitivity. MRD is usually found in the bone marrow. Previous studies have shown that cellular adhesion of leukemia and multiple myeloma to extracellular matrix (ECM) component, fibronectin via β 1 integrin is responsible for increased drug resistance. Integrin contains 17 α and 18 β subunits. VLA-4 (α 4 β 1) and VLA-5 (α 5 β 1) are most common integrin receptors found in multiple myeloma (MM), acute myeloid leukemia (AML) and chronic myelogenous leukemia (CML). Thus inhibition of β 1 integrin mediated cell adhesion has been of great interest to various research groups. Previous studies have shown that a D-amino acid peptide HYD1 inhibits α 4 β 1 mediated adhesion of myeloma cells to fibronectin. Herein we propose the synthesis of

cyclic HYD1 peptide (cHYD1) which inhibits β 1 integrin mediated cell adhesion. The extended conformation of the cyclic HYD1 peptide is believed to increase the activity of the parent HYD1 peptide.

MEDI 439

Design and synthesis of novel phospho-tyrosine mimetics

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Protein phosphorylation is a post translational modification of proteins in which a serine, a threonine or a tyrosine residue is phosphorylated by an enzyme, kinase. Phosphorylation of proteins is a reversible and very important regulatory mechanism that occurs in both prokaryotes and eukaryotes. Phosphorylation turns many protein enzymes on and off, preventing or causing many diseases such as diabetes, cancer and rheumatoid arthritis. The phosphorylation on tyrosine residues of proteins is essential for transmission of signals for cell growth, proliferation and differentiation. Protein tyrosine phosphatases (PTPs) in concert with protein tyrosine kinases (PTKs) regulate many signal transduction pathways by regulating the degree of phosphorylation of tyrosine residues within the protein. While the roles and mechanisms of protein tyrosine kinases are well documented, our present understanding of protein tyrosine phosphatases is very less. In this regard we still have much more to understand about PTPs. Here we propose the design and synthesis of novel protein tyrosine phosphatases mimetics which we hope could be very helpful in significantly improving the current understandings about the roles and mechanisms of the PTPs. These proposed tyrosine phosphatases inhibitors are believed to work effectively in treating the diseases by modulating the phosphorylation in signal transductions pathways.

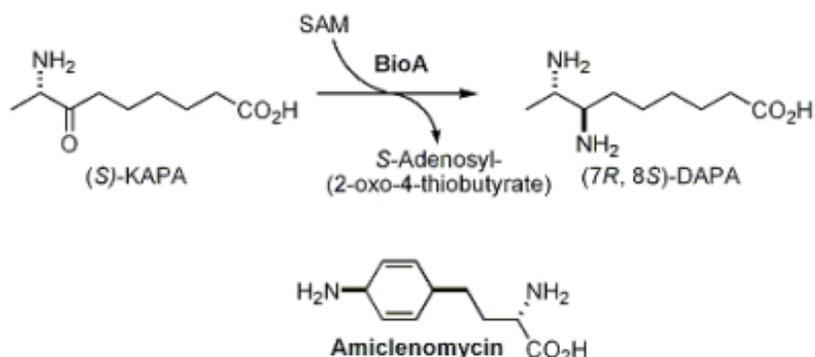
MEDI 440

Design of mechanism-based inhibitors of biotin biosynthesis in *Mycobacterium tuberculosis*

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Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) is the leading cause of bacterial infectious disease mortality and new drugs, ideally with new

mechanisms of action, are urgently needed to combat the emergence of multidrug resistant TB strains. Several lines of evidence suggest that biotin biosynthesis is essential for Mtb. Biotin biosynthesis is carried out by four enzymes (BioF, BioA, BioD and BioC) and we have focused our efforts on BioA, which catalyzes the second step of biotin biosynthesis due to availability of the three dimensional structure of BioA and aminclenomycin, a known covalent inhibitor of BioA. BioA is a typical pyridoxamine phosphate (PMP)-dependent transaminase and catalyzes the conversion of 7-keto-8-aminopelargonic acid (KAPA) to 7,8-diaminopelargonic acid (DAPA) and concomitant oxidation of the PMP cofactor to pyridoxal phosphate (PLP). While aminclenomycin has served as an excellent tool compound, it suffers from poor chemical and metabolic stability. We will describe the design, synthesis, and evaluation of a series of mechanism-based irreversible inhibitors of BioA as a potential new class of antitubercular agents.



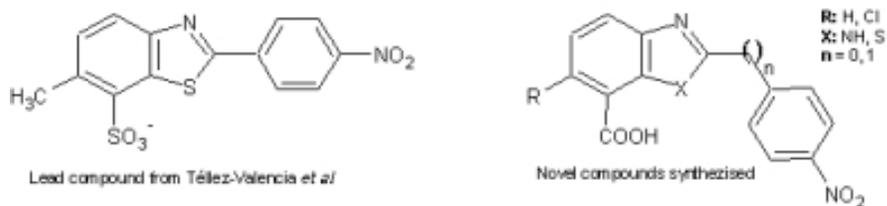
MEDI 441

Docking studies and synthesis of new benzimidazole analogs as selective inhibitors of Triosephosphate isomerase from *Trypanosoma cruzi*

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In this work we present the docking studies and synthesis of new benzimidazole analogues designed to selectively inhibit the enzyme Triosephosphate isomerase (TIM) from the protozoan *Trypanosoma cruzi*, Chagas disease causing agent, which is endemic in the American continent and causes severe health problems during the patient's life. Briefly, 40 benzimidazole and benzothiazole derivatives were designed based on a lead compound reported previously by Téllez-Valencia *et al* (J. Mol. Biol. 2004). The designed compounds were docked *in silico* to the crystallographic structures from human and parasite TIMs using Autodock 4.0. From this study, 2 compounds showed better selectivity and affinity than the lead compound to both TIMs. These compounds, along with 6 more having

different theoretical profiles (ranging from low to mild selectivity) were selected to be synthesized from commercially available starting materials to be finally evaluated *in vitro* with both enzymes.

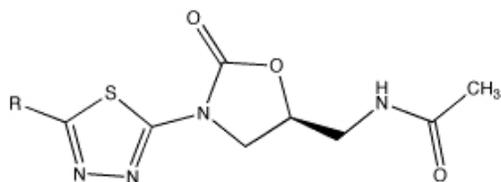


MEDI 442

Effects of thiadiazoles on oxazolidinone activity

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Amino substituted thiadiazoles were used as starting materials to synthesize novel oxazolidinones [see figure 1] in six steps. The electron withdrawing ability of the thiadiazole ring not only effected the activity of the resulting oxazolidinone but adversely effected several of the steps in the synthetic route. The pKa of one of the starting materials and a carbamate intermediate was measured in order to explain the poor yields and production of a bis-carbamate byproduct in one of the steps. This data was also utilized to design conditions to increase the yield of this step. The antimicrobial effectiveness of the new oxazolidinones was tested against *Staphylococcus aureus* and compared to Linezolid.



MEDI 443

Synthesis and analysis of promethazine sulfoxide, an oxidation product of promethazine

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Promethazine is used for prevention of nausea and vomiting, for sedation, for treatment of allergy symptoms, and for prevention and treatment of motion sickness. Previous research by this group has shown that Promethazine in saline solution degrades after 12 hours, resulting in a number of unknown byproducts. Promethazine Sulfoxide was deduced to be a principal decomposition product in the saline solution due to an earlier HPLC retention time than promethazine, it being more polar than promethazine. Other studies have concluded that when Promethazine degrades in blood, Promethazine Sulfoxide is formed. Pure Promethazine Sulfoxide was synthesized by oxidation. The HPLC retention time of Promethazine Sulfoxide was compared to the retention time of the decomposition products observed in stored saline-Promethazine solutions.

MEDI 444

Modifications to the quinoline ring system of reversed chloroquinines to enhance activity against chloroquine-resistant malaria

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Resistance of *Plasmodium falciparum* malaria to chloroquine-based antimalarial drugs is a continuing problem, particularly in the developing world. Previously in our laboratory, we have synthesized a novel class of quinoline-based antimalarials, which we termed reversed chloroquinines (RCQs), consisting of a chloroquine-like portion connected to a chemosensitizer (Reversal Agent, RA) against chloroquine resistance (CQR). We now examine the effect of modifications to the quinoline ring system of these RCQs, varying the position and nature of its substituents. *In vitro* testing against chloroquine sensitive and chloroquine resistant *P. falciparum* malaria reveals, in some cases, improved activity relative to the 7-chloro analogues, with IC₅₀ values in the sub-10 nanomolar range.

MEDI 445

Exploring a general approach to improve the brain exposure of peptidic small-molecule therapeutics

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The blood-brain barrier (BBB) of animals effectively excludes most small molecules from the brain. Hydrogen bond donor (HBD) functions limit passive

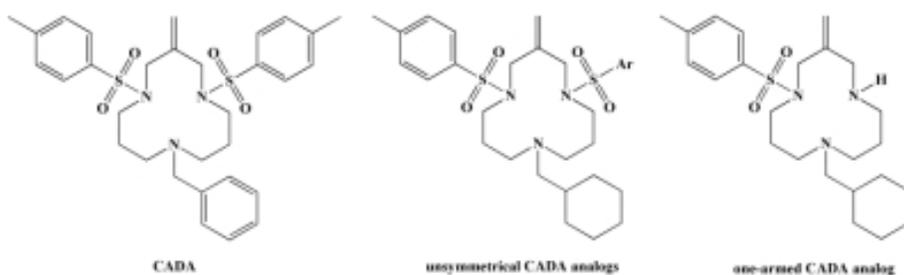
transcellular transit across the BBB. A possible approach to mitigate this unfavorable effect is to introduce hydrogen bond acceptor (HBA) functionality that enables intramolecular hydrogen bond formation, thereby reducing the energetic costs of desolvation upon entering a membrane. To investigate this approach, we synthesized a set of peptidic compounds bearing various natural or unnatural amino acid side chains. Comparator analogs were synthesized in which an HBA atom was introduced in strategic positions to enable hydrogen bonding. In the majority of cases, the HBA-containing analogs exhibited superior permeability in a Parallel Artificial Membrane Permeability Assay (PAMPA). We examined whether these permeability effects could be predicted de novo using a physics-based algorithm that considers conformational preferences. Correlation of the predicted and experimental PAMPA data are also discussed.

MEDI 446

Unsymmetrical CADA analogs as CD4 down-modulators

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Cyclotriazadisulfonamide (CADA) is able to inhibit entry of HIV into cells by down-modulating cellular CD4, which is the primary receptor recognized by the virus. Structural modifications of CADA have been made to increase potency, reduce toxicity, and improve physical properties. These CADA analogs have shown strict correlation between the anti-HIV and CD4 down-modulating activities. However, unsymmetrical analogs having two different arenesulfonyl side-arms have not been fully explored. Only two unsymmetrical analogs have been prepared previously. Using a 6-step synthesis starting with 1,3-diaminopropane, seven new unsymmetrical analogs have now been prepared. These analogs have the benzyl tail of CADA replaced by a cyclohexylmethyl group and one tosyl side-arm replaced by a different arenesulfonyl group. All of these analogs are able to down-modulate the CD4 receptor in T-cells. Also, to determine if both side-arms are needed for the analog to exhibit CD4 down-modulation, a “one-armed” CADA analog is being synthesized.



MEDI 447

Blind predictions of relative passive membrane permeabilities of cysteine protease inhibitors using a physics-based approach

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There is an urgent need to treat tropical diseases like leishmaniasis, trypanosomiasis, etc. The currently available therapies suffer from significant toxicity and/or limited efficacy – problems that require expensive and time-consuming medicinal chemistry optimization. To quicken this lead optimization process, we developed a computational approach to predict relative passive membrane permeabilities. To estimate relative passive membrane permeabilities, we apply a computational atomistic model that uses conformational sampling in combination with an all-atom force field and implicit solvent model. The model does not require the use of training data for rank-ordering compounds, and as such represents a different approach from the more commonly employed QSPR models. A central theme in several prior studies of this type has been the importance of conformational flexibility and internal hydrogen bonding in facilitating passive membrane permeability. As conformational flexibilities of ligands are likely to change upon entering the membrane, we improved our protocol to include calculation of ligand entropy changes. The utility of this approach has previously been demonstrated for a set of FDA-approved drugs. To test our model, we have synthesized a series of 21 peptidomimetic compounds that may function as cysteine protease inhibitors and compared our blind predictions to permeabilities measured in a parallel artificial membrane permeability assay (PAMPA).

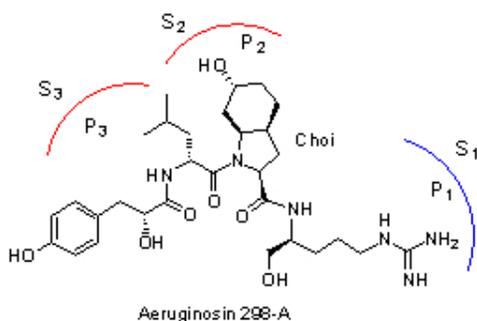
MEDI 448

Synthesis and serine protease inhibition activities of Aeruginosin 298-A analogs

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Aeruginosins are a class of naturally occurring oligopeptides that exhibit interesting biological activities. These oligopeptides contain an unusual bicyclic amino acid, 2-carboxy-6-hydroxyl octahydroindole (Choi), as the common core structure. Many compounds in the aeruginosin family are inhibitors to trypsin and important blood coagulation factors such as thrombin and factor VIIa. In order to understand the structure activity relationship (SAR) of the aeruginosins and to optimize the thrombin inhibition potency and selectivity, we have synthesized a series of analogs of the aeruginosin 298-A and analyzed their serine protease inhibition activities. These analogs contain novel synthetic bicyclic amino acids

for the P₂ binding unit, and various functional groups for the P₁ and P₃ groups. The preparation of these novel analogs and their thrombin and trypsin inhibition activities will be presented.

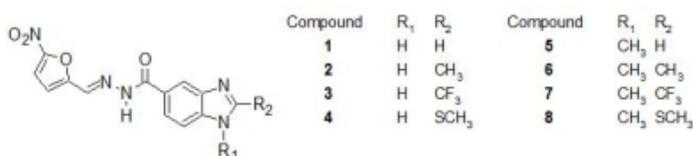


MEDI 449

Design, synthesis, and biological activity of novel hybrids of benzimidazole and 5-nitrofurfural hydrazone

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A series of novel *N*-[(5-nitrofurán-2-yl)methylidene]-1*H*-benzimidazole-5-carbohidrazidas derivadas (**1-8**) fueron sintetizadas y probadas *in vitro* contra *Trypanosoma cruzi*, *Giardia intestinalis*, *Trichomonas vaginalis*, *Trichinella spiralis* and *Entamoeba histolytica*. We also determinate the cytotoxic activity. These compounds were designed having in mind the features of Nifurtimox, a potent antichagasic agent, and some 1*H*-benzimidazole derivatives that we have found to have antiprotozoal activity. Thus, the novel molecules are carbohidrazidas, híbridos de 5-nitrofurfural hidrazona and 1*H*-benzimidazole-5-carboxylic acids.



Biological activity of the new carbohydrazides against *T. cruzi* was carried out using the Pizzi Method. For *G. intestinalis*, *T. vaginalis* and *E. histolytica* we used the subculture method. The cytotoxic activity was performed on Hela Cells. IC₅₀ was calculated in uM. Against *Trypanosoma cruzi* (trypomastigote form) compound **4** was 13 times more potent than Nifurtimox (Lampit®) and 20 times more potent than Benznidazole (Rochagan®). The syntheses, spectroscopic data, biological assays and results will be presented.

MEDI 450

HTS, design, synthesis and pharmacological evaluation of tetrahydroindazole based ligands as novel antituberculosis agents

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The resurgence of tuberculosis (TB), the incidence of multiple-drug-resistant strains of *Mycobacteria* and the synergy between TB and HIV have led to serious infections, high mortality and a global health threat, resulting in the urgent search for new classes of antimycobacterial agents. Herein, we report the identification of a novel class of tetrahydroindazole based compounds as potent and selective inhibitors of *M. tuberculosis*. Compounds **5a**, **5m**, and **5q** exhibited activities in the lower micromolar range against the replicating *M. tuberculosis* (R-TB), with minimum inhibitory concentrations (MICs) of 1.7, 1.9 and 1.9 μ M, respectively, while showing no toxicity to Vero Cells. Moreover, studies aimed to assess the metabolic stability of **5a** and **5m**, both in plasma and mouse liver microsomes, gave satisfactory results, thus making *in vivo* administration of these derivatives as the obvious next step for further investigation. This research suggests that tetrahydroindazole based anti-TB compounds can serve as a promising lead scaffold in developing new drugs to combat tuberculosis infections.

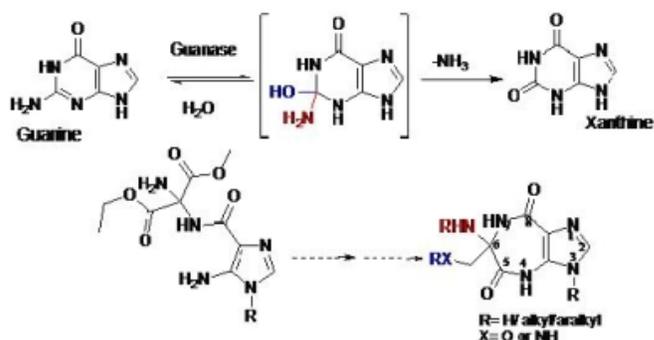
MEDI 451

Use of diaminomalonates as synthons for novel transition state analog inhibitors of guanase

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Guanine deaminase or guanase (GDA, EC 3.5.4.3) is an important enzyme in purine salvage pathway of nucleotide metabolism and, therefore, is an important target for anticancer, antiviral, and antibacterial therapy. Azepinomycin is a known, naturally occurring inhibitor of the enzyme, but is not nearly as potent as cofomycin, also a natural product, that inhibits another purine-based deaminase

called adenosine deaminase. Both azepinomycin and cofomycin are viewed as transition-state analogue inhibitors of the respective enzyme-catalyzed hydrolysis of guanine and adenosine into xanthine and inosine. In order to design better transition state analogue inhibitors of the guanase-catalyzed reaction, we considered placing geminal hydroxyl/amino functionalities at the quaternary carbon where the hydrolysis takes place. We present herein our synthetic efforts to access such compounds employing diaminomalonates as useful synthons.



