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J. Zablocki, Program Chair

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J. Breitenbucher, Organizer; S. McAlpine, Organizer; J. Breitenbucher, Presiding; S. McAlpine, Presiding Papers 497-501

THURSDAY AFTERNOON

General Oral Session

J. Zablocki, Organizer; J. Zablocki, Presiding Papers 502-515

MEDI 1

2-Aminothiazoles derivatives as potent γ -secretase modulators

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Alzheimer's disease (AD) is the major cause of dementia that affects 35 million people worldwide. Compelling genetic, biochemical and pathological evidence indicate that fibrillar A β 42 is the peptide species in the brain directly linked to the pathogenesis of Alzheimer's Disease (AD). Using a cell based assay, we have identified a novel series of γ -secretase modulators that lowered A β 42 levels without inhibiting NOTCH proteolytic processing (NICD generation). γ -secretase modulators shift the cleavage toward shorter A β peptides resulting in the selective inhibition of A β 42 while increasing the production of shorter A β peptides (e.g. A β 37, A β 38). Starting from a weak hit identified from a high-throughput screen, we developed SAR and identified low nanomolar lead compounds with good in vitro and in vivo activity. Concurrent optimization of the drug properties have produced analogs that are orally bioavailable and achieve high concentrations in the brains of animals. The in vitro and in vivo γ -secretase modulating profiles of these 2-aminothiazoles derivatives and a review of the SAR which led to the clinical candidate NGP-328 will be presented.

MEDI 2

New aminohydantoins as BACE1 inhibitors

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Alzheimer's Disease (AD) is a progressive, degenerative disease of the brain and most common form of dementia. Increasing evidence implicates the amyloid beta-peptide (beta-amyloid, 39–43 residues) in the neurodegenerative pathogenesis. Beta-amyloid is produced in vivo through proteolytic cleavage of the membrane-bound beta-amyloid precursor protein (APP) by beta- and gamma-secretases sequentially. The beta-amyloid peptide is neurotoxic and the principal component of the neuritic plaque found in the brains of AD patients. Inhibition of secretases responsible for beta-amyloid formation may stop or slow

AD progression by preventing its production.

The design and synthesis of highly potent and selective inhibitors of beta-secretase (BACE1) was based on the HTS hit W-1 ($IC_{50} = 40 \text{ nM}$). The initial aminohydantoin beta-secretase inhibitors, exemplified by W-2 ($IC_{50} = 10 \text{ nM}$), were potent and selective, but demonstrated only weak to moderate brain permeability. As a result, the in vivo efficacy of these inhibitors was very modest. Two major issues have impacted the poor pharmacokinetic properties of these compounds; the high topological polar surface area, and high susceptibility for the P-glycoprotein transporter protein. In order to overcome these issues, we have identified the areas that have contributed to poor brain permeability and synthesized new aminohydantoin with superior permeation properties. Modification of the P3 side chain of W-2, and optimization of the S2' pocket ligand-protein interactions have led to compounds with lower TPSA, decreased affinity for P-glycoprotein and superior pharmacokinetic properties. Our SAR design strategy supported by X-ray structures of BACE1 co-crystallized with various ligands, molecular modeling studies, and *in silico* methods. Several compounds have demonstrated excellent activity in the cell-based assay (ELISA; $EC_{50} \sim 10 \text{ nM}$), and were orally efficacious in vivo, near normalizing plasma beta-amyloid and significantly reducing beta-amyloid and solAPPbeta levels in the brain. Lastly, these compounds reversed the cognitive deficits exhibited by Tg2576 mice, as assessed by compound-mediated increased % freezing vs. vehicle in the contextual fear-conditioning model for hippocampal-mediated memory. These new orally active BACE1 inhibitors will contribute toward the understanding of APP processing, as well as the development of disease-modifying AD therapeutics.

MEDI 3

New potent and selective PDE10A inhibitors for the treatment of schizophrenia

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Schizophrenia is a chronic and debilitating psychiatric disorder affecting approximately 1% of the general population. Current therapies treat predominantly the positive symptoms of the disease, creating a need for therapies effectively targeting the negative symptoms and cognitive deficits. Furthermore, most current therapies have unwanted side effects. These include extra-pyramidal side effects (EPS) and weight gain. Thus, there is a need for

drugs that treat symptoms with a better side effect profile. The phosphodiesterase PDE10A, primarily a brain specific protein, is highly expressed in GABAergic medium spiny neurons in the striatum, with expression evident in the hippocampus and cortex as well. Inhibition of PDE10A elevates cAMP and cGMP in the MSNs and leads to an increase in striatal output, which could be of benefit in schizophrenia. Indeed, we have previously shown in preclinical animal models that inhibition of PDE10A has the potential to treat not only the positive symptoms of schizophrenia, but also the negative symptoms and cognitive deficits.

In this paper, we report the design and synthesis of new potent and selective PDE10A inhibitors following a traditional SAR approach that was supported by X-ray structures and molecular modeling studies to expedite the discovery process. Several compounds have demonstrated picomolar potency for human PDE10A and good selectivity against the other PDEs. In vivo, these inhibitors have shown robust activity in a range of preclinical models of antipsychotic efficacy (e.g. Conditioned Avoidance Responding model) and cognition (e.g. Novel Object Recognition model). Furthermore, these PDE10A inhibitors produce low levels of catalepsy, suggesting a minimal risk of EPS. In conclusion, PDE10A inhibitors are predicted to treat all three domains of schizophrenia, from our pre-clinical studies, without the side effect liabilities that are associated with several currently marketed atypical antipsychotics.

MEDI 4

Amino imidazoles as β -secretase inhibitors for treatment of Alzheimer's disease

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A major pathophysiology of Alzheimer's disease (AD) is the presence of amyloid plaques which are primarily composed of the Ab peptide. The formation of the Ab peptide is the result of sequential enzymatic cleavage of the Amyloid Precursor Protein (APP) by β -secretase (BACE) and subsequently by γ -secretase. BACE is a membrane bound aspartyl protease which is characterized by a large hydrophilic binding pocket. We have designed a series of amino imidazole inhibitors using a fragment based drug design strategy that bind directly to the catalytic aspartic acids through hydrogen bonding interactions. Chemical modification using a parallel medicinal chemistry strategy allowed for modification

of prime and non-prime substituents yielding improvements in potency and properties. Details of the SAR guided by structure based drug design will be described.

MEDI 5

Development of TRPM8 selective antagonists for the treatment of inflammatory and neuropathic pain

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TRPM8 is a ligand-gated, nonselective cation channel from the Transient Receptor Potential (TRP) ion channel super family that is activated by both cold and chemical stimuli *in vitro*. TRPM8 has been implicated in inflammatory and neuropathic pain based on DRG-selective expression, upregulation in preclinical models of pain, and knockout mouse studies. This presentation outlines the SAR of our lead series including strategies for the implementation of desired pharmaco-kinetic profiles. Selected compounds were further profiled *in vivo* utilizing two TRPM8 specific pharmaco-dynamic assays, icilin-induced jumping in mice and icilin-induced wet dog shakes in rats. Compounds exhibiting full target coverage in both biochemical challenge models with ED₅₀ values <1mg/kg were identified. When tested in preclinical models of inflammatory or neuropathic pain, no significant therapeutic effect was observed. This lack of efficacy suggested that TRPM8 antagonism may not provide significant benefit in the clinical indications predicted by these models.

MEDI 6

Discovery of new high-affinity PDE10 inhibitors using fragment based lead generation and knowledge-based design

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Inhibitors of PDE10 have been widely investigated as treatments for schizophrenia. In order to rapidly and efficiently enter this field we employed fragment screening in parallel with rational design.

New high concentration screening protocols were developed using BIND and SPR methodologies. Using crystallographic knowledge, we designed a probe compound that bound with high affinity to PDE10 and then attached that compound via an extended tether to the BIND or SPR chip surface. This robust screening system was rapid and very sensitive; detection of binding as weak as 1 μ M was possible. Next we selected 3000 fragments (compounds with mw <250) based on the following considerations: (1) ligand knowledge, (2) target knowledge, (3) diversity metrics, and (4) chemical tractability (novelty, physical properties, etc.). A hit rate of 10% was achieved and structural analysis of the hit set provided valuable new pharmacophore knowledge. To be able to rapidly advance weak starting points as hits it is critical to validate those hits by multiple orthogonal methods. We profiled our hits in an enzymatic assay, an NMR competition assay, and by screening against related targets.

