32\textsuperscript{nd} Annual National Medicinal Chemistry Symposium

June 6-9, 2010
Willey Hall
University of Minnesota
Twin Cities Campus
2010 National Medicinal Chemistry Symposium
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OPENING REMARKS

Date       Sunday, June 6
Time       2:00 PM

General Chair: Carston R. Wagner
University of Minnesota

ORAL SESSION 1

Targeting Neurodegeneration

Date       Sunday, June 6
Time       2:10 PM

Session Chair: Casey McComas
Merck

2:15 PM   Discovery, Characterization, and Antiparkinsonian Effect of a
          Series of Heterobiarylamides as Positive Allosteric Modulators of
          Metabotropic Glutamate Receptor 4
          Corey Hopkins, Vanderbilt University

2:55 PM   Hsp90 Inhibitors in Neurodegenerative Diseases
          Gabriela Chiosis, Memorial Sloan Kettering Cancer Center

3:35 PM   Discovery of 2,2-Difluoro-2-Phenylethyl-Piperidines as NR2B-
          Subtype Selective NMDA Receptor Antagonists
          Mark Layton, Merck Research Laboratories

4:15 PM   BREAK

4:30 PM   Targeting Dendritic Spines in CNS Disorders: Developing
          inhibitors of p21-activated kinase (PAK) for the treatment of
          Fragile X mental retardation syndrome
          Sergio Duron, Afraxis

5:10 PM   Selective Neuronal Nitric Oxide Synthase Inhibitors for the
          Prevention and Treatment of Neurodegenerative Diseases
          Richard Silverman, Northwestern University

5:50 PM   Opening Reception
          Willey Atrium
ORAL SESSION 2

GPR119 as a Target for the Treatment of Type 2 Diabetes

Date  Sunday, June 6  Session Chair: Robert Jones
Time  6:50 PM  Arena Pharmaceuticals

6:55 PM  New G Protein-Coupled Receptors as Therapeutic Targets for the Treatment of Type 2 Diabetes
Andrew Howard, Merck Research Laboratories  Page 6

7:35 PM  Discovery of GSK1292263A, a GPR119 Agonists for the Treatment of Type 2 Diabetes
Andrew Carpenter, Glaxo Smith Kline  Page 7

8:15 PM  PSN821: A Novel Oral GPR119 Agonist for the Treatment of Type 2 Diabetes Producing Substantial Glucose Lowering and Weight Loss in Rodents
Simon Swain, Prosidion/OSI Pharmaceuticals Inc.  Page 8

8:55 PM  BREAK

9:10 PM  Discovery of GPR119 Agonists for the Treatment of Type 2 Diabetes Using an Information Based Lead Generation Approach
Sherrie Pietranico-Cole, Roche  Page 9

9:50 PM  The Discovery of Novel Agonists of GPR119 Receptor for the Treatment of Type 2 Diabetes
Charles McWherter, Metabolex Pharmaceuticals  Page 10

10:30 PM  Adjournment
BREAKFAST
Time  7:00 - 8:30 AM

ORAL SESSION 3

Apoptosis Based Therapies

Date  Monday, June 7  Session Chair: Saul Rosenberg
Time  8:30 AM  Abbott Pharmaceuticals

8:35 AM  Dissecting and Drugging Apoptotic Pathways with Stapled Peptides of the BCL-2 Family
Loren Walensky, Harvard University  Page 11

9:15 AM  Discovery of ABT-263, an Orally Bioavailable Inhibitor of Bcl-2 Family Proteins
Milan Bruncko, Abbott Laboratories  Page 12

9:55 AM  BREAK

10:10 AM  Targeting Key Apoptosis Regulators for New Cancer Therapeutics
Shaomeng Wang, University of Michigan  Page 13

10:50 AM  Inducing Programmed Cell Death in Cancer Cells
John Flygare, Genetech  Page 13

11:30  Lunch Break
*UofM Alumni Luncheon, Carlson School of Management
*(former graduate students, post docs and visiting professors at the University of Minnesota are invited)
ORAL SESSION 4

Natural Product Based-Drug Design

Date: Monday, June 7
Time: 1:00 PM
Session Chair: Dale L. Boger
Scripps Research Institute

1:05 PM  A Tale of Two Tails: Modulation of the Hsp90 N- and C-Terminus by Small Molecules
Brian S. J. Blagg, University of Kansas
Page 14

1:45 PM  Function-Oriented Biosynthesis of Beta-Lactone Proteasome Inhibitors
Brad Moore, University of California, San Diego - Scripps Institute of Oceanography
Page 15

2:25 PM  Natural Products as Leads for Anticancer Drug Discovery
Gunda I. Georg, University of Minnesota
Page 16

3:05 PM  BREAK

3:20 PM  Himbacine-Based Drug Discovery Efforts - From Antiplatelet Agents to Antiobesity Agents
Sam Chackalamannil, Schering Plough Corporation
Page 17

4:00 PM  Vinblastine: Synthetic and Mechanistic Studies
Dale L. Boger, Scripps Research Institute
Page 18

4:45 PM  Adjournment

POSTER SESSION

Holiday Inn Metrodome
7:30 – 10:00 P.M.
BREAKFAST
Time 7:00 - 8:30 AM

ORAL SESSION 5

Recent Advances in Drug Metabolism and Pharmacokinetics

Date Tuesday, June 8  Session Chair: Michael Sinz
Time 8:30 AM Kenneth Santone
Bristol-Myers Squibb
- Wallingford

Terry Stouch, Duquesne University  Page 19

9:15 AM  PXR/CYP3A4 Transgenic Mouse Model
Frank Gonzales, National Institutes of Health  Page 20

9:55 AM  BREAK

Page 20

10:10 AM  Perspectives on Reactive Metabolic Intermediates
Gary Skiles, Amgen

10:50 AM  Transporter Biology in Drug Discovery and Development: Impact of SLCs/ABCs on PK/PD from Mouse to Man
Joseph Ware, Genentech  Page 21

11:30 AM  Lunch
ORAL SESSION 6

Recent Advances in Scale Up and Process Chemistry

Date Tuesday, June 8          Session Chair: Robert Larsen
Time 12:30 PM                  Amgen
Note Early Start              Presiding: Matt Bio
                               Amgen

12:35 PM  New Methods for Heterocycle Synthesis and Applications to the
          Chemical Development of Drug Candidates
          Jonathan Reeves, Boehringer-Ingelheim

1:15 PM  Pracitcal Arene Metallation Chemistry
          Matt Bio, Amgen

1:55 PM  Development and Scaleup of Heck, Suzuki-Miyaura and
          Metalation Reactions
          Marv Hansen, Eli Lilly & Company

2:35 PM  Break

2:50 PM  Process Development for Indazylurea Based TRPV1 Inhibitors
          Kirill Lukin, Abbott Laboratories

3:40 PM  The Development of a Biocatalytic Manufacturing Process for
          Sitagliptin
          Jacob Janey, Merck Research Laboratories

4:20 PM  Development of a Scalable Synthesis of Sulopenem: A β-lactam
          Antibacterial Candidate
          Jade Nelson, Pfizer

5:00 PM  Adjournment

6:30 PM  Awards Banquet
American Chemical Society Medicinal Chemistry Award

Wednesday, June 9
BREKFAST
Time  7:00 - 8:30 AM

8:30 – 8:45 a.m.  Session Chair:  Lawrence Hurley, Univ of Arizona
Chair, Div. of Medicinal Chemistry
American Chemical Society

8:45 – 9:35 AM
Zhaoning (Johnny) Zhu, Merck Research Laboratories
"Discovery and Development of Cyclic Acylguanidines as Potent and Selective
BACE1 Inhibitors"

9:35 – 10:20 AM
2010 Division of Medicinal Chemistry Award
Malcolm MacCoss, Bohicket Pharma Consulting LLC - Recipient
"Discoveries of Emend and Januvia - from Bench to Marketed Products"

10:20 – 10:35 AM  BREAK

10:40 – 11:30 AM
Hiroaki Mitsuya, Experimental Retroviorology Section, HIV & AIDS, National
Cancer Institute
"Development of Antiviral Therapeutics of AIDS:
From AZT to Darunavir"

11:35 AM – 12:15 PM
2010 IUPAC Richter Award
Arun K. Ghosh, Purdue University, Recipient
"Behind the Design of Darunavir for HIV/AIDS and β-Secretase Inhibitors for
Alzheimer's Disease"
ORAL SESSION 7

Fragment Based Drug Discovery

Date  Wednesday, June 9  Session Chair: David Rees
Time  1:15 PM  Astex, UK

1:20 PM  Scaffold Based Discovery of Indeglitazar, a Pan PPAR Treatment for Metabolic Diseases
Jack Lin, Plexxikon Pharmaceuticals

2:00 PM  Fragment-Based Discovery of the HSP90 Inhibitor, AT13387
Chris Murray, Astex Pharmaceuticals

2:40 PM  BREAK

2:55 PM  Fragment-Based Drug Discovery: Novel Opportunities for Well-Known Targets
Wolfgang Jahnke, Novartis Institute for Biomedical Research

3:35 PM  Evolving Trends and Opportunities for Fragment Based Screening
Chaohong Sun, Abbott

4:15 PM  Substrate Activity Screening: A Fragment-Based Method for Inhibitor Discovery
Jon Ellman, University of California, Berkeley

5:00 PM  Closing Remarks

ADJOURNMENT
Speaker Abstracts
ORAL SESSION 1

Targeting Neurodegeneration

2:15 PM  Discovery, Characterization, and Antiparkinsonian Effect of a Series of Heterobiarylamides as Positive Allosteric Modulators of Metabotropic Glutamate Receptor 4
Corey Hopkins, Vanderbilt University Medical Center
Department of Pharmacology
corey.r.hopkins@vanderbilt.edu

Using a functional high-throughput screening and subsequent parallel synthesis approach, we have discovered a novel series of selective heterobiaryl amides as positive allosteric modulators of mGluR4. These compounds potentiate hmGluR4 with EC50 values in the 240 nM – 5 μM range, and the rmGluR4 with EC50 values in the 80 nM – 1 μM range, with selected compounds having unprecedented, clean ancillary pharmacology (no substantial activity at 10 μM across a large panel of targets). A number of the more active compounds were next evaluated for their ability to shift the glutamate response curve to the left; and many produced robust fold shifts, giving this series several compounds with fold shifts >15. Optimized compounds, such as VU0361737, provide excellent brain exposure after subcutaneous dosing and have robust in vivo efficacy in reversing haloperidol-induced catalepsy, an anti-Parkinsonian rodent model. This series of selective positive allosteric modulators of mGluR4 provides critical research tools to further probe the mGluR4-mediated effects in Parkinson’s disease.
Hsp90 is a molecular chaperone with important roles in regulating pathogenic transformation. In addition to its well-characterized functions in malignancy, recent evidence from several laboratories suggests a role for Hsp90 in maintaining the functional stability of neuronal proteins of aberrant capacity, whether mutated or over-activated, allowing and sustaining the accumulation of toxic aggregates. In addition, Hsp90 regulates the activity of the transcription factor heat shock factor-1 (HSF-1), the master regulator of the heat shock response, mechanism that cells use for protection when exposed to conditions of stress. These biological functions therefore propose Hsp90 inhibition as a dual therapeutic modality in neurodegenerative diseases. First, by suppressing aberrant neuronal activity, Hsp90 inhibitors may ameliorate protein aggregation and its associated toxicity. Second, by activation of HSF-1 and the subsequent induction of heat shock proteins, such as Hsp70, Hsp90 inhibitors may redirect neuronal aggregate formation, and protect against protein toxicity. This talk will summarize our current knowledge on Hsp90 in neurodegeneration and will focus on the potential beneficial application of Hsp90 inhibitors in neurodegenerative diseases.
Discovery of 2,2-Difluoro-2-Phenylethyl-Piperidines as NR2B-Subtype Selective NMDA Receptor Antagonists
Mark Layton, Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA

The N-methyl-D-aspartate (NMDA) receptor is a ligand-gated, ionotropic glutamate channel expressed throughout the CNS. Overstimulation of NMDA receptors within the striatum is believed to contribute to the neurodegeneration associated with Parkinson's disease. The clinical effectiveness of non-selective NMDA receptor antagonists is limited by motor coordination and cognitive side effects with little or no therapeutic window. NR2B-selective antagonists are effective in animal models of Parkinson's disease without the side effects of non-selective compounds. Our research program targeted orally bioavailable NR2B-subtype selective antagonists culminating in the discovery of MK-0657. The backup program focused on identifying structurally diverse oral agents with improved in vivo potency and pharmacokinetics. The design and development of highly potent and selective NR2B antagonists with improved profiles over the lead compound will be presented.
Fragile X syndrome is an X-linked genetic disorder caused by mutations in the Fmr1 gene and characterized by severe cognitive dysfunction and in many cases autism. There is currently no treatment available. Defects in dendritic spines, postsynaptic structures which mediate cortical excitatory synaptic transmission and plasticity, are present in both the human disease as well as Fmr1 knock-out mice, a well established model of human Fragile X mental retardation syndrome. In particular, these defects are marked by a reduced proportion of "mature" dendritic spines coupled with an increased proportion of filopodia-like, "immature" dendritic spines. It is thought that the defects in synaptic function, which are at the core of the disease, are a direct result of defective dendritic spines and recent evidence suggests that alterations to p21-activated kinase (PAK), an actin cytoskeleton-regulating enzyme, may play a central role in the disease phenotypes.

Our group identified for the first time small molecule inhibitors of PAK as potential novel treatment modalities for Fragile X. Starting from a 12,000 compound kinase-focused library, we developed highly potent small molecule PAK inhibitors representing several chemical scaffolds. Currently, our most advanced compounds inhibit Group I PAKs with an IC50 below 10 nM. These compounds demonstrate good overall PK properties, show high CNS exposure and support QD dosing. Treating acute cortical slices from Fmr1 KO mice with our PAK inhibitors reversed dendritic spine defects and normalized the population of "mature" and "immature" dendritic spines. In addition, we observed normalization of cortical long-term potentiation (LTP), which is otherwise depressed in Fmr1-KOs. Following 5-hour treatment with a PAK inhibitor, theta-burst stimulation induced cortical LTP that was indistinguishable from untreated wild-type slices and significantly elevated above vehicle-treated
Fmr1 KO controls. Taken together, these results show that short-duration pharmacological inhibition of PAK can address the synaptic defects in Fragile X that are thought to be at the core of the disease. Consistent with these observations, treatment of Fmr1 KO mice with small molecule PAK inhibitors reversed behavioral defects in these animals including stereotypy, anxiety and ambulatory activity that are all increased compared to wild-type litter mates. These results represent the first disease modifying agent for Fragile X and provide a path forward for the treatment of Fragile X patients.
Nitric oxide (NO) is a ubiquitous biological messenger involved in a variety of physiological processes that acts as a signal transducer but also exerts a variety of regulatory and cytostatic functions. Nitric oxide synthase (NOS) is a family of homodimeric enzymes that catalyzes the oxidation of L-arginine to L-citrulline and nitric oxide in a NADPH- and O2-dependent process. The constitutive endothelial isozyme (eNOS) is involved in the regulation of smooth muscle relaxation and blood pressure and in the inhibition of platelet aggregation. A second constitutive isozyme is neuronal NOS (nNOS), which is important for neurotransmission. A third isozyme is the inducible NOS (iNOS), which is located in activated macrophage cells and acts as a cytotoxic agent in normal immune responses.

The use of NOS inhibitors in pathologically elevated synthesis of NO has great therapeutic potential. NO overproduction by nNOS has been associated with neurodegeneration during stroke, spinal transmission of pain, migraine headaches, Parkinson's disease, Alzheimer's disease, Huntington's disease, and cerebral palsy. Compounds that inhibit nNOS would decrease the production of NO in the brain. However, because of the importance of NO to physiological functioning, potent as well as nNOS-selective inhibitors are essential.

This lecture describes the design of the first class of potent and highly dual-selective nNOS inhibitors and their modification for enhanced potency, selectivity, and lipophilicity. After the first selective inhibitors were obtained, X-ray crystallography and computer modeling guided additional modifications, and de novo structure-based design led to a new class of potent and selective nNOS inhibitors. Results of animal testing of some of these compounds for peripheral pain and cerebral palsy will be described.
GPR119 as a Target for the Treatment of Type 2 Diabetes

6:55 PM  New G Protein-Coupled Receptors as Therapeutic Targets for the Treatment of Type 2 Diabetes
Andrew Howard, Department of Metabolic Disorders-Diabetes, Merck Research Laboratories, Rahway, New Jersey, USA

In recent years, there has been an alarming increase in obesity worldwide (20-25% of the U.S. population, 10-25% of the European population and 2-3% for Japan). Co-morbidities associated with obesity include hypertension, dyslipidemia and cardiovascular disease, which significantly reduce life expectancy. At present, safe and effective therapies are clearly lacking. Type 2 diabetes mellitus (T2DM) also represents a major and growing health threat to the world and continues to be a huge, unmet medical need. The prevalence of T2DM is projected to increase from 194 million today to over 333 million by 2025. Despite the availability of a range of agents for T2DM (i.e., sulfonylureas, metformin, PPARα-selective agonists, and DPP-4 inhibitors), a high proportion of the diabetic patients fail to achieve or maintain glycemic targets. In addition, most current therapies have significant limitations and/or liabilities, particularly in terms of disease modification and durability. As obesity and diabetes have become more prevalent, opportunities for pharmacological intervention have also grown, especially in the area of novel target discovery. G protein-coupled receptors have traditionally been an attractive class for therapeutic intervention. This talk will focus on progress made and challenges faced in identification and validation of emerging GPCR targets implicated in metabolic disorders, including GPR40 and GPR119, among others.
GPR119 is a recently discovered GPCR expressed in enteroendocrine cells in the GI tract and in pancreatic islets. Evidence from small molecule activation of this receptor suggests GPR119 plays a role in glucose homeostasis and may have utility in the treatment of type 2 diabetes.

In addition to compounds disclosed in the literature, several small molecule agonist classes were uncovered during our investigation of this target. Evidence suggested that replacement of the central core of the agonists may produce alternative chemotypes. An internally-developed web-based search tool, the Drug Rings Database, was successfully used to identify a series containing biaryl functionality. Lead optimization of this series led to the discovery of GSK1292263A, which progressed into clinical trials for the treatment of type 2 diabetes and is currently in Phase II. Details of the discovery of this class of GPR119 agonists will be presented.
GPR119 is a G-protein coupled receptor expressed in both pancreatic ß-cells and incretin producing cells in the gastrointestinal tract. Agonists of GPR119 demonstrate substantial glucose lowering in rodent models of diabetes and in addition, some GPR119 agonists have been shown to offer significant effects on food intake reduction and body weight loss. Hence, GPR119 agonists demonstrate the potential for both glucose lowering and meaningful body weight loss in patients with type 2 diabetes.

Herein, we describe the identification and SAR around early tool and subsequent lead compounds which ultimately led to the discovery of PSN821, a novel orally-active agonist of the GPR119 receptor. PSN821’s in vitro effects on insulin and GLP-1 secretion, sustained glucose control in prediabetic ZDF rats and substantial body weight lowering in DIO rats will also be described.
Discovery of GPR119 Agonists for the Treatment of Type 2 Diabetes Using an Information Based Lead Generation Approach


Discovery Chemistry, Hoffmann-La Roche Inc., Nutley, NJ, 07110.
Sherrie_L.Pietranico@roche.com

GPR119 is a 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. An information based lead generation approach was employed to discover potent and efficacious lead GPR119 agonists derived from pyrazolopyrimidines. Strategies to eliminate hERG activity and glutathione addition associated with the lead structures led to the design of significantly improved GPR119 agonists in the related pyrrolopyrimidine and dihydropyrrolopyrimidine series.
The Discovery of Novel Agonists of GPR119 Receptor for the Treatment of Type 2 Diabetes

Charles McWherter, Metabolex Pharmaceuticals
Apoptosis Based Therapies

8:35 AM Dissecting and Drugging Apoptotic Pathways with Stapled Peptides of the BCL-2 Family

Loren Walensky, Harvard University

Protein interactions mediate innumerable cellular activities in health and disease. Whether fleeting or stable, homeostatic or pathologic, protein partnerships and their sites of contact form the basis for discovery of biological pathways, disease mechanisms, and opportunities for therapeutic intervention. Harnessing Nature’s evolutionarily-honed peptides to investigate and subvert disease-causing protein interactions has been hindered by their loss of natural architecture, vulnerability to degradation, and cellular impermeability. We have applied a chemical strategy termed “hydrocarbon-stapling” to remedy the shortcomings of synthetic peptides, yielding unique discovery tools and prototype therapeutics for dissecting and targeting pathologic protein interactions.