MEDI 452

Addition of arginine to pyropheophorbide-a

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To enhance the effectiveness of photosensitizers in photodynamic therapy (PDT) treatments of cancer, the water solubility, absorbance in the red region of the electromagnetic spectrum, and uptake in mitochondria of cancer cells to cause cell death by apoptosis must be enhanced. To this end, an arginine-substituted derivative of pheophorbide-a was synthesized. This target compound was prepared using a peptide coupling reaction, in which tert-butyloxycarbonyl (boc)-protected L-arginine was reacted with pyropheophorbide-a. The reaction was monitored by TLC to determine if the starting material completely reacted. The boc-protected compound was purified and characterized by ^1H NMR and UV visible spectroscopy revealing an absorption band of high intensity at 666 nm. The boc group was removed by refluxing the protected pigment in HCl dioxane. The UV/Vis spectrum of the deprotected photodrug shows an unshifted Q-band at 666 nm. It incubated in LNCaP cancer cells, thereby revealing properties for an improved photosensitizer.

MEDI 453

Repurposing compound collections for specific drug discovery approaches

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In the past, large collections of compounds have been gathered for high throughput screening and parallel synthesis. As new rules and methods for drug discovery have emerged – even beyond the Rule of 5 – many of these collections need to be revised, and a one-collection-fits-all approach seldom succeeds. We examined several compound collections with a variety of alternate and specialized approaches to drug discovery in mind (Drugs in other Drugs, Biologically Relevant Cores, CNS Active Compounds) while also avoiding known bad moieties (Rishton filters, frequent hitters, aggregators). From this study, we developed useful, automated methods to allow quick parsing of a large collection when looking for specific libraries of interest. We then generated a unique set of compound subsets that are more applicable to specific types of screening methods.

MEDI 454

Syntheses of 8-substituted xanthine adenosine receptor antagonists

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Dimethoxystyryl xanthine KW-6002, now commonly known as istradefylline, has recently been investigated as a target therapeutic in the treatment of Parkinson's disease. Based on the xanthine skeleton, this lead compound is one of many that act as an A_{2A} Adenosine receptor antagonist, and it has been shown to suppress the onset of clinical symptoms with co-administration of levodopa in phase I trials. (Bromodimethyl)sulfonium bromide-mediated coupling of 5,6-diaminouracils and carboxaldehydes was used to synthesize new analogues of the KW-6002 antagonist. This new synthetic process which produces good yields, is mild, efficient, and eliminates the need for external oxidants, will be presented as well as the preparation of several of the new analogues. The bromination of aryl substituted analogues in situ will be depicted as well as the synthesis of analogues which feature built in functionality for easy radio-labeling for use in PET and SPECT imaging.

MEDI 455

***trans*-2-Aminocyclohexanol-based lipids as pH-sensitive conformational switches for the PEG-grafted liposomes**

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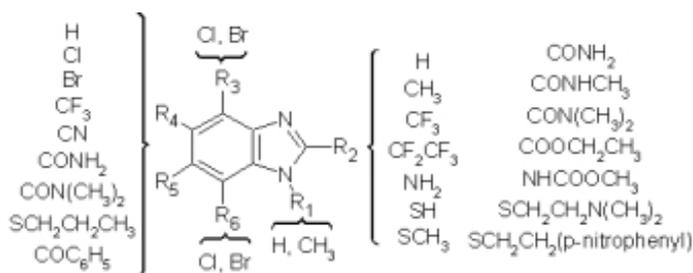
Recently we described a novel strategy to render pH-sensitive lipid amphiphiles and their colloids: a protonation-induced conformational change of the built-in *trans*-2-aminocyclohexanol moiety. In liposomes, this ring flip loosens packing of the attached lipid tails, leading to contents leakage. Herein we report our latest studies on the pH-sensitivity of various PEG-grafted (sterically hindered) liposomes comprising *trans*-2-aminocyclohexanol-based lipids. These liposomes are stable at pH 7.4 and yet release their content in a few seconds at pH 5.3-5.5.

MEDI 456

Comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) of some benzimidazole derivatives with trichomonocidal activity

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Mucosal infections caused by protozoan *Trichomonas vaginalis* add to more than 170 millions people. The symptoms in some women are principally inflammatory; also, it has been associated with preterm labor, low-birth weight, sterility, cervical cancer and predisposition to VIH infection. As part of our efforts to find new benzimidazole derivatives as antiparasitic agents, we have synthesized and tested these type of compounds as trichomonocides. With this information we constructed a data base of 68 active compounds to study the structure-activity relationships by CoMFA and CoMSIA methodologies.



General formula of benzimidazole derivatives and some substituents considered in this study

4 CoMFA models and 8 CoMSIA models were generated, 11 of them had values of $q^2 < 0.5$ and $r^2 < 0.6$. The models were generated using different types of charges (Mulliken, Gasteiger-Huckel and electrostatic potential atomic charges), conformations (minimum energy conformations and rapid overlay of chemical structures) and properties (steric, electrostatic, hydrophobic, hydrogen-bond

donor or acceptor); finally, all models were validated using a test set molecules. The contour maps generated show the most important features to design new benzimidazole derivatives with potential trichomonocidal activity.

MEDI 457

High-throughput, reduced-cost screening collection monitoring

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Through the use of parallel synthesis and aggressive compound acquisition programs, many corporate and academic screening collections have grown to hundreds of thousands or even millions of compounds. To ensure the reliability of the results of expensive high throughput biological assays, the purity of initial samples and integrity of stored compounds is of utmost importance. With such large collections, however, the time and cost of analyzing these collections can become prohibitive. To minimize the time and costs associated with reviewing these collections, we have carefully examined and optimized all aspects of our high throughput LCMS methods. Points considered include column selection, guard column usage, solvent selection (ACN vs. MeOH), ramp rate, overall run time and sample type. These efforts have resulted in dramatic cost saving while also allowing rapid sample analysis – including 1.5 minute run times without the use of UPLC.

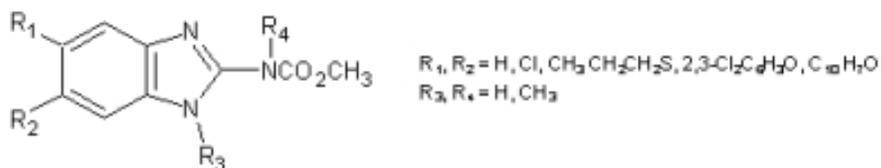
MEDI 458

Synthesis and antiparasitic activity of methyl (*N*-methyl-1*H*-benzimidazol-2-yl) carbamate derivatives

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In addition to the anthelmintic activity of the benzimidazole 2-carbamates, it has been found that this type of compounds also have antiprotozoal activity. In order to have more information about the structural requirements for the antiparasitic activity (antiprotozoal and anthelmintic), during the last decade we have been working on the synthesis of 1*H*-benzimidazole derivatives of the general formula shown below. Most of the compounds have been synthesized already in our laboratory and tested in vitro against the protozoa *Giardia intestinalis*, *Trichomonas vaginalis*, *Entamoeba histolytica* and the helminth *Trichinella spiralis*. We now present the synthesis and antiparasitic activity of the last series, the methyl (*N*-methyl-1*H*-benzimidazol-2-yl)carbamate derivatives. Our

presentation will focus on the synthesis of this series, the in vitro evaluation against the above parasites, and the in vivo activity against *T. spiralis*.



MEDI 459

Employing a multidetector approach in flash chromatography improves purity in target submissions

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During synthetic transformations, chemists continuously monitor their reactions using TLC spotting and manual UV detection as indicators of reaction completion. Complementary detection represents mass balance better than UV alone, giving the chemist more confidence about the relative amounts of the target compound being synthesized, unreacting starting materials, and reaction by-products being collected. UV detection alone provides the false or misleading impression of reaction component masses. Multiple signals are detected and monitored to trigger collection of crude mixtures. The results will show greater information about the crude mixture including relative amounts of target product and impurity levels by comparing the relative peak size. Uncertainty in final target compound purities can be minimized using the multiple detector approach. The data will show that maximum sample recoveries are possible with this technique compared to traditional UV-directed approaches. Finally, more universal detection and better fractionation result in improved mass purity and reduced contaminant concerns in post submission testing.

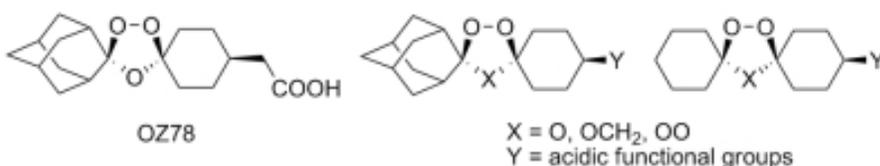
MEDI 460

Activity of dispiro synthetic peroxides against *Fasciola hepatica*

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The liver flukes *Fasciola hepatica* and *F. gigantica* are pathogenic trematodes infecting an estimated 2.4-17 million people. Evidence of drug-resistance to triclabendazole, currently the sole drug used to treat human fascioliasis, provides an impetus for the discovery and development of new drugs against fascioliasis. Although the artemisinins are best known for their powerful antimalarial properties, it is not surprising that they and other peroxidic compounds possess

both antiplasmodial and trematocidal activities, since both plasmodia and several trematodes including *Fasciola* spp. degrade hemoglobin to generate free heme, a possible target for bioactive peroxides. We report an investigation of 1,2,4-trioxolane, 1,2,4-trioxane, and 1,2,4,5-tetraoxane derivatives of OZ78 in an effort to identify more effective trematocidal synthetic peroxides. The only trioxolane with efficacy equal to OZ78 was an acyl sulfonamide derivative, although partial cures were obtained for four carboxylic acid and ester analogs and for the glycine conjugate. The position of the carboxylic acid functional group in OZ78 seems to be optimal since removing or extending the connecting alkyl link reduced efficacy. Substituting the spiroadamantyl substructure of OZ78 with a spirocyclohexyl completely abolished activity. The 1,2,4-trioxane and 1,2,4,5-tetraoxane isosteres of OZ78 had better efficacy than OZ78.



MEDI 461

Best in class DHODH inhibitors: Evolution of clinical compounds

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Inhibitors of the enzyme dihydroorotate dehydrogenase (DHODH) show clinically relevant beneficial immunosuppressant and antiproliferative effects in human diseases that are characterized by abnormal and uncontrollable cell proliferation causing chronic inflammation and tissue destruction. DHODH catalyzes the fourth step in the *de novo* biosynthetic pathway to pyrimidine bases, namely the conversion of dihydroorotate to orotate, with concomitant transfer of an electron to ubiquinone (cofactor Q) *via* a flavin mononucleotide intermediate. Mammalian cells have an additional pathway to pyrimidines (salvage pathway). During homeostatic proliferation, the salvage pathway, which is independent of DHODH, is sufficient for the cellular supply of pyrimidines. Only cells with a high turnover, and particularly T and B lymphocytes, need the *de novo* pathway to proliferate. In these cells, DHODH inhibition stops cell cycle progression by suppressing DNA synthesis and consequently cell proliferation. The pro-drug Leflunomide, sold under the trade name Arava, was the first DHODH inhibitor to reach the market place for the treatment of rheumatoid arthritis and psoriatic arthritis. Moreover, teriflunomide, its active metabolite has shown efficacy in multiple sclerosis and is currently in Phase III clinical trials. Herein we describe the discovery and structural biology guided evolution of a totally novel family of DHODH inhibitors - **amino(iso)nicotinic acid derivatives**, a structural class of potent, orally

bioavailable DHODH inhibitors that avoids known structural alerts and has an impressive safety/efficacy profile. The lead optimization exercise shown has led to the identification of compounds suitable for clinical development.

MEDI 462

Collaborative drug discovery tuberculosis database (CDDTB) and 1D, 2D and 3D computational model development

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Collaborative Drug Discovery hosts a widely used drug discovery data cloud platform that supports a global tuberculosis researcher community, as well as commercial researchers in private groups. The search for molecules with activity against Mycobacterium tuberculosis (Mtb) is employing many approaches in parallel including high throughput screening and computational methods. We have developed a database (CDD TB) to capture public and private Mtb data while enabling data mining and collaborations with other researchers. We have also applied several cheminformatics approaches to datasets from the CDD TB to describe active and inactive compounds. We have compared these datasets to those for known FDA approved drugs and between Mtb active and inactive compounds. The distribution of polar surface area and pKa of active compounds was found to be a statistically significant determinant of activity against Mtb. Bayesian classification models for 220,463 molecules were generated and tested with external molecules, and enabled the discrimination of active or inactive substructures from other datasets in the CDD TB. Computational pharmacophores based on known Mtb drugs were able to map to and retrieve a small subset of some of the Mtb datasets, including a high percentage of Mtb actives. The combination of the database, dataset analysis, Bayesian and pharmacophore models provides new insights into molecular properties and features that are determinants of activity in whole cells. This study provides novel insights into the key 1D molecular descriptors, 2D chemical substructures and 3D pharmacophores related to Mtb activity. We illustrate how we can mine the chemistry space using these different models, prioritizing those molecules with a higher probability of activity against Mtb and proteins.

MEDI 463

One pot synthesis of tertiary carbinamines

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High throughput synthetic methodologies including the synthesis of tertiary carbinol esters and the three-component one-pot synthesis of tertiary

carbinamines will be presented. Sequential addition of a carbon nucleophile into a nitrile, silylation of the resultant imine anion followed by addition of a second carbon nucleophile to yield a tertiary carbinamine will be discussed. The scope and limitations of this methodology will also be presented. These methodologies gave efficient access to numerous analogs to understand SAR around tertiary carbinamine chemotype.

MEDI 464

Cruzain inhibitory activity of chalcones and hydrazones

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Human parasitic diseases are the foremost threat to human health and welfare around the world. American trypanosomiasis, or Chagas' disease, is a neglected disease against which the efficacy of currently available drugs ranges from limited to none. Thus, there is an urgent need for new chemotherapeutic agents. Cruzain is the major cysteine protease of *Trypanosoma cruzi*. This enzyme is relevant to a key biochemical path of the parasite's life-cycle and also to the parasite-host relationship. In this context, cruzain is an attractive target for antitrypanosomal chemotherapy. We tested 20 compounds (9 chalcones and 11 aryl hydrazones) as potential cruzain inhibitors. All derivatives tested were active with 50% inhibitory concentration (IC₅₀) between 3.38 ± 0.35 and 12.78 ± 3.8 mmol. The compound 4-methyl-*N*'-(5-nitrothiophen-2-yl)methylene)benzohydrazide showed to be the most active of the series. The structural scaffold of the molecules studied herein suggests a good starting point for the design of new potent inhibitors against cruzain.

MEDI 465

Acceleration in lead generation and optimization by parallel investigation of target biology and pharmacokinetic properties

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Two case studies focused on the discovery and optimization of novel Sphingosine phosphate receptor subtype-1 (S1P1) agonists and optimization of Hepatitis-C viral polymerase inhibitors will be presented. In the first case, scaffold-hopping followed by rapid fire optimization of potency and pharmacokinetic criteria led to identification of potent pre-clinical leads with oral bioavailability and *in vivo* efficacy in less than one year. Against HCV

polymerase, an HTS hit with micromolar potency and very poor PK was optimized to three leads worthy of clinical development in 2-years time.

MEDI 466

Pyridinium derivatives as modulators of carbonic anhydrase activity

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The zinc enzyme carbonic anhydrase catalyzes the reversible hydration of carbon dioxide to yield a bicarbonate ion and a proton. Through its isozymes, carbonic anhydrase is involved in respiration and CO₂ transport between the metabolizing tissues and the lungs, pH and carbon dioxide homeostasis, electrolyte secretion, etc. Its inhibitors were exploited for more than five decades in the treatment of edema, glaucoma, obesity, cancer, epilepsy and osteoporosis, while its activators were recently shown to enhance synaptic efficiency, memory and spatial learning. An overview of the use of pyridinium moiety in the design of isozyme selective inhibitors and activators will be presented, emphasizing the structure-activity relationship correlations observed in each case.

MEDI 467

Probing the phosphopeptide binding site on BRCT(BRCA1): A peptidomimetic approach

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The carboxy terminus domains of BRCA1 (BRCT) plays an important role in several cellular functions that include, DNA repair, checkpoint regulation and lipogenesis. It is well known that BRCT(BRCA1) domains bind proteins through the pSXXF consensus recognition sequence. We recently showed that the tetrapeptide pSPTF binds BRCT(BRCA1) with low micromolar affinity. We have conducted extensive structure-function studies on the tetrapeptide and have defined a pharmacophore. Also we have identified a peptide with nanomolar affinity that inhibits BRCT(BRCA1) in a target and mechanism specific manner.

MEDI 468

Linear enediyne bioconjugates as photo-activated cytotoxins

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The enediyne family of naturally occurring antitumor agents continue to stimulate new areas of medicinal chemistry research. Mylotarg[®] (a monoclonal antibody

conjugate of calicheamicin) is now used clinically for the treatment of acute myeloid leukemia, represents the first FDA approved Mab-cytotoxin conjugate. Our program has focused on synthetic enediynes, most recently on applications of photo-activated variants of the Bergman cycloaromatization. An over-arching goal is to apply nanoparticle targeting techniques in order improve the specificity of photo-activated enediyne conjugates. Accordingly, a number of enediyne prodrugs were coupled to select antibodies using heterobifunctional PEG linkers, and the synthetic methodology expanded to include surface modified Au nanoparticles. The affinity ligands retain immunocompetence and undergo photo-activation on demand. Second generation agents with improved transport properties and variants incorporating functionality to allow functional imaging will also be presented.

MEDI 469

Structure-activity relationships of sulfonamide- and ester-based inhibitors of plasminogen activator inhibitor-1

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Plasminogen activator inhibitor-1 (PAI-1) is an endogenous serine protease inhibitor, pathologic levels of which have been implicated in a variety of conditions, including myocardial infarction, cancer, atherosclerosis, and type 2 diabetes. The development of potent and selective inhibitors of PAI-1 has therefore become a priority. A variety of polyphenolic compounds based on sulfonamide and ester linking units have been synthesized and found to be potent and selective inhibitors of PAI-1. The synthesis and structure-activity relationships of these compounds with PAI-1 and related mammalian serpins will be discussed.