One representative fragment hit bound with IC₅₀ = 800 μ M. We mined our company compound collection for larger compounds that contained related elements of this fragment as a core. This immediately led to the identification of a larger compound with IC₅₀ = 3 μ M. This hit was evolved using target based knowledge to deliver a lead with IC₅₀ = 16 nM; this was achieved though the synthesis of fewer than 40 compounds.

MEDI 7

Discovery of potent and orally bioavailable phthalazinone Bradykinin B1 receptor antagonists for chronic pain

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The Bradykinin B1 receptor is rapidly induced upon tissue injury and inflammation, stimulating the production of inflammatory mediators resulting in plasma extravasation, leukocyte trafficking, edema, and pain. B1 receptor expression is enhanced in the synovial tissue of patients with osteoarthritis and rheumatoid arthritis. We have previously reported on sulfonamide and sulfone based B1 antagonists containing a privileged bicyclic amine moiety leading to the potent oxopiperazine AMG 327. The suboptimal PK and physicochemical properties of the oxopiperazines led us to seek B1 antagonists with improved drug-like properties. Using a pharmacophore model containing the bicyclic amine as anchor, we designed a series of amide antagonists with restrictions on polar surface area, molecular weight and the number of hydrogen bond donors. This approach led to a novel series of potent phthalazinone B1 antagonists. SAR studies revealed compounds with sub-nM B1 affinity. These compounds demonstrate excellent PK properties in rats with oral bioavailability in the 60-90% range. SAR, PK and rabbit in vivo efficacy studies in a biochemical challenge model and a carrageenan-induced mechanical hyperalgesia model with the phthalazinones will be discussed.

MEDI 8

Rational design, synthesis and structure-activity relationships of novel bicyclic azole-amines as negative allosteric modulators of Metabotropic Glutamate Receptor 5

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A novel series of diaryl bicyclic azole-amines that are potent selective negative modulators of metabotropic glutamate receptor 5 (mGluR5) were identified through rational design. An initial hit compound **5a** of modest potency ($IC_{50} = 1.2 \mu M$) was synthesized. Evaluation of structure-activity relationships (SAR) on the left hand side of the molecule revealed a preference for a 2-substituted pyridine group linked directly to the central heterocycle. Variation of the central azolo-amine portion of the molecule revealed a preference for the [4,5c]-oxazoloazepine scaffold, while right-hand side variants showed a preference for *ortho*- and *meta*-substituted benzene rings linked directly to the tertiary amine of the saturated heterocycle. These iterations led to the synthesis of **29b**, a potent ($IC_{50} = 16 \text{ nM}$) and selective negative modulator that showed good brain penetrance, high receptor occupancy and respectable duration of action in rat when administered intraperitoneally. Formal PK studies in rat and Rhesus

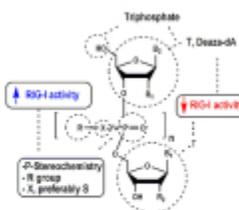
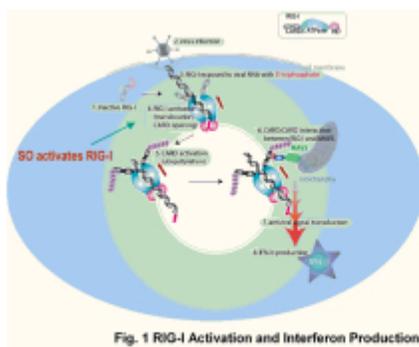
monkey revealed a short half-life that was attributable to high first-pass clearance.

MEDI 9

Activation of retinoic acid inducible gene (RIG-I) by nucleotide analogs: A potential novel mechanism for antiviral discovery

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Retinoic acid inducible gene (RIG-I), a host cellular protein, acts as a “sensor” of viral RNA. Activation of RIG-I results in interferon (IFN) expression and induction of antiviral effects. Using a novel translocation assay of RIG-I on RNA template, we have discovered that short oligonucleotides (SO) cause activation of RIG-I. The RIG-I actives had specific structural and stereochemical attributes. The lead compounds had EC₅₀ (of 1~2 micromolar) against HCV (genotypes 1a, 1b HCV replicons) and had synergistic antiviral activity with polymerase and protease inhibitors, as well as, IFN and Ribavirin.



MEDI 10

Discovery of the 1,7-diazacarbazole class of inhibitors of checkpoint kinase 1

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Checkpoint kinase 1 (Chk1) is a serine/threonine kinase which functions as a central mediator of the S and G2/M phase checkpoints by blocking the G2/M transition to allow for repair of damaged DNA. Inhibition of Chk1 is an emerging strategy for selectively potentiating the cytotoxicity of chemotherapeutic agents on checkpoint defective tumor cells while minimizing toxicity to normal, checkpoint competent cells. High throughput screening identified the diarylpyrazines as a promising lead series, which through structure-based design led to the discovery of the novel 1,7-diazacarbazole class of potent and orally bioavailable inhibitors of Chk1. The evolution of this novel scaffold, together with initial SAR findings, will be presented.

MEDI 11

Rapid discovery of a DP1 antagonist series with good developability characteristics

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Prostaglandin D2 (PGD2) modulates a number of biological functions through its action at the DP1, TP and DP2 (CRTH2) receptors. The prosecution of several areas of research with differential risks led to the identification of a high-quality lead series of DP1 antagonists possessing low plasma-related activity shift and good developability properties. A pre-candidate molecule was thus identified within 12 months of programme start. Herein we describe:

i) Key early activities

- Data analysis, conformational modelling, capture of rationale and use of predictive tools
- Efficient use of chemistry resource to achieve programme objectives in short order

ii) The key features of the series and pre-candidate:

- *In vitro* and *in vivo* data - focussing on activity in plasma and PKPD

· Developability and toxicology profile

iii) Lessons learned

MEDI 12

Discovery and optimization of benzylphenoxyethyluracil to yield non-nucleoside inhibitors of HIV-1 reverse transcriptase using virtual screening and free-energy calculations

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Non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs) are very important constituents of HIV treatment regimes. Rapid emergence of drug resistant mutant strains compromise the effectiveness of most NNRTIs. Particularly troublesome mutations which affect most NNRTIs are Tyr181Cys (Y181C) and Lys103Asn (K103N). Computer-aided drug design techniques including virtual screening by docking and Monte Carlo/free-energy perturbation (MC/FEP) calculations closely coupled with synthetic chemistry have been used to generate and optimize benzylphenoxyethyluracil derivative (JLS007) to a very potent compound (JLJ334), which is active against both wild type (WT) and common HIV-1 mutant strains in cell based assays.



MEDI 13

Medicinal chemistry in opioid research: Looking back

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The present opioid research program is one of the oldest continuous programs at NIH having been in progress since 1939 under the sequential leadership of Drs. Lyndon Small, Nathan Eddy, Everette May, Arnold Brosi and the present author. Many fundamental discoveries in the organic and medicinal chemistry and pharmacology of narcotic analgesics, their antagonists, and other drugs of abuse have resulted during this work. The discovery of metopon provided the proof of principle of the original hypothesis that specific chemical modification of the morphine molecule could separate the beneficial and detrimental effects of morphine. Other studies provided tools for PET imaging of opioid receptors, clinical treatment of pain and narcotic addiction, and diverse lines of investigation in elucidation of the opioid receptor endorphin system. The development of the NIH Opiate Total Synthesis as a practical route to both opioid enantiomers rendered the natural enantiomers available independent of the opium poppy and the unnatural enantiomers available as valuable research tools and potential drugs. These and other discoveries emanating from the NIH program will be reviewed.

MEDI 14

Targeting O-GlcNAc cycling: Impact on the epigenetics of diabetes and immunity

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Reversible O-GlcNAcylation of key components of the transcriptional machinery is emerging as a key epigenetic regulator of gene expression. O-GlcNAc cycling at promoters and functioning through Polycomb group repression represent concrete mechanisms by which nutritional information may be transmitted across generations in the intra-uterine environment. Thus, the nutrient-sensing-hexosamine signaling pathway may be a key contributor to the metabolic deregulation resulting from prenatal exposure to famine, or the 'vicious cycle' observed in children of mothers with type-2 diabetes and metabolic disease. The enzymes of O-GlcNAc cycling are attractive drug targets that may be causally related to diabetes and neurodegenerative disease

MEDI 15

Membrane trafficking complexes of the ESCRT pathway

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Structural biology using a fully integrated approach that ranges from crystallography, cryoelectron microscopy, protein-protein and protein-lipid interactions, to in vitro reconstitution and cell imaging. Monoubiquitination and Lys-63 linked polyubiquitination direct protein cargo to the ECSRT pathway, which is hijacked by HIV-1.