BCL-2 family protein interactions constitute a critical control point for the regulation of programmed cell death or apoptosis. Whereas multidomain anti-apoptotic proteins such as BCL-2 guard against cell death, multidomain pro-apoptotic proteins such as BAX constitute a gateway to cell death through mitochondrial damage. The BH3-only proteins function as death sentinels situated throughout the cell, poised to transmit signals of cell injury to multidomain members. Cancer cells often exploit the apoptotic pathway and achieve immortality by overexpressing BCL-2 family survival proteins. Thus, pharmacologic targeting of BCL-2 proteins to reactivate the death pathway is a promising strategy for subverting cancer. Each BCL-2 family member contains a critical interaction motif called the BH3 death helix, which mediates the crosstalk of the protein network. By chemically “stapling” this key binding motif, we have generated a molecular toolbox of Stabilized Alpha-Helices of BCL-2 domains (SAHBs) to dissect apoptotic signaling pathways and explore the pharmacologic effects of “BH3 replacement” in cancer cells. The sensitivity and specificity of stapled peptide helices in identifying and discriminating among protein targets is best exemplified by their capacity to uncover new protein interactions, such as our use of a BIM BH3 helix to identify the elusive trigger site on pro-apoptotic
BAX and a stapled phospho-BAD BH3 helix to determine how BAD toggles between its apoptotic and metabolic functions. Our recent studies have focused on defining the molecular mechanism of BH3-mediated direct BAX activation and on deploying pro-apoptotic SAHBs to overcome the chemoresistance of relapsed and refractory malignancies.
Apoptosis, or programmed cell death, is an evolutionarily conserved and highly regulated process that plays a role in the careful removal of aged, damaged and unnecessary cells. Impairment of this function often leads to the development of several diseases, including cancer. B-cell lymphocyte/leukemia 2 family proteins (Bcl-2) are important regulators of programmed cell death. Bcl-2 was discovered in follicular lymphomas, where the t(14;18) chromosomal translocation resulted in the over-expression of Bcl-2 mRNA and its encoded protein. The Bcl-2 family of genes encodes a large family of anti-apoptotic and pro-apoptotic proteins that share up to four Bcl-2 homology (BH) domains. The pro-survival family consists of Bcl-2, Bcl-XL, Bcl-w, Mcl-1 and A1 proteins, all of which contain four BH domains (BH1-BH4). The pro-apoptotic proteins can be divided into two groups. One group is characterized by the possession of three BH domains (BH1-BH3) (Bax, Bak), while the second group contains proteins with one BH3 domain (BH3-only; Bad, Bik, Bid, Bim, Hrk, Bmf, Noxa and Puma). The involvement of Bcl-2 proteins in oncogenic processes collectively makes them an attractive target for cancer therapy, as small molecule inhibitors of anti-apoptotic Bcl-2 proteins that could mimic the function of various BH3-only proteins should bias the cell towards apoptosis. In this presentation, the SAR development towards the discovery of ABT-263, a BH3-only protein mimic, will be disclosed. Our first generation Bcl-2 family protein inhibitor - ABT-737, was effective in various tumor models, but lacked oral bioavailability. Therefore extensive SAR studies were initiated in order to identify a second-generation compound that could be dosed orally, an effort that culminated in the identification of ABT-263. This compound is a best-in-class, orally bioavailable inhibitor of Bcl-2 family proteins with high affinities (Ki < 1 nM). Additionally, ABT-263 has excellent preclinical, single-agent antitumor efficacy in small cell lung cancer, lymphoma, and leukemia, and recently is in several phase II clinical trials.
10:10 AM  Targeting Key Apoptosis Regulators for New Cancer Therapeutics  
*Shaomeng Wang, University of Michigan*

10:50 AM  Inducing Programmed Cell Death in Cancer Cells  
*John Flygare, Genetech*

Apoptosis, or programmed cell death, is a cell suicide mechanism with a major role in development and homeostasis in vertebrates and invertebrates. Inhibition of apoptosis can lead to the absence of physiological cell death and contribute to development and progression of various malignancies. Apoptotic cell death can be initiated through the engagement of cell-surface pro-apoptotic receptors by their specific ligands or by changes in internal cellular integrity. Both of these pathways converge at the activation of effector caspases. Blockage of programmed cell death enhances cell survival and contributes to escape from cytotoxic therapies. This well regulated process is governed by a series of protein/protein interactions including Bcl-2 family proteins and inhibitor of apoptosis (IAP) proteins. Specific interactions that are amenable to small molecule intervention will be presented. Examples will include small molecule mimetics of the second mitochondrial activator of caspases (Smac) that have been developed as clinical candidates for our oncology program. Evaluation of these compounds against a number of cancer cell lines indicated that they caused single agent cell killing by inducing apoptosis. The work leading to the discovery of clinical compound GDC-0152 will be presented. Our current efforts are focused on creating isoform-selective backup leads in order to investigate the efficacy/toxicity profile versus GDC-0152. These selective compounds also give us insight into the mechanism of action of IAP inhibition. These data suggest that regulation of apoptosis may represent a useful approach to improve the current management of this serious disease.
ORAL SESSION 4

Natural Product Based-Drug Design

1:05 PM  A Tale of Two Tails: Modulation of the Hsp90 N- and C-Terminus by Small Molecules

Brian S. J. Blagg, University of Kansas

The 90 kDa heat shock proteins (Hsp90) are molecular chaperones required for the refolding of denatured proteins and the maturation of nascent polypeptides into their biologically active, three-dimensional structures. In fact, numerous proteins represented in all six hallmarks of cancer are dependent upon Hsp90 for conformational maturation. Hsp90 inhibition provides a combinatorial attack on multiple pathways responsible for malignant cell growth and proliferation. Consequently, Hsp90 has emerged as a promising target for the development of cancer chemotherapeutics.

Hsp90 contains two ATP binding sites, and in order to fold nascent polypeptides into biologically active proteins, Hsp90 catalyzes the hydrolysis of ATP. ATP hydrolysis provides the Hsp90 protein folding machinery the requisite energy for folding “client” proteins into their correct three-dimensional conformation. Disruption of this folding process results in the destabilization of Hsp90 “client” protein complexes, which leads to ubiquitination and proteasome-mediated degradation of the protein substrate.

The C-terminal ATP binding site was only recently elucidated and studies demonstrated that the coumarin antibiotics, including novobiocin, inhibit the C-terminal ATP binding site and lead to the degradation of Hsp90 client proteins similar to that of N-terminal inhibitors. Unfortunately, novobiocin’s activity is not sufficient for further clinical evaluation and thus provides a new opportunity for the development of more effective Hsp90 inhibitors. We have developed the most potent C-terminal inhibitors of Hsp90 yet discovered and have demonstrated that Hsp90 inhibitors possess potent neuroprotective properties for potential use against Alzheimer’s, Parkinson’s and Multiple Sclerosis, in addition to some that exhibit excellent anti-tumor activity. Delineation of these two attributes by the conduction of structure–activity relationships provided two novel classes of Hsp90 inhibitors. Background, development, and future directions for Hsp90 C-terminal inhibitors will be provided.
1:45 PM  Function-Oriented Biosynthesis of Beta-Lactone Proteasome Inhibitors

Bradley S. Moore, Scripps Institution of Oceanography and the Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, CA
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The natural proteasome inhibitor salinosporamide A from the marine bacterium Salinispora tropica is a promising drug candidate for the treatment of multiple myeloma and mantle cell lymphoma. Its unusual \( \delta \)-lactam-\( \delta \)-lactone ring structure is biosynthesized by a unique metabolic process incorporating novel biochemical precursors that contribute to the drug's selectivity and potency. Using a comprehensive approach combining chemical synthesis and metabolic engineering, we generated a series of salinosporamide analogues with altered proteasome binding affinity. In this presentation, I will outline our strategy to design and develop a focused biosynthetic library of salinosporamide analogues that resulted in the production of a derivative equipotent to salinosporamide A in inhibition of the chymotrypsin-like activity of the proteasome, yet, superior in the cell-based HCT-116 assay.
Natural products continue to be an excellent source as drugs or leads for drug discovery efforts. However, natural products often need chemical modification in order to become effective therapeutic agents, involving either the semi-synthesis or total synthesis of analogues. Efforts in that regard with the natural products triptolide, phenanthropiperidines, and oximidine II will be discussed.
Total synthesis of himbicine and himbicine-based drug discovery research in three different therapeutic areas will be discussed. This research has led to two successful lead optimization programs and identification of an antiplatelet agent SCH 530348 which is currently undergoing Phase-III clinical studies for acute coronary syndrome.
Vinblastine: Synthetic and Mechanistic Studies

Dale L. Boger

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Abstract. A summary of studies providing a first generation and second generation (asymmetric) total synthesis of vindoline based on the implementation of a powerful [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles will be presented along with its extension to the preparation of a series of key analogs. The development of a single-step biomimetic Fe(III)-promoted coupling of vindoline with catharanthine and subsequent in situ oxidation to provide vinblastine, its extension to the total synthesis of related natural products and key analogs, and new mechanistic insights into the reactions will be presented. Key studies addressing the structural features of vinblastine contributing to its tubulin binding and antitumor properties will be discussed.
Recent Advances in Drug Metabolism and Pharmacokinetics

Terry Stouch, Duquesne University

ADME/Tox properties are critical to a drug’s success. in silico approaches to estimating these properties are attractive since hypothetical molecules can be evaluated even before synthesis. More importantly, one hopes that in silico approaches ('models') might help to guide 'repair' of compounds with liabilities. These models, based on many technologies and from many laboratories, have been available for quite some time. However, despite extensive effort in their development, reports on the success of these models has been mixed and range from accounts of great success to some of total failure. Possible reasons for this are the actual adequacy of the models, the interpretation of their results, and the predilection of the user, among others. In fact, even a "good" model can actually "fail", a successful model could be perceived to fail depending on interpretation of the results, and a "good" result for one user might be "bad" for another. In this talk, I will expand on and update observations provided in "In silico ADME/Tox: why models fail," T. R. Stouch, et al. J Comput. Aided Mol Des 2003, 17 (2-4), 83. Current best principals practice in model development, model deployment, and model use will be discussed with examples. "Model-independent" paths forward to addressing ADME/Tox will be discussed.
9:15 AM  PXR/CYP3A4 Transgenic Mouse Model
         Frank Gonzales, National Institutes of Health

10:10 AM  Perspectives on Reactive Metabolic Intermediates
          Gary Skiles, Amgen
With the advent of metabolic stability screening and an increased emphasis on the elimination of cytochrome P450 interactions, inadvertently, many molecules in drug development are high affinity substrates of drug transporters. In particular, membrane transporters expressed in the intestine, liver, kidney, and at the blood-brain barrier (BBB) are now recognized as determinants of ADME, drug-drug interactions, and drug response. Over 400 membrane transporters in two major super-families, Solute Carrier (SLC) and the ATP-Binding Cassette (ABC) in the human genome have been discovered. SLC and ABC’s maintain cellular physiology and are known to import and efflux a vast array of drugs and xenobiotics. Knowledge of drug transporter function and SAR has been derived in vitro using polarized monolayer cells and in vivo through the utilization of slc or abc knock-out mice. However, due to variable levels of SLC/ABC expression, interplay between drug metabolism and drug transport, and the promiscuity of substrate/transport interactions, it remains difficult to define an optimal drug discovery screening strategy without recognition of the caveats of each preclinical model used to define membrane transporter interactions. Moreover, considerable debate exists with respect to the prediction of clinical DDI risk that an NME or marketed drug may have. To better clarify the ‘how’, ‘when’, and ‘why’ of transporter biology, an International Transporter Consortium (ITC) has recently convened and published recommendations on drug transport evaluation. The objective of this presentation will be to provide a balanced and critical review of the current knowledge of transporter biology and the ITC’s recommendations within the drug discovery and development continuum.
ORAL SESSION 6

Recent Advances in Scale Up and Process Chemistry

12:35 PM  New Methods for Heterocycle Synthesis and Applications to the Chemical Development of Drug Candidates
Jonathan Reeves, Boehringer-Ingelheim
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Novel methodologies for the synthesis of substituted pyrroles, aza- and diazaindoles, pyrroloquinoxalines and related heterocycles will be described. The application of these methodologies to the development of practical syntheses of drug candidates will also be described.
The regioselective metallation of heterocycles is a powerful synthetic tool for the creation of complex molecules, including those of interest as human therapeutic agents. Unfortunately, the conditions required for regioselective metallation of heterocycles are often impractical for large-scale application either due to cost, safety or the kinetic stability of the metallated species generated. We report on two recent examples in which these limitations were overcome such that practical and efficient metallations were achieved and applied in synthetically useful ways. In particular, we have demonstrated the regioselective magnesiation of thiophenes and benzothiazoles with iso-propylmagnesium chloride under non-cryogenic conditions as an alternative to cryogenic conditions typically required to generate and use the lithiated analogs of these molecules. In a second example we report on the generation of 5-metallo-1-benzyl-1H-tetrazoles under practical conditions and application to the synthesis of tetrazole-containing complex molecules. The construction of tetrazoles often requires use of hazardous reagents that limit the application of existing synthetic methods due to safety concerns. The ability to safely generate and utilize tetrazoles as synthetic building blocks avoids the hazards of associated with common methods of tetrazole synthesis.
This lecture will detail process development of three common organic transformations as applied to the synthesis of several pharmaceutical intermediates. First a novel double-Heck reaction was used to generate a trisubstituted alkene with high stereocontrol. Elaboration of the Heck acrylate products required a Suzuki-Miyaura coupling to afford the desired triaryl substituted alkene. It was found that high loading of triphenylphosphine as a Pd ligand afforded improved results in the Suzuki-Miyaura reaction, in direct contrast to literature reports. In the final section, the application of metal-halogen exchange reactions in benzothiophene chemistry was optimized through correct choice of metal and by blocking proton transfer from more acidic sites on the benzothiophene. Ultimately this benzothiophene metalation strategy was replaced with a new thiophenol dianion route to afford a significantly cheaper approach to the key intermediate.
Process development for indazylurea based TRPV1 inhibitors
Kirill Lukin, GPRD Process Chemistry. Abbott Laboratories, R-8, North Chicago, IL

Process development for indazylurea based TRPV inhibitor 1 will be presented with focus on asymmetric synthesis of 5-tert-butylaminoindan, a new method for the preparation of indazoles from o-flourobenzaldehydes, and catalytic amination of haloindazoles with ureas.
A new biocatalytic process using a highly evolved R-selective transaminase enzyme is described. This new manufacturing process was developed to replace the current catalytic, asymmetric enamine hydrogenation used to manufacture the anti-diabetic DPP-IV inhibitor sitagliptin, the active ingredient in Januvia®. Using a combination of "substrate walking" and a variety of directed evolution approaches, an industrial useful enzyme was produced starting from absolutely no activity in the parent transaminase. The resulting enzyme is not only capable of producing sitagliptin on industrial scale, but it has proven to be a broadly applicable catalyst towards the direct conversion of ketones to enantiopure R-amines. This work clearly demonstrates that biocatalysis is a mature, manufacturing ready technology with broad utility and application from discovery through commercial supply.
The sulopenem intravenous program has a storied history within Pfizer. During a collaboration between the Groton and Nagoya sites during the late 1980s and early 1990s, sulopenem API was manufactured on multi-kilogram scale and successfully administered to approximately 1,200 patients as a lyophilized sodium salt. Despite a positive clinical outcome, the development program was discontinued in the late 1990s, but was recently renewed with the goal of developing orally available prodrugs that would decrease hospitalization time for patients.

Containment guidelines for the safe handling of β-lactam antibacterial agents required Pfizer scientists to support technology development and implementation for the sulopenem program across three continents. Multiple synthetic routes were evaluated in our laboratories during progression from gram- to kilogram-scale and two distinct processes were utilized for API manufacture at up to 4,000 L scale. Our API sub-team has recently nominated a third API process for potential commercialization. This new process addresses many of the challenges associated with synthesis of these complex targets on large scale. An overview will be presented.
Wednesday, June 9

American Chemical Society Medicinal Chemistry Award

8:30 – 8:45 a.m.  Session Chair: Lawrence Hurley, Univ of Arizona Chair, Div. of Medicinal Chemistry American Chemical Society
Zhaoning (Johnny) Zhu, Merck Research Laboratories
"Discovery and Development of Cyclic Acylguanidines as Potent and Selective BACE1 Inhibitors"

"Discovery and Development of Cyclic Acylguanidines as Potent and Selective BACE1 Inhibitors"

Alzheimer’s disease is caused by widespread neuronal dysfunction and cell death that is believed to be initiated by synaptic deposition of Aβ42 oligomers related to their overproduction, decreased clearance or enhanced aggregation. Aβ42 is generated from the membrane bound Amyloid Precursor protein (APP) via sequential cleavages first by γ-secretase-1 (BACE1) followed by γ-secretase. BACE inhibition has been viewed as an attractive path for potential treatment of Alzheimer’s disease through reduction of Aβ42 production.

A unique structural class of cyclic acylguanidine BACE inhibitors was designed and validated as highly potent and selective and CNS penetrant BACE inhibitors, starting from a fragment based protein NMR screening lead with extensive use of X-ray crystallography and CADD technologies. Here we will discuss the SAR work evolving from 5-membered iminohydantoins (1 and 2) to 6-membered iminopyrimidinone (3) with special emphasis on optimization of overall molecular profile guided by rat in vivo efficacy data.
2010 Division of Medicinal Chemistry Award
Malcolm MacCoss, Bohicket Pharma Consulting LLC - Recipient
"Discoveries of Emend and Januvia - from Bench to Marketed Products"

This presentation will address the discoveries of two marketed drugs, Emend (aprepitant), the first small molecule orally active, highly potent, Substance P Antagonist for the treatment of Chemotherapy Induced Nausea and Vomiting (CINV); and of Januvia (sitagliptin) the first orally active dipeptidyl peptidase 4 (DPP-IV) inhibitor for the treatment of Type 2 Diabetes Mellitus.

In both cases, the rationale for addressing the target and the medicinal chemistry approach which led to the selection of the final candidate molecules, will be detailed - including the scientific hurdles overcome on the way to the candidates. In addition, the activities in the pre-clinical animal models and the early human clinical data will be presented. The overall goal is to demonstrate two case histories from the early chemistry leads to the final marketed products from a medicinal chemistry perspective.
Development of Antiviral Therapeutics of AIDS: From AZT to Darunavir

Since the first three reverse transcriptase inhibitors including AZT, developed at the National Cancer Institute, proved to be efficacious in patients with HIV infection, a number of antiviral agents have been added to our armamentarium in the fight against AIDS. Combination chemotherapy or HAART has had a major impact on the morbidity and mortality of patients with HIV infection. However, we have faced multiple major problems, which represent the challenges different than we faced in the development of the first drugs. They include (i) drug-related toxicities, (ii) emergence of drug-resistant HIV variants, (iii) only partial restoration of immunologic functions, and (iv) increased cost of therapy. More efficacious and less toxic anti-HIV agents are needed. One new area in the development of anti-HIV agents is predictive modeling, which maximizes our chances of success. We recently discovered that darunavir and a group of agents block the dimerization of HIV protease, an essential step in the replication cycle of HIV. Further improved approaches to explore new treatment modalities should make it possible to control HIV diseases more effectively.
Behind the Design of Darunavir for HIV/AIDS and β-Secretase Inhibitors for Alzheimer's Disease

Aspartic acid proteases are implicated in the pathogenesis of many of human diseases. As a consequence, aspartic acid proteases have become important drug-design targets. The use of HIV protease inhibitors in highly active antiretroviral therapy (HAART) with reverse transcriptase inhibitors continues to be the major treatment regimen for HIV infection and AIDS. One of the major challenges of HAART-therapy however, is the emergence of multidrug-resistant HIV-1 variants. In this context, our structure-based design strategies targeting the protein backbone led to diverse classes of potent HIV-1 protease inhibitors. Darunavir, designed based upon our ‘backbone binding concept’ has been approved for the treatment of HIV/AIDS patients harboring multidrug-resistant HIV. Another aspartic acid protease, memapsin 2 (beta-secretase, BACE-1), has been a focus of our efforts as an important drug-design target for Alzheimer's disease. Our structure-based design has led to the development of a number of potent and selective inhibitors of memapsin 2 for clinical development. This presentation will focus on design-concepts, general (structure-based design) strategies and development tools for HIV-1 protease and beta-secretase inhibitors.
Diabetes patients often suffer from obesity, hypertension, elevated cholesterol, hyperlipidemia - symptoms commonly associated with Metabolic Syndrome (also known as Syndrome X). To address the various challenges of treating NIDDM patients in a single therapeutic, a pan PPAR agonist would address many symptoms of Syndrome X such as dyslipidemia (PPARα), insulin sensitization (PPARγ), and dyslipidemia/HDL (PPARδ). Using our Scaffold Based Discovery platform, we identified a weakly active scaffold/fragment with > 200 μM activity on PPARγ. Using structural binding information from co-crystallography, we rapidly advanced a medicinal chemistry effort toward optimization of the weakly active scaffold toward pan PPAR activity for NIDDM. After 2 rounds of chemistry, we identified Indeglitazar, a pan-PPAR active agent, with partial PPARγ and PPARδ agonism. Indeglitazar demonstrated glucose- and lipid-lowering without the side effects that plague existing PPARα, PPARγ, and PPARα,δ - dual agonists in pharmacology studies. Evidence of partial activation of PPARγ was supported by the observation that adiponectin levels were very modestly increased in vivo. Indeglitazar also showed an excellent safety margin: while efficacy is achieved at 10 mg/kg daily doses, rats survived a 28 day daily dosing at 500 mpk and cynomolgus monkeys survived 28 day daily dosing at 400 mpk. Indeglitazar has advanced to phase 2 clinical trials.
2:00 PM  Fragment-Based Discovery of the HSP90 Inhibitor, AT13387  
Chris Murray, Astex Pharmaceuticals

2:55 PM  Fragment-Based Drug Discovery: Novel Opportunities for Well-Known Targets  
Wolfgang Jahnke, Novartis Institute for Biomedical Research

3:35 PM  Evolving Trends and Opportunities for Fragment Based Screening  
Chaohong Sun, Abbott

4:15 PM  Substrate Activity Screening: A Fragment-Based Method for Inhibitor Discovery  
Jon Ellman, University of California, Berkeley
Poster Session

32nd National Medicinal Chemistry Symposium
Expanding the Scope of the Cu Assisted Suzuki Reaction: Application to Aryl Chlorides and Polyhalo Aryl Boronates

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Compounds containing biaryl and heterobiaryl subunits are of great interest to the pharmaceutical industry; improved protocols for their synthesis, therefore, can accelerate lead ID and lead optimization programs. Recent advances in the development of the copper facilitated suzuki reaction for the improved preparation of such compounds are described. Improvements include expansion of the scope of substrates to include aryl chlorides and polyhalo aryl boronates as well as demonstration of the generality of the transformation to simple aryl boronates and highly hindered coupling partners. Through a short ligand screen, it was found that S-Phos and X-Phos could successfully accomplish the coupling of 2-pyridyl boronates to aryl chlorides and bromides at lowered temperatures, shorter reaction times, and in higher yield than previously described. Control reactions (no copper) showed little to no productive couplings for 2-heteroaryl boronates and lowered yields for the polyhalo, simple, and hindered aryl boronates.