MEDI 470

5, 6-Dimethyl-seco-Himbacine analogs as potent Thrombin receptor antagonists

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The Thrombin receptor plays important roles in platelet aggregation and vascular smooth muscle cell proliferation. Thrombin receptor antagonists have the

potential to treat various cardiovascular disorders such as thrombosis, restenosis and atherosclerosis with a low probability of bleeding as a side effect. The 5, 6-dimethyl seco-Himbacine analogs were explored in order to find a receptor antagonist possessing good activity, without the enzyme induction, poor clearance and hERG activity of some previous Himbacine derived analogs. The following discussion will focus on substitution at the lactone carbonyl and changes to the phenyl ring.

MEDI 471

QM/MM study of the interaction between thrombin and its protein inhibitors

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Thrombin is a human protein converting fibrinogen into fibrin, which can lead to strokes and heart attacks. It has been discovered that a meta-chloro benzyl side chain of a protein inhibitor (ligand), is responsible for high binding affinity in the thrombin S1 pocket. We have calculated the interaction energy between the ligand and the protein for a series of the most reported potent thrombin inhibitors, which consisted of a meta halogen (X), as well as a second halogen at the ortho position (Y). The calculations have been performed using a large-scale quantum-mechanical molecular-mechanical (QM/MM) approach, which is based on a long molecular dynamics (MD) followed by a series of individual QM/MM calculations, randomly selected from a MD trajectory. The MD simulations have been performed for the protein with the ligand in a TIP3P water sphere of a radius 50Å, for 10ns at constant temperature and volume using AMBER program. The similar MD has been performed for the ligand alone in TIP3P water solution for 5ns. After MD, 600 protein structures have been randomly selected and for each protein snapshot, geometry of the ligand has been QM optimized in the fixed MM protein matrix using Q-Chem program. The similar QM/MM calculations have been performed for the ligand alone in water solution. The interaction energy was calculated as an energy difference between an average energy of the ligand in the protein and an average energy of the ligand in water. The overall correlation was observed in our study between the calculated interaction energy and the measured ITC enthalpy of binding for the selected thrombin inhibitors. The unusual binding affinity of the meta-chloro ligand is explained in our study by its small desolvation energy.

MEDI 472

SAR studies of chroman-3-amides as potent, selective inhibitors of Rho kinase

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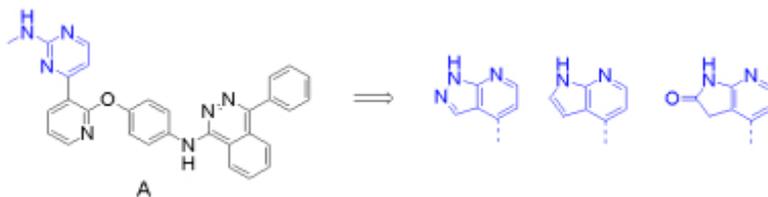
Rho kinase (ROCK) is an important regulator of cytoskeletal reorganization and smooth muscle contraction. Various studies have shown that inhibition of ROCK may serve as a viable method to treat diseases such as cerebral vasospasm, hypertension, and glaucoma. Recently, we reported SR3850 (N-(2-(2-(dimethylamino)ethoxy)-4-(1H-pyrazol-4-yl)phenyl)-6-methoxychroman-3-carboxamide) as an effective ROCK inhibitor which demonstrates excellent potency in a cell-based myosin light chain *bis*-phosphorylation (ppMLC) assay and blood pressure reducing effects in a rat model of hypertension. Herein, we present the enantioselective preparation of SR3850, their biological effects, and an extensive optimization study to enhance selectivity against MRCK, a closely related kinase, and also to improve DMPK properties.

MEDI 473

Phthalazine based inhibitors of Aurora A/B kinase: Variations at the hinge-binding motif

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We recently disclosed a series of highly potent, selective and orally bioavailable methylaminopyrimidine phthalazine-based Aurora A/B kinase inhibitors (e.g., compound A). Herein, we present three new hinge-binding motifs, 7-azaindazole, 7-azaindole, and 7-azaoxindole. The synthesis, structure-activity relationships, and pharmacokinetic properties of these new phthalazine-based dual Aurora A/B kinase inhibitors are described.

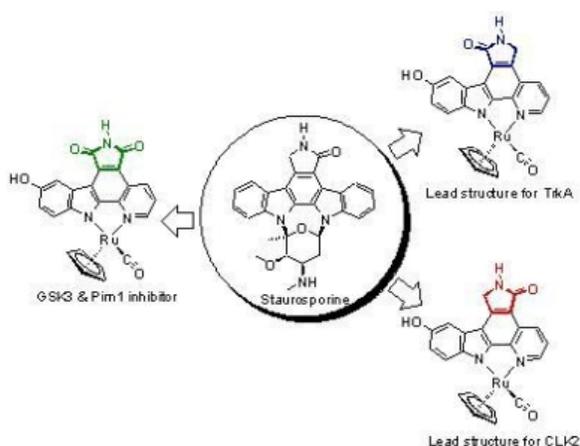


MEDI 474

From imide to lactam metallo-pyridocarbazoles: Distinct scaffolds for the design of selective protein kinase inhibitors

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Organometallic pyridocarbazole scaffolds are investigated as protein kinase inhibitors. Whereas our previous designs employed solely a maleimide pharmacophore for achieving the two crucial canonical hydrogen bonds to the hinge region of the ATP binding site, we have now extended our investigations to include the related lactam metallo-pyridocarbazoles.



The synthetic access of the two regioisomeric lactam pyridocarbazoles is described and the distinct biological properties of the two lactam scaffolds are revealed by employing a ruthenium half sandwich complex as a model system, resulting in organometallic lead structures for the inhibition of the protein kinases TrkA and CLK2. These new lactam metallo-pyridocarbazoles expand our existing molecular toolbox and assist towards the generation of metal complex scaffolds as lead structures for the design of selective inhibitors for numerous kinases of the human kinome.

MEDI 475

Discovery of LIM kinase-1 inhibitors

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LIM kinase-1 (LIMK1) is a downstream effector of Rho kinases and controls actin dynamics by phosphorylating members of the cofilin protein family. The actin depolymerizing function of cofilin is inactivated upon phosphorylation, which results in stabilization of actin filaments and aggregates. While the role of LIMK1 in the regulation of cytoskeletal structure is important for numerous cellular functions, overexpression of LIMK1 is observed in malignant prostate and breast cancer cell lines, and increased LIMK1 activity has been shown to promote metastatic properties of human breast and prostate cancer cells. Despite the therapeutic potential of LIMK1, there are few reports of small molecule inhibitors in the literature. In this presentation, we describe the development of aryl sulfonamides as LIMK1 inhibitors. Optimization methods by traditional medicinal chemistry and rational design resulted in the identification of compounds with enzyme potency in the low nanomolar range.

MEDI 476

Exploring binding modes of small drug-like molecules to the polo-box domain of human polo-like kinase 1

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Purpurogallin (PPG) and Poloxin were reported as inhibitors of the polo-box domain (PBD) of human polo-like kinase 1 (Plk1). However, our ELISA competition assay indicated only PPG could bind to the phospho-binding pocket of the PBD. Induced fit docking results suggest that PPG may likely fill the SpT pocket by forming five hydrogen bonds and a p-p stacking interaction, thus providing a rationale for designing PBD inhibitors. In contrast, Poloxin may fill another site by forming a covalent bond with a cysteine residue.

MEDI 477

Fragment based drug design approach for the identification and optimization of potent inhibitors of 5'-AMP-activated protein kinase, AMPK

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We have previously reported that 5'-monophosphate-activated protein kinase (AMPK) has a functional role in many solid tumors. We successfully designed inhibitors of AMPK using ImagiroTM protein modeling and the fragment-based drug design (FBDD) software, CharretteTM. We prioritized the compounds for synthesis based on their calculated binding affinities and their ADME properties. The analoging was achieved *via* a 2 steps synthesis in good yield. After S_N2 type

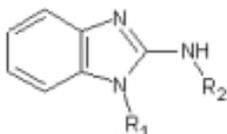
reaction to put in place the solubilizing group, the final analogs were prepared via a Suzuki cross-coupling. The synthesis of a small set of compounds (17) led to the discovery of potent inhibitors of AMPK. In particular five compounds were more potent than reported dorsomorphin at 200 nM. We also broadened our chemical series from the pyrazolopyrimidine core of dorsomorphin to 2 new chemical series, the 2,5-pyridine series and 2-aminooxazole series. The synthesis of the 2,5-pyridine series was achieved *via* an S_NAr type reaction, followed by a Suzuki coupling. The 2-aminooxazole scaffold was built through an intermolecular cyclization of an isothiocyanate and an acyl azide in good to moderate yields.

MEDI 478

Docking study of benzimidazole derivatives and pyruvate kinase of *Leishmania spp*

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Leishmaniasis is a parasitic infection caused by the protozoan *Leishmania spp.* It mainly affects the population of the third world with high morbidity and mortality indexes. The WHO considers this infection among the most important neglected diseases. Therapy for the control of this infection with antimony compounds have severe side effects and in some cases resistance by the parasite have been reported. Therefore, the search for new therapeutic agents is of the utmost importance. As part of our research interest to have information about the structural requirements of benzimidazole derivatives for antiparasitic activity, a docking study using the pyruvate kinase enzyme of *Leishmania mexicana* as potential target was carried out to find new compounds against this kind of infection. From this study the compounds in the table below were found to bind preferently to the catalytic site of the enzyme. These compounds will be synthesized and tested in vitro against *L. mexicana* to validate the model.



Compound	R ₁	R ₂	ΔG (Kcal/mol) <i>L. mexicana</i>	ΔG (Kcal/mol) <i>H. sapiens</i>
1	2,5-Dimethylbenzyl	Ethyl	-5.92	-4.77
2	2-(1-Piperidinyl)ethyl	2,5-Dimethoxybenzyl	-6.74	-4.15
3	Ethyl	3,4,5-Trimethoxybenzyl	-5.81	-4.49
4	1-Butyl	2-Hidroxy-5-methylbenzyl	-5.79	-4.72
5	<i>N,N</i> -Diethylaminomethyl	1-Naphthylmethyl	-6.27	-5.08
6	Benzyl	3,4-Dimethoxybenzyl	-5.93	-4.76

MEDI 479

Design and synthesis discussion of compound 1, a triazolopyrazine, as an exquisitely selective and potent inhibitor of c-Met receptor tyrosine kinase

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c-Met is a protooncogene that encodes for a protein MET (mesenchymal-epithelial transition factor), a membrane receptor tyrosine kinase. Met receptor kinase is activated by the binding of heparocyte growth factor (HGF). Upon this activation, Met induces several cellular responses including cell proliferation, migration, and survival, all important in the normal development and wound healing. Abnormal Met activation in cancer cell correlates with poor prognosis. High level of cMet expression was found in many cancer cell types i.e. renal cell carcinoma and gastronomas, etc. There are several compounds currently in clinical trials inhibiting c-Met. 6-[1,2,4]Triazolo[4,3-b][1,2,4]triazin-3-ylmethyl-quinoline has been identified as a class of potent and exquisitely selective c-Met inhibitors at Pfizer. However, this class of compounds is susceptible for metabolism. Compound 1 2-(4-(3-((7-fluoroquinolin-6-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyrazin-5-yl)-1H-pyrazol-1-yl)ethanol was identified during the lead optimization process by using structure base drug design. It demonstrated low nM potency against cMet in both the *in vitro* cell assay and *in vivo* target modulation studies, good PK/PD properties, and negative in Ames & micronucleus assay. This poster presented the total synthesis of this compound, an exquisitely potent and selective inhibitor of cmet.

MEDI 480

Characterization of both allosteric and ATP-competitive kinase inhibitors with TR-FRET binding assays

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Kinase activity assays are cost-effective and widely used to drive early drug discovery and lead identification. However, activity-based assays have limitations both in terms of the extent of target coverage and the type of information they can provide about test compounds. We have developed a competitive TR-FRET binding assay platform based on Alexa Fluor® 647 conjugated to kinase inhibitor scaffolds for characterization of protein kinase inhibitors. This platform has advantages over traditional activity-based assays by eliminating the need for substrate or an activated kinase preparation, the ability to measure binding events in real-time, and overall simplicity of the assay. Binding of the conjugate to a kinase is detected by addition of a europium-labeled anti-tag antibody, which binds specifically to the kinase. Binding of both the tracer and antibody to a

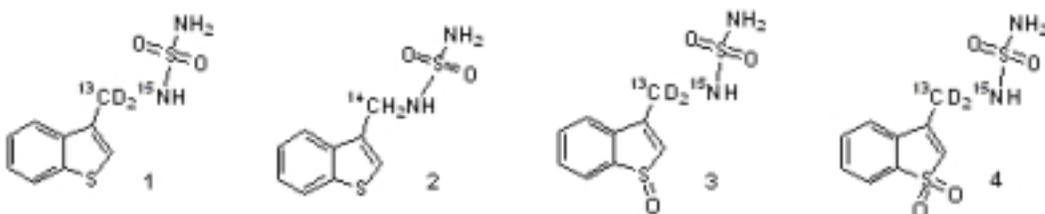
kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET. This assay has been validated for more than 200 kinases using both Type I and Type II inhibitors. The ability of this assay format to detect “allosteric” kinase inhibitors has been examined and, although these compounds have been described as non-competitive or un-competitive with respect to ATP, the clear majority are detected in this assay format, indicating that the binding sites are either close to the ATP site or that they elicit a conformation change impacting the ATP site. Thus, in addition to measuring Type I and Type II kinase inhibitors, this assay format is able to detect and provide mechanistic insight into many allosteric kinase inhibitors.

MEDI 481

Expedient syntheses of isotopically labeled anticonvulsant agent *N*-(benzo[*b*]thien-3-ylmethyl)-sulfamide (JNJ-26990990) and its metabolites

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Syntheses of stable and radioactive isotopically labeled anticonvulsant agent *N*-(benzo[*b*]thien-3-ylmethyl)-sulfamide (JNJ-26990990) and its metabolites (**1-4**) are described. [$^{13}\text{C}^{15}\text{N}$]Benzo[*b*]thiophene-3-carbonitrile was first prepared by coupling of 3-bromo-benzo[*b*]thiophene with [$^{13}\text{C}^{15}\text{N}$]-copper (I) cyanide. The resultant [$^{13}\text{C}^{15}\text{N}$]benzo[*b*]thiophene-3-carbonitrile was reduced with lithium aluminum deuteride to give [$^{13}\text{CD}_2^{15}\text{N}$]benzo[*b*]thiophen-3-yl-methylamine; which was then coupled with sulfamide to afford [$^{13}\text{CD}_2^{15}\text{N}$]-*N*-(benzo[*b*]thien-3-ylmethyl)-sulfamide, the stable-isotope labeled compound with four stable isotope atoms. Direct oxidation of [$^{13}\text{CD}_2^{15}\text{N}$]-*N*-(benzo[*b*]thien-3-ylmethyl)-sulfamide with hydrogen peroxide and peracetic acid gave the stable isotope labeled sulfoxide and sulfone metabolites. Synthesis of ^{14}C -radiolabeled *N*-(benzo[*b*]thien-3-ylmethyl)-sulfamide was prepared conveniently by sequential coupling of 3-bromo-benzo[*b*]thiophene with [^{14}C]copper(I) cyanide, reduction of the resulting nitrile to carboxaldehyde, and reductive amination with sulfamide.



MEDI 482

Phosphonoglutamate analogs: Synthesis and in vitro pharmacological evaluation at select glutamate transporters

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The metabotropic glutamate receptors (mGluRs) are a family of G-protein coupled receptors that are expressed in the central and peripheral nervous systems. (L)-2-Amino-4-phosphonobutyric acid (AP4), a phosphonic acid isostere of glutamate, has been found to be a specific agonist of the group III mGluRs in cells expressing mGluR4a and mGluR8a but is largely inactive at group I and group II mGluRs. Recently, we began to develop substituted analogs of AP4 to test pharmacologic differences among the glutamate transporters, particularly the excitatory amino acid transporters (EAATs), the vesicular glutamate transporter (VGLUT), and system X_c⁻. In this work, a series of γ -substituted AP4 analogs were synthesized and evaluated for their activity against different glutamate transporters. This work will present our synthetic strategies, in vitro data showing the pharmacology of the AP4 analogs to act as glutamate transport inhibitors, and an example of pharmacologic differences among a set of AP4 enantiomers.

MEDI 483

Tricyclic 3,4-dihydropyrimidine-2-thione derivatives as potent TRPA1 antagonists

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The Transient Receptor Potential A1 (TRPA1, formerly named ANKTM1) channel is a polynodal nociceptor of various noxious stimuli including pungent chemicals such as allylisothiocyanate present in mustard oil, thiosulfinates present in garlic, cinnamaldehyde, and tear gases. Antagonists of the TRPA1 receptor could find possible therapeutic use as antinociceptive agents or be used as protective agents against irritant chemicals and tear gases. In a high throughput screen aimed at the identification of TRPA1 antagonists, 4-phenyl-2-thioxo-1,2,3,4-tetrahydro-indeno[1,2-d]pyrimidin-5-one was identified as a potent TRPA1 receptor antagonist. A series of analogues has been prepared via the multi-component Biginelli reaction and subsequent derivatization. Using a screening assay with benzylisothiocyanate as agonist, tricyclic 3,4-dihydropyrimidine-2-thiones were discovered with potencies up to 10nM for both rat and human derived TRPA1 receptors. In comparison, analogous 3,4-dihydropyrimidines without annulation on the dihydropyrimidine 5,6-double bond, which have been claimed as TRPA1 antagonists in WO-2007/073505, were ~;500 fold less active

in the same assay. In addition, the activity was shown to reside exclusively in the 4*R*-enantiomers.