MEDI 16

G Protein-coupled receptor signaling pathways in pancreatic beta-cells

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G protein-coupled receptors regulate many important aspects of beta-cell function. To assess the physiological relevance of the different beta-cell G protein signaling pathways in vivo, we employed mutant M3 muscarinic acetylcholine (ACh) receptors (M3 mAChRs) which are unable to bind the endogenous ligand, ACh, but can activate different classes of G proteins when treated with the pharmacologically inert compound, clozapine-N-oxide. Studies with transgenic mice selectively expressing these modified M3 mAChRs in pancreatic beta-cells led to novel insights into the *in vivo* roles of distinct G protein signaling pathways in beta-cell function. Recent data suggest that strategies aimed at enhancing signaling through beta-cell M3 mAChRs may be beneficial for the treatment of type 2 diabetes by promoting glucose-stimulated insulin secretion. We recently identified several proteins that act as negative regulators of M3 mAChR signaling in pancreatic beta-cells. These findings may be relevant for the development of novel strategies for the treatment of type 2 diabetes.

MEDI 17

New frontiers for selective agonists and antagonists of adenosine and P2Y receptors

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Ligands of G protein-coupled

purine and pyrimidine receptors have entered and passed clinical trials, despite associated challenges. Novel drug delivery, prodrug approaches, allosteric modulation, and biased agonism could overcome side effects, seen even

with receptor subtype-selective ligands. A₃ adenosine receptor (AR) agonist IB-MECA is efficacious in psoriasis, dry eye, and rheumatoid arthritis. Novel A₃AR agonists and antagonists containing a methanocarba ribose-ring substitution constrained in the receptor-preferred North (N) conformation have improved pharmacological profiles. Novel selective agonists and antagonists of the less explored P2Y receptors include nucleotides and uncharged or nonhydrolyzable

compounds. UDP-activated cytoprotective

P2Y₆ receptor requires an unusual South (S) conformation of ribose demonstrated through modeling and synthesis. Multivalent GPCR Ligand Dendrimer (GLiDe) conjugates are designed as smart drugs. Attachment of GPCR

functionalized congeners to tree-like polyamidoamine (PAMAM) dendrimer carriers

has greatly increased selectivity and affinity. Fluorescent and other reporter groups incorporated into ligands provide new assay and imaging possibilities.

MEDI 18

First disclosure of PF-03715455: An inhaled p38 inhibitor for the treatment of chronic obstructive pulmonary disease

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The global prevalence of chronic obstructive pulmonary disease (COPD) has reached epidemic proportions and is now one of the leading causes of death in the developed world. Existing treatments for COPD patients are dominated by long acting bronchodilators, with anti-inflammatory agents such as inhaled corticosteroids, being largely ineffective. With COPD exhibiting a significant inflammatory component to the symptoms and progression of the disease there

is an acute medical need for an effective anti-inflammatory agent with a suitable therapeutic index (TI) for chronic administration. p38 Mitogen activated protein (MAP) kinase is a well studied regulator of inflammatory cytokines, with oral p38 inhibitors such as VX-745 and BIRB-796 demonstrating efficacy in a Phase II trial for rheumatoid arthritis, a disease with a strong inflammatory component. Studies have demonstrated that p38 is activated in the alveolar macrophages of COPD patients and hence p38 inhibition represents a promising approach towards treating the symptoms and progression of this disease. In fact, oral p38 inhibitors have progressed to Phase II clinical trials in COPD patients, with findings from these studies expected imminently.

Historically the progression of many of the oral p38 inhibitors to phase III studies, and beyond, has been hampered by adverse findings. However, there is of course the possibility that oral agents with improved AE profiles may yet emerge, but this is far from a certainty. With COPD being a disease of the lung, it represents an opportunity to deliver a p38 inhibitor directly to the site of action, via the inhaled route, with potential to minimise systemic driven adverse events and therefore an improved TI over an oral agent. This talk will focus on the first disclosure of PF-03715455, a potent and selective inhaled p38 inhibitor, with physical properties commensurate with inhalation. This talk will also highlight many of the 'inhalation by design' principles which are aimed at delivering sustained lung efficacy, whilst minimising systemic exposure and drug-drug interactions.

MEDI 19

Discovery of PSI-352938 and PSI-353661: Purine nucleotide prodrugs for the treatment of HCV

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Hepatitis C is a global health problem with over 180 million individuals infected with the hepatitis C virus (HCV). HCV infection can lead to chronic liver disease, cirrhosis and eventually hepatocellular carcinoma. Since the current standard of care, interferon- α and ribavirin, is only effective in approximately 50% of genotype 1 infected patients and is associated with a number of undesirable side effects, the search for direct acting antiviral agents has become a priority. The HCV NS5B polymerase is an essential enzyme associated with RNA replication and several nucleosides which target this polymerase are currently in clinical

development. The S282T mutation has been demonstrated in the lab to produce some level of resistance to these nucleosides. We have identified two distinct purine nucleotide prodrug analogs (PSI-352938 and PSI-353661) of the 2'-deoxy-2'-F-2'-C-methyl class of nucleosides that demonstrate potent activity against both wild-type and S282T mutant virus. PSI-352938 and PSI-353661 are currently in development for the treatment of HCV. The discovery and characterization of these novel nucleotide HCV inhibitors will be discussed.

MEDI 20

Discovery and early development of ALKS-33, an opioid modulator for treatment of reward disorders

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Design, preclinical evaluation and early clinical development of ALKS 33 (RDC-0313; 17-(cyclopropylmethyl)-4,14-dihydroxy-6-oxo-morphinan-3-carboxamide), a novel carboxamide isostere of the phenolic –OH in various opioid classes, is disclosed. The chemistry design goal was to maintain high affinity for opioid receptors and achieve high oral bioavailability with metabolic stability. RDC-0313 was identified as an agent to treat various psychiatric and CNS conditions, including reward disorders. RDC-0313 is a potent μ antagonist while functioning as a partial agonist/antagonist at both δ and κ receptors. A dealkylation metabolite of RDC-0313 was identified across species, with no evidence of metabolites from biotransformations at the C6 ketone or C3 amide. Phase I pharmacokinetic studies showed that ALKS 33 is safe, well tolerated across a wide dose range and achieved desired oral bioavailability. Pharmacologic endpoints in man established duration beyond one day following QD dosing. ALKS 33 is currently in a Phase II study for alcohol dependence.

MEDI 21

Discovery of a new class of SGLT2 inhibitors

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Inhibition of sodium glucose cotransporter 2 (SGLT2) has emerged as a compelling glucose-dependent mechanism for the treatment of type 2 diabetes. In this presentation, the discovery of a new class of SGLT2 inhibitors harboring a dioxo-bicyclo[3.2.1]octane-2,3,4-triol motif will be discussed. In particular, the

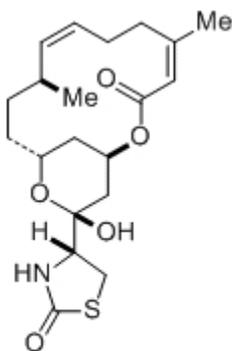
structure of our SGLT2 inhibitor currently in phase 2 will be disclosed as well as some related phase 1 clinical data. Emphasis will be placed on key elements that led to the rapid identification of this compound. Enabling features of the strategy were the development of innovative synthetic routes to challenging targets, and the development of a PK/PD model that proved critical in candidate selection.

MEDI 22

INS115644 (latrunculin B): A potential new treatment for glaucoma

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A summary of Inspire's approach to addressing the effect of agents that act upon the trabecular meshwork and their potential to lower intraocular pressure will be given. The company's experience with the synthesis, purification, preclinical development, as well as results from an initial proof of concept clinical study to evaluate safety, tolerability and intraocular pressure (IOP) lowering effects of INS115644 (latrunculin B) in subjects with bilateral ocular hypertension or early primary open angle glaucoma will be presented.