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\text{R-H} + \underset{\text{incl. hindered and hetAr halides}}{\text{R-X}} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{CuCl, Pd(OAc)}_2, \text{DMF, 70-100 °C, 15 min}} \underset{\text{incl. } 2,6\text{-diF, hindered and hetAr boronates}}{\text{R-Y}}
\]

\[
Y = \text{N, w/ Cu: } 69-95%
\]

\[
Y = \text{N, w/o Cu: } 0-12%
\]

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The well documented deregulation of the PI3K/AKT/mTOR pathway in numerous tumor types has established a significant desire for PI3K inhibitors with drug-like properties. Our program directed toward identifying potent and orally available molecules that selectively inhibit PI3 kinase has previously disclosed GDC-0941. This poster will discuss the identification of new PI3 kinase inhibitors. Topics highlighted will include structure-guided design, physicochemical property optimization, and PI3K inhibitory selectivity.
Design and Synthesis of Orally Bioavailable Kv1.5 Antagonists for the Treatment of Atrial Fibrillation

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Nathan R. Kett, a Ahren Green, a Zhicai Wu, a Christopher P. Regan, b Joseph J. Lynch, b Gary L. Stump, b Laszlo Kiss, c Jixin Wang, d Gong Cheng, d Matthew J. Cato, e Rebecca B. White, e Suzie Yeh, e Stefanie A. Kane, d George D. Hartman, a Mark T. Bilodeau a and B. Wesley Trotter a
Departments of a Medicinal Chemistry, b Central Pharmacology, c In Vitro Sciences, d Pain Research, and e Drug Metabolism and Pharmacokinetics
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Atrial fibrillation (AF) is the most common sustained arrhythmia observed in clinical practice. Blood stasis resulting from AF is a major contributor to stroke incidence in the affected population. Intervention with non-selective ion channel blockers can be effective in treating and preventing AF, but currently available drug therapies carry a significant risk of potentially lethal ventricular proarrhythmia. The potassium current $I_{Kur}$ selectively contributes to atrial repolarization via its underlying potassium channel, Kv1.5. We have pursued Kv1.5 antagonists because of their potential to terminate or prevent AF without exhibiting the proarrhythmic side effects of current drugs, all of which inhibit ventricular currents. We present here a multidimensional optimization of a series of Kv1.5 antagonists that addresses elimination of specific undesirable ion channel activities, incorporation of essential P-gp transport properties, and refinement of pharmacokinetic profiles.
Plant Natural Products in a Drug Discovery Program: From the Ground-Up

Mark O'Neil-Johnson\textsuperscript{1}, Jin-Feng Hu\textsuperscript{1}, Courtney Starks\textsuperscript{1}, Russell Williams\textsuperscript{1}, Gary Eldridge\textsuperscript{1} and Peter Raven\textsuperscript{2}

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Natural product chemistry has traditionally been a long and time-consuming process for drug discovery research. From extraction, isolation and purification to structure elucidation of biologically active compounds, Sequoia Sciences has created a patented extraction and isolation method to create purified natural product fractions that fit into HTS screening platforms. Utilizing the CapNMR probe and ACD database and structure elucidation software, it is now possible to routinely elucidate structures on mass limited or microgram quantities of purified natural product compounds.

Sequoia has accelerated the discovery of active and novel compounds from plant sources. In addition, Sequoia's process has also allowed it to produce focused screening libraries based on selective plant species that may be either underrepresented due to insufficient material or that may produce unique compounds necessary for their survival. Introduction of new NMR probe technologies has allowed for increase through-put of complete NMR data sets resulting in the discovery of preferred, neglected and novel scaffolds. A review of our natural product discovery process using working examples of microgram quantities of material to perform isolation and structure elucidation to unravel an active lead compound, as well as the introduction of unique NMR capabilities will be presented.
Discovery of MK-7725, a Potent and Selective BRS-3 Agonist for the Treatment of Obesity

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Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Desirable outcomes for the treatment of obesity include weight loss, weight management to improve cardiovascular and metabolic health, and reduction of obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic parameters, such as blood glucose, blood pressure, and lipid levels.

To this end, studies were undertaken towards discovering a novel, potent agonist of the bombesin receptor subtype-3 (BRS-3). BRS-3 is an orphan G-protein coupled receptor that is expressed primarily in the hypothalamus region of the brain. The BRS-3 mechanism has been implicated through rodent genetics and pharmacology to regulate food intake and metabolic rate. Rodents lacking the BRS-3 receptor were found to be obese, hypometabolic, and insulin resistant.

This poster will outline the medicinal chemistry effort leading to the identification of MK-7725, as well as the use of a high throughput PD assay to guide the lead optimization process. Approaches to increase binding affinity, improve pharmacokinetic profile, and address PXR activation with the aid of molecular modeling will be detailed along with the unusual chirality exhibited by MK-7725.

MK-7725
SYNTHESIS AND ANTIMICROBIAL EVALUATION OF A-SUBSTITUTED-N-ACETYL DERIVATIVES OF CIPROFLOXACIN AND NORFLOXACIN

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Abstract:
The continuous emergence of fluoroquinolone-resistant bacterial strains, in addition to
the withdrawn or restricted use of some fluoroquinolones were the driving forces for the
design and synthesis of a series of novel α-substituted N-acetyl derivatives of
ciprofloxacin and norfloxacin. In this work twenty four derivatives were synthesized and
assayed for their antibacterial activity against Pseudomonas aeruginosa, Escherichia coli,
Staphylococcus aureus, and Bacillus subtilis. In addition, their activity was evaluated
against *Candida albicans*. The α-chloroamides, 1a, 1b and 2b showed better activity than their parent drugs against both *S. aureus* and *B. subtilis*.

The ciprofloxacin derivatives 3e, 3g and 3h exhibited MICs values in the range of 0.36-0.91 μM against *S. aureus*, compared to ciprofloxacin (2.2 μM). In addition, compound 3h has better activity, 0.1 μM, against *B. subtilis* compared to, for ciprofloxacin (0.28 μM). Still, compounds 3e, 3d, 3f, 3c and 3g showed MIC values below 1.0 μM against this bacterium.

None of the norfloxacin derivatives showed better activity than norfloxacin itself (MIC = 1.14 μM) against *S. aureus*, although 4e and 4d showed MIC values less than 2 μM. On the other hand, two norfloxacin derivatives, 4e (MIC = 0.55 μM) and 4d (MIC = 0.68) have comparable activity against *B. subtilis* to norfloxacin. Compound 4h and 4f have showed MIC values less than 1.0 μM against *B. subtilis*.

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R_1 = \text{Ethyl or Cyclopropyl} \\
R_2 = \text{H or phenyl} \\
R_3 = \text{Phenyl or substituted phenyl}
\]

Compounds 3e-h, 4e-h, 5,6,7 and 8
NOVEL POLYCYCLIC BASED MACROCYCLIC COMPOUNDS HIGHLY EFFECTIVE AS HCV INHIBITORS

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Hepatitis C virus (HCV) is the major causative agent for most cases of non-A, non-B hepatitis, and it is a single-stranded positive RNA virus in the Flaviviridae family. It includes a nucleocapsid protein (C), envelope proteins (E1 and E2), and several non-structural proteins (NS1, NS2, NS3, NS4a, NS5a, and NS5b). NS3 protein possesses serine protease activity and is considered essential for viral replication and infectivity. The essentiality of the NS3 protease was inferred from the fact that mutations in the yellow fever virus NS3 protease decreased viral infectivity. This presentation discloses the discovery of novel polycyclic based macrocyclic compounds highly effective for inhibiting HCV replication. Currently, several novel polycyclic compounds has been determined to be very potent in inhibiting HCV NS3-NS4A proteases and developed as valuable lead compounds (IC₅₀ for NS3-NS4A: 0.1nM-5nM). Moreover, preparation of new polycyclic building blocks and 14-16 membered macrocyclic compounds have been reported. Further SAR study and preclinical development are ongoing to provide alternative potent and non-toxic HCV inhibitors.
Synthesis and biological evaluation of novel 3-(ferrocenylmethyl)-naphthoquinone derivatives as antiplasmodial agents

Pedro M García-Barrantes¹; Guy V. Lamoureux²; Alice L. Pérez³; Rary N. García Sánchez², Antonio R. Martínez Fernández², Arturo San Feliciano³

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Malaria, caused by Plasmodium parasites, is perhaps the greatest health problem for developing countries in the tropics. Naphthoquinones, such as atovaquone, have been studied as antiplasmodial drugs, and have shown important activity against this parasite. Additionally, substances such as ferroquine (ferrocene plus the chloroquine nucleus) are active against chloroquine resistant Plasmodium falciparum strains.

The aim of this study is to produce novel biologically active substances based on a nucleus of naphthoquinone plus ferrocene. Several compounds were synthesized and different derivatives of 3-(ferrocenylmethyl)-naphthoquinone were obtained, with different substitution in the methylene link between the ferrocene and the naphthoquinone groups. Their structures were established using IR, ¹H and ¹³C NMR, and HRMS techniques. Antiplasmodial activity was assessed in vitro against Plasmodium falciparum 3D7 and Dd2 strains (chloroquine sensible and resistant respectively) employing a fluorimetric microtest with SYBRGreen® I; and on ferriprotoporphyrin IX biocrystallization inhibition assay (FBIT). Nonspecific cytotoxicity of the compounds was assayed on murine macrophages J774.

Preliminary results show that compounds CRQ121, CRQ125 and CRQ127 were active against the parasite, and had IC₅₀ values similar to chloroquine. Their activity was not influenced by the parasite strain; and did not inhibit the ferriprotoporphyrin IX biocrystallization process, which suggests that these compounds work through a different mechanism of action than chloroquine and other aminoquinolines. Furthermore, the cell viability test on macrophages showed low cytotoxicity.

The high activity of these compounds, and their low toxicity, make these compounds suitable for in vivo tests and further research.
Discovery of Pyridazinopyridinones as Potent and Selective p38 Mitogen-Activated Protein Kinase Inhibitors

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The p38 mitogen-activated protein kinase (MAPK) plays an important role in the production of proinflammatory cytokines, making it an attractive target for the treatment of various inflammatory diseases. A series of pyridazinopyridinones was designed as novel p38 kinase inhibitors. A structure-activity investigation identified several compounds possessing excellent potency in both enzyme and human whole blood assays. The leading compound also exhibited good pharmacokinetics and showed excellent selectivity against other related kinases. Herein a detailed SAR investigation and profile of this lead molecule is presented.
1,2-Dihydro-Quinolines as Selective Estrogen Receptor-beta Ligands

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The estrogen receptor (ER) is a ligand-activated nuclear hormone receptor that is widely distributed throughout the tissues of both men and women. Industry wide efforts continue to develop novel nonsteroidal selective estrogen receptor modulators (SERMs) that elicit the desired effects of hormone replacement therapy (HRT) without inducing the negative effects of HRT. As part of a program aimed at the development of selective estrogen receptor modulators (SERMs), a novel series of 4-hydroxy-benzenesulfonyl-2,2-dimethyl-1,2-dihydro-quinoline analogs have been prepared. We will summarize the chemistry and structure activity relationships utilizing a novel binding mode for this series to demonstrate 100x fold selectivity against ERα.
Discovery of N-Methyl Piperidine Analogs as Potent DPP-4 Inhibitors

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Sitagliptin (Merck) was approved by the FDA in 2006 as the first dipeptidyl peptidase IV (DPP-4) inhibitor for the treatment of type 2 diabetes. Saxagliptin (BMS) was also approved recently by the FDA. In addition, several other major pharmaceutical companies have reported clinical candidates in various stages of development. In order to study novel ring constrained DPP-4 inhibitors, novel N-methyl piperdine analogs with different functional groups such as sulfonamide, amide, carbamate and urea were synthesized and evaluated as DPP-4 inhibitors. In order to maintain our leadership in this area, cyclohexane, tetrahydropyran and piperidine analogs were designed as novel ring constrained DPP-4 inhibitors. In this presentation, details of syntheses and the SAR of these N-methyl piperidine analogs will be discussed.
Balancing potency and off target activities: Discovery of Cav2.2 blockers for treatment of chronic pain

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Cav2.2 calcium channels are key components in nociceptive transmission pathways. Ziconotide (Prialt™) is a peptide inhibitor of Cav2.2 channels approved for the treatment of refractory pain. However, the peptide needs to be administered via intrathecal infusion. As a state-independent Cav2.2 blocker, ziconotide affords a narrow therapeutic index over neurologic side effects. In this program, we sought to discover an orally available, state-dependent Cav2.2 blocker that might afford analgesic efficacy without neurologic activity. Starting from the HTS screening lead compound 1, a potent but non-selective Cav2.2 blocker, SAR studies were carried out to improve ion channel selectivity. This effort led to discovery of compound 2, a selective Cav2.2 blocker with an improved PK profile and in vivo efficacy. However, formation of a long lasting primary sulfonamide metabolite precluded this lead class from further development. Sulfonamide replacements were investigated, leading to the discovery of the structurally novel sulfone series. Systematic optimization of the aromatic substitution led to a series of compounds that were devoid of iKr, PXR and Pgp substrate issues. Among these compounds, compound 3 showed the best in vivo efficacy and was profiled extensively as a potential development candidate.
OXOPYRROLYLIDENE BENZOHYDRAZIDE CB\textsubscript{2} AGONISTS

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The cannabinoid G-protein coupled receptor (GPCR) family comprises two well-characterized subtypes. Cannabinoid 1 (CB\textsubscript{1}) receptors exist primarily in the central nervous system (CNS) and also in peripheral tissues. Activation of CB\textsubscript{1} receptors produces a variety of effects, including sedation, euphoria, and appetite stimulation. Cannabinoid 2 (CB\textsubscript{2}) receptors are expressed peripherally in tissues associated with the immune system. Cannabinoid receptors couple primarily to G\textsubscript{i/o} proteins and activation inhibits cAMP production, but the roles of cannabinoid receptors in pain states remains under investigation. Activation of CB\textsubscript{1} or CB\textsubscript{2} receptors can produce analgesia, but agonists that lack selectivity for CB\textsubscript{2} over CB\textsubscript{1} cause the undesirable effects associated with Δ\textsuperscript{9}-tetrahydrocannabinol (Δ\textsuperscript{9}-THC). Abbott pursues CB\textsubscript{2}-selective agonists for pain management, and a series of CB\textsubscript{2} agonists derived from the oxopyrrolylidene core will be described.
Novel CB2 Agonists: Optimization of CB2/CB1 Selectivity and Implications for In Vivo Analgesic Efficacy

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The known analgesic effects of natural cannabinoids and the identification of the CB1 and CB2 cannabinoid receptors have engendered a large and active area of research aimed at agonists of these receptors. Due to undesirable psychotropic effects associated with CB1 agonism, many have focused efforts on identification of selective CB2 agonists, which might demonstrate analgesic efficacy without CB1-mediated side effects. We report here two novel and structurally distinct series of imidazopyridine CB2 agonists. Structural optimization improved CB2/CB1 selectivity in each series and conferred physical properties that facilitated high in vivo exposure, both centrally and peripherally. Administration of very highly selective CB2 agonists and moderately selective CB2/CB1 agonists in a rat model of analgesia provided results indicating that CB2 agonism alone may not be sufficient for pain relief.
The Synthesis of Novel, Fluorinated P1 HCV NS3 Protease Inhibitors

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Abstract - Hepatitis C virus (HCV) is an infectious agent that causes chronic infection in over 85 percent of infected patients, often leading to chronic liver diseases such as cirrhosis and hepatocarcinoma. The current standard of care (SOC) for the treatment of HCV is a combination of pegylated interferon-α and ribavirin. The main objective with this regimen, neither of which are specific antiviral agents, is to achieve a sustained elimination of HCV RNA from blood. Unfortunately, the current SOC demonstrates a poor response rate (~40%) in genotype 1-infected patients and demonstrates a wide range of undesirable side effects that afflicts almost all patients. Additional modalities for the treatment of HCV infection are urgently needed. At BMS, we have had an enduring interest in identifying and developing novel therapeutic agents to tackle this significant health problem. In this poster presentation, we will focus on chemical modifications to the P1 vinylcyclopropane element of a series of potent HCV NS3 protease inhibitors. Here we will describe our synthetic efforts in modifying this very challenging region of the molecule. Relevant structure-activity relationship (SAR), along with molecular modeling studies will be discussed.
Diverse Steviol and Isosteviol Templates for Pilot Scale Libraries

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Abstract: Stevioside is the primary natural product isolated from the leaves of \textit{Stevia rebaudiana} Bertoni plant, which is sold commercially as an artificial sweetener. Enzyme-mediated hydrolysis of the glycosidic bonds of stevioside forms the aglycone steviol, which has shown to be pharmacologically active. Acid hydrolysis of stevioside yields the Wagner-Meerwein rearranged product isosteviol, which has been used to develop anti-diabetic drugs. The manipulation of the D-ring of both steviol and isosteviol diterpene scaffolds provides diverse templates for small molecule libraries that explore sparsely populated areas of chemical space. The libraries are then submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR) to analyze their potential biological activity.
Discover and Synthesis of Novel N-(Hetero-biaryl) Piperazine Adenosine A2a Receptor Antagonists

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Adenosine is an important neuromodulator in the central and peripheral nervous systems. Adenosine modulates its effects through the activation of four subtype receptors located on cell membranes, known as A1, A2a, A2b, and A3. The adenosine A2a receptor is a member of the G-protein-coupled receptor family and is abundant in discrete brain regions, such as the striatum. Antagonism of the A2a receptor may provide a means of modulating the dopaminergic system without the associated motor side effects of direct dopamine D2 receptor interaction. Thus, adenosine A2a receptor antagonists could provide treatment of neurodegenerative diseases such as Parkinson’s disease. The design, synthesis, and evaluation of N-(hetero-biaryl) piperazine adenosine A2a antagonists will be presented. Highly potent A2a receptor antagonists were discovered with excellent selectivity versus the A1 receptor and exhibited good in vivo activity.
(+)-3-Hydroxymorphinan (3-HM), a metabolite of dextromethorphan (DM), was found to be a potent anti-Parkinsonian agent. 3-HM was demonstrated to have more potent neuroprotective activities than either levodopa/carbidopa or levodopa alone, and comparable to ropinirole in LPS and MPTP induced models of PD (Parkinson’s disease). Daily injections with 3-HM represented that dopamine neurons in substantia nigra were restored or protected. However, 3-HM was only efficacious if administered intraperitoneally or intravenously, suggesting that 3-HM has poor oral bioavailability. In order to improve the oral bioavailability, prodrugs of 3-HM were prepared and their oral absorptions were evaluated by cell permeability test in MDCK cells. The oral administration of GCC1290K, one of the prodrugs, showed high oral bioavailability (92 %) and in vivo efficacy in PD models. GCC1290K was well tolerated in single dose toxicity studies at dose up to 1,000 mg/kg and 25 mg/kg in rats and dogs, respectively. A process chemistry was successfully developed, suitable for the bulk production of GCC1290K for the clinical test. US FDA has approved Green Cross’s Investigational New Drug (IND) application for GCC1290K, a novel therapeutic product for the treatment of Parkinson’s disease.
One-pot synthesis of trisubstituted ureas as potent and selective mPGES-1 inhibitors

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Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is a common prostanoid with a variety of bioactivities and has been found to be a major mediator of pain, fever and inflammation. PGE<sub>2</sub> is produced by sequential conversion of arachidonic acid to PGH<sub>2</sub> by cyclooxygenase (COX) followed by the isomerization of PGH<sub>2</sub> to PGE<sub>2</sub> by a protanglandin E synthase (PGES). Characterisation of the different PGES led to the identification of mPGES-1, a microsomal, glutathione-dependent, inducible enzyme responsible for PGE<sub>2</sub> production as the key component present in inflammation. Selective inhibition of mPGES-1 would preclude PGE<sub>2</sub> production but, unlike NSAIDs and coxibs, would not inhibit the biosynthesis of PGD<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub> and TXA<sub>2</sub>.