MEDI 484

Novel bispidine derivatives: Synthesis and structure-affinity relationships for nicotinic acetylcholine receptors (nAChRs)

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Cytisine is an invaluable template in the development of bioactive compounds. Particularly its bispidine framework has been used as a core structure for the synthesis of ligands for numerous biological targets including nAChRs. It is accessible by double Mannich reaction from *N*-*t*Boc-piperidone, formaldehyde and benzylamine and subsequent reduction of the carbonyl group yielding *N*-benzyl-*N'*-*t*Boc-bispidine. After cleavage of the benzyl protective group *N*-*t*Boc-bispidine served as a starting material for the synthesis of diverse bispidine analogs including amides, sulfonamides and urea derivatives. The obtained bispidine derivatives were tested for their affinities for different nAChR subtypes by competition assays with [³H]epibatidine ($\alpha 4\beta 2^*$, $\alpha 3\beta 4^*$ and muscle type) and [³H]methyllycaconitine ($\alpha 7^*$), respectively, using membrane fractions of native tissues (rat brain, calf/pig adrenals and *Torpedo californica* electroplax). Most compounds showed subtype selectivity for $\alpha 4\beta 2^*$. A broad spectrum of affinity (e.g. *K_i* values from 1.2 nM to > 10,000 nM for $\alpha 4\beta 2$) provided important insights into structure-affinity relationships.

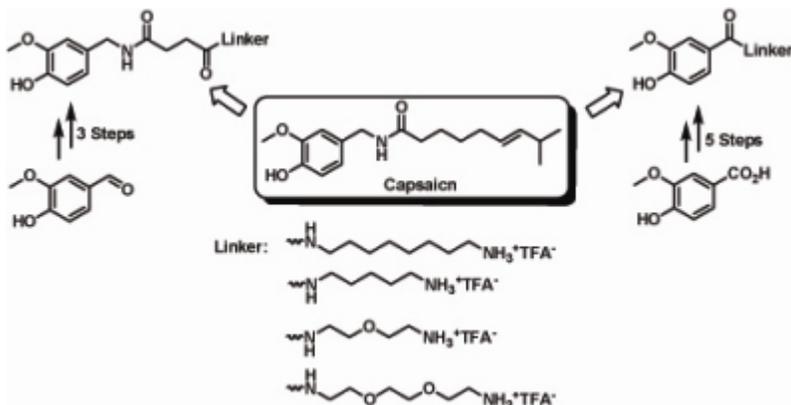
MEDI 485

Synthesis and biological properties of capsaicin-like compounds functionalized with tethers suitable for coating applications.

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Capsaicinoids are an effective chemical defense produced by chili pepper plants against herbivores and have acceptable toxicity towards marine life in aquatic systems. The purpose of this study was tethering these compounds to a solid support and comparing them with the biological properties of the non-tethered species. The goal of constructing a solid support containing compounds with relative low toxicity demonstrates an eco-friendly approach towards marine

coatings. Two strategies were employed producing gram quantities of compounds for attachment to various surfaces.



MEDI 486

$\alpha 6$ nAChR Benzazepine derivatives as psychotherapeutics

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The discovery of nicotinic acetylcholine receptor (nAChR) partial agonists for smoking cessation focused on the development of $\alpha 4\beta 2$ selective compounds, many of the compounds in this effort derived from efforts in the Bicyclic Aryl Piperidine (BAP, or benzazepine) structural class. Further studies revealed that some compounds within this class of derivatives exhibit activity at the alpha 6 nAChR subtype. Alpha 6, the " $\alpha 6$ " nAChR, presumably exists as a heteropentamer containing $\alpha 6\alpha 4\beta 3\beta 2$ subunits, and possibly others, has been shown to mediate norepinephrine (NE) in central catecholaminergic neurons of the prefrontal cortex and other brain areas. We describe here continued investigations of structures that probe the relationships within this type of ring architecture within the BAP structural framework and their activity in neurochemical and behavioral models relevant to antipsychotic treatment paradigms.

MEDI 487

Synthesis and pharmacological evaluation of azetidine and pyrrolidine derivatives as dual norepinephrine reuptake inhibitors and 5-HT_{1A} partial agonists

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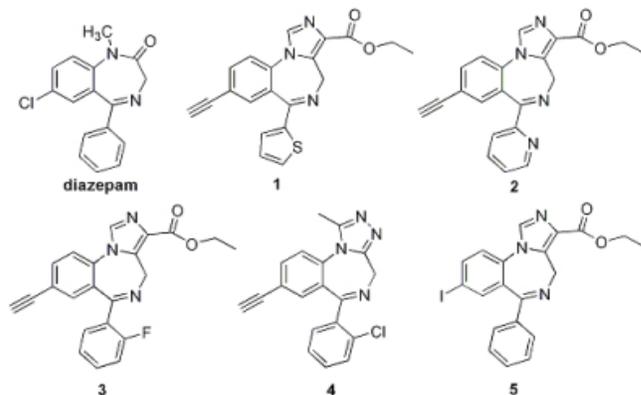
Data from preclinical studies indicate that compounds with combined norepinephrine reuptake inhibitor (NRI) and 5-HT_{1A} partial agonist pharmacology may be useful for treating symptoms of neuropsychiatric disease including depression, anxiety and ADHD. A novel chemical series was discovered that exhibited promising dual NRI and 5-HT_{1A} partial agonist activity in vitro, as well as in vivo efficacy in preclinical disease models. Select compounds from this series have good selectivity for the norepinephrine transporter over the dopamine and serotonin transporters. The synthetic strategy which enabled development of in-vitro SAR along with relevant in vivo pharmacology for key compounds will be discussed.

MEDI 488

Novel non-sedative agents to treat epilepsy: Benzodiazepine-related ligands that do not develop tolerance

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The antiseizure activity of benzodiazepines (BDZs) **1-5** in mice and rats as animal models is described. These BDZs have selective efficacy for $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$ GABA_A-receptors. Significant anticonvulsant activity with little or no motor impairment and therapeutic indexes (TI) of 2.8-44 (mice, ip) were observed for compounds **2-4** in the subcutaneous metrazole seizure (scMET) test. In rats orally (po) the TI was >5 to 105. These compounds represent novel leads in the search for anticonvulsants devoid of sedative, ataxic and amnestic side effects.



MEDI 489

¹¹¹In-labeled Deltorphan II targeting the δ -opioid receptor for SPECT imaging

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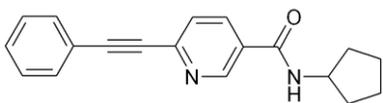
Development of selective radioligands targeted to opioid receptor is an active area of research for studying the cell receptor-ligand interactions. Targeted *in vivo* SPECT imaging provides insight into clinical trials and enables better understanding of these interactions. Our studies are focused on the opioid receptor which plays a role in a variety of cancers, cardiovascular diseases, and gastrointestinal disorders. Recent research promises newer paradigms of opioid analgesia acting outside the central nervous system. With such recognition, we have started developing radioactive labels for opioid ligands and establishing solid-phase synthetic strategies. Here we present the synthesis of ¹¹¹In-DOTA linked Deltorphan II ligand for SPECT imaging. *In vitro* competitive binding of the ¹¹¹In-labeled Deltorphan II to HCT116 tumor cells expressing δ -opioid receptors (δ -OR) revealed that the ligand retains its activity after radiolabeling (IC₅₀ = 18 nM). *In vivo* SPECT imaging of HCT116/ δ -OR xenografts in mice will also be discussed.

MEDI 490

Allosteric modulators of the metabotropic glutamate 5 receptor (mGluR5)

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The metabotropic glutamate receptors (mGluRs) are class C GPCRs for which eight subtypes are known. They mediate the modulating effects of glutamate on neuronal function in the CNS. In particular, the mGluR5 subtype has attracted a lot of attention because it has been implicated in a number of psychiatric and neurological disorders, including anxiety, Parkinson's disease, and fragile X mental retardation and activation of this receptor has been postulated to ameliorate both positive symptoms and cognitive deficits in schizophrenia. We recently discovered a series of mGluR5 positive allosteric modulators and identified the lead compound **1**. Here, we describe expanded structure-activity relationships in this series.



1

MEDI 491

Pyrrolopiperidine NK1 receptor antagonists

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The NK₁ receptor is present in both the central and peripheral nervous systems. Substance P (SP) is the natural ligand for the NK₁ receptor. The binding of SP to the NK₁ receptor is associated with the transmission of stress signals and pain, contraction of smooth muscles and inflammation. It has been selected as a therapeutic target for the treatment of pain, chemotherapy-induced emesis, urinary incontinence and other disorders. Design, synthesis and biological data of a new class of potent NK₁ receptor antagonists with a pyrrolopiperidine core will be presented.

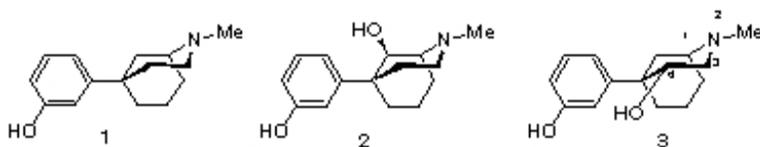
MEDI 492

Probes for narcotic receptor mediated phenomena: Synthesis and opioid receptor affinity of 4-hydroxyphenylmorphans

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In 1955, May and co-workers introduced 5-(3-hydroxyphenyl)-2-methylmorphan (1) as a novel, potent narcotic analgesic. Since then numerous pharmacologically interesting research tools based on 1 and derivatives have been described. For example, we have found that 1R,5R,9S-(-)-2 had subnanomolar affinity ($K_i = 0.19$ nM) for the mu-opioid receptor and was at least 500x more potent than morphine

as an antinociceptive. As part of our ongoing studies towards understanding opioid receptor mediated effects on a molecular level, a general approach to the synthesis of 3 and related 4-hydroxyphenylmorphans was undertaken. A detailed study on the synthesis of this molecule and the accompanying opioid receptor binding studies will be presented.



MEDI 493

Discovery and SAR of non-competitive antagonists of mGlu₅ with activity in rodent models of disease

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Glutamate is the major excitatory transmitter in the mammalian CNS, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlu_s) belong to family C of the G-protein-coupled receptors (GPCRs). The eight mGlu_s discovered to date have been further divided according to their structure, preferred signal transduction mechanisms, and pharmacology (Group I: mGlu₁ and mGlu₅; Group II: mGlu₂ and mGlu₃; Group III: mGlu₄, mGlu₆, mGlu₇, and mGlu₈). Whereas orthosteric ligands of mGlu_s bind in the amino-terminal domain of the receptor, known allosteric binding sites are located in the 7TM domain. Orthosteric ligands often suffer from poor selectivity among the mGlu_s due to a highly conserved binding site. The discovery of non-competitive antagonists, also known as negative allosteric modulators (NAMs), has offered a potential solution to such selectivity issues. We have been interested in the discovery of non-competitive antagonists of mGlu₅ from new chemical scaffolds. Potential therapeutic applications of mGlu₅ NAMs include pain, anxiety, gastroesophageal reflux disease (GERD), Parkinson's disease (PD), and fragile X syndrome. This report will detail our progress toward the identification of new mGlu₅ NAM chemical scaffolds and their SAR in our functional cell-based assay, which measures the ability of compounds to block the mobilization of calcium by an EC₈₀ concentration of glutamate in HEK293A cells expressing rat mGlu₅. The characterization of select

compounds in radioligand binding, selectivity, and additional *in-vitro* cell based assays will be presented. Profiling of compounds in both *in-vitro* and *in-vivo* DMPK assays will also be discussed. Finally, the activity of a few compounds in rodent behavioral models of disease will be described.

MEDI 494

Classification of drugs according to presence or absence of CNS activity based on mechanistic QSAR models of the rate and extent of brain delivery

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This study presents a simple classification scheme for *in silico* evaluation whether brain penetration of novel compounds is sufficient to exhibit central action. Classification is performed taking into account both kinetic and thermodynamic characteristics of drug transport across blood-brain barrier. The calculation procedure for the brain penetration rate expressed by permeability-surface area product ($\log PS$) was described previously (Lanevskij K, Japertas P, Didziapetris R, Petrauskas A. Ionization-specific prediction of blood-brain permeability. *J Pharm Sci.* 2009 Jan;98(1):122-34). The extent of brain penetration was represented by experimentally determined steady-state brain/blood distribution ratios ($\log BB$) for about 500 compounds collected from literature. These data were split into two terms corresponding to drug binding to plasma proteins and brain constituents – the two major processes that influence partitioning between brain and plasma under the assumption of passive diffusion-driven transport. Brain tissue binding affinity of drugs was then described by a nonlinear model in terms of key physicochemical determinants – octanol/water $\log P$ and pK_a . Prediction of CNS activity was performed on the basis of calculated $\log BB$ and supplementary parameter brain/plasma equilibration rate defined as $\log PS$ corrected for unbound fraction in brain. It was shown that a simple combination of the respective models allows correctly classifying more than 90% of drugs in the literature data set comprised of about 1600 diverse molecules with experimentally assigned CNS activity categories (CNS+/CNS-). Moreover, as demonstrated by several examples, the proposed classification scheme provides an insight on the onset and duration of action of central drugs.

MEDI 495

Identification of potent and selective 3-sulfonylindazole derivatives as 5-HT₆ antagonists

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Cognitive dysfunction is a characteristic of various forms of dementia such as Alzheimer's disease (AD) and a core feature of schizophrenia. Among the potential therapeutic targets for the development of cognitive enhancers for AD and schizophrenia, the 5-HT₆ receptor is of special interest based on its brain-exclusive localization and unique pharmacology. 5-HT₆ receptor antagonism enhances neurotransmission at cholinergic and glutamatergic neurons, as well as in other pathways. Studies have shown that 5-HT₆ receptor blockade improves cognition in a number of rodent behavioral models. More recently, evidence of cognitive efficacy has been reported from several 5-HT₆ antagonists undergoing phase 2 clinical trials for AD and schizophrenia. As part of our continuing efforts to develop agents for cognitive enhancement, we have been focused on the 5-HT₆ receptor in order to identify potent and selective ligands for this purpose. Herein we report the identification of a novel series of 3-sulfonylindazole derivatives as potent and selective 5-HT₆ antagonists. The synthesis and detailed SAR of this class of compounds are reported.

MEDI 496

Potent piperaziny lindazole derivatives as potent and selective 5-HT₆ ligands

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As part of our continuing efforts to identify therapeutics for CNS diseases, such as schizophrenia and Alzheimer's disease (AD), we have been focused on the 5-HT₆ receptor in an attempt to identify ligands as a potential treatment for cognitive dysfunction. Herein we report the identification of a novel series of piperaziny lindazole derivatives as potent and selective 5-HT₆ antagonists. The synthesis and SAR of this class of compounds are reported.

MEDI 497

Mechanism of action and pharmacokinetics of Sansalvamide A derivatives: Preparing them for mice models

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Sansalvamide A (San A) is a macrocyclic depsipeptide that has shown cytotoxicity against cancer cell lines. Over 100 derivatives of San A have been synthesized and using affinity purification assays, binding studies, and cell based

assays we have determined their mechanism of action. Our work describes the synthesis, affinity purification, target identification, and pharmacokinetic studies of several lead compounds. These studies include our compounds' solubility in a number of excipients: Tween 80, cremaphore EL, and DMSO. Studies were also run to determine our derivatives' stability in plasma, their cell permeability, and their clearance rate in hepatocytes. Upon collecting these data we determined which compound has the most promising profile to be tested in mice models.

MEDI 498

Design, synthesis, and evaluation of novel metabotropic glutamate receptor subtype-2 (mGluR2) positive allosteric modulators (PAMs): A fragment matrix approach to focused libraries of analogs

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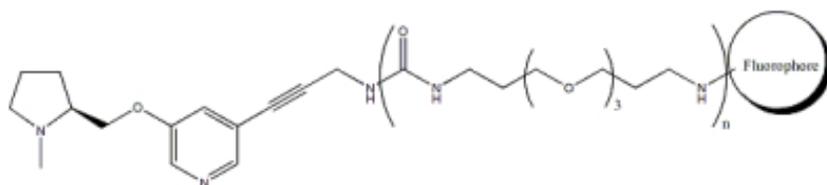
Group II metabotropic glutamate receptors (mGluR2 and mGluR3) are found both pre- and postsynaptically and couple to G_i and G_o-proteins to negatively regulate the activity of adenylyl cyclase. In particular, Group II mGluRs function as glutamate autoreceptors that modulate presynaptic glutamate release. Thus, modulation of Group II mGluRs by small molecules represents a promising approach for the treatment of diseases caused by aberrant glutamatergic transmission such as schizophrenia, anxiety or drug addiction. Our ongoing program is focused on the design, synthesis and *in vitro* and *in vivo* evaluation of small molecule modulators of Group II mGluRs. We identified several key fragments from a series of mGluR2 positive allosteric modulator (PAM) scaffolds and combined the fragments in a matrix approach to generate a focused library of new structures. In addition to selectivity testing against other mGluR subtypes, the most potent mGluR2 PAMs identified in this way were characterized in assays predictive of ADME/T and pharmacokinetic properties with the goal of identifying new mGluR2 PAMs with the potential to be systemically active *in vivo*. This presentation will provide an update on our progress towards new potent and selective, systemically active mGluR2 PAMs and their characterization in relevant tests, including rat models of cocaine dependence.

MEDI 499

Synthetic studies on fluorescent ligands for nicotinic receptors based on A-84543.

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Fluorescent ligands are of utility for the microscopic study of proteins and may serve as non-radioactive adjuncts for ligand binding assays for drug screening. Our interest in nicotinic acetylcholine receptors has led us to examine high potency derivatives of A-84543, a hybrid structural analog of nicotine and epibatidine. We report here our synthetic studies toward fluorescently labeled PEG-based homologs and preliminary labeling studies in cultured cells.



MEDI 500

Identification of novel pan-caspase irreversible inhibitors and their evaluation in Huntington's disease models

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Huntington's Disease (HD) is a dominantly inherited neurodegenerative disorder characterized by progressive deterioration of neurons in the striatum and cortex. HD is caused by a mutation in the Htt gene encoding glutamine repeats in the N-terminus of huntingtin (Htt). A neuropathological hallmark of HD in human and mouse models is the accumulation of N-terminal Htt fragments leading to cytotoxicity, suggesting that Htt proteolysis is a critical pathological event. The Substrate Activity Screening (SAS) method was utilized against caspases-3 and -6 and led to the identification of three novel, non-peptidic pan-caspase irreversible inhibitors that blocked proteolysis of Htt at caspase-3 and caspase-6 sites, suppressed Hdh^{111Q/111Q}-mediated toxicity, and rescued HttN90Q73-induced degeneration of rat striatal and cortical neurons.