Latrunculin B

MEDI 23

Making agonists from antagonists: SAR106881, a breakthrough in FGFRs activation and a potential treatment to improve peripheral revascularization and reduce neuropathic pain

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Due to their broad spectrum of activities on vascular cells, the Fibroblast Growth Factor (FGF) family plays a key role in the induction of angiogenesis in ischemic conditions. FGFs trigger the activation of FGFRs by bringing them in pair in the presence of heparane sulfates. We aimed to develop a small molecule capable of inducing such an activation *via* the dimerisation of the FGFRs.

The design of chemical inducers of dimerisation (CIDs) of the FGFs receptors was investigated from our protein-protein interaction FGFRs antagonists, and led to the development of the first FGFR agonist SAR106881 in pre-clinical phase [WO2007080325]. The approach of designing agonists from antagonists was unprecedented and remains as a unique example. The concept is attractive and could be applied to other receptors.

In vivo, SAR106881 has pro-angiogenic activity and represents a novel class of therapeutic agents aimed at reversing impairment of revascularization and reducing neuropathic pain in patients with end-stage PAOD.

MEDI 24

Using irreversibility to achieve enhanced potency and selectivity against the HCV protease

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Designing potent and selective inhibitors of viral proteases has proven problematic, in part because pharmacophores that confer potency typically exploit the catalytic apparatus, a feature often shared by host proteases. We have developed a fundamentally different approach to design covalent irreversible inhibitors targeting a non-catalytic residue, where the lack of structural homology between viral and host proteases may confer exceptional selectivity. Using structure based drug design, we identified a class of small molecules that are able to irreversibly bond to a non-catalytic amino acid residue, cysteine 159 (C159), in HCV NS3 protease. This residue is conserved across all HCV genotypes and therefore enables a means to create a pan-genotype drug without bonding to host proteases. The irreversible inhibitors have greatly enhanced binding affinity and exhibit high potency in biochemical ($IC_{50} = 2$ nM) and replicon ($EC_{50} = 6$ nM) *in vitro* assays. More importantly, the inhibition of protease activity was prolonged for 24 hours after brief exposure to the covalent

irreversible inhibitor. In contrast, similar brief exposure to a clinically advanced NS3/4A reversible inhibitor resulted in rapid return of protease activity. In addition, as predicted from the design strategy, the compound was found to be very selective against many host proteases.

MEDI 25

Chemical biology of chromatin regulation: The first small molecule antagonists of MBT domains

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Epigenetics refers to the heritable changes in how the genome is accessed in different cell-types and during development and differentiation. Knowledge of the mechanisms and pathways which regulate the epigenome holds great promise for our understanding of diseases such as cancer as well as cell-fate and pluripotency.

While the genetic blueprint that directs the construction of proteins is encoded in the sequence of the DNA bases, many processes such as transcription, recombination and DNA replication are controlled by the epigenome. One template upon which the epigenetic code is written is histone proteins of which the amino-terminal tails are subject to more than 100 covalent post-translational modifications (PTM). Among these chemical marks, the methylation of lysine residues plays a central role in development, differentiation and cellular response to the environment through its influence on activation and repression of gene expression. While small molecule antagonists to the enzymes that “write” and “erase” the methylation marks on histone lysine residues have been developed, synthetic ligands interacting with the “readers” are currently unprecedented. We have undertaken the development of potent and selective small molecule probes disrupting the interaction between Malignant Brain Tumor (MBT) domains and methylated lysine residues in histone tails.

We will present the first small molecule antagonists of MBT domains demonstrating low μM potency. We have identified key interactions from a structure-based design approach including the use of computational analyses of the binding pocket. Our studies include structure-activity relationships (SAR) and selectivity screening against multiple MBT domains and other methyl-lysine binding proteins.

MEDI 26

PXR agonism and drug-drug interactions: Structure based design to eliminate PXR mediated CYP induction

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Pregnane X receptor (PXR) belongs to the nuclear receptor (NR) superfamily and is mainly expressed in liver, intestine, and colon where most drug metabolizing enzymes are also highly expressed and regulated. CYP3A4 is one of the most prominent of the CYP enzymes that are upregulated by PXR. CYP3A4 has garnered much attention because its high liver expression leads to metabolize majority of prescription drugs. Therefore, compounds with PXR liability may potentially lead to drug-drug interactions.

Overcoming PXR affinity using structure based SAR had not previously been reported due to promiscuous nature of the large binding pocket. This binding pocket is largely hydrophobic and located in the ligand binding domain (LBD) of the protein. *In silico* models were developed based on the limited co-crystal data and were used to guide SAR investigations. These models were deemed unreliable given the large and flexible binding cavity coupled with the possibility of multiple binding orientations. GlaxoSmithKline is in unique position to generate co-crystal structures of LBD in real time to support SAR investigations. Crystallographic binding information of multiple chemotypes was used to generate a pharmacophore model.

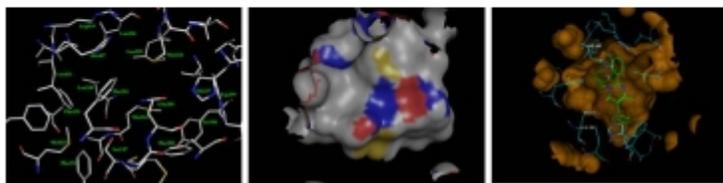


Figure: 1) Active site of LBD of h-PXR 2) Site surface of binding pocket – color coded as carbon – white; oxygen – red; nitrogen – blue; sulfur – yellow 3) Co-crystal structure with a small molecule

The presentation describes structure activity relationships developed in order to mitigate the h-PXR liability in indentifying the lead analog. In addition, a description of how pharmacophore model was generated is detailed and it's utility, and how it compares to the reported understanding of the binding pocket.

MEDI 27

Discovery of CRM1-mediated nuclear transport inhibitors as novel modulators of epigenetic enzymes

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Transport of macromolecules across nuclear membrane is fundamental to the proper functioning of living cells. Molecular transport between the nucleus and the cytoplasm through the nuclear pore complex is mediated by transport receptors called karyopherins. One such well-recognized receptor is CRM1 (XPO1, chromosomal region maintenance 1), which is essential to the nuclear export of various “cargo” proteins (e.g., p53, c-Abl, IκB, FOXO) and epigenetic histone deacetylases (HDACs) including HDACs 1, 3, 4, 5, 6, 7 and SIRT proteins. Moreover, histone acetyl-transferase (HAT) and HDACs modulate p53, NFκB and AKT pathways. Therefore, inhibition of CRM1 may alter the epigenetic activity of HDAC and HAT. Abnormal CRM1 expression is well correlated with the prognosis of various human cancers including pancreas, glioma, liver, ovarian, cervical and osteosarcoma. Moreover, CRM1 has been validated in animal models as a novel target for cancer. CRM1 inhibitors such as Leptomycin B (LMB) are efficacious in xenografts, but exhibit dose limiting toxicities that have prevented successful testing in human clinical trials. Karyopharm Therapeutics is taking the lead in this field to discover small molecule CRM1 inhibitors that are devoid of toxicities seen with other compounds. Employing the power of *in-silico* screening and structural biology, we discovered a variety of chemotypes with potent CRM1 inhibition. We will describe the design of several chemotypes using our integrated computational and medicinal chemistry strategies, and their biological activities. Our compounds have shown CRM1-mediated HIV-rev (IC₅₀ = 360 nM), FOXO, IκB and p53 nuclear export inhibition similar to LMB. In addition, our small molecule irreversible inhibitors were shown to act at the CRM1 Cys528 position, and exhibited potent cytotoxicity in hematologic and solid tumor cancer cell lines. Pharmacokinetic and *in-vivo* efficacy studies are on-going and results will be presented at the meeting.