We recently reported the synthesis and characterization of potent and selective phenanthrene imidazole mPGES-1 inhibitors (Biorg. Med. Chem. Lett. 2009, 19, 5837; Biorg. Med. Chem. Lett. 2007, 17, 6816). In an ongoing effort for the identification of a structural distinct series of selective mPGES-1 inhibitors, a HTS was conducted. A new trisubstituted urea 1 was identified as a viable lead (88% enzyme inhibition at 10 μM) from this sample collection screen. SAR was undertaken on this urea scaffold, rigidifying the core with an alkyne such as in inhibitor 2 gave us a 10 fold increase in potency. Rigidifying these inhibitors further, exemplified by compound 3, led to inhibitors with excellent potency profiles. The complete SAR of this new structurally distinct series will be presented. Furthermore, the efficient and versatile one-pot synthesis for the preparation of these inhibitors will be described.
Inhibition of Gp130 Homodimerization: An Approach towards Treatment of Prostate Cancer by Design of Selective IL-6 Inhibitors

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Interleukin-6 (IL-6), a pleiotropic cytokine, has been shown to be a candidate mediator of prostate cancer progression and morbidity. IL-6 first binds to IL-6Ra, then presented to gp130 to form trimeric complex (IL-6/IL-6Ra/gp130). Interactions of IL-6 of one trimeric complex to the D1-domain of gp130 of other trimeric complex lead to homodimerization of two trimeric complex into high-affinity, signaling-competent hexamer. Gp130 is a shared surface cell receptor for a family of cytokines and homodimerization of gp130 induces Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway. The JAK2/STAT3 pathway mediates gene transcription and thereby cancer progression. Interactions of IL-6 and D1-domain of gp130 are unique for IL-6 and IL-11 cytokines. Thus, inhibition of IL-6 and gp130 interaction would give specificity to IL-6 type cytokines. We have investigated the binding pocket on the D1-domain of gp130 surface by MMPBSA (Molecular mechanics/Poisson-Boltzmann surface area) methods and screened compound libraries using GLIDE program (Schrödinger L.L.C.). The high ranked compounds were then tested for biological effect using a panel of human tumor cell lines. Of the eight selected compounds, a consistent anti-proliferative effect was observed with one compound, compound 6, which reduced cell proliferation after 72 hours to 64 ± 4%, and 53 ± 5% of controls at 10 and 100μM respectively. Heterogeneity of tumor cell responses was also noted in consistency with biological effects. Therapeutic targeting of IL-6 and its receptor in cancer has strong biologic rationale, and there is preliminary evidence suggesting that targeting of the IL-6 system may be beneficial in the treatment of prostate cancer. Our strategy of inhibiting gp130 homodimerization by inhibiting IL-6 and D1-domain of gp130 would provide specificity for IL-6 cytokine dependent signaling, and our initial hits may be useful for optimization to modulate IL-6 effect on tumor cell growth.
Design and Synthesis of Novel NNRTIs with Activity Against the Clinically Important K103N and Y181C RT mutations

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HIV reverse transcriptase (HIV-RT) plays an essential role in the life cycle of HIV replication. The emergence of resistant strains of human immunodeficiency virus type 1 (HIV-1) requires new anti-HIV agents that are effective against mutated forms of the virus. Previously, it was shown that 5-chloro-3-(phenylsulfonyl)indole-2-carboxamide (1) is a potent NNRTI against wild-type enzyme (IC_{50} = 0.8 nM). However, potency against strains expressing the K103N or Y181C mutation decreased by 150-fold and 15-fold, respectively. Further investigation by this group and others focused on replacing substituents and modifying the parental indole structure to enhance activity against the K103N and Y181C mutants. Modeling studies based on a co-crystal structure of WT RT and 1 suggested structural modifications to the indole core template that could lead to improvements in potency against these key mutants. These studies led to the discovery of the phenylsulfonylpyrrole 2,5-dicarboxamide series, which had good potency vs WT and K103N enzymes. A key interaction that was engineered into the new series of inhibitors involved a hydrogen bond between the pyrrole 5-carboxamide carbonyl group and the backbone NH of the K103 residue. Notably, a similar H-bond interaction occurs in many NNRTIs that have good potency vs the K103N mutation. The binding mode of this new series of NNRTIs was confirmed by a co-crystal structure with RT. Many compounds in this new series displayed potency shifts < 3-fold in the K103N enzyme assay as well as in cell culture. Further SAR studies optimized activity against the Y181C mutation, giving compounds with IC_{50} shifts less than 3 to 5-fold. The design, synthesis, enzyme inhibition and in vitro antiviral activity of this novel series of NNRTIs will be presented along with the pharmacokinetic evaluation of key compounds in the series.
Multivalent Antibodies Using DHFR-anti-CD19 scFv Fusion Proteins

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We have shown that dihydrofolate reductase (DHFR)-DHFR fusion proteins spontaneously self-assemble into highly stable nanorings upon the addition of the chemical dimerizer bis-methotrexate (Bis-MTX). Varying the length of the peptide linker between the two DHFR proteins, allows the assembly of rings consisting of between two and eight fusion proteins. These protein nanorings can be used for the multivalent display of anti-CD3 scFv proteins to target T-leukemia cells. We hypothesize that, by replacing the anti-CD3 scFv with anti-CD19 scFv, these fusion proteins can be used for the targeting of B-leukemia cells. In this poster, we present the preparation of our DHFR-anti-CD19 scFv fusion proteins and their in vitro binding studies using Daudi cells. By displaying multiple copies of the anti-CD19 scFv, the formation of these rings offer benefits of increased avidity for the target cell.

Nanoring assembly, tissue targeting, and induced disassembly.

References:
Development of *Yersinia pestis* protein tyrosine phosphatase (YopH) inhibitors using a substrate activity screening approach

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Abstract

Tyrosyl phosphorylation is controlled by reversible actions of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Deregulation of PTPs is linked to diseases ranging from diabetes to cancer. *Yersinia pestis* (*Y. pestis*) is an organism which has been classified by the CDC as category A pathogen and has gained attention as a possible biological warfare agent for use as a weapon of mass destruction. *Y. pestis* produces diseases ranging from pneumatic to bubonic plaque. The pathogenicity of *Y. pestis* involves its virulence protein “YopH”, which is a highly active PTP. Because development of YopH inhibitors may represent a new approach to anti-plague therapeutics, this enzyme represents an exciting target for drug development. However, discovery of PTP inhibitors, including inhibitors of YopH, has traditionally been hampered by a high incidence of “false positives” arising through inhibition of enzyme function by “promiscuous” mechanisms that do not represent valid leads for further development. In an effort to develop *Y. pestis* inhibitors while minimizing promiscuous inhibition, we have utilized a new approach that employs a library of nitrophenylphosphate substrates which are optimized using a concept of "substrate activity screening (SAS)". High affinity substrates identified through this process provided the molecular frameworks for inhibitor design by replacement of phosphoryl ester with non-hydrolysable phosphate mimetics. Continued optimization beyond this point made use of aminooxy-aldehyde based click chemistry. This provided oxime libraries that exhibited bidentate interactions with the catalytic pocket and proximal secondary sites. This approach allowed the identification of low micromolar affinity bidentate inhibitor whose inhibitory profile was found to be independent of detergent concentration. This latter characteristic is taken to indicate that inhibition is "bonafide" and not promiscuous.
Synthesis and Biological Properties of Raloxifene Fragments

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Some selective estrogen receptor modulators (SERMs) are of great interest because they are able to have both selective agonistic and antagonistic features at the estrogen receptors (ER) alpha and beta. The development of novel SERMs requires an understanding of current SERM molecules and their interactions at both ER subtypes. Raloxifene is a SERM molecule that is an agonist at ERβ and an antagonist at ERα, thus allowing it to be used as a treatment for osteoporosis and as a preventative medication for breast cancer, respectively. It is effective with a lower incidence of side-effects than most other SERMs currently in the marketplace. In this study we are examining a portion of raloxifene, namely its 4-[2-(1-piperidinyl)ethoxy]benzoic acid adduct, to determine the latter’s role on the effectiveness and selectivity of the overall molecule. This presentation will focus on the synthetic routes being used to prepare this compound and its derivatives containing substitutions at both the carboxylic and piperidine ends of the molecule. Discussion will also include the biological and SAR studies that will be conducted to gain information on the contributors of this side-chain and to determine the effects of the derivatives.
Calcium ion (Ca\(^{2+}\)) is a versatile, ubiquitous intracellular signal responsible for controlling a number of cell processes, including fertilization, cell proliferation and differentiation, apoptosis, secretion and contraction. Despite the many regulatory functions Ca\(^{2+}\) controls, relatively little is known about the processes of Ca\(^{2+}\) release from intracellular stores. Originally, the discovery of inositol trisphosphate (IP3) and its related receptor exemplified that Ca\(^{2+}\) signaling in the cell was due to, in part, endogenous molecules. Additionally, and more recently, dinucleotides, specifically cyclic-adenosine diphosphate ribose (cADPR) and nicotinic acid dinucleotide phosphate (NAADP), were found to play a major role in Ca\(^{2+}\) mobilization. To date, NAADP is the least characterized and most potent of the above endogenous molecules, with its binding protein yet to be fully characterized. The subject of this investigation is to probe receptor activity through synthetic and chemoenzymatic means. Through the synthesis of NAADP derivatives, we hope to produce a variety of pharmacological “tools” probing receptor activity in sea urchin egg homogenates and mammalian cell lines, including a true competitive antagonist. In the sea urchin system, activity is determined in a cell-free extract system, eliminating the need to cross cell membranes. In mammalian cell lines, this is not the case. By placing a photolabile “caged” moiety on analogs, we can control the exact time in which compound can be released, causing effect. Caged NAADP derivatives will be tested using microinjection or patch clamp diffusion and photoactivation.
Structural Evolution of Aporphinoids: Identification of Novel Compounds with Dopamine D2 and Serotonin 1A Receptor Dual Agonists

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Accumulating evidence has indicated that alteration of serotonin 1A (5-HT\textsubscript{1A}) receptor function is associated with a number of neuropsychological disorders, including anxiety and depression, pain, neuroprotection, schizophrenia, Parkinson’s disease, and Alzheimer disease. More importantly, 5-HT\textsubscript{1A} receptor agonists have been found effectively reducing L-dopa induced dyskinesia (LID). To this end, a series of aporphinoids have been developed based on structural evolution of apomorphine, a typical D\textsubscript{2} receptor full agonist marketed as anti-Parkinsonian drug in 2004. Compounds active at D\textsubscript{2} and 5-HT\textsubscript{1A} receptors were selected for functional assays, and several analogues with full agonism at these two receptors were identified for further evaluation. One compound with a long side chain at the C11 position should significant anti-Parkinsonian effect on the 6-HODA lesioned rats model. Meanwhile, the development of dyskinesias of this compound itself is minor at different doses. When co-treated with L-dopa, it reduced L-dopa induced dyskinesia (LID) significantly. However, the metabolic stability and glucuronidation potential rendered further development of this compound.

![Chemical Structures](image)

\textbf{References}

Discovery of Prolyl 4-Hydroxylase Inhibitors that are Potent Oral Erythropoietin Secretagogues


HIF prolyl 4-hydroxylases (PHD) are a family of enzymes that mediates key physiological responses to hypoxia by modulating the levels of hypoxia inducible factor 1-α (HIF1α). A number of benzimidazole-2-pyrazole carboxylates were discovered to be PHD2 inhibitors using ligand- and structure-based methods, and found to be potent, orally efficacious stimulators of erythropoietin secretion in-vivo.
Small molecules with polycyclic skeletons are widespread in nature and often show interesting activity. These frameworks can be employed as scaffolds to elaborate additional structures having an extensive array of biological properties. Here, we describe the enantioselective synthesis of the tricyclic compound, 2-isopropenyl-2,3-dihydro-7H-furo[3,2-g]chromene. This molecule is made up of a 2-isopropenyl-2,3-dihydrobenzofuran and a 2H-chromene ring. The 2-isopropenyl-2,3-dihydrobenzofuran contains an asymmetric center at the 2-position and is seen in a number of biologically active toxins including tremetone and fomannoxin. The broad-spectrum insecticide rotenone also contains this unit. Alternatively, the 2H-chromene ring system is widely observed as an intermediate during the synthesis of various natural products and medicinally relevant compounds. For example, 2H-chromenes act as precursors in the synthesis of the second largest group of isoflavonoids called the pterocarpans. These compounds play an important role as phytoalexins and exhibit strong antifungal and estrogenic activity. In our synthetic strategy, we start by generating the 2H-chromene ring. This is followed by the formation of the benzofuran unit containing the 2-isopropenyl substituent using a chiral Trost ligand. These chiral building blocks will be used to assemble various pterocarpans, which will then be extensively evaluated for their biological properties.
Substrate based inhibitors of PlsY, an essential Gram-positive bacterial acyltransferase

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Abstract:
The widespread occurrence of bacterial resistance by Gram-positive bacteria, including methicillin resistant Staphylococcus aureus (MRSA), Vancomycin resistant Enterococcus (VRE) and macrolide resistant Streptococcus has warranted the identification of novel targets for antibacterial therapy. One such target is the recently discovered acyltransferase PlsY which catalyzes the synthesis of phosphatidic acid, an essential intermediate in the biosynthesis of bacterial membrane phospholipids. 1 Our goal is to develop inhibitors of PlsY with antimicrobial activity.

Biosteric replacement of the long chain acylphosphate substrate of PlsY by non-hydrolyzable mimics such as acylphosphonates, acyl α, α – difluoromethyl phosphonates, acylphosphoramides, reverse amide phosphonates, acylsulfamates and acylsulfamides led to the identification of several inhibitors of PlsY from Streptococcus pneumoniae and Bacillus anthracis. Antimicrobial testing showed these compounds to have generally weak anti Gram-positive activity but showed potent activity against multiple strains of Bacillus anthracis. 2 Additional structure-activity relationship (SAR) studies on these inhibitors in attempts to improve their potency against PlsY, their antimicrobial activity and to integrate more drug-like characteristics are currently underway and will also be reported herein.

References:

Development of Novel Cucurbitacin Analogs as Kinase Inhibitors for the Treatment of Hepatocellular Carcinoma

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Liver cancer is the fourth leading cause of cancer related deaths worldwide. Cucurbitacins, a natural product with known hepatoprotective and anti-cancer activities, have been studied for their use as a hepatocellular carcinoma (HCC) treatment. However, due to their extreme cytotoxicity, a molecular docking approach was adopted to identify novel cucurbitacin analogs that have been modified for optimized activity. These molecules have been docked with the active epidermal growth factor receptor (EGFR) tyrosine kinase, which has not been previously investigated as a target of the cucurbitacins. An in vitro STAR ELISA assay has been performed and shows the cucurbitacins to have a significant effect on the EGFR/tyrosine kinase concentration. More specifically, treatment of serum deprived HepG2 cells with iso-cucurbitacin B doubles the amount of EGFR detected relative to treatment with EGF. In other words, treatment with cucurbitacins forces the cell to up-regulate EGFR present in the cell, which clearly indicates that cucurbitacin analogues can deregulate the signaling of tyrosine kinase, which will inhibit cell growth. A number of synthetic routes have been employed in order to conduct semi-synthesis of these novel analogs including: Heck reaction, Friedel-Crafts type arylation, indium catalyzed arylation, and surface-mediated hydrohalogenation, among others. Synthesis of these novel analogs and anti-HCC activity will be presented.
Synthesis and Structure-Activity Relationship Study of meso-Heterocycle-Substituted Metalloporphyrins

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Abstract:
Novel meso-heterocycle-substituted metalloporphyrins were designed, synthesized, and evaluated as potential catalytic antioxidants. Several new analogues (8) have exhibited greatly enhanced SOD activity over previously reported metalloporphyrins like MnTBAP (1), glyoxylate-derived metalloporphyrins 2a–d, and meso-pyridinium substituted metalloporphyrin 3.

8a: \( R^3 = R^4 = CH_3, R^5 = H \)
8b: \( R^3 = R^4 = CH_3CH_2, R^5 = H \)
8c: \( R^3 = CH_3, R^4 = CH_2CH_3, R^5 = H \)
8d: \( R^3 = R^4 = CH_3CH_2CH_3, R^5 = H \)
8e: \( R^3 = R^4 = R^5 = CH_3 \)
In(0)-mediated Allylation of Isatins: An Environmentally Friendly Route to 3-hydroxy-2-oxindole Derivatives for Use in Natural Product Synthesis

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The occurrence of 3-hydroxy-2-oxindole derivatives in natural products presents a very interesting task for the synthetic chemist. Couple that with the fact that many of these have good biological activity, and their appeal increases. Of the many compounds which fall under this category, a significant number can be made by direct alkylation or allylation of the 3-keto position of isatin or isatin-based derivatives. Previous methods using organocatalysis or toxic palladium catalysis are low yielding, either in overall yield or enantiomeric excess, and are potentially unattractive to pharmaceutical development of such compounds. In our group, we have developed an environmentally benign system utilizing indium metal, which allows for enantioselective allylations of isatin. Using these as precursors, a plethora of synthetic transformations can be used to functionalize into further products of interest. As representatives of the profile, donaxaridine and arundaphine will be shown featuring the In⁰-allylation chemistry.
The University of Toledo’s Center for Drug Design and Development (CD3) serves as a core resource to translate new biological and clinical discoveries into small molecule diagnostic, treatment or preventative agents for various human diseases including, in particular, cancer. After highlighting key aspects about the CD3’s general operation, two programs pertaining to cancer research will be described. The first involves the CD3’s collaboration with the USDA wherein we have identified an interesting family of natural products produced by the common soybean plant when it is stressed by specific elicitor agents. These natural products display pronounced anticancer activity that should be useful in the treatment and prevention of breast cancer. This technology is presently being considered by a private sector party for the purpose of marketing it as a medical food. The second research program involves the CD3’s discovery of a novel compound that can inhibit an enzyme called ‘PAM.’ PAM becomes over-expressed in human prostate cancer during its late and most devastating stages wherein growth continues to occur even when male hormones are ablated. Thus, PAM may play a role in activating local growth hormones. Preliminary data from both cell culture and animal implant studies indicate that our PAM inhibitor can reduce cancer growth during this type of late stage disease.
Design and Synthesis of a New Class of MCD Inhibitors with Anti-Obesity and Anti-Diabetic Activities


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Obesity has become a worldwide pandemic over the last several decades. As it is associated with increased risk of type II diabetes, cardiovascular and cerebrovascular diseases, and increased mortality, obesity is a major contributor to the global burden of chronic disease and disability. However, only limited treatments are available today for obesity despite the severity of this health problem.

The fatty acid intermediate malonyl-CoA is a key fuel sensor in signaling satiety in the brain as well as a potent endogenous inhibitor of CPT-I, a key enzyme involved in fatty acid oxidation (FAO). In the brain, inhibition of malonyl-CoA decarboxylase (MCD), which leads to an increase of the malonyl-CoA level, has been shown to reduce food intake in mice. In peripheral tissue, inhibition of MCD has been shown to shift energy metabolism from FAO toward glucose oxidation. Thus, it is feasible to develop small molecule MCD inhibitors for the treatment of obesity and/or diabetes.

This presentation will outline medicinal chemistry efforts leading to the discovery of a new class of potent small molecule MCD inhibitors. Approaches to improve PK and brain penetration properties will be addressed. POC results from chronic food intake/body weight studies and in vivo mouse glycolysis models will be discussed.
The Discovery Highly Potent and Selective EP₄ Antagonists for the Treatment of Inflammatory Pain

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Arthritis is a chronic inflammatory condition that ultimately leads to the destruction of bone and cartilage. Prostaglandin E₂ (PGE₂) plays an important role in the pathogenesis of this disease, and inhibition of PGE₂ production by NSAIDs and COX-2 inhibitors relieves arthritis symptoms. PGE₂ is the ligand of four subtype Prostaglandin E receptors (EP₁-₄). In a mouse model of collagen-antibody induced arthritis (CAIA), EP₄⁻/− mice, unlike EP₁⁻/− mice, showed remarkable inflammatory symptom resistance when compared to the wild type controls (J. Clin. Invest. 2002, 110, 651). This suggested that the proinflammatory effects of PGE₂ are predominantly mediated by the EP₄ receptor. Furthermore, Lin et al. demonstrated that EP₄, not EP₁-₃, contributed to inflammatory pain hypersensitivity in rats (J. Pharmacol. Exp. Ther. 2006, 319, 1096). Using highly selective EP₁, EP₃ and EP₄ antagonists, we have recently demonstrated that EP₄, not EP₁ or EP₃, is the primary receptor involved in joint inflammation and pain in rodent models of rheumatoid and osteoarthritis (Pharmacol. Exp. Ther. 2008, 325, 425).