MEDI 501

Discovery of a potent nicotinic acid receptor agonist for the treatment of dyslipidemia

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Nicotinic acid has been used to treat dyslipidemia and it has been known to lower very low-density lipoprotein (VLDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and lipoprotein (LP), and is also an effective drug to raise high-density lipoprotein (HDL)-cholesterol. However, nicotinic acid has shown a number of liabilities in clinical use. The most notable side effect is several cutaneous flushing sensation from patients' upper body and face, which sometime is unbearable. We discovered pyranopyrimidinedione series as potent nicotinic acid receptor agonist with better PK profile than nicotinic acid, but no flushing side effect. The synthesis and SAR of these compounds will be discussed in the presentation

MEDI 502

Discovery of *N*-[(4*R*)-6-(4-chlorophenyl)-7-(2,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-yl]-5-methyl-1*H*-pyrazole-3-carboxamide (MK-5596) as a novel cannabinoid-1 receptor (CB1R) inverse agonist for the treatment of obesity

L. Yan¹, lin_yan@merck.com, P. Huo¹, J. S. Debenham¹, C. B. Madsen-Duggan¹, J. J. Hale¹, J. Lao², R. Z. Chen², J. C. Xiao², C.-P. Shen², D. S. Stribling³, L. P. Shearman³, A. M. Strack³, N. Tsou⁴, R. Ball⁴, J. Wang⁵, X. Tong⁵, T. J. Bateman⁵, V. B. G. Reddy⁵, and T. M. Fong². ¹Departments of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, United States, ²Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, United States, ³Department of Pharmacology, Merck Research Laboratories, Rahway, NJ, United States, ⁴Department of Pharmaceutical Research and Development, Merck Research Laboratories, Rahway, NJ, United States, ⁵Department of Drug Metabolism and Pharmacokinetics, Merck Research Laboratories, Rahway, NJ, United States

This paper describes the discovery of *N*-[(4*R*)-6-(4-chlorophenyl)-7-(2,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-4-yl]-5-methyl-1*H*-pyrazole-3-carboxamide (MK-5596) as a novel cannabinoid-1 receptor (CB1R) inverse agonist for the treatment of obesity. Structure activity relationship (SAR) studies of lead compound **3**, which had off-target hERG inhibition, led to the identification of several compounds that not only attenuated hERG inhibition but also allowed for direct glucuronidation of the parent compound, providing the potential for multiple metabolic clearance pathways. Among them, pyrazole **12c** (MK-5596) was found to be a highly selective CB1R inverse agonist that inhibited body weight gain and food intake in DIO (diet-induced obese) rat model through CB1R mediated mechanism. Although **12c** was a substrate of the P-glycoprotein (P-gp) transporter, its good *in vivo* efficacy in rodents, good pharmacokinetic properties in preclinical species, good safety margin, and a potentially balanced metabolism profile in humans allowed for its further evaluation in the clinic.

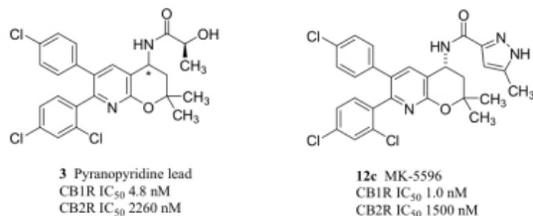


Figure 1. Structures of compound 3 and 12c

MEDI 503

Highly selective low molecular weight 5-hydroxytryptamine 2C receptor agonists showing antifeeding properties and reduced cocaine-induced locomotor activity

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5-hydroxytryptamine (5-HT) mediates a wide variety of behaviors including cognition, emotion, attention and appetite through at least 14 different receptor subtypes in humans. The 5-HT_{2C} receptor has emerged as a promising target in the treatment of depression, anxiety, obesity, chronic pain control, and epilepsy. A series of potent (EC₅₀ < 10 nM for most potent compounds) highly subtype selective (no activation of B and C subtypes at ≤ 10 nM for most selective compounds) 5-HT_{2C} agonists of low molecular weight (≥ 230 u) have been developed and biologically evaluated. Compounds have been demonstrated to possess anti-feeding effects and to decrease cocaine-induced locomotor activity.

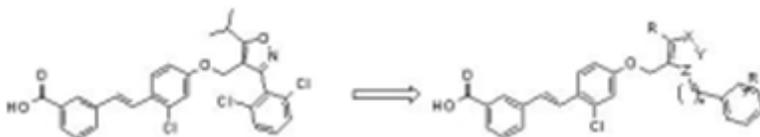
MEDI 504

Novel isoxazole analogs of GW4064 as farnesoid X receptor agonists

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Research, Biological Reagents & Assay Development, GlaxoSmithKline, Inc.,
Research Triangle Park, NC, United States

Novel analogs of GW4064 varying the isoxazole ring were synthesized and evaluated as modulators of the farnesoid X receptor (FXR). Several novel ring replacements were discovered exhibiting good potency. The most interesting analogs include pyrazole- and oxazolone-containing moieties with varying lengths to the substituted aromatic ring.



MEDI 505

Design of imidazo[4,5-c]pyridin-4-one derivatives with dual action as angiotensin II type 1 receptor (AT1) antagonists and partial PPARgamma agonists

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Hypertension is commonly associated with an array of other risk factors for cardiovascular disease including obesity, insulin resistance, elevated plasma glucose, and dyslipidaemia. They are collectively referred to as the metabolic syndrome. Angiotensin II type 1 receptor blockers (ARBs) are clinically effective, well tolerated agents for the treatment of hypertension. Among the ARBs, telmisartan (Micardis®), an approved ARB with well documented efficacy in blood pressure reduction, demonstrated improvements in glucose and lipid metabolism in small clinical trials. This activity was associated with weak partial agonism of PPAR γ . Compounds possessing the dual pharmacology of AT1 receptor antagonist/partial PPAR γ agonist could potentially treat several recognized cardiovascular risk factors including hypertension, insulin resistance and hypertriglyceridemia in patients with metabolic syndrome. Our group recently embarked upon a search of novel agents possessing this novel dual pharmacology. This poster will describe the design, synthesis, and in vitro biological evaluation of a series of imidazo[4,5-c]pyridin-4-ones with the desired dual pharmacology.

MEDI 506

Small molecule inhibitors of estrogen receptor α /coactivator binding: Synthesis and in vitro and cell-based biological evaluation

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We report here a series of small molecules (coactivator binding inhibitors, CBIs) block estrogen signaling by directly inhibiting the interaction of the estrogen receptor (ER) with coactivator proteins of the p160 class (steroid receptor coactivators, SRCs). This approach to blocking estrogen action is fundamentally different from traditional antagonism because the endogenous estrogen need not be replaced by an antagonist ligand. We investigated two high-throughput screening hits 1, 2 and analogs of them we have prepared. These compounds are active as CBIs in a luciferase reporter gene assay, but their potencies to now are unable to reach below micromolar levels, and thus are not better than the activities of existing ER CBIs that discovered using de novo design methods. Analysis of the X-ray structure of a bound SRC by molecule modeling strongly suggests that all four hydrophobic side chains within the nuclear receptor box of an SRC are critical binding elements. Thus, insufficient water displacement as the CBIs bind at the expansive complexation site may be responsible for the low micromolar limit in the potency range of compounds in these series.

MEDI 507

Identification of selective glucocorticoid receptor modulators: Design and synthesis of nonsteroidal pyrazole sulfones

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Traditional glucocorticoids, such as dexamethasone and prednisone, are highly effective therapeutic agents for the treatment of a variety of inflammatory and immunological disorders. However, their clinical use, especially when administered at higher doses, or prescribed for long-term use, can be limited due to dangerous systemic side effects that often include skin thinning, diabetes, osteoporosis and others. A selective glucocorticoid receptor modulator that is non-steroidal, equally efficacious, and has reduced adverse effects as compared to current glucocorticoids is highly desirable. It is theorized that the GR-mediated transcriptional profile of such a ligand would provide nearly equivalent transrepressive activity to traditional glucocorticoids, but with a marked reduction in the transactivative activity that causes the various adverse effects. A novel

class of pyrazole sulfones has been identified that offers such a selective transcriptional profile, and the design, synthesis and *in vitro* biological evaluation of these compounds will be described.

MEDI 508

Discovery of novel cyanamide-based inhibitors of cathepsin C

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Cathepsin C is member of the papain family and is a lysosomal cysteine exopeptidase. The enzyme is co-expressed with certain serine proteases, which are released from inflammatory cells recruited to sites of inflammation, and acts as a physiological activator of these proteases. Once activated, these proteases are capable of degrading various extracellular matrix components, which can lead to tissue damage and chronic inflammation. A Cathepsin C inhibitor would be useful for the treatment of chronic inflammatory diseases, such as Chronic Obstructive Pulmonary Disease ("COPD"). A cyanamide lead compound, picked from our compound collection, was found to be moderately active at cathepsin C and somewhat selective over other cathepsins. The result of efforts to investigate the structure activity relationships around its template led to the identification potent selective compounds and plasma stable compounds with moderate PK in the mouse and significant *in vivo* activity.

MEDI 509

Synthesis and SAR of 1-phenyl-3-(1-propionylpiperidin-4-yl)urea inhibitors of human and murine soluble epoxide hydrolase

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The soluble epoxide hydrolase (sEH, E.C. 3.3.2.3) is a pharmaceutical target for anti-inflammatory, cardioprotective and antihypertensive therapies. Inhibiting sEH leads to elevated levels of lipid epoxides, most notably arachidonic acid-derived epoxyeicosatrienoic acids (EETs), which gives rise to therapeutic effects. A series of sEH inhibitors possessing a 1,3-disubstituted urea with a N-acyl piperidine substituent was synthesized to investigate SAR and with the goal of improving *in vivo* performance. Multiple structures exhibited low nanomolar to picomolar IC₅₀ *in vitro* against recombinant human and murine sEH. Electron withdrawing, hydrophobic and sterically large substituents were positively correlated with inhibitor potency. Oral administration to mice of some analogues showed improvements in pharmacokinetics over adamantane-based inhibitors. For example, 1-(4-Chlorophenyl)-3-(1-propionylpiperidin-4-yl)urea showed a

1300-fold and 5200-fold improvement in C_{max} and AUC, respectively, over 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (AUDA). This new series of inhibitors provides additional analogues to probe the biological role of sEH and presents advances towards viable therapeutic molecules.

MEDI 510

Synthesis, structure-activity relationships, and biological profiles of a thiadiazole class of histamine H₃ receptor antagonists

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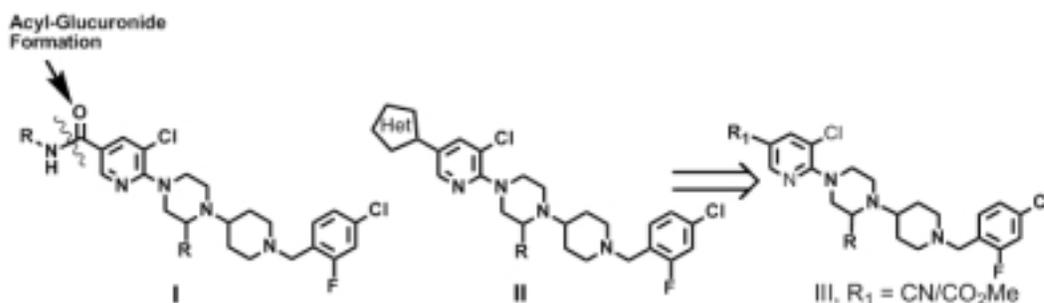
A new series of thiadiazole derivatives was synthesized and evaluated as non-imidazole H₃ receptor antagonists. A preliminary SAR study identified 4-(5-(1,4'-bipiperidin-1'-yl)-1,3,4-thiadiazol-2-yl)-2-(pyridin-2-yl)morpholine (**1**) as a potent H₃ antagonist following optimization of key parameters. The synthesis and SAR of this new class of H₃ receptor antagonists will be discussed.

MEDI 511

Novel CXCR3 Antagonists with heterocycles as amide surrogates: SAR development

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A CXCR3 antagonist offers promise as an anti-inflammatory agent for conditions such as rheumatoid arthritis, multiple sclerosis, psoriasis, and transplant rejection, where upregulation of CXCR3+ T lymphocytes is implicated. Recently we have disclosed compounds of the structure type **I** as potent CXCR3 antagonists. One of the major metabolic pathway observed in the structure type **I** is the cleavage of the left hand side amide moiety to the corresponding acid which can form an undesirable acylglucuronide conjugate. In an effort to overcome this potential metabolite issue, heterocycles were synthesized as amide surrogates. This poster will discuss the SAR development of heterocyclic analogs of type **II**. Synthesis of many heterocycles from nitrile/ ester intermediate **III** will be discussed.



MEDI 512

Structure-based design of TACE inhibitors

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A series of potent, non-hydroxamate TNF- α converting enzyme (TACE) inhibitors containing a hydantoin moiety has been discovered. X-ray crystal structures of inhibitor-enzyme complexes reveal a binding motif involving monodentate coordination of the hydantoin group to zinc. Structure-based design from an initial screening hit gave rise to a number of compounds with excellent binding affinity and good selectivity over other MMPs.

MEDI 513

Synthesis of potential new cathepsin K inhibitors

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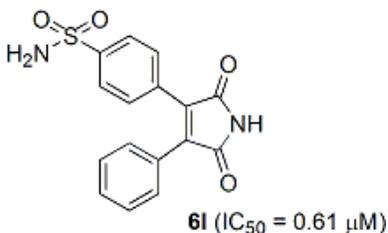
Cathepsin K has recently been identified as the major cysteine protease expressed in osteoclasts. The abundance and selective location of cathepsin K in cells responsible for bone resorption has led to a new interest in design of cathepsin K inhibitors for the treatment of osteoporosis. Increased bone resorption may release factors from the extracellular matrix that contribute to tumor growth. In fact, recent reports indicate that interactions between prostate cancer cells, osteoblasts, osteoclasts, and bone matrix are essential in the formation of bone metastases. The design and synthesis of cyclic thiones that have a substituted N-aromatic piperazino group to accommodate the S₃ subsite of cathepsin K subsite is reported.

MEDI 514

Synthesis and PGE₂ production inhibition of 1*H*-furan-2,5-dione and 1*H*-pyrrole-2,5-dione derivatives

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3,4-Diphenyl-substituted 1*H*-furan-2,5-dione and 1*H*-pyrrole-2,5-dione derivatives were synthesized and evaluated for the inhibitory activities on LPS-induced PGE₂ production in RAW 264.7 macrophage cells. Both 1*H*-furan-2,5-dione and 1*H*-pyrrole-2,5-dione rings as main scaffolds were easily obtained using one of three synthetic methods. Among the compounds investigated, 1*H*-3-(4-sulfamoylphenyl)-4-phenyl-pyrrole-2,5-dione (**6I**) showed a strong inhibitory activity (IC₅₀ = 0.61 μM) of PGE₂ production.



MEDI 515

Discovery of novel tartrate-based TNF-α converting enzyme (TACE) inhibitors

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A novel series of TNF-α convertase (TACE) inhibitors which are non-hydroxamate have been discovered. These compounds are bis-amides of *L*-tartaric acid (tartrate). The tartrates are the first reported tridentate ligand to the active site zinc of TACE. They are selective for TACE over other MMP's. The SAR of the optimization of the initial screening hits and key pharmacophoric elements of the tartrate series are discussed.

MEDI 516

Chiral soluble epoxide hydrolase (sEH) inhibitors

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Soluble epoxide hydrolase (sEH) is involved in the metabolism of endogenously derived fatty acid epoxides, such as epoxyeicosatrienoic acids (EETs). EETs are the cytochrome P450 epoxygenase products of arachidonic acid, which are known modulators of blood pressure and inflammation. Therefore sEH has emerged as a cross-functional target, in the areas of hypertension, inflammation, and organ-protection. Urea and amide-based compounds have well developed as sEH inhibitors. Interestingly, we found that these compounds contain a benzyl group do not follow a general SAR of sEH inhibitors. When this position became a stereogenic center, the two enantiomers showed different potency. In general, the (S)-isomer was more potent than the (R)-isomer. In the case of non-urea chiral inhibitors that contain hetero atoms on the benzylic position beta to the NH group, only one of isomers was active. The SAR of chiral inhibitors and the role of residues at the active site will be presented.

MEDI 517

Pharmaceutical candidates for anti-inflammatory and anti-vesicant utility

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Inhibitors of acetylcholinesterase (AChEIs) promote an anti-inflammatory effect by activating the *cholinergic anti-inflammatory pathway*. The well-known non-steroidal anti-inflammatory drugs (NSAIDs) have also been employed both topically and systemically in treating inflammation. Our group has synthesized and tested two classes of anti-inflammatory/anti-vesicant pharmaceuticals containing either choline mimics (-CO-O-CH₂-CH₂-X(CH₃)₃, X = C, Si, N⁺) or AChEIs (such as galanthamine or pyridostigmine) conjugated to NSAIDs. The two pharmacophores were attached either via a *p*-hydroxybenzyl carbonate linker (Class 1) or directly, via a simple ester linkage (Class 2). Both types prevented chemically-induced inflammation in a mouse ear model, with Class 1 compounds showing a more potent therapeutic effect as well as a lower IC₅₀ against acetylcholinesterase (AChE). Class 1 agents inhibited AChE in the μM range and provided prophylaxis for phorbol ester and sulfur mustard-induced edema and inflammation up to 98%, more than 50% greater than the sum of the pharmacophores which constitute them.

MEDI 518

Design, synthesis, and biological evaluation of MMP-14 inhibitors

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Matrix metalloproteinase-14 (MT1-MMP or MMP-14) is an internalized cell-surface protease implicated in various metastatic cancers. The ability to detect MMP-14 tumor cells *in vivo* would be useful in diagnosing early stage cancers. Our design of small-molecule probes for *in vitro* detection of MMP-14 positive cells includes a MMP-14 inhibitor linked to a fluorescent dye. Analogs of known MMP-14 inhibitors such as hydroxamate-containing sulfonamides as well as a new class of phosphoramidates are currently under investigation. Progress toward the development of these probes as well as results for the inhibitory potency of fluorescent MMP-14 inhibitors and *in vitro* cell labeling as detected by confocal microscopy will be presented.