MEDI 28

Identification of the pharmacophore of 4EGI-1, an inhibitor of translation initiation with anti-cancer activity

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Inhibition of translation initiation represents a novel mechanism-based approach for developing more effective and safer anti-cancer drugs. High throughput screening of a diversity chemical library led to the discovery of 4EGI-1, a thiazol-2-yl hydrazone, as an inhibitor of eIF4E/eIF4G protein-protein interaction and consequently a preferential inhibitor of cap-dependent translation of weak mRNAs. 4EGI-1 inhibits tumor growth in animal models of human cancer. Combination of structural studies of eIF4E--4EGI-1 complex with NMR and molecular docking suggested hydrophobic interactions between the small molecule and a hydrophobic hot spot on eIF4E located at the interface between eIF4E and eIF4G. Structure-activity relationship studies identified the pharmacophore essential for activity and led to the development of KY-615, KY-383, and KY-689 which display 4-fold higher binding affinity to eIF4E than 4EGI-1, the parent 4-substituted-thiazol-2-yl hydrazone. Taken together, these results represent the first step toward hit-to-lead optimization.

MEDI 29

High-affinity binding of small-molecules to the intrinsically disordered c-Myc oncoprotein

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Intrinsically disordered (ID) proteins or domains lack a stable, folded structure in their native form but often undergo coupled folding and binding. These ID proteins are dramatically over represented in disease pathways and many are appealing drug targets. We have demonstrated multiple examples of small molecules that bind to specific, short segments of the ID oncoprotein c-Myc. These molecules bind to the disordered monomer of the c-Myc bHLHZip protein and disrupt the extensive interface formed between c-Myc and its heterodimerization partner Max. By linking two structures that target independent binding sites within the HLHZip region of Myc, we found inhibitors that bind 1000 fold tighter to c-Myc than its normal binding partner Max.

MEDI 30

Design and synthesis of HDAC inhibitors for property based optimization

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Histone deacetylase (HDAC) and histone acetyltransferase (HAT) are important enzymes on epigenetic controls and play an important role in regulating of DNA expression by histone modification. It is reported that HDACs are associated with carcinogenesis and considered as anti-cancer agent. Many HDAC inhibitors are developed clinical trials as monotherapy or combitherapy with other anti-cancer agents. SAHA (Zolinza®, Vorinostat) and depsipeptide (Istodax®, Romidepsin) are approved US FDA for treatment of cutaneous T-cell lymphoma in 2006 and 2009 respectively.

We designed and synthesis of novel lactam based HDAC inhibitors, composed of cap group, lactam core and zinc binder. Cap groups are hydrophobic moieties and a wide variety of substituents in aromatic ring were introduced. Lactam cores are consisting of δ -lactam or γ -lactam and linked to cap group by 1~4 carbon chain length. Zinc binder is hydroxamic acid, which is chelated to zinc ion in active site of HDAC. The series of lactam core HDAC inhibitors showed a good *in vitro* HDAC enzyme inhibitory activities, and *in vitro* and *in vivo* cancer cell growth inhibitory activities. The result of docking study showed lactam core HDAC inhibitors are similar binding mode of SAHA. KBH-A118, the initial candidate among δ -lactam analogues, however, appeared severe problems in pharmacokinetics study; poor oral exposure and oral bioavailability. KBH-A118 showed a good permeability in caco-2 cell permeability test and it showed high metabolic instability with or without NADPH. This result rationalized that the poor oral bioavailability is caused by microsomal instability. Thus, for improving the microsomal stability, various approaches were performed changing δ -lactam to γ -lactam, reducing carbon chain length, and introducing substituents on cap group for blocking NIH shift. Consequently, KBH-A247, metabolically stable of γ -lactam based HDAC inhibitor, showed good oral exposure and excellent oral bioavailability.

MEDI 31

Identification of the b-amyloid PET ligand candidate MK-3328

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Miller⁽²⁾; James J Mulhearn⁽¹⁾; Stacey S O'Malley⁽²⁾; Christine Ryan⁽²⁾; Sandra Sanabria⁽²⁾; Cyrille Sur⁽²⁾; Scott E Wolkenberg⁽¹⁾; David L Williams⁽²⁾; Zhizhen Zeng⁽²⁾. (1) Department of Medicinal Chemistry, Merck & Co., Inc., West Point PA 19486, United States (2) Department of Imaging, Merck & Co., Inc., West Point PA 19486, United States (3) Department of Chemistry Modeling and Informatics, Merck & Co., Inc., West Point PA 19486, United States

The direct, non-invasive detection of b-amyloid (A β) plaque deposits using Positron Emission Tomography (PET) imaging shows promise as a means to accurately diagnose Alzheimer's disease (AD) prior to the onset of severe cognitive decline. Because diagnosis of AD is a challenge at the early mild cognitive impairment (MCI) stage, such a technique may prove invaluable for identifying patients most likely to benefit from novel disease-modifying therapeutics and may provide an opportunity to measure changes in plaque load over time. This presentation will delineate our medicinal chemistry campaign which culminated in the discovery of the A β PET clinical candidate [¹⁸F]MK-3328. Parallel chemistry techniques were employed to quickly evaluate several chemical series, generating SAR for both A β plaque binding affinity as well as logP. Ultimately, the fluoro-azabenzoxazole scaffold was identified which exhibited moderate logP, high affinity for A β plaque deposits, high blood-brain barrier permeability, and allowed for facile ¹⁸F radiolabeling.

MEDI 32

Long-residence time kinase inhibitors: Binding kinetics in fragment-based design

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Fragment-Based Lead Discovery is an established strategy for lead generation within the pharmaceutical industry. Fragment hits are most effectively evolved if high-resolution structure data become available within the course of the optimization campaigns.

This presentation highlights a novel kinase inhibitor design approach, notably the "retro-design concept". Main advantage of the retro-design strategy is that it avoids seed fragments that are hinge-directed. Distinct binding kinetic attributes can be pre-engineered into the resulting lead structures on a fragment basis yielding kinase inhibitors with slow dissociation rates (k_{off}), i.e. long residence times on the target kinases. It has been shown that the desired binding kinetic properties translate into candidates with high in-vivo efficacy. This presentation will introduce the underlying enzymology, design of a tailor-made fragment library, medicinal chemistry routes for fragment confirmation and fragment evolution, as well as fragment-directed protein crystallography.

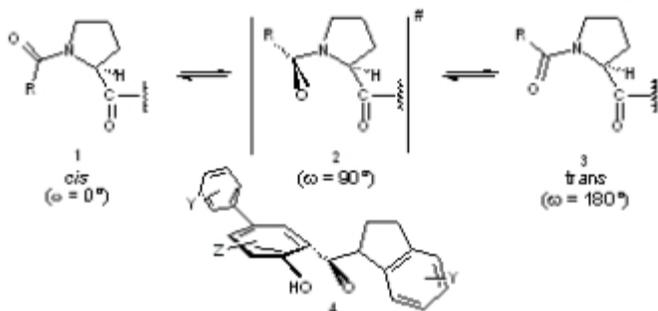
MEDI 33

Novel and efficient inhibitors of peptidyl-prolyl-cis/trans-isomerases Pin1 and cyclophilin

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Peptidyl-prolyl-cis/trans isomerases (PPlases) are enzymes that catalyze the interconversion of *cis*-**1** to *trans*-**3** isomer of the peptide bond preceding proline. This rotation about the amide bond from $\omega = 0$ to 180° is assumed to involve the transition state **2** ($\omega = 90^\circ$). Among the different PPlase families, the human Pin1 is of particular interest inasmuch as Pin1 exhibits essential regulatory function in the mitosis. As a consequence, substances that act as PPlase inhibitors are considered as potential chemotherapeutics in the treatment of diseases with errors in the regulation of cell proliferation.^[1] Overexpression of Pin1 promotes tumor growth, whereas its inhibition leads to tumor cell apoptosis. Thus, Pin1 is considered as an anticancer target.^[2]

Guided by the idea, that compounds mimicking the twisted-amide transition state **2** may act as PPlase inhibitors, we developed biaryl-indanyl ketones **4** as potent, reversible inhibitors of Pin1. As shown by their crystal structures, they feature a perpendicular arrangement of the biaryl-carbonyl and the indanyl plane. Therefore, they can be considered as analogs of the transition state **2**.^[3]



In addition, biaryl-indanyl ketones exhibit an isoform-specific inhibition of cyclophilins, another group of PPlases. Thus, a discrimination between Cyclophilin A and B was observed, the corresponding K_i values differing by more than two orders of magnitude.^[4]

In summary, a new class of efficient, cell-penetrating, reversible PPlase inhibitors has been developed. Aside from in-vitro inhibition, they shown various biological activities and seem to be promising candidates for the development of anticancer drugs.