Our efforts to identify selective EP₄-antagonists for the treatment of inflammatory pain has led to the discovery of a novel series of compounds based on a N-benzyl indole/indoline scaffold. This poster will summarize the SAR optimization and pharmacological profiling that led to the identification of MF-766. MF-766 exhibited good pharmacokinetics in a number of animal species and unprecedented in vivo potency in a pre-clinical rat model of inflammation.

\[
\begin{align*}
&\text{MF-766} \\
&\text{O} \\
&\text{N} \\
&\text{H} \\
&\text{COOH} \\
&\text{CF}_3
\end{align*}
\]
Spirocyclic Ureas: Orally Bioavailable 11β-HSD1 Inhibitors identified by
Computer-Aided Drug Design

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Joan Guo, Paula M. Krosky, Barbara A. Kruk, Jennifer Berbaum, Richard K. Harrison,
Judith J. Johnson, Yuri Bukhtiyarov, Reshma Panemangalore, Boyd B. Scott, Yi Zhao,
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Abstract

Structure-guided drug design led to the identification of a class of spirocyclic ureas which
potently inhibit human 11β-HSD1 in vitro. Lead compound 10j was shown to be orally
bioavailable in three species, distributed into adipose tissue in the mouse, and its (R)
isomer 10j2 was efficacious in a primate pharmacodynamic model.
DISCOVERY OF 8-PHENYLAMINO-DHI ANALOGS AS POTENT DLK INHIBITORS FOR THE POTENTIAL TREATMENT OF ALZHEIMER'S DISEASE

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The mixed lineage kinase family (MLK1, MLK2, MLK3 and DLK (dual leucine-zipper kinase)) are a critical upstream activating component of the stress-activated protein kinase-signaling cascade regulating c-Jun N-terminal kinase (JNK) activation and subsequent c-Jun phosphorylation, leading to neuronal cell death. DLK, which is located almost exclusively in the brain, induces activation of JNK via MKK7 and inhibition of DLK has been shown to closely correlate with blockade of c-Jun phosphorylation and prevention of cell death. Our efforts in the design and synthesis of MLK inhibitors in the indolocarbazole class identified CEP-1347 as a first generation molecule that advanced through Phase III clinical trials. Recently we reported the identification of MLK1/3 subtype-selective dihydronaphthyl[3,4-a]pyrro[3,4-c]carbazole (DHN) analogs with neuroprotective properties and favorable pharmacokinetic profiles. Our subsequent objective was to design in DLK potency and advance pan-MLK inhibitors with acceptable pharmacokinetic properties and brain exposure for the potential treatment of Alzheimer’s disease. Structural modification to the DHN core with the aid of molecular modeling identified a novel series of 8-phenylamino-12,13-dihydroindazolo[5,4-a]pyrrolo[3,4-c]carbazole (DHI) inhibitors. The synthesis, optimization and characterization of a lead candidate will be presented.
Noncompetitive Delayed Onset TRPV1 Antagonists

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The characteristics and functional role of the rodent and human TRPV1 receptor have been greatly illuminated by a number of studies in the past decade. This receptor, which is widespread in many tissues of the body, seems to be principally involved in mediating nociceptive responses to heat, low pH and vanilloid agonists such as capsaicin and resiniferatoxin. The possibility that endogenous vanilloids resulting from tissue injury or inflammation may be acting via stimulation of TRPV1 has led to the pursuit of a variety of chemical structures that possess TRPV1 antagonist properties. Such compounds may have usefulness as analgesic agents in the treatment of certain types of pain.

A series of compounds (Template I) has been designed that was intended to meet the requirements of the TRPV1 antagonist pharmacophore. Previous studies of vanilloid agonists have identified the importance of an aromatic A region, a polar B region, and a hydrophobic C region. In addition, our compounds have included a heteroatom (X = alcohol or amide) intended to interact with a proposed D region.

The target compounds were evaluated by inhibition of [3H]resiniferatoxin binding to rat TRPV1, which provides a measure of affinity for TRPV1 under equilibrium conditions, and by inhibition of ⁴⁵Ca²⁺ uptake in response to capsaicin, which provides measures of potency and efficacy (agonism / antagonism). In addition to a usual incubation time of 5 min for ⁴⁵Ca²⁺ uptake, some compounds were assayed with a 1 hour incubation, to determine the potential consequences of slow penetration. Likewise, for some compounds which displayed antagonism, the inhibition of agonist stimulated ⁴⁵Ca²⁺ uptake was measured.
uptake was also probed using a large excess of agonist, to determine if the inhibition was competitive with agonist or non-competitive. A striking feature of some of the 3,4-methylenedioxy derivatives was non-competitive inhibition of the capsaicin response, evident at 1 hour of incubation, at concentrations approximating their $K_i$ values for TRPV1 binding. Further exploration of the mechanism for this antagonism will be required. A preliminary finding was that the extent of partial agonism with a short incubation time was diminished in antagonism assays with a 1-hour incubation. Feedback regulation of TRPV1 may thus complicate the pharmacology of partial agonists. Further details on the syntheses of these compounds and the results of the biological testing
SYNTHESIS OF ANTICANCER AGENTS THAT SELECTIVELY TARGET DRUG RESISTANT CANCER

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Bcl-2 proteins play a key role in apoptosis. Overexpression of anti-apoptotic Bcl-2 proteins inhibits apoptosis and is a major cause for development of multiple drug resistance (MDR). Since MDR poses a major obstacle in the treatment of cancer, developing inhibitors for anti-apoptotic Bcl-2 proteins is a promising strategy. HA 14-1 (1) is the first small-molecule reported to inhibit anti-apoptotic Bcl-2 proteins. It selectively eliminates cancer cells overexpressing anti-apoptotic Bcl-2 proteins and demonstrates synergism with a variety of chemotherapeutic agents. However, previous work in our lab revealed that 1 is unstable and decomposes within 15 minutes. Efforts to develop a stable analog lead to the synthesis of sHA 14-1 (2), which was 100-fold more stable, but 2 fold less active than 1. A thorough structure-activity relationship (SAR) study was carried out to improve the anti-cancer efficacy of 2, leading to the identification of CXL017 (3), which is 23 fold more potent than 2. Furthermore, 3 selectively targets drug resistant cell lines that are cross-resistant to a variety of known chemotherapeutic agents in vitro. More importantly, 3 shows significant anti-tumor activity against resistant tumors in vivo. These results suggest that 3 is a potential candidate for the treatment of drug-resistant cancers. This presentation will discuss the results and implications of the research.

Rational drug design to develop stable potent analogs of HA 14-1
N-Aryl Pyrrolidinone/Pyrrolidine Carboxamides as Potent NPY5 Antagonists

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Abstract: Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in the central and peripheral nervous systems possessing a diverse array of biological functions including influencing blood pressure, food intake, circadian rhythms, and stress sensitivity. NPY exerts its effects through interaction with specific receptors of the GPCR superfamily. Five NPY receptor subtypes have been identified to date (Y1, Y2, Y4, Y5, and Y6). The N-aryl pyrrolidinone carboxamide 1 was identified as a lead in our efforts to design potent NPY5 antagonists. Lead optimization generated a new class of sub-nanomolar N-aryl pyrrolidine carboxamides exemplified by 2. This work will be presented along with our efforts to optimize microsomal stability, CYP profile, Pgp efflux liability and subsequent in vivo PK profile.

\[ hY5\text{Ki} = 90\text{ nM} \]

\[ hY5\text{Ki} = 0.53\text{ nM} \]
Alkyl Amino Sulfonamides as Potent NPY5 Antagonists

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Abstract: Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in
the peripheral and central nervous system and a member of the pancreatic polypeptide
family, which includes pancreatic polypeptide (PP) and peptide YY (PYY). The
biological effects of NPY and related peptides are mediated through interactions with
receptors belonging to the GPCR super family. A total of five corresponding receptor
subtypes were cloned and pharmacologically characterized (Y1, Y2, Y4, Y5, and Y6).
The Y5 receptor is well known for its role in appetite. Based on expression in the limbic
system, we hypothesized that the Y5 receptor might also modulate stress sensitivity.
Recently we disclosed compound Lu AA33810 as a highly potent and selective NPY5
antagonist with anti-depressant like activity in rat behavioral models. Synthesis, SAR and
physico-chemical properties of a novel linear alkyl aminothiazoles series (I) will be
presented.

\[ \text{Lu AA33810 hY5 Ki 1.5 nM} \rightarrow \] (I) hY5 Ki 12 nM
Discovery of Lu AE00654: An Orally Efficacious NPY5 Antagonist with Anti-depressant like Behavior

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Abstract: Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in the peripheral and central nervous system and a member of the pancreatic polypeptide family, which includes pancreatic polypeptide (PP) and peptide YY (PYY). The biological effects of NPY and related peptides are mediated through interactions with receptors belonging to the GPCR super family. A total of five corresponding receptor subtypes were cloned and pharmacologically characterized (Y1, Y2, Y4, Y5, and Y6). The Y5 receptor is well known for its role in appetite. Based on expression in the limbic system, we hypothesized that the Y5 receptor might also modulate stress sensitivity. Recently we disclosed compound Lu AA33810 as a highly potent and selective NPY5 antagonist with anti-depressant like activity in rat behavioral models. Initial SAR studies with linear alkyl aminothiazoles resulted in potent Y5 antagonists with high in vitro clearance. Here we describe compound Lu AE00654, an orally bio-available and highly efficacious Y5 antagonist with anti-depressant efficacy in rat behavioral models. Synthesis, SAR studies and in vivo data will be presented.
Identification of N-Aryl Amino 2-Thiazoles as Potent Small Molecule NPY5 Antagonists

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Abstract: Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in the peripheral and central nervous system and a member of the pancreatic polypeptide family, which includes pancreatic polypeptide (PP) and peptide YY (PYY). The biological effects of NPY and related peptides are mediated through interactions with receptors belonging to the GPCR super family. A total of five corresponding receptor subtypes were cloned and pharmacologically characterized (Y1, Y2, Y4, Y5, and Y6). The Y5 receptor is well known for its role in appetite. Based on expression in the limbic system, we hypothesized that the Y5 receptor might also modulate stress sensitivity. Screening of compounds from a mini-library collection resulted in the identification of aminothiazole derivative (I) with good affinity at the Y5 receptor. Optimization of the initial hit led to the identification of potent Y5 antagonists with acceptable PK properties. A detailed SAR study of the 2-aminothiazoles will be discussed.
A pharmacophore for acetylcholinesterase inhibition using curcumin derivatives

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The extract of *Curcuma longa* has been used for years in traditional medicine for the treatment of several illnesses. One of its most important constituents, curcumin, is a beta-diketone which possesses antiinflammatory, hypolipemic, antimicrobial, anticarcinogenic, anticoagulant, antioxidant and mild acetylcholinesterase inhibition activities. These two latter activities make curcumin a molecule of interest for the treatment of Alzheimer’s disease. It is the aim of our group to design curcumin derivatives with enhanced potency as acetylcholinesterase inhibitors. We present a pharmacophore generated for such purpose that includes curcumin derivatives. The predictive ability of our model was tested with a new set of curcumin derivatives.
Development of an Oxazolobenzimidazole Class of Positive Allosteric Modulators of mGluR2 for the Treatment of Schizophrenia

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Normalization of excessive glutamate neurotransmission through activation of the metabotropic glutamate receptor 2 (mGluR2) represents a novel and promising approach for the treatment of schizophrenia. This strategy has gained support through the evaluation of dual mGluR2/3 agonists that act directly at the glutamate (orthosteric) binding site. Importantly, clinical validation of the mechanism was achieved in a Phase II study in schizophrenia patients with mGluR2/3 agonist LY404039, dosed orally as its prodrug LY2140023. Selective positive allosteric modulators (potentiators) of mGluR2 that bind to the transmembrane region of the receptor have shown efficacy in rodent models predictive of antipsychotic activity, but have yet to be evaluated in the clinic. Allosteric mGluR2 potentiators may offer advantages over orthosteric mGluR2 agonists as a result of their unique mode of action and ability to achieve superior mGluR2 selectivity. Herein we describe the hit-to-lead discovery of a potent N-aryl oxazolidinone mGluR2 potentiator (1) that through ring-constraint was transformed into a novel oxazolobenzimidazole lead (2). Further optimization of 2 with a focus on metabolic stability and physical properties provided 3 as an orally bioavailable and brain penetrant compound. The synthesis and in-depth profile of 3 will be presented, including its efficacy in reducing the psychomotor activating effects of MK-801 in rats.

\[
\begin{align*}
1 & : \text{N-aryl oxazolidinone mGluR2 potentiator} \\
2 & : \text{Novel oxazolobenzimidazole lead} \\
3 & : \text{Orally bioavailable and brain penetrant compound}
\end{align*}
\]
N-Heteroaryl Glycinamides as Potent NPY5 Antagonists

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Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in the central and peripheral nervous systems possessing a diverse array of biological functions including influencing blood pressure, food intake, circadian rhythms, and stress sensitivity. NPY exerts its effects through interaction with specific receptors of the GPCR superfamily. Five NPY receptor subtypes have been identified to date (Y1, Y2, Y4, Y5, and Y6). In our effort to identify novel NPY5 antagonists, the benzothiazepine glycinamide 1 was identified as a promising lead. Optimization efforts will be described targeting improvements in potency, microsomal stability, and PK properties.

1

\( hY5 \text{ Ki} = 27 \text{ nM} \)
Synthesis of Tritium Labeled Queuine, PreQ₁ and Related Azide Probes for Determining the Prevalence of Queuine in RNA

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Queuine, the aglycone of queuosine, is one of the approximately one hundred modified nucleotides found in RNA. It is unusual in that, unlike the majority of modified nucleotides that result from modifications of the genetically encoded nucleotides, it is incorporated into RNA by transglycosylation. In order to determine the prevalence of the queuine modification it was important to consider that queuine modification differs depending on the type of organism under consideration. Eukaryae incorporate queuine, whereas eubacteria incorporate preQ₁, which then undergoes modification to yield queuine. This work seeks to determine the prevalence of queuine in eubacteria and eukaryae to better understand its physiological importance as well as give a better understanding of the enzyme responsible for its incorporation, tRNA guanine transglycosylase. Tritium-labeled probes that allow for following the incorporation of queuine into RNA were prepared to determine the prevalence of the modification in general terms, the amount of modification and type of RNA affected by the modification. In addition, azide congeners of queuine were prepared to allow for isolation and identification of RNA fragments to implicate specific sites of queuine incorporation. Concise routes to generate tritium labeled versions of queuine, preQ₁ as well as the azide congeners will be presented.
Structure based design of cyclic sulfone hydroxyethylamine BACE1 inhibitors

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Alzheimer's disease (AD) is a progressive neurodegenerative disease that is the leading
cause of dementia. Although the cause of AD is still unclear, deposition of β-amyloid
peptide (Aβ) in the brain is a hallmark of AD pathogenesis, and it is believed that
therapeutic agents that lower Aβ will be beneficial in the treatment of AD. Aβ is
produced from membrane-bound β-amyloid precursor protein (APP) by sequential
proteolytic cleavage by β-secretase (BACE1) and γ-secretase. Therefore, BACE1 is an
attractive therapeutic target for AD.

A structure-based design approach and the synthesis of novel cyclic sulfone hydroxy-
thylamine BACE inhibitors that penetrate the CNS and acutely lower brain A-beta levels
in APP transgenic mice will be disclosed.
Inhibiting NIK (NF-κB-Inducing Kinase): Discovery, Structure-based Design, and the First Co-crystal Structure of NIK Inhibitors

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Nuclear factor (NF)-κB is a group of conserved eukaryotic transcription factors that regulate the expression of genes critical for both innate and adaptive immune responses. As a member of the mitogen-activated protein kinase kinase kinase (MAP3K) family, the NF-κB-inducing kinase (NIK) is a serine/threonine protein kinase essential for the activation of a second major NF-κB (NF-κB2) pathway. A small-molecule inhibitor specific for NIK may provide a novel approach to the intervention of NF-κB2 signaling and the modulation of the immune system. Our work began with HTS hits such as imidazopyridinyl pyrimidinamine 1, utilized homology modeling and conformational analysis to carry out SAR around the indole scaffold, and underwent structure-based design leading to the discovery of novel and potent conformatinally constrained NIK inhibitors such as compounds 24 and 27. Compound 24 was co-crystallized with NIK protein to provide the first reported NIK co-crystal structure. In this poster the SAR, synthesis and co-crystal structure will be presented.
Discovery of Pyrimidoaxazines as Novel DGAT1 Inhibitors Efficacious in a Mouse Diet-Induced Obesity Model

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Disorders or imbalances in triglyceride metabolism are implicated in the development of obesity, insulin resistance syndrome, type II diabetes and coronary heart disease. DGAT1 is a micosomal enzyme that catalyzes the final step in triglyceride synthesis. DGAT1 plays a major role in the absorption of triglyceride from the intestine and deposition of triglyceride into adipose tissue. DGAT1/- mice have reduced adiposity, are resistant to diet-induced obesity and have increased insulin and leptin sensitivity. A high-throughput screen of our small molecule library resulted in the discovery of pyrimidooxazine 1 as a moderately potent DGAT1 inhibitor. Investigation of the SAR of the three rings of 1 provided highly potent carboxylate 44. Pyrimidoaxazine 44 was shown to be very selective against other acyl transferases and demonstrated good PK properties across several species. In vivo studies were conducted with 44 that demonstrated its ability to inhibit the absorption of triglycerides (TG) from the intestine of mice and rats, as well as, inhibit the synthesis of TG in the fat pads of mice. Dosing 44 to obese mice in food for 30 days resulted in a significant decrease in body weight compared to vehicle in a diet-induced obesity model.

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\begin{align*}
\text{DGAT1 IC}_{50} &= 0.5 \mu M \\
\text{DGAT1 IC}_{50} &= 0.006 \mu M
\end{align*}
\]
The discovery of structural hybrid p38 inhibitors with enhanced binding and efficacy as inhaled inhibitors of neutrophilia

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A general goal of our group has been the treatment of respiratory diseases through local administration of anti-inflammatory agents to the lung. As part of these efforts we chose to evaluate oral p38 inhibitors as lead structures. The 6-{3-carboxamidephenyl}-3-pyridinecarboxamides 1, and 8, 4, 2 trisubstituted pyrido[2,3-d]pyrimidin-7(8H)-ones 2, are distinct classes of orally active p38 inhibitors which utilize several non-equivalent binding sites. By analyzing co-crystal structures of the separate inhibitor classes with p38α, hybrid molecules were proposed which had the potential for interacting with p38α by means of the binding sites available to each of the inhibitor classes. Using a synthetic approach which was suitable for high throughput syntheses, examples of these new p38 inhibitors were prepared. These were effective for the treatment of an animal model of neutrophilia through intratracheal administration. Two of these hybrid molecules co-crystallized with p38α and X-ray crystallography confirmed that they bound to the enzyme using binding sites derived from both structural classes.
SAR studies on potent and selective indole-based MMP-13 Inhibitors: ester replacement

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This poster will present the SAR studies to replace the ester group of a series of potent and selective novel MMP-13 inhibitors (1), which were discovered by a fragment-based lead identification approach. While the ester group was important for potency, it also presents a potential metabolic liability. SAR studies, guided by X-ray co-structures, identified a number of different heteroaromatic groups that replaced the ester and maintained similar potency. The preferred group is 1,2,4-oxidazol-5-yl group which improved the potency by 5 fold and provided compound 2 with good oral exposure in mouse.

![Diagram of ester replacement]

- **1**: MMP-13 IC₅₀: 0.45 nM
- **2**: >400 fold selective over MMP-1,2,3,7,8,9,10,12,14 (all tested)
Indole- and Indazole-Based Inhibitors of Dipeptidyl Peptidase IV for the Treatment of Type 2 Diabetes

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Two new series of \( \beta \)-aminoamides (A and B) have been developed as potent and selective inhibitors of dipeptidyl peptidase IV (DPP-IV), a proven target for the treatment of type 2 diabetes.

The \( \beta \)-aminoamide motif is shared with the sitagliptin (MK-0431), the first marketed DPP-IV inhibitor, and through careful design the indole and indazole groups afforded viable alternatives to the trifluorophenyl group of sitagliptin. Routes were devised to racemic mixtures of indoles (A) and indazoles (B), and the two series were initially progressed in parallel. From the latter set, PK44 emerged as the lead compound, for which a route to the single enantiomer was developed. PK44 is a potent inhibitor of DPP-IV (IC\(_{50}\) 15.8nM), with more than a thousand-fold selectivity over DPP-8 and DPP-
9 and ten thousand-fold selectivity over FAP. DPP-8 and -9 have been associated with toxicity. It showed no adverse effects in hERG and cytotoxicity screens. In a preliminary oral glucose tolerance assay in mice PK44 showed significant improvements in glucose tolerance.
ONE-POT SYNTHESIS OF 2-AMINOBENZIMIDAZOLES USING 2-CHLORO-1,3-DIMETHYLIMIDAZOLINIUM CHLORIDE (DMC)

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2-Chloro-1,3-dimethylimidazolinium chloride (DMC or DMC-Cl) effectively and rapidly generates 2-aminobenzimidazoles from 1,2-diaminoaranes and isothiocyanates in moderate to good yields using a room-temperature, one-pot procedure. 2-Aminobenzimidazoles are an important chemotype in medicinal chemistry, and this method offers the advantage of ease of use and relatively low toxicity over the usually employed iedomethane or metal-based procedures.
SYK (Spleen Tyrosine Kinase) is a non-receptor tyrosine kinase that is involved in coupling activated immunoreceptors to signal downstream events that mediate diverse cellular responses, including proliferation and differentiation. Inhibition of SYK mediated Ig Fc epsilon and gamma receptor and B-cell receptor signaling leads to mast cell, macrophage and B-cell inhibition. Accordingly, SYK kinase inhibitors have attracted interest in a number of therapeutic areas, including the treatment of rheumatoid arthritis, B-cell lymphoma and asthma / rhinitis.