MEDI 519

Discovery of novel potent and selective A_{2B} adenosine receptor antagonists

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The synthesis and SAR of *N*-(5,6-diarylpyridin-2-yl)amide derivatives as potent A_{2B} receptor antagonists is described. Several compounds showed good selectivity vs. other adenosine receptors. Pharmacokinetic profile of a lead compound will be presented. Additionally, new potent and selective A_{2B} antagonists have been prepared in which the aryl-amide moiety has been replaced by bioisosteric bicyclic moieties which retain the hydrogen bond-donating group of amide series. Although the majority of compounds had generally improved microsomal stability compared to amides, this was not translated to overall improvements in the pharmacokinetic behavior of a representative set of compounds.

MEDI 520

Synthesis and biological activity of pyrido[3',2':4,5]furo[3,2-d]pyrimidine derivatives as novel and potent PDE4 inhibitors

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Phosphodiesterases (PDE's) comprise a superfamily of enzymes responsible for the hydrolysis and inactivation of the second messengers cAMP and cGMP. Eleven different PDE families have been identified to date. Among them the PDE4 isoenzyme family exhibits a high affinity for cyclic AMP. Increased levels of cAMP caused by PDE4 inhibition are associated with the suppression of cell activation in a wide range of inflammatory and immune cells. Moreover, PDE4 inhibitors decrease the release of the cytokine $TNF\alpha$. Therefore, the major therapeutic areas that have been investigated for PDE4 inhibitors are asthma and chronic obstructive pulmonary disease (COPD), although inflammatory bowel disease, atopic dermatitis, psoriasis and rheumatoid arthritis are also within the scope. Thus, several PDE4 inhibitors such as **roflumilast** or **oglemilast** are in active development for the oral treatment of such diseases. We report herein some pyrido[3',2':4,5]furo[3,2-d]pyrimidines derivatives (PFP) as novel structural class of potent and efficacious PDE4 inhibitors, based on a lead compound which was identified in an HTS exercise. The optimization process was driven by X-ray crystallography.

MEDI 521

Tricyclic histamine H₄ receptor antagonists

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Tetrahydrobenzofuranopyrimidine and tetrahydrobenzothienopyrimidine analogs have been synthesized and identified as potent antagonists of the histamine H₄ receptor. The H₄ receptor influences the chemotaxis of hematopoietic cells and cytokine production, rendering it an important target for the treatment of inflammatory diseases. Methyl- and fluoro- substituents on the saturated rings of the tricyclic compounds were synthesized to examine pharmacokinetic properties. Diamine substituents on the aminopyrimidines were also demonstrated to be important for potent antagonistic activity.

MEDI 522

Triamino pyrimidines and pyridines as histamine H₄ antagonists

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Histamine H₄ is a 390 amino acid G-protein coupled receptor implicated in the treatment of inflammatory diseases based on the expression of the H₄ receptor on eosinophils, mast cells, dendritic cells and other leukocytes. Design, synthesis, and SAR development led to the identification of triamino pyrimidines

and pyridines as potent and selective Histamine H₄ antagonists. The binding affinity and functional activity of three heteroaromatic cores will be discussed.

MEDI 523

Marine natural-derived inhibitors of glycogen synthase kinase-3 β phenylmethylen hydantoin: In vitro and in vivo activities, pharmacophore modeling, and virtual screening studies

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The Red Sea sponge *Hemimycale arabica* afforded the known (*Z*)-5-(4-hydroxybenzylidene)-hydantoin (**1**). This natural phenylmethylen hydantoin (PMH) **1** and the synthetic (*Z*)-5-(4-(ethylthio)benzylidene)-hydantoin (**2**) showed potent in vitro and in vivo anti-growth and anti-invasive properties against PC-3M prostate cancer cells in MTT, spheroid disaggregation, and in mice models. To explore a possible molecular target of PMHs, the most potent synthetic analogue **2** has been virtually screened against various protein kinases. Molecular modeling study has shown that **2** can be successfully docked within the binding pocket of glycogen synthase kinase-3 β (GSK-3 β) similar to the well-known GSK-3 β inhibitor I-5. Several PMHs showed potent in vitro GSK-3 β inhibitory activity with an IC₅₀ range of 4–20 μ M. The most potent analogue **3** showed a significant increase in liver glycogen level at the 5, 15, and 25 mg/kg dose levels, in vivo. Pharmacophore model was built and validated using in-house database of active and inactive GSK-3 β inhibitors. New lead identification was carried out by performing virtual screening using the validated pharmacophoric query and three chemical databases namely NCI, Maybridge and our in-house database. Surfex Dock-based molecular docking study was used for final screening. New highly potent GSK-3 β inhibitors with IC₅₀ as low as 3 nM was discovered based on the marine-derived GSK-3 β inhibitors pharmacophore model.

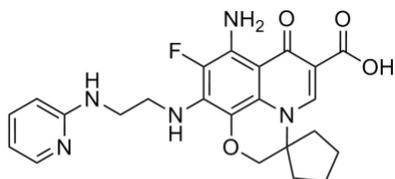


MEDI 524

Synthesis and structure-activity relationship of 4-quinolone-3-carboxylic acid based inhibitors of glycogen synthase kinase 3 β

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C. Zhang¹, A. Aban¹, A. K. Szardenings¹, J. W. Kozarich¹, Y. Kohno², and K. R. Shreder¹. ¹ActivX Biosciences, La Jolla, CA, United States, ²Kyorin Pharmaceutical Co. Ltd, Nogi, Japan



1

GSK3 β IC₅₀ = 12 nM

Inhibitors of glycogen synthase kinase 3 β (GSK3 β), a serine/threonine protein kinase, offer promise as therapeutic agents to treat GSK3 β mediated diseases such as diabetes, Alzheimer's disease, and various CNS disorders. The synthesis and GSK3 β IC₅₀ values of bicyclic and tricyclic derivatives of the 5,7-diamino-6-fluoro-4-quinolone-3-carboxylic acid scaffold are presented. Selected potent inhibitors based on this core were shown to have insignificant anti-microbial activity. Finally, KiNativ™ kinase profiling in HL-60 lysate indicated that members of this class (e.g., compound **1**) were highly selective GSK3 inhibitors.

MEDI 525

Design, synthesis, and characterization of the novel analogs of chimeric AGRP- melanocortin peptide targeting melanocortin receptors

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The melanocortin system belongs to the family of G- protein coupled receptors and consists of five receptor subtypes (MC1R-MC5R). The MC3R and MC4R are located in the brain and have been identified in knockout mice to play important role in regulating energy homeostasis, obesity, and metabolism and are potential drug targets for the treatment of obesity and related diseases. Based on the studies that bioactive conformation of agonist at melanocortin receptor involves β -turn containing "His-Phe-Arg-Trp" core sequence, it was hypothesized that incorporation of turn mimetic into biologically active peptides might restrict the conformational mobility, increase potency and enhance selectivity. A thioether cyclized peptidomimetic scaffold was introduced to the AGRP-melanocortin chimeric peptide template by systematic solid phase synthesis. By using positional walking approach, we identified novel analogues with nanomolar potencies at melanocortin receptor subtypes. Conformational analysis was performed on the selected analogues using 2D ¹H NMR and computer assisted molecular modeling.

MEDI 526

Ligand based screening tools for identification of insulin receptor activating compounds

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²Department of Pharmacognosy, University of Vienna, Vienna, Austria

The binding of insulin to its receptor starts a signalling cascade leading among other effects to glucose uptake. Activation of the insulin receptor could therefore be a possible target for the treatment of type 2 diabetes mellitus. In 1999, Zhang et. al. identified a small molecule activator of the insulin receptor. The molecule is known to interact directly with the intracellular domain of the receptor, but the exact interactions are still unknown. Li et. al. proposed a pocket at the N-terminal lobe to which a small molecule could bind, thereby preventing the receptor from autoinhibition. Combining several in silico screening methods such as self-organizing maps with 2 types of descriptors (VSA and 2D autocorrelation vectors), Tanimoto similarity of 8 different fingerprint types (including MACCS and pharmacophore based fingerprints) and shape similarity search revealed a total of 367 compounds out of more than 600.000 compounds of the ChemDiv database as potential insulin receptor activators. Ligand-based studies were complemented by docking studies on the activated tyrosine kinase domain of the insulin receptor (PDB-Code: 1IR3). Biological evaluation of selected compounds demonstrates the usability of the different approaches to identify new insulin receptor activating compounds. Daniela Digles is recipient of a DOC-fORTE-fellowship of the Austrian Academy of Science at the Department of Medicinal Chemistry, University of Vienna.

MEDI 527

Optimization of anthranilimide based glycogen phosphorylase inhibitors: Replacement of the naphthoic acid core

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Hepatic glucose output is elevated in Type 2 diabetic patients, and evidence suggests that drugs which lower hepatic glucose output are effective antihyperglycemic agents. Glycogenolysis, which is the release of monomeric glucose from its polymeric storage form called glycogen, is a key contributor to hepatic glucose output. Glycogen Phosphorylase is the enzyme that catalyzes

this process. The optimization of lead glycogen phosphorylase inhibitor anthranilimide **1** will be presented, with a focus on key heterocyclic replacements of the naphthoic acid core.

MEDI 528

Discovery of novel glucagon receptor antagonists

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Glucagon is a peptide hormone secreted by the α -cells of the pancreatic islets in response to falling blood glucose levels. Upon binding to its G protein coupled receptor, it stimulates hepatic gluconeogenesis and glycogenolysis resulting in increased blood glucose levels. In concert with insulin, which decreases blood glucose levels, glucagon plays a critical role in maintaining glucose homeostasis. In Type II diabetics, excessive hepatic glucose production is a key contributing factor to loss of glycemic control. Glucagon receptor antagonists, therefore, have potential as novel agents for the treatment of type II diabetes. We have discovered a series of novel glucagon receptor antagonists with low nano-molar binding and functional activity and good efficacy in rodent diabetes models. This poster will describe the synthesis and SAR of these potent antagonists.

MEDI 529

Discovery of potent, selective and orally efficacious glycogen synthase activators as a potential treatment for type 2 diabetes

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The key step in the synthesis of glycogen is the addition of UDP-glucose to the growing glycogen chain, and is catalyzed by the enzyme glycogen synthase (GS). There is substantial clinical and genetic evidence linking GS to various metabolic disorders. Basal and insulin-stimulated GS activities as well as glycogen content in muscle cells from diabetic subjects are significantly lower than in cells from lean non-diabetic subjects. Thus, an activator of GS has potential as a novel therapeutic agent for the treatment of metabolic diseases,

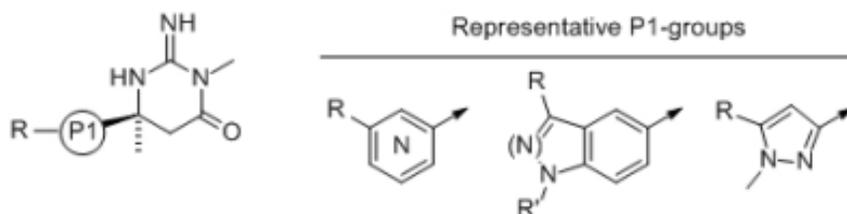
such as type 2 diabetes and cardiovascular diseases. High throughput screening identified a biphenyl-furanoic acid derivative which activated the GS enzymatic activity. Lead optimization enhanced the enzymatic potency of the screening hit and improved cellular activity, metabolic stability, protein binding and solubility. Structure-activity relationship studies of these biphenyl-based GS activators as well as their pharmacokinetic and pharmacologic properties will be presented.

MEDI 530

Novel iminopyrimidinone β -secretase (BACE1) inhibitors: Part 2. P1-azoles

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β -Secretase (BACE-1) is a membrane-bound aspartic protease responsible for the cleavage of amyloid precursor protein (APP) to generate A β 40/42 peptide fragments. Deposition of these A β -fragments ultimately leads to plaques associated with Alzheimer's disease. Therefore, inhibition of BACE is thought to be a potential therapeutic target for the treatment of AD. A structure-based design approach and the synthesis of novel iminopyrimidinone BACE inhibitors will be disclosed.



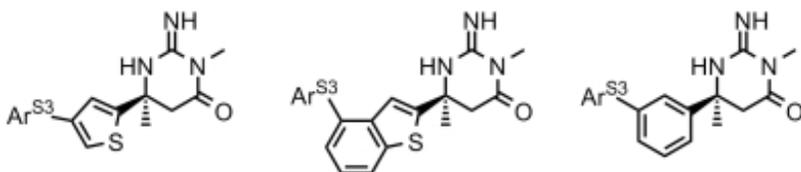
MEDI 531

Novel iminopyrimidinone β -Secretase inhibitors: Part 1. P1-P3 SAR

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β -Secretase (BACE1) inhibition remains a key focus of Alzheimer's disease (AD) research due to its potential slow or halt disease progression without mechanism-based toxicity. Through rational, structure-based design, we identified an iminopyrimidinone binding motif that produces BACE1 inhibitors with good potency and moderate cell shifts. SAR for a variety of P1-P3 biaryl analogs in this series, as well as selected *in vivo* activity and chemistry to generate these structures will be presented.



MEDI 532

Identification of spirocyclic pyrrolidines as novel BACE inhibitors

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X-ray based screening of the proprietary fragment collection led to identification of a novel BACE binder featuring spiropyrrolidine framework. Analysis of the binding mode and early hit expansion efforts allowed to establish a productive fragment growing direction. Hit assessment highlighted promising ligand efficiency profile and a potential for good brain penetration in more advanced analogs. Initial SAR work resulted in potency improvement from millimolar to single digit micromolar range while maintaining ligand efficiency and properties predictive of good permeability and low P-gp liability.

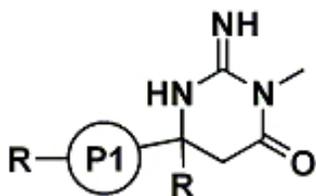
MEDI 533

Novel iminopyrimidinone β -secretase (BACE) inhibitors: Part 3. C5 substitution

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Madison¹, B. A. Mckittrick¹, T. Lee², T. Meng¹, J. Misiaszek¹, J. Pan¹, E. Parker¹, G. Qian², K. Saionz², A. Stamford¹, C. Strickland¹, D. Tadesse², J. Voigt¹, L. Wang¹, J. Wong¹, Y. Wu¹, J. Zhao², Z. Zhu¹, Z.-Y. Sun¹, L. Hyde¹, P. Leach¹, L. Zhang¹, Q. Zhang¹, and L. Favreau¹. ¹Schering Plough Research Institute, Kenilworth, NJ, United States, ²Ligand Pharmaceuticals, Cranbury, NJ, United States

The pathogenesis of Alzheimer's disease (AD) is intimately related to the presence of neurotoxic amyloid- β peptide ($A\beta$) in the brain. Peptides $A\beta$ -40 and $A\beta$ -42 are produced by the proteolysis of amyloid precursor protein (APP), first by the membrane-associated aspartic protease β -secretase (BACE), and then further processed by gamma-secretase. Therefore, inhibition of BACE is thought to be a potential therapeutic target for the treatment of AD. A structure-based design approach and the synthesis of novel iminopyrimidinone BACE inhibitors will be disclosed.

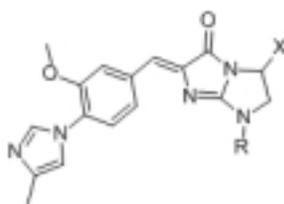


MEDI 534

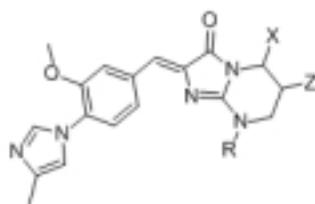
Novel bicyclic iminohydantoins as γ -Secretase modulators

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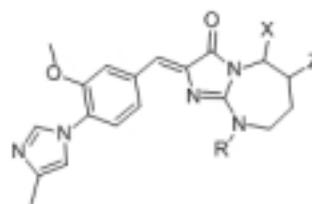
The cleavage of amyloid precursor protein (APP) via γ -secretase leads to the production of amyloid- β peptide ($A\beta$) of various chain lengths. This production of $A\beta$ is thought to be a leading factor in the development of Alzheimer's disease. Of the various $A\beta$ fragments generated, $A\beta$ -42 is more prone to forming amyloid plaques in the brain. The development of γ -secretase modulators provides a means to alter the production from $A\beta$ -42 to shorter, more soluble $A\beta$ fragments. In addition, γ -secretase modulators provide an attractive alternative to γ -secretase inhibitors since they do not block cellular signaling such as Notch processing. The following compounds are representative examples of novel bicyclic iminohydantoins that display a modulator profile.



X = 4-fluorophenyl



1. X = 4-fluorophenyl, Z = H
2. X = H, Z = 4-fluorophenyl



1. X = 4-fluorophenyl, Z = H
2. X = H, Z = 4-fluorophenyl

MEDI 535

Landomycins P-W: Eight new angucycline antibiotics isolated from *Streptomyces cyanogenus* S136

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Streptomyces spp. play significant roles in the production of bioactive secondary products. Numerous classes of these metabolites have a great bio-functional diversity (as antibiotics, antifungal, antiviral, anticancer, immunosuppressant agents, insecticides, herbicides etc.) and diverse chemical structures as well. Many of them are potentially useful as pharmacologically and agriculturally active agents. *Streptomyces cyanogenus* S136 is the producer of landomycins A, B and D, which were previously reported. Repeated fermentation (6 liter shaker cultures) of the same strain afforded 6.4 g of a reddish powder crude extract. Isolation and purification of the crude extract using different chromatographic techniques led to isolation of 18 angucyclines, among them eight new landomycins (P-W). Structures of the new compounds were unequivocally established by 1D and 2D NMR data and mass spectrometry, while the stereochemistry was confirmed by NOESY experiments, coupling constants and comparison with related structures. Landomycins consist of an angucycline polyketide backbone decorated with diverse sugar side chains and show unusual broad antitumor properties. The antitumor activity of landomycins depends on the length of the sugar side chain. Landomycin A is the largest member of this group, containing a hexasaccharide side chain, and is the most active compound. The results presented here provide more insights into the structure activity relationship (SAR) of landomycins, particularly with regard to the oxygenation patterns of the aglycon.