[1] Fischer, G.: *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1415. [2] G. G. Xu, F. A. Etzkorn, *Drug News Perspect.* **2009**, 22, 399. [3] G. Fischer, M. Braun et al, *Angew. Chem. Int. Ed.* **2006**, 45, 7454. [4] C. Schiene-Fischer, M. Braun et al, *Biochemistry* **2009**, 48, 6268.

MEDI 34

Spirocyclic sulfamides as β -secretase inhibitors for treatment of Alzheimer's disease

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A major pathophysiology of Alzheimer's disease (AD) is the presence of amyloid plaques which are primarily composed of the A β peptide. The formation of the A β peptide is the result of sequential enzymatic cleavage of the Amyloid Precursor Protein (APP) by β -secretase (BACE) and subsequently by γ -secretase. BACE is a membrane bound aspartyl protease which is characterized by a large binding pocket designed to recognize 6-8 amino acid residues of APP. Identification of small molecule development candidates that inhibit BACE remains a major hurdle due to challenges in identifying compounds with the appropriate balance of potency, clearance and CNS penetration. Optimization of a series of spirocyclic sulfamides was accomplished by achieving protein contacts in P1/P3 pockets. Analogs that penetrate the CNS and acutely lower brain A β levels in wild type mice will be presented.

MEDI 35

Amyloid beta aggregates as intrinsic platforms for assembling a non-conjugated non-bioengineered FRET pair

Chongzhao Ran⁽¹⁾, cran@nmr.mgh.harvard.edu, RM2301 Blg149, 13th Street, Charlestown MA 02129, United States ; Anna Moore⁽¹⁾. (1) Martinos Center for Biomedical Imaging, Mass General Hospital/Harvard Medical School, Charlestown MA 02129, United States

Förster resonance energy transfer (FRET) is a widely used technical tool for biological studies, particularly for protein/protein interactions

and DNA/RNA folding. In general, these studies require construction of a FRET pair by chemical conjugation of two chemical fluorophores or bioengineering of two fluorescent proteins. However, the non-conjugated non-bioengineered FRET in biological studies has not been demonstrated yet. Here we demonstrated that amyloid beta (A β) aggregates could be used as intrinsic platforms for assembling a non-conjugated non-bioengineered FRET pair. By simply mixing two structurally similar curcumin derivatives with Ab40 aggregates, we observed apparent FRET signal in solution. We believe that this FRET technique could potentially be used as a tool for detection of A β aggregates in biofluids such as cerebrospinal fluid (CSF), serum of Alzheimer's disease patients, and in vivo imaging of A β plaques in transgenic mice. In addition, we also believe that this concept could be generalized to other misfolding proteins/peptides such as amylin in diabetes, prion in mad cow disease, tau protein in AD, and α -synuclein in Parkinson disease.

MEDI 36

Curcumin analogs as “turn-on” fluorescent probes for a wide variety of amyloid beta species and in vivo imaging with transgenic mice

Chongzhao Ran⁽¹⁾, cran@nmr.mgh.harvard.edu, RM2301 Blg 149, 13th street, Charlestown MA 02129, United States ; **Anna Moore**⁽¹⁾. (1) Martinos Center for Biomedical Imaging, Mass General Hospital/Harvard Medical School, Charlestown MA 02129, United States

Early/presymptomatic diagnosis of Alzheimer's disease (AD) is an immense challenge. One of the major hurdles in the way is the lack of imaging probe capable of detecting biomarkers at the early/presymptomatic stage. Amyloid β (Ab) species, which include monomers, dimers, oligomers, fibrils and plaques, are widely believed to be important biomarkers for AD diagnosis. Much progression has been achieved for imaging insoluble Ab species such as fibrils and plaques; however probes that are able to detect both the soluble species such as monomers, dimers and oligomers and the insoluble species are still urgently needed. Here we reported that the curcumin derivative CRANAD-3 was able to detect a wide range of Ab species from plaques down to monomers and even the core fragment (KLVFF) of Ab40/42. Meanwhile, we also found that amino acid K16 of the peptide was the hot spot for CRANAD-3 binding, and the diketone moiety of curcumin and its derivatives were crucial for the interaction. Moreover, in vivo two-photon imaging results showed that CRANAD-3 was specific to Ab plaques and able to label cerebral amyloid angiopathy (CAA). Remarkably, our in vivo near-infrared imaging (NIR) indicated that CRANAD-3 was capable of differentiating transgenic mice and wild type mice both at old and very young ages. We believe CRANAD-3 has the potential capability to monitor the full

course of amyloidosis pathology of AD, and we also believe that CRANAD-3, along with its analogues that include their ^{18}F or ^{11}C derivatives, will be very important tools for realizing the goal of the early/presymptomatic diagnosis of AD.

MEDI 37

Structure-activity relationship of dual target inhibitors of amyloid-beta self-assembly

Abha Sood⁽¹⁾, abha6sood@gmail.com, 100, Morissey BLVD., dorchester MA 02125, United States ; Aditya Kulkarni⁽¹⁾; Dmitry Borkin⁽¹⁾; Seema Bag⁽¹⁾; Sujaya Dasgupta⁽¹⁾; Harry LeVine III⁽¹⁾; Bela Torok⁽¹⁾; Marianna Torok⁽¹⁾. (1) Green Chemistry, UMASS Boston, Dorchester MA 02125, United States

The aggregation of misfolded amyloid b peptide into plaques is a common symptom of Alzheimer's disease and the harmful effects of these fibrils were thought to be the major cause of the disease. More recently, however, the even stronger neurotoxicity of smaller oligomers was also described. Accordingly, the development of dual target inhibitors that can interfere with the formation of both oligomers and fibrils is highly desirable. In this work, a broad group of structurally diverse molecules have been evaluated in the self-assembly of amyloid b. The major goal was to observe general structural features that characterize the oligomer and fibril inhibitors, and ultimately find lead structures for further, focused inhibitor design.

A broad range of potential small molecule inhibitors were synthesized and tested by standard methods, such as Thioflavine T-fluorescence assay for following fibril formation, biotinyl-A β (1-42) single-site Streptavidin-based assay for observing oligomer formation and atomic force microscopy for morphological studies. The assays yielded a small number of structures that showed significant inhibition and efficiency against both fibril and oligomer formation; all belong to one particular group of compounds, indicating that these molecules may serve as a prototype for the further development of dual inhibitors against amyloid self-assembly.

MEDI 37

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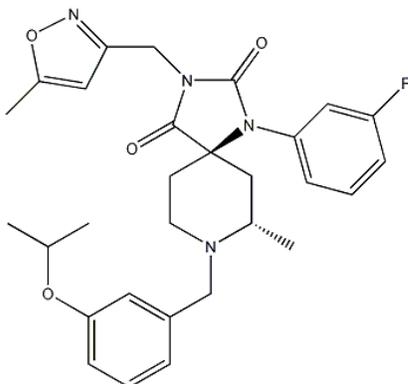
MEDI 38

Development of hydantoin spiropiperidines as potent BACE1 inhibitors

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Inhibition of the aspartyl protease BACE1 (b-APP Cleaving Enzyme) is of considerable interest as a therapeutic target for the treatment of Alzheimer's disease. We have explored a hydantoin spiropiperidine series as potential BACE1 inhibitors. Extensive SAR studies were conducted using rapid analog synthesis via alkylation, Mitsunobu and Ullmann coupling chemistry. The chemistry, SAR and PK properties of the hydantoins will be presented. The X-ray

crystal structure of a potent hydantoin, compound A, co-crystallized with BACE1 will also be shown.



compound A

MEDI 39

Evaluation of virtual screening methods towards the discovery of new functional transthyretin amyloid inhibitors

Carlos J. V. Simões⁽¹⁾⁽²⁾, csimoes@qui.uc.pt, Departamento de Química, Universidade de Coimbra, Coimbra Coimbra 3004-535, Portugal ; Trishna Mukherjee⁽²⁾; Richard M. Jackson⁽²⁾; Rui M. M. Brito⁽¹⁾. (1) Department of Chemistry, Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra 3004-535, Portugal (2) Institute of Molecular and Cellular Biology, University of Leeds, Coimbra 3004-535, Portugal

Amyloid fibrils are a product of deviant protein-protein interactions and assembly of conformational intermediates found along the unfolding pathway of certain proteins. Inhibition of fibril formation by stabilization of the native form of transthyretin (TTR) is an appealing approach for the treatment of Familial Amyloid Polyneuropathy. We undertook a benchmark of five virtual screening techniques to identify novel TTR stabilizers: (1) 2D similarity searches with chemical hashed fingerprints, pharmacophore fingerprints and UNITY fingerprints, (2) 3D-searches based on shape, chemical and electrostatic similarity, (3) LigMatch, a ligand-based method employing multiple templates, (4) 3D-pharmacophore searches, and (5) docking to consensus X-ray crystal structures. Moreover, a narrow subset of molecules was retrieved from a tailored library of 2.3 million compounds and identified as representative of multiple series of potential leads. According to our predictions, amongst these are molecules holding better solubility, halogen fraction and binding affinity than the TTR stabilizers discovered to date.