The lead optimisation of the diaminopyrimidine carboxamide series will be described. The initial strategy focussed on optimising the physicochemical properties, particularly modification of pKa and PSA, to deliver adequate pharmacokinetics and low hERG activity. The series was subsequently optimised to overcome mutagenicity whilst maintaining SYK potency and broad kinase selectivity.
The Discovery of 2-Aminoquinolines and 2-Aminopyridines as Potent Beta-Secretase Inhibitors

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β-secretase (BACE1) is believed to play a crucial role in the initiation of the amyloid cascade leading to the pathogenesis of Alzheimer’s disease (AD). The development of BACE1 inhibitors to lower the production of amyloid peptides (Aβ) thus represents an attractive therapeutic approach for the treatment of AD. Using the fragment based lead generation strategy we identified 2-aminoquinoline as an initial fragment hit that displayed potency in the millimolar range with excellent ligand efficiency. Structure guided evolution of this fragment using X-ray crystallography has resulted in 2-aminoquinoline derived BACE inhibitors with potent activities in enzymatic and cellular assays. The analogous 2-aminopyridine derived inhibitors were also explored. In this poster, detailed structure-activity relationships in both series will be discussed.
Identification of novel non-hydroxamate anthrax toxin lethal factor inhibitors


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Abstract

Anthrax is an infectious disease caused by Bacillus anthracis, a Gram-positive, rod-shaped, anaerobic bacterium. The lethal factor (LF) enzyme is secreted by B. anthracis as part of a tripartite exotoxin and is chiefly responsible for anthrax-related cytotoxicity. As LF can remain in the system long after antibiotics have eradicated B. anthracis from the body, the preferred therapeutic modality would be the administration of antibiotics together with an effective LF inhibitor. Although LF has garnered a great deal of attention as an attractive target for rational drug design, relatively few published inhibitors have demonstrated activity in cell-based assays and, to date, no LF inhibitor is available as a therapeutic or preventive agent. Here we present a novel in silico high-throughput virtual screening protocol that successfully identified 5 non-hydroxamic acid small molecules as new, preliminary LF inhibitor scaffolds with low micromolar inhibition against that target, resulting in a 12.8% experimental hit rate. This protocol screened approximately 35 million nonredundant compounds for potential activity against LF and comprised topomeric searching, docking and scoring, and drug-like filtering. Among these 5 hit compounds, none of which has previously been identified as a LF inhibitor, three exhibited experimental IC₅₀ values less than 100 μM. These three preliminary hits may potentially serve as scaffolds for lead optimization as well as templates for probe compounds to be used in mechanistic studies. Notably, our docking simulations predicted that these novel hits are likely to engage in critical ligand-receptor interactions with nearby residues in at least two of the three (S1', S1-S2, and S2') subsites in the LF substrate binding area. Further experimental characterization of these compounds is in process. We found that micromolar-level LF inhibition can be attained by compounds with non-hydroxamate zinc-binding groups that exhibit monodentate zinc chelation as long as key hydrophobic interactions with at least two LF subsites are retained.
Anthranilic acid derivatives as potent, orally bioavailable DHODH inhibitors devoid of hepatotoxicity

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Inhibitors of the enzyme dihydroorotate dehydrogenase (DHODH) have shown beneficial immunosuppressant and antiproliferative effects in human diseases that are characterised by abnormal and uncontrollable cell proliferation causing chronic inflammation and tissue destruction.

DHODH catalyzes the fourth step in the de novo pathway of pyrimidine biosynthesis. Cells with a high turnover rely on this pathway to proliferate – eg, lymphocytes in chronic immune-mediated diseases. In these cells, DHODH inhibition stops cell cycle progression by suppressing DNA synthesis and consequently cell proliferation is prevented.

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 evolution of anthranilic acid derivatives as a novel, potent, orally bioavailable family of DHODH inhibitors which have an outstanding safety/efficacy profile. The lead optimization exercise shown has led to the identification of compounds suitable for clinical development..
Leukotrienes (LTs) are pro-inflammatory lipid mediators derived from arachidonic acid which play pivotal roles in various biological and pathological processes. Recent studies suggest a crucial role of 5-LO products in cell proliferation and survival particularly of prostate and pancreatic cancer cells. Additionally, the cardiovascular actions of LTs have also been well recognized for many years, especially in atherosclerosis and in myocardial infarction in which each disease is characterized by an inflammatory component at some stage of the associated vascular pathology. Therefore, the inhibition of LT formation became an attractiveness pharmacological strategy to intervene with these diseases. In present study, we show that certain derivatives of 1,5-darylpyrazole-3-propanoic acid inhibit LTB₄ biosynthesis in intact human neutrophils when stimulated with ionophore A23187. Our efforts for structural optimization resulted compounds with IC₅₀ values between 1.2 and 4.8 μM. Interestingly, the compounds showed no considerable inhibition of 5-LO product formation in a cell-free system suggesting that the compounds may interfere with a regulatory mechanism of 5-LO in intact cells resulting in inhibition of LT formation rather than directly acting on the 5-LO enzyme. We are currently studying the identification of the exact mode of action underlying inhibition of the cellular LT formation. Based on their high selectivity and efficacy, these novel structures might represent promising candidates for further development as suitable inhibitors of 5-LO product synthesis (This work is supported by a TUBITAK Research Grant 108S210).
Synthetic routes to a cardioprotective (N)-methanocarba phosphate and phosphonate analogues of 5'-AMP derivative

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Cardiac P2X receptors represent a novel and potentially important therapeutic target for the treatment of heart failure. MRS2339, is an (N)-methanocarba monophosphate derivative of 2-chloro-AMP that contains a rigid bicyclo[3.1.0]hexane ring system in place of ribose, activates this cardioprotective channel. Synthesis of MRS2339 involves twelve synthetic steps starting from commercially available L-ribose. Among these are a few steps that are either low yielding or requiring a laborious workup. However, the cardioprotective properties of MRS2339 justified devising an alternative route, with fewer steps than the previously reported route and easier workup. This route also provided a common intermediate for the synthesis of phosphonate analogues. Although a (N)-methanocarba nucleoside monophosphate was shown to be a poor substrate of nucleotidases, replacement of the phosphoester group of MRS2339 with a phosphonate would be expected to further increase the invivo half-life because of the stability of the C-P bond. Hence we synthesized the two phosphonate analogues of MRS2339 viz, MRS2775 and MRS2776. After chronic administration of these phosphonates via a miniosmotic pump (Alzet), they significantly increased intact heart contractile function in calsequestrin-overexpressing mice (genetic model of heart failure) compared to vehicle-infused mice (20.25% and 16.23%, respectively, versus 13.78% in controls). These phosphonate analogues were inactive at the P2Y₁ receptor, which excludes the possibility that the observed cardiovascular effects of the phosphonate derivatives were a result of activation of an endothelial P2Y₁ receptor.
Chemically controlled assembly of anti-CD3 antibody nanorings

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Due to the enhancement in avidity of a polyvalent ligand for its receptor over the monovalent ligand, single-chain antibodies (scFv) oligomers are increasingly being used as clinical therapeutic reagents. Based on our development of a highly efficient protocol for the chemical dimerization of dihydrofolate reductase (DHFR) by a methotrexate dimer (MTX2), we have recently discovered a method for the preparation of self-assembling DHFR based protein nanorings. We have sought to exploit our methodology for the controlled assembly of polyvalent antibody nanorings for tissue imaging and drug delivery. This assembly is reversible in vitro with the clinically available antibiotic trimethoprim.

References

Acknowledgements
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RGD4C-DHFR Fusion Proteins for the Cellular Delivery of Therapeutics

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We have shown that dihydrofolate reductase (DHFR)-DHFR fusion proteins spontaneously self-assemble into highly stable nanorings upon the addition of the chemical dimerizer bis-methotrexate (Bis-MTX). Varying the length of the peptide linker between the two DHFR proteins, allows the assembly of rings consisting of between two and eight fusion proteins (Figure 1A). These protein nanorings can be used for the multivalent display of anti-CD3 scFv proteins to target T-leukemia cells. Replacing the scFv with RGD4C peptides allows for the targeting of solid tumors such as breast and prostate cancers. We hypothesize that DHFR-RGD4C fusion proteins can be used to carry MTX-therapeutic constructs into these cells. Towards this we have shown that these DHFR-RGD4C proteins can be used to carry bis-MTX ligands labeled with a dye into MDA-MB-231 and MIA PaCa-2 cells (Figure 1B). The formation of these rings offer benefits of increased avidity for the target cell (by displaying multiple copies of the RGD4C).

![Figure 1A](image1.png) Schematic showing nanoring assembly. B) DHFR-RGD4C fusion proteins delivering fluorescein-MTX conjugates to MIA PaCa-2 (prostate cancer) cells.

References:
Pharmacokinetics studies of anti-cancer gallotannin penta-O-galloyl-beta-D-glucose (PGG) in mice

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Studies by our group and others have shown that 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucose (PGG) exhibits in vivo anti-cancer effects against prostate and breast cancer xenograft or lung cancer allograft when administrated by i.p injection or oral gavage. PGG has also been shown in several studies to exhibit anti-diabetic activities both in vitro and in vivo. However, no data have been published on the absorption, distribution, metabolism and elimination (ADME) to provide mechanistic correlates to account for the biological activities. In this study, we developed a method for the analysis of PGG in mouse plasma, using tea polyphenol epigallocatechin gallate (EGCG) as an internal standard (IS). A liquid–liquid extraction (LLE) protocol originally developed for tea polyphenol analyses was optimized for the extraction of PGG from mouse plasma. In brief, plasma (0.2 ml) was acidified with an equal volume of 2% acetic acid, and ethyl acetate was then applied to extract PGG and EGCG (IS). After LLE, PGG was quantitated by HPLC with a UV detection at 280 nm. The method was validated according to FDA guidelines. The extraction efficiency for spiked PGG was ~70 % in mouse plasma. The limit of detection (LOD) for PGG was approximately 100 ng/ml and the limit of quantitation (LOQ) around 200 ng/ml when using 200 µl mouse plasma. The linear range of the method was 0.2 -25 μg/ml in mouse plasma.
Pharmacokinetics of PGG following a single i.p. injection in mice was studied. The peak plasma PGG concentrations (C\text{max}) were found to be approximately 4 and 11 μM at administered dose of 20 and 80 mg/kg of PGG, respectively. The apparent half life of the elimination phase for PGG is 3 h. Addition of glucuronidase and sulfatase to plasma did not change extractable PGG. These data suggest that PGG exists in plasma mostly as free extractable form after a single i.p. injection and that the plasma resident time for PGG is several hours.
Opioid agonists are the first-choice analgesics used for the treatment of pain. However, they produce undesired side effects such as tolerance and physical dependence that complicates their use. It has been suggested that delta antagonists attenuate tolerance and dependence produced by mu opioid agonists. To address this, along with the mounting evidence for oligomerization of opioid receptors, our group previously described the synthesis of a bivalent series of MDAN compounds with mu agonist/delta antagonist pharmacophores tethered together via a spacer of varied lengths. The bivalent ligand with a spacer length of 21 atoms (MDAN-21) proved optimal and did not produce any tolerance or dependence in mice. Here we provide evidence that MDAN-21 selectively activates, and is bridging mu-delta heteromeric receptors using intracellular calcium release and immunofluorescence imaging studies in HEK-293 cells. We also investigated the clinically employed monovalent ligand, buprenorphine, which has limited tolerance and dependence liabilities. We observed that it also selectively activates mu-delta heteromeric receptors, but it is an antagonist at delta opioid receptors. These results suggest a strong link between the signal transduction of mu-delta heteromeric opioid receptors and behavioral side effects like tolerance and dependence. The parallels between MDAN-21 and buprenorphine, along with the implications for the design of analgesics devoid of tolerance and dependence will be discussed.
3-Oxa-7-Azabicyclo[3.3.1]nonane GPR119 Receptor Ligands

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GPR119 is a promising target for the treatment of type II diabetes. This derives from the ability of GPR119 agonists to stimulate both an incretin response in the gut and to stimulate insulin release in the pancreas in a glucose dependent fashion. To elicit a maximal response from receptors at both sites of action, a good balance of agonist pharmacology and drug like properties will be needed. Herein we closely examine two isomeric 3-oxa-7-azabicyclo[3.3.1]nonanes and show that small conformational changes can lead to profound differences in both the biopharmaceutical properties and the agonist pharmacology of the molecules.
Synthesis and SAR of a novel class of tetrahydroisoquinoline-based potentiators of NR2C/D containing NMDA receptors

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The N-methyl-D-aspartate (NMDA) receptor is a member of the ionotropic glutamate receptor family and plays a prominent role in many processes, including learning and memory, synaptic plasticity, and neuronal development. Dysfunction of these receptors has been implicated in a wide range of neurological disorders including schizophrenia, Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea and neuropathic pain. The four different NR2 subunits (A-D) each endow the receptor a specific and distinguishable open probability, single channel conductance, and deactivation time course. This, along with their differential expression, strengthens the therapeutic rationale for the development of subunit-selective modulators of this receptor. A novel NR2C/D subunit selective potentiator (1), with an EC50 of 11.4 μM and a max of 156%, was identified through a high-throughput screening assay. A structure activity relationship (SAR) was developed around the screening hit. Synthesized analogs are accounted for in the generic structure, 2. Bischler-Napieralski reaction conditions were employed for the conversion of acyclic amides to the corresponding tetrahydroisoquinoline containing analogs.
NOVEL SILICON DERIVATIVES FOR INDOMETHACIN: GENERATION OF POTENT COX-2 SELECTIVE AGENTS WITH IMPROVED ANTICANCER ACTIVITY

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Elevated tumor cyclooxygenase-2 is associated with poor overall survival in patients with a variety of cancers. Patients with elevated COX-2 that receive a COX-2 inhibitor have demonstrated improved survival. Indomethacin (IM) is a COX-non-selective inhibitor with demonstrated anticancer activity in patients. The anticancer effects of IM are related to inhibition of COX-2 as well as COX-independent targets. We now report the synthesis and activity of novel IM-sila-amide derivatives where strategic silicon addition results in COX-2 selective IM derivatives that demonstrate activity in mouse models of human cancers and are devoid of the COX-1 associated toxicities. The sila-IM compounds demonstrated improved inhibition of purified human COX-2, IC₅₀ 0.2 μM and limited inhibition of COX-1 up to 10 μM. Sila-IM derivatives were also found to be potent inhibitors of NFkB transcription activating function at concentrations below 1.0 μM. A sila-IM derivative Silexsyn was tested in various animal models of human cancer following oral administration. Significant activity was observed in models of non-small cell lung cancer and pancreas cancer. Potent synergism was observed for Silexsyn in combination with EGFR inhibitors. A synthetic methodology incorporating a heteroatom in the amino-functional silane has been developed and used to generate second-generation sila-IM derivatives that could have improved pharmacological properties. The introduction of silicon into an approved scaffold represents an efficient strategy for the rapid production of biologically relevant therapeutics for the treatment of cancer.
Cytosolic phospholipase A2α (cPLA2α) is the major enzyme which liberates arachidonic acid and lysophospholipid from membrane phospholipids. It plays an important role in the production of inflammatory mediators such as prostaglandins, leukotrienes, platelet-activating factor, and therefore inhibition of cPLA2α would be a very attractive target field to treat or prevent various inflammatory diseases. We have been searching for novel cPLA2α inhibitors, and recently identified a new class of N-aryl-indole derivatives (1) as potent small molecule inhibitors, which we originally designed based on a hit compound from our random screening. SUN13333 is the representative of these new potent cPLA2α inhibitors, and orally efficacious in in vivo model. Herein we will describe the design, the syntheses and the structure-activity relationships of this series of compounds.
Efforts Toward Recombinant NMDA GluN2C/D Subunit Selective Antagonists

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N-methyl-D-aspartate receptors (NMDARs) mediate the slow component of excitatory synaptic transmission in response to co-agonist binding of glutamate and glycine. NMDARs are hetero-tetrameric receptors composed of two GluN1 and two GluN2 subunits, of which there are four types (GluN2A-D). The differential expression patterns associated with each particular NR2 subunit type suggest a pharmacological rationale for intervention in diseases such as Parkinson's, schizophrenia, and ischemic cell death. We have described a new class of subunit-selective antagonists of NMDA receptors that
contain the (E)-3-phenyl-2-styrylquinazolin-4(3H)-one backbone. This class of compounds resemble CP-465,022 ((S)-3-(2-chlorophenyl)-2-[2-((6-diethylaminomethyl-pyridin-2-yl)-vinyl]-6-fluoro-3H-quinazolin-4-one), however some members are 100-fold selective for NMDA over both AMPA and kainate receptors. In addition, at least two members of this class have been identified that are up to 50-fold selective for NR2C/D containing NMDARs. We have described the structure-activity relationship around this class of molecules, which has led to modest improvements in the IC\textsubscript{50} values and GluN2 subunit-selectivity. A predictive quantitative structure-activity relationship (QSAR) model has been developed, and efforts to understand the mechanism of antagonism and molecular determinants of action are ongoing.

CP-465,022, a known AMPA antagonist

General structure of novel NMDA antagonist
Minimization of Bioactivation Potential of 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors in Lead Optimization

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11β-Hydroxysteroid dehydrogenase type 1 (11β–HSD1), a short chain reductase expressed mainly in the adipose and the liver, catalyzes the reduction of the inactive glucocorticoid cortisol to the active glucocorticoid cortisol using the cofactor NADPH. The 11β-HSD1 knockout mouse is protected from hyperglycemia associated with stress or obesity through reduced hepatic expression of phosphoenolpyruvate carboxy kinase (PEPCK), which controls the rate limiting step of gluconeogenesis, as well as other glucose mobilizing enzymes such as glucose-6-phosphatase (G6Pase). Inhibition of 11β-HSD1 activity provides an opportunity to reduce glucocorticoid levels specifically in the liver and splanchnic circulation. Thus, inhibition of 11β-HSD1 activity is a potentially attractive approach to treat diabetes. The N-(pyridin-2-yl) arylsulfonamide PF-915275, a potent 11β–HSD1 inhibitor ($K_i = 2 \text{ nM, } EC_{50} = 15 \text{ nM}$) was identified as a clinical candidate. During discovery efforts, a bioactivation screen showed that PF-915275 and other members of the N-(pyridin-2-yl) arylsulfonamide series formed glutathione conjugates. This poster presents the results of the risk-benefit analysis of the reactive metabolite formation with PF-915275 and the design efforts made to circumvent this issue in this series of compounds.

![PF-915275](image)
Discovery and SAR of novel pyrazole-based thioethers as cathepsin S inhibitors

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Cathepsin S (CatS) is a cysteine protease of the papain family that is involved in the presentation of antigens to the cell surface of certain antigen-presenting cells (APCs) for recognition by CD4⁺ T-cells. The main target of the proteolytic activity of CatS is the invariant chain (Ii), a chaperone molecule for major histocompatibility complex class II molecules (MHC II). Inhibition of CatS activity slows the removal of Ii and attenuates antigen presentation to CD4⁺ T-cells, resulting in immunosuppression with specificity for these T-cells.

We have previously reported our efforts to identify novel noncovalent inhibitors of CatS based on a tetrahydropyrido-pyrazole heterocycle. More recently, we became interested in exploring substitution that would access S1 binding, ultimately discovering novel arylalkynes that bind to this region of the enzyme. Concurrent efforts to explore alternative binding elements led to the preparation of analogs containing aryl thioethers as a replacement for these arylalkynes. Synthesis development and SAR of these thioethers will be discussed.
Title:
‘Optimization of 2,3-Dihydro-1,4-Benzoxazine VEGFR-2 Inhibitors: Discovery and Preclinical Studies of AMG 429’

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Vascular endothelial growth factor (VEGF) plays a key role in tumor angiogenesis by stimulating the proangiogenic signaling of endothelial cells through activation of the VEGF receptor (VEGFR) tyrosine kinases. A series of substituted 2,3-dihydro-1,4-benzoxazines was identified as potent inhibitors of the tyrosine kinase activity of VEGFR-2. Although several of these compounds were found to be inhibitors of the hERG ion channel, structure activity relationship studies revealed a subset of heterocyclic amine analogs with mitigated hERG activity and low nanomolar inhibition of both VEGFR-2 kinase and VEGF-induced proliferation of human umbilical vein endothelial cells (HUVECs). A key analog (AMG 429) was identified which exhibited efficacy in models of vascular permeability, VEGF-induced angiogenesis, as well as significant antitumor efficacy against several cancer xenografts implanted in athymic mice. The synthesis, biological activity, and optimization of the 2,3-dihydro-1,4-benzoxazines that led to the discovery of AMG 429 will be described herein.

Author list should read as follows:

Design and Synthesis of Deuterated Vicriviroc Analogs with Enhanced Metabolic Stability

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CCR5 receptor antagonists are a novel class of HIV anti-retroviral drugs, represented on the market by the first-in-class agent maraviroc/Selzentry™ (ViiV, formerly Pfizer) and in late-stage clinical trials by vicriviroc (Merck, formerly Schering-Plough.) These agents block the CCR5 receptor on CD4+ macrophages and T-cells, thereby preventing recognition of M-tropic HIV-1 and subsequent entry of the virus into cells. Merck has pursued vicriviroc, which has been granted Fast Track designation by the FDA, in both treatment-experienced and treatment-naive patient populations in combination with an optimized background therapy which includes a ritonavir-boosted protease inhibitor. CoNCERT Pharmaceuticals has prepared novel deuterium-modified analogs of vicriviroc in which certain key hydrogen atoms have been selectively replaced with deuterium atoms. Deuterium effects on metabolism are unpredictable, even when deuterium is inserted at a known site of metabolic oxidation. In select cases, however, deuterium substitution has the potential to significantly enhance a drug’s metabolic properties while preserving its pharmacological activity. Our research has led to the identification of multiple novel compounds with enhanced metabolic stability. The design and synthesis of these compounds via routes which allow for precise deuterium incorporation with high levels of isotopic purity will be described. Studies were undertaken to compare vicriviroc and our precision-deuterated analogs with respect to metabolic clearance, and these data will be presented.
3-(phenylsulfonyl)-4H-pyrido[1,2-a]pyrimidin-4-imines and -4-ones as novel classes of selective, brain penetrant, potent 5-HT6 antagonists

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Since its discovery in the early 1990s, the G-protein coupled receptor 5-HT6 has generated enormous interest in the pharmaceutical industry, as inhibitors of this receptor have potential in the treatment of CNS-mediated diseases such as Alzheimer’s disease, schizophrenia and obesity. 5-HT6 is almost exclusively expressed in the central nervous system (CNS) and is the most recent addition to the mammalian 5-HT receptor family. To date two 5-HT6 receptor antagonists, Lu-AE58054/LY-483518 and SB-742457, have entered Phase II clinical trials for the enhancement of cognitive function, while
antagonists PRX-07034 and BVT74316, have recently entered studies for the treatment of obesity. An early screening effort at BMS led to the discovery of 1 as a selective, and potent 5-HT6 antagonist (IC$_{50}$: 4 nM). Herein, we report SAR in this structural class wherein potency and ADME properties were optimized.