MEDI 536

Synthesis and biological evaluation of the first pentafluorosulfanyl analogs of mefloquine

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The pentafluorosulfanyl (SF₅) group is of increasing interest as a functional group in pharmaceutical and agrochemical research, and was recently labeled as the “substituent of the future”. It imparts unique properties to organic compounds and enhances their biological activities because of its high electronegativity, substantial steric effect, significant hydrophobicity and high chemical resistance. To improve the activity and alleviate the neurotoxicity of the anti-malarial drug mefloquine, we introduced the SF₅ group into the quinoline methanolamine scaffold in place of the trifluoromethyl (CF₃) group. Three novel mefloquine analogs were synthesized in high yields from simple phenyl SF₅ building blocks through short synthetic routes. Two analogs were found to have improved activity and selectivity against malarial parasites, and one analog demonstrated lower membrane permeability, which is potentially advantageous for the reduction of the neurotoxic side effects. We also report the first SF₅-containing quinoline heterocycles and the first *ortho*-substituted SF₅ aniline.

MEDI 537

Resistance and activity of multivalent antimicrobial peptides

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Department of Chemistry, New York University, New York, NY, United States

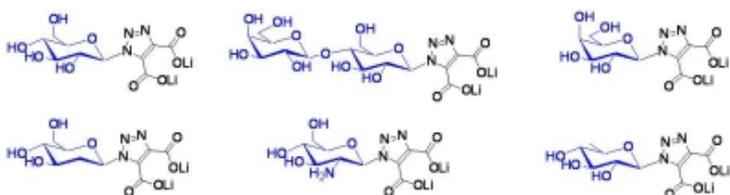
As multidrug-resistant bacterial strains emerge in increasing numbers, the need to identify different kinds of antibiotics is growing. Antimicrobial peptides (AMPs) have been proposed as prospective antibiotics agents because their effect is rapid, broad spectrum and indifference to resistant towards standard antibiotics. Among the promising approaches, multivalent designs by polymerizing AMPs can enhance the potency and efficacy of existing antimicrobial monomeric peptides. However, the mechanism and ability to develop resistance of multivalent AMPs for killing bacterial pathogen has yet to be explored. In the present study, antimicrobial and spectroscopic studies were carried out to understand the possible mode of action for these new antibacterial agents. Both multivalent and monomeric AMPs were much less affected over extended exposure to continuous growing bacterial strains up to 400 generations when compared conventional antibiotics. Also, the mechanism by which multivalent AMPs are able to overcome resistance appears to be different than their monomeric AMPs.

MEDI 538

Synthesis and evaluation of carbohydrate based 1,2,3-triazoles as potential therapeutics for the treatment of gram-positive bacterial infections

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Vancomycin is a glycopeptide antibiotic used in the clinical setting as a last resort for the treatment of methicillin-resistant *Staphylococci* and *Enterococci*. Over the past two decades strains of vancomycin-resistant bacteria have appeared, raising serious public health concerns. Recent research has focused on investigating the inhibition of peptidoglycan biosynthesis by using small carbohydrate derivatives that target the transglycosylation step. Here we present the progress towards the synthesis of several small carbohydrate analogs based on Garneau-5. The evaluation of their antimicrobial activity *in vitro*, and the characterization of the binding interactions between these derivatives and the transglycosylase region of penicillin-binding protein 2 from *Staphylococcus aureus* will also be presented.



MEDI 539

Discovery and development of GI181771X, an orally active CCK-1 receptor agonist

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Numerous experiments have demonstrated that agonist-induced activation of the cholecystokinin-1 (CCK-1) receptor induces shortening of meal duration and reduction of meal size, suggesting that chronic CCK-1 stimulation may be an appropriate target for the treatment of human obesity. We identified a series of 1,5-benzodiazepines that functioned as CCK-1 agonists via screening of compounds for contractile activity on the isolated guinea pig gallbladder. Optimization of these initial compounds led to the discovery of potent, selective, orally active CCK-1 agonists that were efficacious in reducing food intake in rats. One of these compounds, GI181771X, was selected for clinical development and was evaluated for effects on food intake in a 24-week trial in obese humans. This lecture will summarize the discovery and establishment of structure-activity relationships in the 1,5 benzodiazepine series of compounds, the selection of GI181771X as a development candidate, and results from clinical studies.

MEDI 540

Value of Free-Wilson Analysis in the discovery of CCK-1 receptor antagonists for the treatment of pancreatitis

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Cholecystikinin (CCK) is a 33 amino acid peptide originally discovered in the porcine gut, and subsequently identified in humans. The physiological effects of CCK are mediated by two GPCR's: CCK1 and CCK2. Selective CCK1-receptor antagonists have been shown to inhibit CCK-stimulated gallbladder contraction, pancreatic enzyme secretion, satiety, inhibition of gastric emptying, and regulation of peristalsis, indicating a potential role in the modification of the physiological integrated gastrointestinal response to a meal. Here we describe the discovery and SAR of a series of CCK1 receptor antagonists, and the use of Free-Wilson additivity calculations to optimize the properties of these compounds. In addition, pharmacology will be presented showing the potential utility of these compounds for the treatment of pancreatitis.

MEDI 541

Discovery of triazolobenzodiazepinone derivatives as orally active, gut-selective CCK1 receptor agonists for the potential treatment of obesity

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Both pre-clinical and clinical studies have demonstrated that CCK1 receptor (CCK1R) agonists act as anorectic agents and therefore have the potential to treat obesity. We have identified a series of triazolobenzodiazepinone CCK1R agonists. SAR studies have led to the discovery of our clinical candidate, CE-326597. CE-326597 is a small molecule CCK1R agonist which exhibits robust food intake effects in rodents with low systemic exposure. CE-326597 has

recently completed Ph2a trials. We will present the discovery of CE-326597 and highlight pre-clinical as well as clinical data.

MEDI 542

Molecular modeling of G protein-coupled receptor-ligand complexes

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The G protein-coupled receptor (GPCR) superfamily represents perhaps the most significant group of therapeutically important receptor proteins. Recent x-ray crystal structures for several GPCR family members have provided important information about the superfamily, but also suggest that there may be more structural variability in this receptor family than assumed initially, especially as regards ligand binding modes and interactions. We have used a protocol of molecular modeling studies and biophysical experiments to characterize important features of GPCR-ligand complexes for a number of years, and believe this strategy will continue to be useful in the design and development of ligands targeted to GPCRs. We will present a few representative examples of our integrated approach for cholecystokinin A receptor and other GPCR superfamily members.

MEDI 543

Molecular basis of ligand binding to the cholecystokinin receptor: Implications for drug development

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The type 1 cholecystokinin receptor is a potentially important drug target mediating physiologic effects that contribute to nutritional homeostasis, including stimulation of pancreatic exocrine secretion, gallbladder emptying, enteric motility, and satiety. While the satiety effects make agonists acting at this receptor candidates as anti-obesity drugs, potential trophic effects on receptor-bearing cells are concerning. Development and refinement of drug candidates, particularly those having functional selectivity, could be enhanced by better understanding of receptor structure and molecular mechanisms of ligand binding and signaling. We utilized photoaffinity labeling to define spatial approximations between receptor residues and sites throughout the pharmacophore of cholecystokinin, as well as a benzodiazepine ligand. We also used fluorescence approaches to understand microenvironments along the docked ligand, and dynamic changes that occur upon receptor activation. Differences in the spectrum of signaling and regulatory events in response to different agents provide insights into opportunities for developing therapeutically useful allosteric modulators of this receptor.

MEDI 544

Discovery of imidazole carboxamides as potent and selective CCK1R agonists

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Cholecystinin (CCK) is a potent peptide hormone secreted by the gut in response to intraluminal nutrients. There are two types of the CCK receptor, and the CCK peptide reduces food intake in a wide variety of species. CCK1R stimulation decreases food intake, delays gastric emptying, increases gallbladder emptying and stimulates pancreatic exocrine secretion. CCK2R is the stomach gastrin receptor that mediates gastric acid secretion and is also widely expressed and functional in the CNS. Since the satiety target is CCK1R, selective CCK1R agonists are an attractive target for the potential treatment of obesity. A HTS screen identified 1,5-diarylpyrazole carboxamides as selective but modest CCK1R agonists. Herein we describe the discovery, SAR studies and biological evaluation of aryl imidazole carboxamides as potent and selective CCK1R agonists.

MEDI 545

Discovery of [¹¹C]MK-4232: The first CGRP-R PET tracer

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The 37 amino acid neuropeptide Calcitonin Gene-Related Peptide (CGRP) has been implicated in the pathophysiology of migraine. CGRP receptor (CGRP-R) antagonists including olcegepant and telcagepant have demonstrated efficacy in the acute treatment of migraine comparable to the “gold standard” triptans in clinical trials. Although a potent vasodilator, CGRP is also thought to interact with centrally located CGRP receptors to mediate pain transmission during the migraine headache. To address the question of the effective site of action of CGRP-R antagonists in migraine, several different methods to estimate receptor engagement in both the periphery and the CNS were explored. Positron Emission Tomography (PET) is a powerful imaging tool to address CNS activity

and the medicinal chemistry effort focused on the identification of a suitable PET tracer to probe central CGRP receptors. The medicinal chemistry strategy included exploration of both ^{11}C and ^{18}F PET tracers and led to the discovery of [^{11}C]MK-4232, a PET tracer suitable for the quantitative determination of central CGRP-R occupancy levels in primates. [^{11}C]MK-4232 is currently in Phase 1 trials. The contributions of potency, free unbound fraction in plasma, csf levels and Pgp transport of CGRP-R antagonists to central receptor occupancy will be discussed.

MEDI 546

Automated docking screens: A feasibility study

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Structure-based docking is the most practical approach to leverage protein structure for ligand discovery, but the technique retains important liabilities that make it challenging to deploy on a large scale. We have therefore created an expert system, DOCK Blaster, to investigate the feasibility of full automation. The method requires a PDB code, sometimes with a ligand structure, and from that alone can launch a full screen of large libraries. A critical feature is self-assessment, which estimates the anticipated reliability of the automated screening results using pose fidelity and enrichment. Against common benchmarks, DOCK Blaster recapitulates the crystal ligand pose within 2Å RMSD 50-60% of the time; inferior to an expert, but respectable. Half the time the ligand also ranked among the top 5% of 100 physically-matched decoys chosen on the fly. Further tests were undertaken culminating in a study of 7,755 eligible PDB structures. In 1,398 cases the re-docked ligand ranked in the top 5% of 100 property-matched decoys while also posing within 2Å RMSD, suggesting that unsupervised prospective docking is viable. DOCK Blaster is available at <http://blaster.docking.org>.

MEDI 547

Discovery of structurally distinct analogs of SCH 420814 (Preladenant) as adenosine A_{2A} receptor antagonists

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Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors classified as A₁, A_{2A}, A_{2B}, and A₃. The adenosine A_{2A} receptor is distributed in the basal ganglia (BG) and expressed abundantly in dopamine-rich areas such as the striatum, and the *globus pallidus*. The

colocalization of adenosine A_{2A} and dopamine D₂ receptors in the striatopallidal neurons led to the hypothesis that A_{2A} receptors might be a target for Parkinson's Disease. Antagonism of A_{2A} receptors has shown to improve the motor symptoms of PD in animal models and in clinical trials. A_{2A} receptor antagonists have thus become an attractive target for resetting the motor imbalance in PD. SCH 420814 (Preladenant) is a highly potent, selective and orally active A_{2A} antagonist that is currently undergoing clinical trials for PD. This presentation will describe the unpublished SAR efforts toward the identification of a potential back-up candidate to SCH 420814. Our goal was to achieve better solubility and rodent PK while retaining the excellent in vitro and in vivo profile of SCH 420814. Herein we describe modifications to the right-side furan and the left-side aryl piperazine structural motifs while retaining the pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine tricyclic core present in SCH 420814.

MEDI 548

Removing fear of genotoxicity of aromatic amines: From molecular mechanisms to practical issues

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Fear of genotoxicity limits the use of aromatic amines as molecular building blocks in drug discovery programs. Analysis of Ames data indicates that particular substitution patterns in aromatic amines are free of genotoxicity. We have investigated the molecular basis for genotoxicity of aromatic amines to provide an understanding of factors that would allow a rational design of non-genotoxic aromatic amines. Correlated *ab initio* calculations of precovalent complexes of different arylnitrenium ions with 9-methylguanine indicate that the positive charge of the arylnitrenium is delocalized over the 9-methylguanine HOMO in addition to its delocalization over the arylnitrenium itself. Correspondingly, the structure of the precovalent complexes of arylnitrenium ions in DNA is determined both by the stability of arylnitreniums and by their structural complementarity with the DNA intercalation site. To remove genotoxicity of aromatic amines one can either destabilize the arylnitrenium ions or make them inconsistent with the intercalation site of DNA.

MEDI 549

Developing halogenated benzimidazole carboxamide antagonists as molecular tools for alpha4beta1 integrin expressed on T- and B-cell lymphomas

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Biomedical Engineering, UC Davis, Davis, CA, United States, ³Department of Internal Medicine, UC Davis, Sacramento, CA, United States

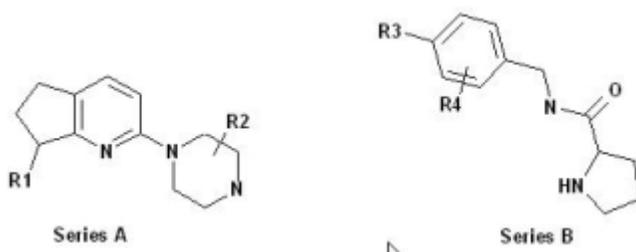
The resting or activated conformations of alpha4beta1 integrin allow for the application of target-selective agents for malignant lymphoid cancers. In accord with our program to discover potent and selective ligands that target various cancers, we are developing a condensed alpha4beta1 integrin radio-targeting agent that not only can be used for imaging but also for therapy. With efforts integrating heterocyclic chemistry, cell adhesion assays, molecular modeling, and radiochemistry, we report herein the discovery of the bromobenzimidazole carboxamide ($IC_{50} = 115 \text{ pM}$), the SAR between the novel halobenzimidazole carboxamides, and the in vivo applications of I-125 derivatives. These high affinity halogenated ligands are attractive tools for medicinal and biological use; the fluoro and iodo derivatives are potential radiodiagnostic or radiotherapeutic agents, whereas the chloro and bromo analogues could provide structural insight due to their heaviness and unique isotopic abundance.

MEDI 550

From functional selective to binding selectivity: Discover orally active 5HT2c agonists for the treatment of obesity

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Two novel series of 5HT2c agonists will be revealed in this talk: series A has good functional but lacking binding selectivity; series B achieved both functional and binding selectivity. Furthermore, series B has more than 1000 fold selectivity against 5HT2b receptor and with good brain penetration. Orally active compounds were found in both series with robust efficacy in our rodent food intake and weight reduction model. ADME data will also be presented in this talk.



MEDI 551

CADA compounds with 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. Recent developments include synthesis of active, dansyl-labeled analogs for studies of cellular uptake, and formulation of CADA as a microbicide gel with preservation of CD-4 down-modulating and antiviral activities. Most recently, CADA resistance in HIV-1 has been found to be associated with increased susceptibility of the virus to neutralizing antibodies. These advances are reviewed, along with improvements in the synthesis of CADA compounds. In particular, macrocyclization yields have been improved by means of palladium catalysis, and a novel route to unsymmetrical CADA analogs has been developed.

MEDI 552

Novel prodrugs of acamprosate: Neopentyl sulfonate esters

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The polar nature of drugs containing charged sulfonic acid functionalities presents a significant hurdle for their effectively traversing biological barriers such as the gut wall resulting in poor oral bioavailability. There remains an apparent lack of practical prodrug strategies for sulfonic acids. Here we demonstrate that acamprosate, protected as substituted neopentyl sulfonate esters bearing a masked heteroatom exhibit greatly improved permeability properties. They undergo enzymatic unmasking of the nucleophilic heteroatom followed by an intramolecular cyclization to effectively release the parent drug. The steric nature of these neopentyl sulfonate esters render them inert to intermolecular nucleophilic attack. This inhibited their reactivity with biological nucleophiles enabling these sulfonate esters to pass in vitro toxicity and mutagenicity screens. In a case study, prodrugs of acamprosate resulted in a more than 20-fold higher exposure to the parent drug in a rat pharmacokinetic study after oral or colonic dosing.

MEDI 553

Synthesis and characterization of novel orally available dopamine D₃ receptor antagonists

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Dopamine receptors are members of the G-protein coupled receptor (GPCR) family and there is substantial evidence, in particular from localization and pharmacological studies, to indicate that the dopamine D₃-receptor subtype plays a key role in the pathophysiology of multiple neurological and neuro-psychiatric disorders such as schizophrenia, Parkinson's disease, and drug abuse. It therefore represents a very attractive drug target in the CNS field in particular for treatment of schizophrenia, a devastating chronic psychotic disorder that affects 1% of the population, which remains poorly managed by existing therapeutics. D₃ receptor antagonists may have therapeutic efficacy in schizophrenia without the side effects associated with D₂ receptor blockade. Efficacy in multiple models predictive of antipsychotic activity, without induction of catalepsy, has been reported for A-437203.¹ This work will describe the lead identification and lead optimization process for a series of highly selective phenylazetidine sulfonamide based D₃ antagonists, and their subsequent characterization and advancement.

References:

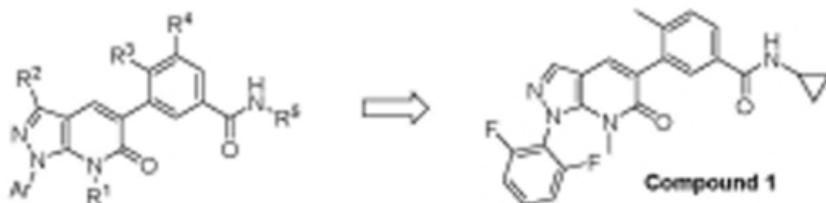
1. Neuropsychopharmacology, 2006, 31, 1382-1392.