MEDI 39

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MEDI 40

Novel amides and ureas as γ -secretase modulators

Hua Zhou⁽¹⁾, hua_zhou2@merck.com, 33 Avenue Louis Pasteur, Boston MA 02115, United States ; **Christian Fischer**⁽¹⁾; **Laura Surdi**⁽¹⁾; **Susan Zultanski**⁽¹⁾; **Paul Tempest**⁽¹⁾; **Bethany Hughes**⁽¹⁾; **Richard Middleton**⁽¹⁾; **Nadya Smotrov**⁽¹⁾; **Nathan Bays**⁽¹⁾; **Sanjiv Shah**⁽¹⁾; **Benito Munoz**⁽¹⁾; **Mark Shearman**⁽¹⁾. (1) Merck & Co., Inc., Boston MA 02115, United States

It is a leading hypothesis that the accumulation of amyloid β -peptide ($A\beta$), specifically $A\beta_{42}$ is a critical step in the pathogenesis of Alzheimer's Disease (AD). γ -Secretase is responsible for the cleavage of $A\beta$ precursor protein (APP) to produce $A\beta$. Thus one therapeutic approach for AD is to find γ -secretase modulators (GSMs) to selectively reduce $A\beta_{42}$ and without affecting Notch. A series of novel amides and ureas were studied as potential GSMs. The structure-activity relationship of these analogs will be discussed.

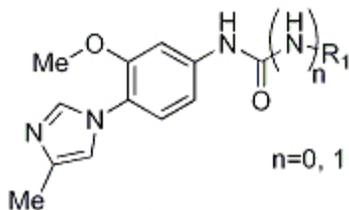


Figure 1

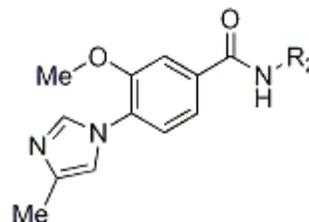


Figure 2

MEDI 41

WITHDRAWN

MEDI 41

WITHDRAWN

MEDI 42

Tetracyclic sulfones as gamma secretase inhibitors

T K Sasikumar⁽¹⁾, sasikumartk@yahoo.com, 2015 Galloping Hill Road, MS: 2800, Kenilworth New Jersey 07033, United States . (1) Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth New Jersey 07033, United States

Inhibition of γ -secretase, one of the enzymes responsible for the cleavage of the amyloid precursor protein (APP) to produce the pathogenic Ab-peptides, is an attractive approach to the treatment of Alzheimer's disease (AD). The disease is characterized by the progressive loss of cognitive function and results in end-stage patients that are bedridden and dependent on custodial care. Because inhibition of γ -secretase blocks the production of Ab, the identification of compounds that block the activity of this enzyme has become a major focus of AD research. This poster describes the synthesis and SAR properties of a tetracyclic sulfone system that showed very good biological profile.

MEDI 42

Tetracyclic sulfones as gamma secretase inhibitors

T K Sasikumar⁽¹⁾, sasikumartk@yahoo.com, 2015 Galloping Hill Road, MS: 2800, Kenilworth New Jersey 07033, United States . (1) Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth New Jersey 07033, United States

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MEDI 43

Novel inhibitors of AHCY for the treatment of Alzheimer's disease

Timothy J Hartingh⁽¹⁾, *timothy_hartingh@merck.com*, 770 Sumneytown Pike WP14-3, PO BOX 4, West Point PA 19486, United States ; Antonella Converso⁽¹⁾; Mark E Fraley⁽¹⁾; Edward J Brnardic⁽¹⁾; Robert M Garbaccio⁽¹⁾; George D Hartman⁽¹⁾; Shaei Y Huang⁽¹⁾; Edward S Tasber⁽¹⁾; Steven D Young⁽¹⁾; Lisa H Gold⁽²⁾; John M Majercak⁽²⁾; Alexander McCampbell⁽²⁾; Sang Jin Na⁽²⁾; William J Ray⁽²⁾; Mary J Savage⁽²⁾; Yuanjiang Yu⁽²⁾; Christine Fandozzi⁽³⁾; Rebecca White⁽³⁾; Suzie Yeh⁽³⁾; Sheila M Galloway⁽⁴⁾; John G DeLuca⁽⁴⁾; Vijay Reddy⁽⁴⁾; Katherine Holloway⁽⁵⁾; Timothy Allison⁽⁵⁾; Sanjeev Munshi⁽⁵⁾; Keith Rickert⁽⁵⁾. (1) Department of Medicinal Chemistry, Merck & Co., Inc., West Point Pennsylvania 19486, United States (2) Department of Alzheimer's Disease, Merck & Co., Inc., West Point Pennsylvania 19486, United States (3) Department of Drug Metabolism, Merck & Co., Inc., West point Pennsylvania 19486, United States (4) Department of Genetic and Cellular Toxicity, Merck & Co., Inc., West Point Pennsylvania 19486, United States (5) Department of Structural Biology, Merck & Co., Inc., West Point Pennsylvania 19486, United States

Elevated plasma homocysteine (Hcy) levels are an independent risk factor for the onset and progression of Alzheimer's disease. High levels of Hcy have also been associated with morphological changes in hippocampal volume and brain atrophy, suggesting a link between elevated Hcy, cognitive decline and AD-related pathologies. Reduction of Hcy to normal levels therefore presents a novel mechanism for disease modification.

Hcy is produced by the cytosolic enzyme S-adenosylhomocysteine hydrolase (AHCY), which converts S-adenosylhomocysteine (SAH) to Hcy and adenosine. Our initial objectives for the program were to identify inhibitors of AHCY and demonstrate reduction of central Hcy levels in vivo. While a rigorous screening campaign produced no tractable non-adenosine leads, we turned our attention to known substrate-based inhibitors of AHCY as starting points for the medicinal chemistry effort. This presentation will focus on the discovery and development of novel, highly potent, orally bioavailable, and brain penetrant inhibitors. Described in particular detail will be how positive exploratory Ames results of our

early adenosine mimetics were overcome. In addition, decreases in central Hcy levels in multiple species were observed, representing an important tool for the study of this novel strategy within the existing preclinical models of Alzheimer's disease.

MEDI 44

Design and synthesis of neuroprotective NO chimeras with GABA_A potentiating activity as Alzheimer's disease therapeutics

Zhihui Qin⁽¹⁾, qinzhh@uic.edu, 833 S. Wood St. Rm539, Chicago IL 60612, United States ; **Jia Luo**⁽¹⁾; **Lawren VandeVrede**⁽¹⁾; **Gregory R.J. Thatcher**⁽¹⁾. (1) Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago IL 60612, United States

Clomethiazole (5-(2-chloroethyl)-4-methyl-1,3-thiazole; CMZ) is a sedative/hypnotic, anticonvulsant, thought to act as a GABA_A potentiator, currently in clinical use for anxiety in the elderly. The anti-inflammatory and neuroprotective properties of CMZ have been widely described in animal models of ischemic stroke and the drug completed Phase 3 clinical trials for this indication. GT-1061 incorporates the methyl-thiazole (MZ) pharmacophore and retains GABA_A potentiating and anticonvulsant activity and attenuated sedative/hypnotic activity. The aliphatic nitrate group of GT-1061 provides nitric oxide (NO) mimetic activity via sGC/cGMP/ERK/CREB signal transduction enhancing synaptic plasticity. GT-1061 has completed Phase 1A clinical trials for Alzheimer's disease. In order to extend structure activity relationships around GT-1061, a library of 40 MZ compounds was designed to construct novel scaffolds having neuroprotective and anti-neuroinflammatory activities. NO chimeras of selected compounds from this library were designed using a variety of prodrug and stable linker strategies. MZ library compounds were assayed in primary cultured rat cortical neuron and glial cells, whereas NO chimeras were studied in bioavailability, sedation, and cognition enhancement tests in mice. Several active NO chimeras were identified.