![Chemical Structures](image)

$1 \quad X = N \text{ or } O$
Phthalazine-Based Inhibitors of Aurora Kinases: Lead Optimization and Identification of AMG 900 as a Clinical Candidate

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The aurora family of serine/threonine kinases (aurora-A, -B, -C) regulate cell-cycle progression in mammalian cells. Aurora-A and aurora-B are essential regulators of mitotic entry and progression, whereas aurora-C function appears restricted to meiosis in males. Aurora-A and aurora-B expression is elevated in a variety of human tumor types and is associated with advanced clinical staging and poor prognosis. Thus, these mitotic kinases have become the subject of much interest as targets for anticancer therapy.

Recently, we reported the discovery of pyridinyl-pyrimidine phthalazines as potent, selective, and orally bioavailable pan-Aurora kinase inhibitors\(^1\). Here, we describe the optimization of this series including SAR, PKDM properties, and pharmacological profiles. The results of these studies led to the identification of AMG 900, a molecule that showed antitumor efficacy in multiple human xenograft models and activity against multidrug resistant tumor cell lines. AMG 900 is currently being evaluated in phase 1 clinical trials for adults with advanced solid tumors.
SYNTHESIS AND BIOLOGICAL EVALUATION OF 2, 6-DISUBSTITUTED PYRAZINES AS ANTITUBERCULOSIS AGENTS

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High throughput screening of commercially available compound libraries against Mycobacterium tuberculosis cell cultures (strain H₃₇Rv) was carried out to search for novel anti-TB agents. Chemical optimization of one hit series led to a set of 2, 6-disubstituted pyrazine derivatives which exhibited sub-micromolar minimum inhibitory concentrations (MICs). Based upon these screening results, structure-activity relationships are described along with cytotoxicity data, microsomal metabolism and cytochrome P450 inhibition of these potent compounds.

Several representative compounds exhibited high potency, all with low to sub-micromolar MICs, and acceptable cytotoxicity against Vero cells. Microsomal stability and pharmacokinetics in mice were also studied. The half-life of these compounds was reasonable both in mice and in human. ITR 514 had good pharmacokinetic profile in mice with the doses at 10 mg/kg and 50 mg/kg. The distribution in lung tissue of mice was also high at 50 mg/kg dose level.

Further efficacy studies are underway. We expect that 2, 6-disubstituted pyrazines can serve as the candidates in developing new drugs to fight tuberculosis infection.
BIOTIN-PROTEIN LIGASE FROM MYCOBACTERIUM TUBERCULOSIS: STRUCTURAL ANALYSIS OF A NEW DRUG DEVELOPMENT TARGET.

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The causative agent of tuberculosis (TB) is Mycobacterium tuberculosis (Mtb) infects over one-third of the world’s population and is the leading cause of bacterial infectious disease mortality. The rise of drug-resistant strains of TB precipitates the need to identify novel chemotherapeutics and validate new Mtb therapeutic targets. One such target is the biotin-protein ligase BirA, which post-translationally modifies the three Mtb-encoded acyl-coenzyme A carboxylases (ACCs) in Mtb. ACCs synthesize the precursors to critical Mtb cell wall components and virulence factors. Here, we present the \(1.7\AA\) crystal structure of Mtb biotin-protein ligase BirA bound to Bio-AMS, a stable analog of the reaction intermediate 5'-biotinyl-AMP with sub-nanomolar affinity. Residues 65-76 and 162-169 undergo a disorder-to-order transition upon ligand binding to make extensive contacts with four regions of the inhibitor: the biotin head group, acyl-sulfamide linkage, adenine ring, and the 2'-hydroxyl of ribose. Residue tyrosine-74 stacks between the adenine ring and alkyl chain of the biotin moiety. Computational methods are being used to design alternative scaffolds and analogs that engage an adjacent surface crevice to increase Mtb specificity.
Synthesis and evaluation of potential chemotherapeutics derived from the natural product silvestrol and closely related methyl rocaglaol

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Silvestrol is a rocaglamide derivative that contains a cyclopenta[b]benzofuran core with a unique dioxanyloxy side chain. It was isolated from the fruit and twigs of the Indonesian plant Aglaia foveolata. The structurally diverse natural product silvestrol has shown promising cytotoxic activity both in vivo and in vitro against several human cancer cell lines, with its mechanism of action believed to be inhibition of translation. Particular
attention has been paid to silvestrol due to its efficacy and \( \beta \)-cell selectivity with respect to both acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL). However, all pharmacokinetic studies to this point have shown that this compound has not only a short half-life but also poor bioavailability. Although various elegant syntheses of silvestrol and the rocaglamide core have previously been reported, we hoped to explore highly modular synthetic approaches to the ring system which would facilitate functional group manipulation and permit deep-seated structural changed to the core ring system. These changes have been designed to improve the pharmacological properties of silvestrol as well as to explore the structure activity relationship (SAR) and mechanism of action of the natural product. Preliminary synthetic studies have focused on elimination or replacement of the dioanyloxy and methyl ester side chains of silvestrol in structurally simplified model systems. This study has also extended to methodology for the asymmetric synthesis of silvestrol itself and related compounds. Future analog development will be based upon the data obtained in these initial studies in concert with molecular docking studies.
Optimization and Evaluation of Curcumin like Analogues as Inhibitors of the JAK2/STAT3 Pathway

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The JAK2/STAT3 pathway is frequently upregulated in both blood cancers and solid tumors in comparison to normal cells. The pathway plays an essential role in transmitting signals which control processes involved in cell growth, differentiation, senescence and apoptosis. Inhibitors of this pathway are attractive targets for the prevention and therapy of cancer. Curcumin, isolated from the rhizome of Curcuma longa, has previously been shown to inhibit both JAK2 and STAT3 in the JAK/STAT pathway, while displaying little toxicity in vivo. Curcumin, itself as a drug however, is somewhat limited due to its poor bioavailability and rapid metabolism. Therefore utilizing this strategy, the aim of this study is to develop derivatives from this lead compound as potential therapeutic agents. Synthetic analogues were designed to increase selectivity, potency and pharmacological profiles. Synthesis of symmetric analogues involved simple condensation of benzaldehydes with acetylaceton to yield curcuminoids. FLLL31 and
FLLL32 are the two most extensively studied analogues and FLLL32 has been shown to selectively inhibit of JAK2/STAT3 in a variety of in vitro assays. Efficacy was compromised in vivo, which is most likely linked to poor water solubility. Computational models also suggested synthesis of non-symmetric analogues by derivatizing one side of the molecule to enhance binding. These reactions were accomplished through two efficient acylation procedures to yield the desired asymmetric curcumin analogues. Currently additional derivatives are being explored to further enhance bioavailability, potency and selectivity.
Development and synthesis of inhibitors of the IL-6/IL6R/GP130 Complex in IL-6 dependent Cancers

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Inhibition of Interleukin-6 (IL-6) activation of the JAK/STAT pathway represents a new potential target for drug discovery. Specifically, IL-6 initiates the JAK2/STAT3 signaling cascade via interaction with the extracellular domain of IL-6R and GP130, resulting in homodimerization of the heterotrimeric IL-6/IL-6R/GP130 complex. Thus, this complex plays a key role in cell proliferation and differentiation in IL-6 dependent cancer cells. Madindoline A was reported to exhibit anticancer activity through blocking IL-6 activity in IL-6 dependent cancer cells. The existing synthetic routes to madindoline A show limited applicability in drug discovery efforts and moreover the extraction from its natural source is no longer possible due to mutation in the bacterial strain. Our efforts focus both on simplification of the madindoline A structure and incorporation of functional groups predicted to provide additional binding interactions with the receptor in order to increase synthetic feasibility and develop potent synthetic analogues. The design, synthesis, and biological evaluation of these analogues in various cancer cells will be reported and discussed.
The Design, Synthesis and Biological Evaluation of Anacetrapib, a Potent and Orally Active Cholesteryl Ester Transfer Protein Inhibitor Currently in Phase III Clinical Trials

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An elevated level of high density lipoprotein cholesterol (HDL-C) in plasma has been identified as a risk-lowering factor for atherosclerosis and coronary heart disease. The beneficial effects of HDL-C are thought to arise from its participation in reverse cholesterol transport (RCT), the process by which HDL-C shuttles cholesterol out of the atherosclerotic plaque to the liver for metabolism or elimination. Cholesteryl ester transport protein (CETP) mediates the transport of cholesteryl ester (CE) from HDL-C to very low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) in exchange for triglycerides (TG) in the opposite direction. Thus, inhibition of CETP mediated cholesteryl ester transport should lead to elevated levels of HDL-C and, it is hoped, increased RCT. However, the recent withdrawal of another drug in this class from Phase III trials has raised concerns over CETP inhibition and it remains to be seen whether a CETP inhibitor will lead to improved outcomes in the clinic.

Anacetrapib is a CETP inhibitor that raises HDL-C and reduces LDL-C when administered alone or in combination with a statin. Adverse effects on blood pressure, electrolytes, and aldosterone levels have not been noted to date and anacetrapib is currently in Phase III clinical trials. The design, synthesis and biological evaluation of anacetrapib will be described in detail during the course of this presentation.
"Total Synthesis and Molecular Docking Studies of a Glabridin Analog having Tyrosinase Inhibitory Activity"

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Tyrosinase, a copper-containing mixed-function oxidase, catalyzes hydroxylation of tyrosine and oxidation of certain phenols. Its inhibition plays an important role in treatment of some dermatological disorders associated with melanin hyperpigmentation (1). European licorice (Glycyrrhiza glabra) is a major source of Glabridin (2), a pyrroloflavon from which a 3',4'-hydroxyglabridin derivative has been found to be a potent tyrosinase inhibitor (1). Several reports have attributed biological activities such as antimicrobial, antioxidant and antiviral, to phenolic constituents in the Glycyrrhiza species (3). Because of the therapeutic potential of isoflavonoids as cancer preventive agents and the recently found tyrosinase inhibitory activity, our lab has undertaken a multi-step total synthesis of 3',4'-dihydroglabridin to produce it in quantities large enough for testing in various cancer cell lines. We have also initiated molecular docking studies to develop SAR for tyrosinase inhibitory activity. Experimental details associated with important chemical and molecular modeling results will be described during the presentation.
The Discovery of a Pharmacologically Active FLAP Inhibitor

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Growing evidence indicates a causative role for proinflammatory cytokines in the progression of atherosclerosis. Characterization of plaques reveals elevated levels of leukotrienes (LT’s) and leukotriene biosynthetic proteins, thereby suggesting LT suppression as a potential therapy. Critical to LT production is the oxidation of arachidonic acid by 5-lipoxygenase (5-LO) and its associated 5-LO activating protein (FLAP). The latter has recently been genetically linked to elevated risk of heart attack and stroke in humans. FLAP inhibition, therefore, could represent a viable target for addressing these clinical outcomes. Presented herein are the principal advances that built off of previous clinical candidate, MK-591, and resulted in the discovery and pharmacological evaluation of the FLAP inhibitor 1.
The Platelet-Activating Factor Receptor Antagonist Program

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Platelet-activating factor (PAF) is a potent inflammatory phospholipid mediator that activates platelet-activating factor receptor (PAFR) to initiate signal transduction for a number of proinflammatory pathways. PAF/PAFR have been implicated in several aspects of the inflammatory response associated with atherosclerosis, although a precise role has not been established. A study indicated that a PAFR antagonist reduced lesion area in Ldlr-/− mice that were fed an atherogenic diet (Circ. Res. 1999, 85, 311). In addition PAF/PAFR has been implicated in numerous other proinflammatory indications, including inflammatory pain (INSM1981, 100, 111), and also neuropathic pain (Pain. 2004, 111, 351-359).

Starting from lead compound 1 (80% inh. @ 1 μM), optimization led to the discovery of antagonist 2 (binding IC₅₀ = 20 nM). SAR investigation led to structural simplification exemplified by antagonist 3, which was evaluated in relevant PD and efficacy models. Presented herein is data supporting a key role for PAFR antagonism in the treatment of pain.
NEW MOLECULES WITH HYPOLIPIDEMIC AND ANTI-HYPERGLYCEMIC ACTIVITY CONSTRUCTED BY INCORPORATING THE PHARMACOPHORE OF FIBRATES INTO RESVERATROL

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Fibrates are known to exhibit their beneficial effects by activating peroxysmal proliferator-activated receptor-a (PPARα) and used in the treatment of dyslipidemia and atherosclerosis and for the prevention of heart failure. Resveratrol is natural antioxidants with cardioprotection activity. By incorporating the pharmacophore of fibrates into molecule of resveratrol, a series of α-alkyl-substituted aryloxyalkanoic acids (Ia) were prepared as agonists of peroxisome proliferator-activated receptors.

![Image of chemical structure](image)

PPAR agonist activity assay revealed that compounds from Ia series exhibited full agonist activity for all subtype PPARs, while fenofibric acid only show activity for PPARα. Compounds with higher agonist activity were further evaluated for in vivo efficacy. Compounds from Ia14 and Ia15 showed excellent oral hypolipidemic activity in three hamster models and anti-hyperglycemic efficacy in KK mouse model. Structure-activity relationship studies indicated that the substituent at the distal benzene ring play key roles in determining the potency of PPAR subtype transactivation and hypolipidemic efficacy.
Development of Substituted Triazoloquinazolinones as Potent and Selective Chk1 Kinase Inhibitors

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Although DNA damaging agents continue to remain central to clinical cancer chemotherapy, their lack of selectivity for killing tumor cells versus normal proliferating cells seriously limits their effectiveness. Therefore, strategies directed at improving their therapeutic index are warranted. In normal cells, DNA damage by these agents can be repaired through cellular arrest induced by both the tumor suppressor protein p53 at the G1 phase and the checkpoint kinase Chk1 at the S and G2 phases. In contrast, a majority of tumor cells have mutated p53 (estimated 50-70% of all cancers) and these damaged tumor cells must therefore rely solely on Chk1 induced arrest and repair for survival. As a result, Chk1 inhibitors have the potential to selectively synergize with clinically-utilized DNA damaging agents in treating p53 deficient cancers and thus widen their therapeutic window. In this presentation, we report the discovery of a triazoloquinazolinone class of Chk1 inhibitors through scaffold hopping from established lead series. The optimization of potency and physical properties that ultimately produced an i.v. development candidate will be described.
Identification of GSK2126458, a Highly Potent Inhibitor of PI3K and mTOR


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Phosphoinositide 3-kinase (PI3K) is a critical regulator of cell growth and transformation and its signaling pathway is one of the most commonly mutated pathways in human cancer. The mammalian target of rapamycin (mTOR), a class IV PI3K protein kinase, is also a central regulator of cell growth, and mTOR inhibitors are believed to augment the antiproliferative efficacy of the PI3K/AKT pathway. GSK1059615, our first PI3K clinical compound, progressed to a dose escalation study in patients with refractory malignancies. Following the discovery of GSK1059615, we sought to identify a second inhibitor with improved potency, selectivity, and pharmacokinetics. Key to our approach to achieving the desired levels of PI3K activity was to pursue structure-based design utilizing crystallography of the more amenable PI3Kγ as a surrogate protein. Following a chemistry lead optimization effort, the pyridylsulfonamide GSK2126458 was identified as a highly potent, orally bioavailable, pan-PI3K and mTOR inhibitor (PI3Kα app Ki = 19 pM; mTORC1 app Ki = 180 pM; mTORC2 app Ki = 300 pM). Consistent with potent PI3K and mTORC2 enzyme inhibition, GSK2126458 decreased cellular levels of phosphorylated AKT (BT474 pAKT IC50 = 180 pM) and inhibited cell proliferation in a panel of cancer cell lines (e.g. BT474 growth IC50 = 2 nM). GSK2126458 showed good exposure in four pre-clinical animal species and exhibited in vivo activity in both pharmacodynamic and tumor growth efficacy models. GSK2126458 is being evaluated currently in human clinical trials for the treatment of cancer. SAR leading to the identification of GSK2126458 will be presented.
IDENTIFICATION AND CHARACTERIZATION OF SMALL MOLECULE INHIBITORS OF THE P70S6K1 (S6K1) PROTEIN KINASE

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P70S6K is a serine/threonin protein kinase responsible for the phosphorylation/regulation of several important targets like S6, BAD, and IRS1/2. It acts downstream of the mammalian target of Rapamycin (mTOR) and mediate regulation of cell growth, proliferation, migration and survival via control of protein translation and a number of important downstream effectors. The over-expression of P70S6K which leads to S6 activation confers clinical aggressiveness in solid tumors and is associated with aggressive disease and poor prognosis for cancer patients (breast, lung, and colorectal cancers). Recent studies showed that patients with breast cancer having increased p70S6K phosphorylation have poor survival and increased metastasis. Constitutive activation of this enzyme is also associated with intrinsic resistance to Cisplatin and other chemotherapies. Furthermore, several finding suggests a critical role for p70S6K signaling in the regulation of invasion and cell motility making selective inhibitors of this kinase a potential for anti-metastatic agents. Beside the importance of this target for the treatment of various types of cancer, selective inhibitors of this enzyme could be potentially useful in the treatment of type II diabetes and obesity. Several reports indicate that prolonged activation of P70S6K by insulin and nutrients leads to inhibition of insulin signaling via negative feedback input to the signaling factor IRS-1. Systemic deletion of S6K protects against diet-induced obesity and enhanced insulin sensitivity in mice.

Due to the multiple potential therapeutic applications that inhibitors of this enzyme could have, we have started a medicinal chemistry program directed toward the design and synthesis of novel phthalazine derivatives that led to the development of potent and selective inhibitors of P70S6K. Rational design, synthesis and SAR will be presented.
Synthesis and SAR of Benzisothiazole- and Indolizine-β-D-glucopyranoside Inhibitors of SGLT2

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A series of benzisothiazole-and indolizine-β-D-glucopyranoside inhibitors of human SGLT2 were synthesized using a Suzuki coupling reaction between a glucal boronate and the corresponding brome heterocycle. These compounds were evaluated for their human SGLT2 inhibition using cell-based functional transporter assays and their structure-activity relationships were presented. Benzisothiazole-C-glucoside 16(d) was found to be a potent SGLT2 inhibitor with an IC50=10nM.
Absorption, Distribution, Metabolism, and Excretion (ADME) Properties of Novel Topoisomerase II Inhibitors

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Dr. David Ferguson’s group at the University of Minnesota recently discovered a series of substituted 9-aminoacridines (Acridine 1 – 4) with potent anti-proliferative activity toward several pancreatic cancer cell lines.¹ The anti-cancer properties of these novel compounds are attributed to the inhibition of topoisomerase II by a unique DNA threading mechanism.² In collaboration, we are characterizing the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of selected 9-aminoacridines by investigating their metabolic stability, Caco-2 permeability, MDCK cell accumulation, Pgp and BCRP efflux transport, plasma protein binding, and tissue distribution in mouse pharmacokinetic studies. Metabolic stability experiments in pooled human liver microsomes indicated good metabolic stability ranging from 2.2 - 4.1 hrs for oxidation and glucuronidation. In addition, all substituted 9-aminoacridine compounds accumulated in MDCK cell uptake experiments and were also shown to be relatively weak substrates for the Pgp efflux transport pump. Interestingly, it was discovered that the 9-aminoacridines were substrates for the organic cation transporter 2 (OCT-2). A mouse pharmacokinetic study following a 60 mg/kg oral dosage with Acridine 1 and 2 has shown penetration into brain (0.25 µM and 0.6 µM), kidney (10 µM and 300 µM), and liver (125 µM and 225 µM), respectively. Bioavailability will be determined following intravenous administration. The lead compound with the best pharmacokinetic properties will be selected for evaluation in a mouse tumor model.