MEDI 554

Pyrazolo-pyridinones as a class of potent, selective and orally available inhibitors of p38a mitogen-activated protein kinase

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The p38a mitogen-activated protein (MAP) kinase is a central signaling molecule in many proinflammatory pathways, regulating the cellular response to a multitude of external stimuli including heat, ultraviolet radiation, osmotic shock, and a variety of cytokines especially interleukin-1b and tumor necrosis factor a. Thus, inhibitors of this enzyme are postulated to have significant therapeutic potential for the treatment of rheumatoid arthritis, inflammatory bowel disease, Crohn's disease and many other diseases where aberrant cytokine signaling is the driver of disease. We describe a novel class of 7-alkyl-1,5-bis-aryl-pyrazolo-pyridinone-based p38a inhibitors, of which Compound 1 is highly selective in the Ambit kinase screen, and efficacious (ED₅₀ = <0.01 mg/kg) in the rat collagen induced arthritis (CIA) model.



MEDI 555

Synthesis and structure-activity relationship studies of 4-(1*H*)-quinolones targeting multi-drug resistant *P. falciparum* malaria

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Multiple series of highly substituted 2-methyl-4-(1*H*)-quinolones have been synthesized and tested against multi-drug resistant *P. falciparum* lines W2 and TM90C2B. Utilizing a Pd/SPHOS catalyst system, we devised synthetic strategies enabling the rapid and reliable preparation of focused libraries of differently substituted 4-(1*H*)-quinolones. One series was designed to probe the 3-position with substituents structurally similar to the side chain of atovaquone. In parallel, a detailed structure-activity relationship (SAR) study in the benzenoid ring was undertaken to further improve the 4-(1*H*)-quinolone's anti-malarial activity. The most potent compounds in the 4-(1*H*)-quinolone series are 450-fold more potent than atovaquone and 60-fold more potent than endochin. The series were simultaneously profiled for physicochemical properties including solubility, permeability, and logD. Results from both SAR and structure property relationship (SPR) studies will be used to advance the best compounds to *in vivo* experiments.

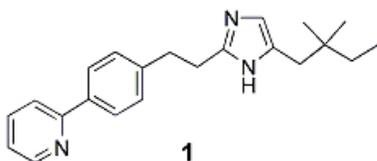
MEDI 556

Synthesis and SAR of derivatives based on 2-biarylethylimidazole as bombesin receptor subtype-3 (BRS-3) agonists for the treatment of obesity

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The bombesin receptor subtype 3 (BRS-3) is an orphan receptor which belongs to the bombesin receptor sub-family of the G-protein coupled receptors, expressed primarily in the central nervous system. Rodent genetic studies implicated that BRS-3 is involved in the regulation of energy homeostasis, and is a potential target for the treatment of obesity. This presentation describes a series of potent and selective BRS-3 agonists containing a biarylethylimidazole pharmacophore. Extensive SAR studies were carried out with different aryl substitutions, leading to the identification of 2-{2-[4-(pyridin-2-yl)phenyl]ethyl} -5-(2,2-dimethylbutyl)-1*H*-imidazole (**1**) with excellent binding affinity ($IC_{50} = 18$ nM, hBRS-3) and functional agonist activity ($EC_{50} = 53$ nM, 99% activation). After oral administration, compound **1** had sufficient exposure in diet induced obese mice and demonstrated mechanism-mediated efficacy in lowering food intake and body weight.



MEDI 557

Macrophage migration inhibitory factor: A novel target for drug discovery in autoimmune and inflammatory diseases

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Macrophage migration inhibitory factor (MIF) is a potent pro-inflammatory cytokine implicated in the pathogenesis of numerous autoimmune and inflammatory diseases (e.g. sepsis and type 1 diabetes). X-ray crystallographic studies have shown that MIF crystal structure possesses a pocket at the interface between the adjacent subunits. Therefore, we reasoned that molecules that targeted this site could be useful to inhibit MIF actions. Indeed, ISO-1 was specifically designed to fit into the pocket of MIF, an interaction confirmed by the crystal structure of the MIF complex with ISO-1. Administration of ISO-1 improves survival during sepsis and treats diabetes. ISO-1 is the first small molecule inhibitor of MIF with therapeutic implications and indicates the potential of the MIF pocket as a novel target for therapeutic interventions in human diseases. We will present our recent studies that generated new potent inhibitors with an IC_{50} of 100 nM, a 200-fold more potent than ISO-1.

MEDI 558

Neglected infectious disease case studies and implications for commercial collaborative drug discovery

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Case studies from scientists working in secure collaborative groups to rapidly develop drug candidates for commercial and humanitarian markets will be presented. In the first case study, the discovery of alternatives to Verapamil, a known chemosensitizer to overcome both tumor and malaria resistance, will be presented using novel collaborative drug discovery technologies.

Chemosensitizers addressing chloroquine resistance was identified combining results from the University of Cape Town with structurally related compounds from the UCSF and similar FDA/Orphan (courtesy Dr. Lipinski) approved drug compounds. CDD provides a cloud-based platform to *securely* register molecules and selectively share sensitive SAR data to develop new treatments. Via collaborative technology researchers build up networks of technical experts around therapeutic or target areas thus facilitating discovery of new drug candidates. Other case studies include: a Malaria Computational and Experimental around large set of historical small molecule animal SAR data case study (UNC, St. Jude), a Malaria UGI-4CC case study (Drexel-Indiana-UCSF), multiple Tuberculosis (TB) Public Private Partnerships, and gene-family wide Ki community databases augment the case studies. For TB where fundamental breakthroughs are needed to overcome resistance and shorten therapy, recent efforts to selectively arrest TB in the dormant phase working with leading researchers and mining SAR data will be presented. A recent example where leading TB researchers selectively share data from WT and nutrient starved screens on natural products will be presented for the first time. Parallels and contrasts to commercial biopharmaceutical research will be emphasized.

MEDI 559

Medicinal agents by self-assembly

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Given the recent explosion of antibiotic resistant strains of bacteria, research into the discovery of novel antibiotics is critical. Recently, our laboratory discovered a novel series of compounds that displayed potent activity against antibiotic resistant Gram-positive microbes. These compounds are bacteriocidal and in vivo testing reveals that they are active in two different animal models of infection. Structure-activity studies have shown that the cationic “tail” region of the molecule is important for activity, as is the length and conformation of the

molecule. Biochemical experiments reveal that these agents display a unique mechanism of action in that they target the bacterial membrane and induce depolarization of the cell. This mechanism implies the formation of a pore, presumably by self-assembly of multiple drug molecules. NMR dilution experiments confirmed the ability of these agents to self-assemble in hydrophobic environments. The self-assembly of these agents was explored by molecular modeling.

MEDI 560

Naphtho[1,2-*d*]thiazol-2-ylamine (SKA-31), a new activator of KCa2 and KCa3.1 potassium channels, potentiates the endothelium-derived hyperpolarizing factor response and lowers blood pressure

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Calcium-activated K channels KCa2/3 modulate calcium signaling and membrane potential in excitable and non-excitable cells. KCa2/3 channel activators constitute useful pharmacological tools and potential new drugs for the treatment of ataxia, epilepsy and hypertension. Using riluzole as template we identified 2 compounds, anthra[2,1-*d*]thiazol-2-ylamine (SKA-20) and naphtho[1,2-*d*]thiazol-2-ylamine (SKA-31), which are 10 to 20 times more potent than riluzole and activated KCa3.1 with EC50 values of 115 and 260 nM and KCa2.1-3 with EC50 values in the range 430 nM-3 μ M. These compounds activated native KCa2.3 and KCa3.1 channels in murine endothelial cells and potentiated EDHF-mediated dilations of carotid arteries from KCa3.1(+/-) mice. Administration of 10 and 30 mg/kg SKA-31 lowered mean arterial blood pressure by 4 and 6 mm Hg in normotensive mice and by 12 mm Hg in angiotensin-II-induced hypertension. In conclusion SKA-31 could be used as a new pharmacological tool to study KCa2/3 channel activation in vivo.

MEDI 561

Discovery of novel, CNS disease-modifying, experimental therapeutics using an efficient discovery engine based on informatics and fragment-based design combined with integrative pharmacology screens for prioritization

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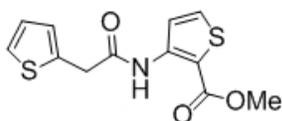
Early assessment of a candidate compound's potential for success in preclinical safety pharmacology and toxicology and early clinical, where failure rates and costs are high, is a focus of contemporary novel compound discovery. Our informatics analyses based on parsed databases of brain penetrant small molecules suggested multidimensional trends to leverage for CNS small molecule leads. We combined emerging trends with specifics about fragments in two distinct CNS drug discovery campaigns. A functional approach rapidly yielded low cost, second generation clinical candidates now in commercial development. The more efficient single molecular target approach used structure assisted design and yielded lead compounds with in vivo function among the first series of compounds synthesized. The initial phases of each of these case studies, including in vivo animal model function, have been reported (Hu et al., 2007 *BMCL*; Munoz et al., 2007 *J Neurosci*).

MEDI 562

In vivo activity of selective thiophene JNK inhibitors

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Herein we describe the evolution of novel thiophene JNK inhibitors from the HTS hit **1**, which demonstrates unusual selectivity over the closely related kinase p38, to a potent JNK compound. The optimized compound lowers levels of phospho-c-Jun in the brain in a Kainic Acid model of neuro-inflammation, and has acceptable pharmacokinetics in rat. Strategies used to improve potency and metabolic stability will be discussed. This compound retains the broad spectrum kinase selectivity of the initial hit, as demonstrated by a kinase panel.



compound **1**
JNK3 IC₅₀ = 2.6 μM
p38 IC₅₀ > 50 μM

MEDI 563

Novel non peptide-nitroxide conjugates for targeting mitochondria

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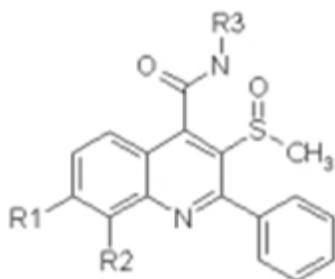
Reactive oxygen species (ROS) generated in mitochondria are thought to play a critical role in various pathologies associated with cell injury, aging, and death. Selective delivery of redox modifiers into these organelles may represent a particularly effective therapeutic strategy, but remains a practical challenge. Recent approaches are based on the tethering of a ROS scavenger to a vehicle with increased selectivity toward mitochondria. Our hemigramicidin-TEMPO conjugates rely on the homology of mitochondrial membranes to bacterial cell walls, and the hypothesis of the use of segments of the antibiotic gramicidin S as selective targeting agents. Among these, the (*E*)-alkene dipeptide isostere XJB-5-131 proved to be a novel and effective mitochondrial ROS and electron scavenging agent. The direct tethering of 4-amino-TEMPO to a shortened peptide isostere sequence of XJB-5-131 provided jp4_039, a lead compound among a unique class of small molecule-nitroxide conjugates that can serve as potent radioprotectors and radiation injury mitigators.

MEDI 564

Application of factorial experimental design (FED) to SAR: Exploration of the SAR at the 7 and 8 positions of the quinoline core for a series of novel potent 2-phenyl, 3-methylsulfoxy, 4-carboxamido quinoline NK3 antagonists

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Novel sulfoxide substituted quinoline derivatives had been shown to have interesting activity as potentially powerful antagonists of the NK3 receptor in the brain for treatment of psychiatric diseases. This led to a need for diverse new drug candidates with desirable activities and physical properties. A set of targets were designed and synthesized based on criteria determined by a factorial experimental design (FED) in order to systematically explore the SAR space with regards to sterics, electronics, and lipophilicity for quinoline substituents at the 7 and 8 positions. Application of palladium catalyzed synthetic methods allowed for the synthesis of most of these FED targets from a common synthetic intermediate. Results of the FED experiment leading to better understanding of the SAR space will be discussed.



MEDI 565

Discovery of novel arylthiadiazole as potent H3 antagonists

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A series novel arylthiadiazole H3 antagonists were designed and synthesized. Extensive SAR study led to the discovery of several potent analogs. Further optimization on pharmacokinetic properties afforded a potent H3 antagonist active in diabetic mouse model.

MEDI 566

Arylsulfanyl pyrazolones block mutant SOD1 aggregation and have potential application for the treatment of amyotrophic lateral sclerosis

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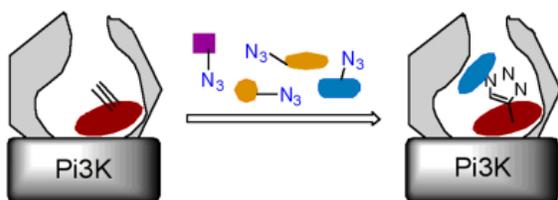
Amyotrophic Lateral Sclerosis (ALS) is an orphan neurodegenerative disease currently without a cure. Active compounds that can be starting points for pursuing potential therapeutics were identified in a cell-based high throughput screening assay targeting ALS. One of the scaffolds assembled from the active hits was the arylsulfanyl pyrazolone (ASP) scaffold. Both potency and bioavailability of the ASP scaffold have been extensively improved *via* chemical modification. Original ASP hit compounds were determined to have poor metabolic/plasma stability, so the direct metabolite was identified. We subsequently synthesized ASP analogs that resolved this rapid metabolism problem. One of the ASP analogues with superior potency and predicted pharmacological properties was tested *in vivo* for pharmacokinetics and brain penetration and subsequently in an animal model of ALS. The analogue showed sustained blood and brain levels *in vivo* and statistically significant activity in the mouse model of ALS, thus validating the scaffold as a therapeutic lead.

MEDI 567

Discovery of isoform specific inhibitors of PI3 kinase by click chemistry

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The use of azide-alkyne cycloaddition “click” chemistry for the discovery of novel isoform-specific inhibitors of phosphoinositol-3 kinase (PI3K) will be presented. Two strategies were employed. The first involves the filling of the active site by *in situ* assembly of candidate inhibitors on the enzyme without catalysis of the cycloaddition reaction (see graphic). The second approach is a more traditional one, requiring synthesis and screening of candidate compounds, enabled by copper-catalyzed click chemistry methods. The first technique proved to be an effective generator of lead compounds for refinement by the second method. Compounds have been created that function as inhibitors of specific isoforms of PI3K as measured by an oncogenic transformation assay in cell culture.



MEDI 568

Chemical synthesis and biological screening of 2-aminoimidazole based bacterial and fungal antibiofilm agents

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Biofilms, which are defined as a surface accreted microbial microcolony that is surrounded by a self-produced extracellular polymeric matrix (EPS), represent a major obstacle in the efforts against infectious disease control. Biofilm induced infections demonstrate an upwards of 1000 times greater resistance to antimicrobial agents and account for approximately 80 % of all infections. This study encompasses the synthesis and biological evaluation of a library of 2-aminoimidazoletriazoleamides that demonstrated the ability to not only inhibit the formation and disperse preformed bacterial biofilms, but also had significant fungal antibiofilm activity. To this date, no 2-aminoimidazole has exhibited fungal antibiofilm properties, making this activity a major development in the efforts to eradicate biofilm related disease.

MEDI 569

Discovery, synthesis and SAR of GIV3727, the first commercially successful bitterness blocker identified using receptor-based technologies

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Taste masking of bitter compounds, whether present in food, nutraceuticals or orally administered pharmaceuticals is a major challenge for developing commercially successful products. We report here the discovery, development and SAR of the first commercially relevant bitterness blocker identified using an HTS, medicinal chemistry-based approach. GIV3727 was found to effectively block TAS2R44 bitter receptor agonists (aristolochic acid and saccharin among others) *in vitro* and its potency correlated well with *in vivo* activity. A significant SAR study lead to a preliminary hypothesis on GIV3727 active conformation; this working hypothesis was independently reinforced through homology receptor modeling. Further application studies showed that GIV3727 effectively blocks the bitterness of noncaloric, non-cariogenic sweeteners in food, beverage and over-the-counter pharmaceutical formulations, greatly improving their organoleptic profile. This approach is expected to provide an unprecedented support for developing orally administered pharmaceuticals with improved acceptability as well as beverages and food applications.

MEDI 570

Investigation of the alpha-7 nicotinic acetylcholine receptor's ligand binding modes and hydrogen bonding patterns

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The $\alpha 7$ subtype of the human nicotinic acetylcholine receptor (nAChR) is the target of studies aimed at identifying features that will lead to the development of selective therapeutics. Benzylidene anabaseine (BA) analogues were synthesized in which the phenyl ring was replaced with pyridine, pyrrole, furan and thiophene (35% to 65% yields) as probes of H-bonding in the ligand binding domain (LBD). Voltage clamp analyses in *Xenopus* oocytes revealed H-bond donor pyrroles were better agonists than H-bond acceptor pyridines. The scanning cysteine accessibility mutagenesis (SCAM) method was used to map ligands' access and orientations within the LBD. Cysteine mutations were made in the LBD of the receptor. Results obtained with five of these mutants (S36C, L38C, W55C, L119C and I165C) and sulfhydryl reagents resembling agonists will be discussed in the context of the present receptor LBD homology model.

MEDI 571

Withdrawn

MEDI 572

Probing the ATP-binding domain of DNA-dependent protein kinase (DNA-PK) with coumarin- and isocoumarin-derived inhibitors

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DNA-dependent protein kinase (DNA-PK) is a nuclear serine threonine protein kinase responsible for the detection of DNA double strand breaks (DSBs) and thus, initiation of the non-homologous end joining pathway for DSB repair. The initiation of DSBs is a key mechanism of action of certain cytotoxic agents and ionizing radiation utilized for cancer chemotherapy. As such, potentiation of the *in vitro* cytotoxicity of such agents has been achieved by the inhibition of DNA-PK. Previous work carried out at the Northern Institute for Cancer Research identified 8-(dibenzothiophen-4-yl)-2-morpholin-4-yl-chromen-4-one (NU7441) as a potent inhibitor of DNA-PK. A pharmacophore mapping approach has been adopted in order to determine the effect of modification of the core chromenone scaffold on DNA-PK activity. Synthetic routes to the isomeric coumarin and isocoumarin scaffolds have been successfully developed to facilitate expedient library synthesis.