The Discovery of Selective, Potent, ATP Competitive Inhibitors of the Mammalian Target of Rapamycin (mTOR)

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The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that plays a key role in the regulation of translation by communication with downstream proteins such as S6K and members of the EIF4 family. In recent years, analogs of the natural product rapamycin, which function as inhibitors of mTOR, have been approved as anti-cancer treatments. This pathway involves two distinct complexes, mTOR/raptor (TORC1), which is inhibited by rapamycin and its analogs, and mTOR/rictor (TORC2), which is unaffected by this class of compounds. The mTOR medicinal chemistry effort at Wyeth resulted in the discovery of pyrazolopyrimidines and triazines that potently inhibit both of these complexes. These compounds also demonstrated selectivity over the upstream lipid kinase PI3K and other PIKKs. The modifications used to achieve such selectivity while maintaining potency against mTOR will be described. Structural alterations that successfully improved microsomal stability will also be summarized. Biomarker data will be presented which shows that these inhibitors reduce the levels of proteins downstream of mTOR which control cellular proliferation. The efficacy of these compounds in nude mouse xenograft models will also be described.
Quantitative HPLC-ESI-MS/MS Analysis of bis-N7-Guanine Cross-Links in White Blood Cells of Cancer Patients Receiving Cyclophosphamide Therapy

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Abstract
Cyclophosphamide (CPA) is a common DNA alkylating agent used in many chemotherapy regimens, including bone marrow transfer conditioning protocols. CPA is metabolized by cytochrome P450 2B6 to 4-hydroxy-CPA, phosphoramidate mustard (PM), normitrogen mustard (NOR), and acrolein. Formation of the DNA-DNA crosslinks, N,N-bis-[2-(7-guaninyl)ethyl] amine (G-NOR-G), through N-7 alkylation of guanine bases in DNA by PM is considered the primary mechanism of action of CPA. However CPA-induced DNA lesions have not been previously quantified in vivo. We employed sensitive and specific isotope dilution HPLC-ESI+-MS/MS methodology to analyze G-NOR-G adducts in blood of Fanconi Anemia (FA) patients and non-FA cancer patients undergoing CPA therapy. Blood samples were collected at different times 2-24 hours following IV administration of CPA (50 mg/kg for non-FA cancer patients and 20 mg/kg for FA patients). CPA was quantified in plasma by HPLC with UV detection, and DNA was isolated from white blood cells for the capillary HPLC-ESI-MS/MS analyses of CPA induced DNA-DNA cross-links. We found that G-NOR-G adduct numbers reach a maximum value (40-50 adducts per 10⁶ nucleotides) 4 and 8 h following drug treatment and are still detectable 24 h post treatment. G-NOR-G concentrations normalized to CPA
levels were greater in FA patients as compared to controls, suggesting that CPA-induced DNA-DNA cross-links are less efficiently repaired in FA. These results suggest that inter-individual differences in sensitivity towards CPA may result from variations in the rates of G-NOR-G cross-link formation and repair.

![Chemical structures and reactions](image)

G-NOR-G
$M = 371.2$

$[^{15}N]_{2}$-G-NOR-G
$M = 381.2$
Design and Synthesis of 1,2,3,4-Tetrahydroisoquinolines (THIQ) as Neurotransmitter Reuptake Transporter Inhibitors

Palladium Catalyzed α-Arylation in the Synthesis of 4-Heteroaryl-THIQ

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Serotonin (5-HT), norepinephrine (NE) and dopamine (DA) are important neurotransmitters that regulate many biological functions. Monoamine reuptake inhibitors, which bind to the monoamine transporters (namely SERT, NET and DAT), increase the concentration of these neurotransmitters in the synapse. Monoamine reuptake inhibitors have been approved for the treatment of many central nerve system disorders such as major depressive disorder (MDD), anxiety disorders, attention-deficit hyperactivity disorder (ADHD), eating disorder/obesity, fibromyalgia (FM) and diabetic peripheral neuropathy. We have discovered a series of novel tetrahydroisoquinolines (THIQ) as monoamine reuptake inhibitors. Here we described the use of an α-arylation as a key step to prepare a series of 4-heteroaryl substituted tetrahydroisoquinolinone derivatives as monoamine reuptake inhibitors.
Large scale practical preparation of 1,2,3,4,6-Penta-O-galloyl-β-D-glucose (PGG) by tannic acid methanolation

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Plants and medicinal herbs contain many bioactive polyphenols. 1,2,3,4,6-Penta-O-galloyl-β-D-glucose (PGG) is a naturally occurring hydrolyzable gallotannin polyphenol with multiple biological activities. It has been shown to differ significantly from its constituent gallate and tea polyphenols EGCG in terms of chemical activity and cellular effects. Recent literature studies reveal that PGG may exert in vivo anti-cancer activities in multiple organ sites including prostate, lung and breast. The low yield of preparation of PGG from botanical and herbal sources has been a bottleneck for rigorous efficacy studies.

Here we present a simple and highly efficient large scale PGG preparation method from tannic acid by selective hydrolysis of galloyl esters groups in the presence of aliphatic esters. The selective ester hydrolysis was achieved by using sodium acetate buffer pH 5, methanol at 65 °C for 5 days. The obtained PGG was characterized by NMR, Mass spectroscopy and HPLC (>99%). The method is highly reproducible and allows multi-gram purification of crystalline PGG. PGG so prepared is being used to investigate its in vivo anti-cancer activity and pharmacokinetic behavior.
Inhibitors of *Plasmodium falciparum* phosphodiesterases for the investigation of malaria

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Malaria is a disease which is caused by parasites of the genus *Plasmodium* that are spread between humans through the bite of infected mosquitoes. There are four species of *Plasmodium* infecting man—*Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. *P. falciparum* is by far the most deadly type of malaria infection, resulting in over a million deaths annually. Cellular differentiation is an important process in the life cycle of the parasite and occurs in the liver erythrocytes; the later rounds of asexual replication correspond to the pathogenic phase of malaria. Cyclic nucleotide signalling, which plays a pivotal role in the growth and differentiation of lower organisms, is essential for parasite survival. It is regulated through cyclic nucleotide production by adenylylate and guanylylate cyclases and hydrolysis by cyclic nucleotide PDEs (phosphodiesterases). Of the reported mammalian PDE inhibitors, only the PDE1/5/9 inhibitor zaprinast has been shown to be a relatively effective inhibitor of PfPDEα with an IC50 of 3.8μM.

This project has sought to investigate novel *Plasmodium falciparum* PDE inhibitors using molecular modelling, including homology modelling and docking, to aid the synthetic design. Generated compounds will be assayed to further influence the synthetic strategy.
Isoform Selective Inhibitors of Phosphodiesterase 3A and 3B

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By selectively inhibiting a specific phosphodiesterase the level of cAMP in tissues where it is expressed will increase and so will the cell’s response. PDE3 or cGMP inhibited cAMP phosphodiesterase has two isoforms; PDE3A is more frequently expressed in platelets, heart and vascular smooth muscle and oocytes while PDE3B is localized in adipocytes, hepatocytes, pancreatic β cells, T lymphocytes and developing spermatocytes. An isoform selective inhibitor of PDE3A or PDE3B could lead to the development of a drug for chronic heart failure, obesity, diabetes or contraception. The true potential of inhibiting these isoforms will remain unknown until the advent of isoform selective inhibitors.

Currently there are very few inhibitors with known selectivity for either isoform of phosphodiesterase 3. Unfortunately interest in PDE3 inhibition waned before the isoforms were distinguished, thus the efforts of some large medicinal chemistry campaigns were limited by unidentified cross inhibition. By reviewing known PDE3 inhibitors that qualified for advanced clinical trials before the identification of two separate PDE3 isoforms, and reinvestigating promising compounds armed with a new perspective of PDE3 inhibition. A selectivity pharmacophore may be elucidated through synthetic studies of analogues related to known PDE3 inhibitors, and these isoforms revalidated as drug targets.

Anagrelide, cilostamide and lixazinone are PDE3 selective inhibitors that were designed and optimized for their activity as PDE3A inhibitors. Whilst being effective inotropic agents, they were held back by an unfavourable side effect profile. Their effect on PDE3B has only been investigated relatively recently. These compounds therefore represent an ideal starting point to develop a series of analogues aimed at identifying an isoform selective inhibitor of PDE3A or 3B.
Psoriasis is an inflammatory skin disorder characterised by excessive skin growth. cAMP is known to be a pivotal second messenger that regulates the inflammatory response. The breakdown of cAMP in inflammatory cells is regulated by the enzyme phosphodiesterase 4 (PDE4). Inhibition of PDE4 has been shown to have an anti-inflammatory action and this enzyme is therefore an important therapeutic target. Given the side effects associated with current therapeutic agents used for inflammatory skin disorders (e.g. steroids), there is a need for new agents with improved safety profiles.

This project has sought to investigate the design and synthesis of novel PDE4 inhibitors. Included in this study has been an investigation of the PDE4 structure using a range of molecular modelling methods. Of the three techniques employed in this study, molecular docking using Glide was found to be superior in its ability to reproduce the binding mode of the ligands. The XP docking method was able to correctly predict the binding mode of 59% of cases when the top binding pose was examined and performed well on the test cases. Both the shape matching algorithm, ROCS, and pharmacophore software, Phase, were disappointing in their ability to predict the binding mode of the test ligands. In addition to the modelling work, a series of novel PDE4 inhibitors based on a thiophene scaffold have been synthesized based on both in-house and existing PDE4 scaffolds. Functional analysis involving the use of PDE4 assays is planned.
Ras-Raf-MEK signaling cascade plays a central role in cell growth, proliferation and survival. Ras mutation occurred in 30% human cancers. Components of the mitogen-activated protein kinase (MAPK) signal pathway are frequently altered in human cancers. Targeting this pathway represents a promising anticancer strategy.

A novel series of substituted hydantoins were discovered as the potent and highly selective non-ATP competitive MEK1/2 inhibitors. \textit{In vitro} RO4920506, one of the most potent analogs, is a non-ATP competitive MEK inhibitor that selectively blocks the MAPK pathway signaling by inhibiting the phosphorylation of both ERK1/2 and MEK1/2 in cancer cells, leading to G1-phase cell cycle arrest and subsequent apoptotic cell death. \textit{In vivo}, RO4920506 exhibits significant anti-tumor activity in a broad spectrum of tumor models. The structure activity relationship of this series of compounds along with the \textit{in vivo} activity will be presented in this poster.
1,2,3-trihydroxy-4-(N-acetylcysteinyl)-butane (THBMA): a novel urinary biomarker of exposure to 1,3-butadiene

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Abstract:

Lung cancer is responsible for 30% of total cancer deaths worldwide, with the majority of cases (87%) resulting from cigarette smoking. 1,3-butadiene (BD) is a known human carcinogen present in cigarette smoke and also observed in urban air and in automobile exhaust. BD undergoes cytochrome P450-mediated metabolism to three epoxide metabolites: 1,2,3,4-diepoxybutane (DEB), 3,4-epoxy-1-butene (EB), and 3,4-epoxy-1,2-butandiol (EBD). The carcinogenicity of BD has been attributed to the reactions of these epoxides with nucleophilic sites in DNA to form covalent adducts. Among the three BD epoxides, EBD is the most abundant; however, no urinary biomarker for EBD formation in humans has been reported. Animal studies suggest that EBD is conjugated with glutathione and is subsequently excreted in urine as 1,2,3-trihydroxy-4-(N-acetylcysteinyl)-butane (THBMA). In the present study, a sensitive and specific HPLC-ESI-MS/MS method for THBMA in human urine was developed. The quantitative analysis of THBMA is achieved by stable isotope dilution with d3-THBMA. Authentic standards of THBMA and d3-THBMA have been prepared synthetically and used for instrument calibration and quantification. In our experimental scheme, urine samples (100 µL) are spiked with d3-THBMA, followed by solid phase extraction on Isolute ENV+ cartridges and HPLC-ESI-MS/MS analysis. The LOQ of our HPLC-ESI-MS/MS method is 1 ng THBMA per 1 ml of human urine. Following full method validation,
urinary THBMA concentrations were determined in a small group of smokers and nonsmokers. We found that urinary concentrations of THBMA in smokers (48 ng/ml urine) are greater than those in non-smokers (18 ng/ml urine). Furthermore, urinary levels of THBMA gradually decreased upon smoking cessation. Based on these results, we propose that THBMA can be used as a biomarker of human exposure to BD and can be effectively monitored in human urine using stable isotope dilution HPLC-ESI-MS/MS methodology.
A Molecular Extender Arm Attached to an Opioid Pharmacophore Leads to Greatly Enhanced Intrathecal Potency without Significant Change at Supraspinal Opioid Receptors: the Concept of Bridging to a Neighboring Site to Selectively Enhance Potency at Spinal Opioid Receptors

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In view of the fact that oligomers are known to exist among a variety of G protein-coupled receptors, we have explored the use of a molecular extender arm attached to an opioid pharmacophore in an effort to reach a group on a neighboring receptor. As the extracellular loops of opioid receptors contain some acidic amino acid residues, we envisaged a protonated amine group at the end of an extender “arm” attached to a kappa opioid receptor pharmacophore (ICI-199441) might associate with a carboxylate group to modify activity. Here we describe such a series of ligands which contain an attached molecular arm that was lengthened incrementally up to 18 atoms. As the number of atoms in the arm was increased, there was virtually no change in the mouse i.c.v. antinociceptive potency. In contrast, the i.t. potency dramatically increased at a chain length of 16 atoms, as reflected by an i.t./i.c.v. antinociceptin potency ratio of ~130, whereupon further lengthening led to a decreased potency ratio. Using different selective antagonists to characterize in vivo pharmacological selectivity revealed that kappa-delta opioid receptor heteromers may be responsible for the increased i.t. potency. In vitro calcium release experiments confirmed that the ligand selectively activated kappa-delta heteromers in co-expressed cells. The combined in vivo and in vitro data are consistent with the reported presence of kappa-delta opioid receptor heteromers in mouse spinal cord but not in the brain. This molecular extender arm approach to spinally selective ligands lends itself to development of analgesics that have fewer supraspinal side-effects.
DNA-PROTEIN CROSS-LINKING BY 1,1,2,2-CIS-DIAMMINEDICHLOROPLATIUM (II) (CISPLATIN)

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Cis-diamminedichloroplatinum (II) (cisplatin) is a bis-electrophile capable of cross-linking cellular biomolecules to form DNA-DNA and DNA-protein cross-links, which are thought to play a central role in its biological activity. The present work combines affinity capture methodology with mass spectrometry-based proteomics and immunological detection to characterize cisplatin-mediated DPC formation in nuclear protein extracts from human cervical carcinoma (HeLa) cells. Nuclear protein extracts from HeLa cells were incubated with biotinylated DNA in the absence or in the presence of cisplatin (50 μM). Following biotin capture enrichment, the cross-linked proteins were separated by SDS-PAGE, and the gel lanes were separated into five fractions encompassing the entire molecular weight range and excised. Proteins in these gel pieces were subjected to in-gel tryptic digestion, and the resulting tryptic peptides were extracted and analyzed by HPLC-ESI+-MS/MS analysis to identify the cross-linked proteins. A total of 133 nuclear proteins were found to form cisplatin-induced DPCs, including proteins participating in DNA replication and repair, transcriptional regulation.
and RNA processing, cell homeostasis and cell cycle and so on. An estimated DNA-protein cross-linking efficiency following treatment with 50 μM Cisplatin was 2-16%, depending on protein identity. HPLC-ESI-MS/MS analysis of total proteolytic digests of cross-linked proteins revealed the presence of 1,1-diammine-2-(6-N-lysyl)-2-(2’-deoxyguanosine-7-yl)-platinum conjugates. These results indicate that cisplatin can form covalent cross-links between chromosomal DNA and nuclear proteins.
Design of Cucurbitacin Analogs As Novel Drug Candidates Against Prostate Cancer

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Prostate cancer is the second cancer-related death in American men and accounts for 25% of new cancer cases. Inhibition of the Androgen Receptor (AR) is one approach used to treat prostate cancer. A strong correlation between cancer and inflammation is also shown. Inflammation creates a microenvironment that is favorable to the development and progression of cancer. Several key enzymes known to be involved in inflammation are Cyclooxygenase II (COX II), Nuclear Factor-κB (NF-κB), and Inducible Nitric Oxide Synthetase (iNOS).

Natural cucurbitacins are recognized as a result of their anti-inflammatory, anticancer, and hepatoprotective properties. The multi-faceted binding of the cucurbitacins make them potential drug candidates to treat prostate cancer. Open Eye molecular modeling software was used to dock over 800 cucurbitacin and hexanor analogs in the AR, Hsp 90, NF-κB, iNOS, COX I and II receptors. From the consensus scores, cucurbitacin analogs were chosen to be synthesized from a natural source. Numerous cucurbitacin and hexanor analogs showed stronger binding than dihydrotestosterone (the natural ligand of the AR). Based on molecular modeling calculations, a new pathway for the laboratory synthesis of the hexanor-type structures starting from commercially available (+) estrone has begun. Additionally, in vitro screening of natural cucurbitacin analogs has shown a wide range of activity against prostate cancer. Cucurbitacins B (IC₅₀ 0.72µM), D (IC₅₀ 0.58µM), E (IC₅₀ 0.50µM), I (IC₅₀ 0.39µM), Analog 1 (IC₅₀ 0.28µM), Analog 2 (IC₅₀ 0.28µM), and Analog 3 (IC₅₀ 0.32µM) have been tested towards the PC3 cell line. Megestrol Acetate (IC₅₀ 0.40µM) was used as a standard. The data indicates the potential of cucurbitacins and their analogs as lead drug candidates for the treatment of prostate cancer.
Biological evaluation of heterocyclic bioisoteres of esters on potency and pharmacokinetics properties in a novel series of allosteric p38 inhibitors.

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p38 MAPK kinase is a serine/threonine kinase that is activated in response to cellular stresses, growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis alpha (TNF-a). The central role of p38 activation in conducting and amplifying pro-inflammatory signals has led to substantial efforts to find inhibitors of this enzyme to treat rheumatoid arthritis. Previously, we have reported design and synthesis of highly potent and selective p38 inhibitors with novel binding mode. In this presentation, we describe our effort to improve the cellular potency and pharmacokinetic properties of this series of novel allosteric p38 inhibitors. Isosteres are often more alike in biological properties than physical properties and are routinely used to modulate pharmacokinetic properties of compounds. By studying the effect of various heterocyclic ester bioisosteres we identified lead compounds with improved PK properties.
A Comparative Assessment of Anti-Inflammatory and Analgesic Activity of Turmeric Oil and Fish Oil in Relation to Aspirin

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Turmeric extracts and fish oil are widely used as food supplements. They have various medicinal properties. Turmeric oil was extracted from freshly dried turmeric powder and fractionated to retain only the major components. Anti-inflammatory and analgesic activities were evaluated by carrageenan induced paw edema and tail flick methods respectively in rats. The percent increase in paw edema was measured. Aspirin was used as a standard for comparison. The turmeric oil formulation at 50 mg/kg significantly inhibited edema whereas at 100 and 200 mg/kg this drug inhibited edema less than the standard drug aspirin. The percentage inhibition was maximum at 3 hours with turmeric oil formulation at 50 mg/kg followed by aspirin at 200 mg/kg. Fish oil did not significantly inhibit edema as compared to control and aspirin. Maximum possible effect (MPE) for tail flick latency was significantly more with turmeric oil formulation at 50mg/kg as compared to control while it was considerably less with fish oil. The results of the present study indicate that turmeric oil formulation has significant anti-inflammatory and analgesic activity in animal models while fish oil did not show significant effect in these models.
Structure-Based Design, Synthesis and Biological Activity of Hsp90 Inhibitors

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The 90 kDa heat shock proteins belong to a family of chaperones that regulate intracellular functions and are required for the refolding of denatured proteins following heat shock, as well as the conformational maturation of a large number of key proteins involved in cellular processes. Inhibitions of Hsp90 disrupt the protein folding process, resulting in client protein degradation via the ubiquitin proteasome pathway. Hsp90 multi-protein complex in tumor cells exhibits a higher affinity for N-terminal ligands and
malignant cells are highly dependent upon the Hsp90 protein folding machinery for cell survival. So, inhibition of Hsp90 could result in the disruption of multiple signaling pathways, which is important for tumor cell survival and brings a potential method for cancer treatment.

Based on Hsp90 crystal structure, we designed a series of new Radicicol-derived compounds (Fig 1) which show great potency in Hsp90 binding and inhibitory effect on human cancer cell growth, indicating further application in anti-tumor drug development.

![Figure 1: Strategy of modification and backbone of leading compound](image)

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Synthesis of Isoform Selective HDAC Inhibitors

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Regulation of gene transcription is paramount for many cellular processes. Disruption of gene regulation is present in a number of autoimmune diseases and malignancies. Histone acetylation and deacetylation is one such mechanism for this regulation. This relies on a pair of enzymes that modify lysines located on the histone tails of the nucleosome. Histone acetyltransferase (HAT) installs acetate on these lysines, which neutralize their positive charge, thus allowing DNA to be loosened for transcription enzymes to read the code. Histone deacetylase (HDAC) hydrolyzes these acetates in the reverse direction resulting in repression of transcription. In humans, 18 HDAC enzymes have been identified and categorized into three main classes based on their homology to yeast deacetylases. Class I enzymes (HDAC1, 2, 3, and 8) are primarily involved in cell proliferation which is the reason they have become the targets for anti-cancer therapy. In some tumors, HDAC enzymes are overexpressed resulting in the silencing of tumor suppressor genes. It has been shown that treatment with HDAC inhibitors results in hyperacetylated histones and activation of these suppressor genes leading to apoptosis of tumor cells. HDAC inhibitors have been designed to incorporate a surface binding group, a hydrophobic linker, and a zinc binding group (ZBG). Suberoyl analide hydroxamic acid (SAHA) is a nanomolar HDACi that has recently been approved by the FDA for treatment of cutaneous t-cell lymphoma. This is a broad spectrum inhibitor. Our group focuses on synthesizing isoform selective HDAC inhibitors. This report will present some of the updates on our ongoing research.
Selective Inhibition of Ras Function in Live Cells using Caged Farnesyltransferase Inhibitors

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Mutant ras proteins are found in 30% of human cancers, and farnesylation is a key step that activates their oncogenicity. Here we report the successful caging of the farnesyltransferase inhibitor L-744,832 with the photolabile protecting groups bromohydroxyquinoline and bromohydroxycoumarin. Both caging groups are attractive for biological studies because they require light of low energy to uncage, as opposed to other uncaging approaches which are more damaging to biological systems. Utilizing caged farnesyltransferase inhibitors, we have blocked ras activity in two different cell types and characterized their one and two-photon kinetics of uncaging. These molecules should be useful for a variety of studies involving ras proteins.