MEDI 45

Common antibiotics used in the treatment of gram negative infectious diseases

Sarita S Mantravadi⁽¹⁾

The paper provides an in-depth review of the commonly used antibiotics in the treatment of infectious diseases caused by gram-negative bacteria. Gram-negative bacterial infections are challenging to treat, as they do not respond

favorably to antibiotic treatment. These pathogens further pose a challenge, as difficulty in their treatment is escalated by the emergence of the so-called “super germs” which on occasion are resistant even to multi-drug treatment. This paper will review and emphasize the chemical structure of the antibiotics used against these virulent strains of bacteria. It will also address the issue of mechanisms of action by these therapeutic agents, which play a key role in controlling these deadly bacterial microorganisms.

MEDI 46

Evidence for the production of novel macrocyclic antibiotics from the marine bacterium *Pseudovibrio denitrificans*

Maria I Vizcaino⁽¹⁾⁽²⁾, vizcain@musc.edu, 331 Ft Johnson Road, Charleston SC 29412, United States ; **Pamela J Morris**⁽¹⁾⁽²⁾⁽³⁾; **Peter D.R. Moeller**⁽²⁾⁽⁴⁾. (1) *Molecular Cellular Biology and Pathobiology, Medical University of South Carolina, Charleston SC 29412, United States* (2) *Hollings Marine Laboratory, Charleston SC 29412, United States* (3) *Belle W. Baruch Institute for Marine and Coastal Sciences, University of South Carolina, Charleston SC 29412, United States* (4) *Toxin/Natural Product Chemistry, NOAA National Ocean Service, Charleston SC 29412, United States*

Antibiotics produced by microorganisms are an important defense against infectious pathogens, and the search for novel antibiotics is of increasing importance due to the emergence of antibiotic-resistant bacteria. Our studies have focused on a Gram-negative *Pseudovibrio denitrificans* strain isolated from a Caribbean octocoral, *Pseudopterogorgia americana*. The methanol extract of *P. denitrificans* cell-free supernatant was subjected to HPLC bioassay-guided fractionation, and resulted in one antibiotic with specific activity against Gram-positive *Bacillus subtilis* and one with activity against two Gram-negative *Vibrio* species. Structural characterization using LC-MS and NMR data suggests the *Bacillus*-inhibiting compound is a macrocyclic peptidic compound (~500 amu). *Pseudovibrio* species have only been isolated from marine environments and little is known regarding their antimicrobial compound production. Our results highlight the potential role of *P. denitrificans* as a source for selective bioactive natural compounds

This work is supported by the National Science Foundation Biodiversity Surveys and Inventories Grant (DEB 0516347 and DEB 0964997) awarded to PJM. MV was supported by the National Institute of Allergy and Infectious Diseases (F31AI084455), the SC Sea Grant Consortium (NOAA), the National Ocean Service (NOS), and NIH's Initiative for Maximizing Student Diversity. The project content is solely the responsibility of the authors and does not necessarily represent the official views of NIAID or NIH

MEDI 47

Design and synthesis of dual CDK2 and CDK7 inhibitors

Elisa Meschini⁽¹⁾, elisa.meschini@ncl.ac.uk, Newcastle University, Newcastle Upon Tyne Tyne and Wear, United Kingdom ; *Jane A Endicott*⁽²⁾; *Bernard T Golding*⁽¹⁾; *Ian R Hardcastle*⁽¹⁾; *David R Newell*⁽³⁾; *Martin E M Noble*⁽²⁾; *Lan-Zhen Wang*⁽³⁾; *Roger J Griffin*⁽¹⁾. (1) School of Chemistry, Bedson Building, Northern Institute for Cancer Research, Newcastle University Newcastle Upon Tyne NE1 7RU, United Kingdom (2) University of Oxford, Department of Biochemistry, South Parks Road Oxford OX1 3QU, United Kingdom (3) Paul O'Gorman Building, Northern Institute for Cancer Research, Newcastle University Newcastle Upon tyne NE1 4HH, United Kingdom

Cyclin-Dependent Kinases (CDKs) play a fundamental role in eukaryotic cell cycle progression, particularly at cell cycle checkpoints, and therefore constitute important targets for anticancer drug discovery.

Previous studies have resulted in the identification of 4-(6-(cyclohexylmethoxy)-9H-purin-2-ylamino)sulfonamide (**1**), a potent and selective CDK2 inhibitor, and N-(4-(2-(4-methylpiperazin-1-yl)ethylsulfonyl)phenyl)-6-(cyclohexylmethoxy)-9H-purin-2-amine (**2**), an equipotent CDK2/7 inhibitor. This project centres on the development of inhibitors based on these two parent structures. While the sulfonamide group of **1** confers potency and selectivity for CDK2, the piperazinyl substituent of **2** improves CDK7 activity; therefore, 4-(6-(cyclohexylmethoxy)-9H-purin-2-ylamino)-N-(2-(4-methylpiperazin-1-yl)ethyl)sulfonamide (**3**) is a potent CDK2 inhibitor with reasonable CDK7-inhibitory activity. Further elaboration of the 2-aryl amino side-chain function has enabled the identification of purines (e.g. N-(4-(2-(benzylamino)ethoxy)phenyl)-6-(cyclohexylmethoxy)-9H-purin-2-amine **4**) exhibiting some selectivity for CDK7.

	IC ₅₀ CDK2 (μM)	IC ₅₀ CDK7 (μM)
1	0.005	4.4
2	0.12	0.23
3	0.012	0.63
4	2.6	0.56

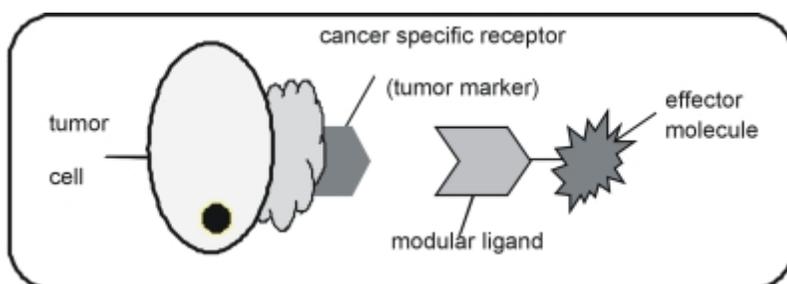
Current synthetic work is focusing on replacing the purine core pharmacophore of **2** with alternative heterocycles.

MEDI 48

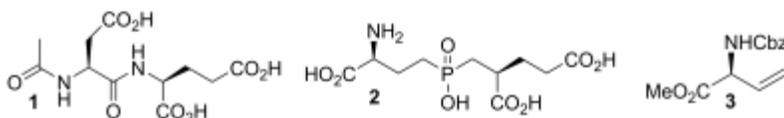
Synthesis of novel carboxypeptidase ligands for tumor imaging

Christian-H. Kuechenthal⁽¹⁾, kuechenthal@org.chemie.uni-giessen.de,
 Heinrich-Buff-Ring 58, Giessen Hesse 35392, Germany ; Wolfgang Maison⁽¹⁾. (1)
 Institute of Organic Chemistry, Justus Liebig University, Giessen Hesse 35392,
 Germany

Differentiation of healthy tissue and cancerous tissue is a major problem in cancer diagnostics and therapy.^[1] In this context, tumor marker like the prostate specific membrane antigen (PSMA),^[2] can be addressed with modular ligands. These ligands bind specifically to the tumor marker and can thus deliver pharmacological effector molecules selectively to cancer cells.



PSMA is a glutamate carboxypeptidase and different PSMA-ligands have been used successfully for tumor imaging according to the above mentioned concept.^[3] Among these ligands, analogs of the natural PSMA-substrate *N*-acetyl-L-aspartyl-L-glutamate (NAAG, **1**) like phosphinic acid derivative GPI **2** have shown the highest potencies.^[4]



We present efficient and stereoselective syntheses of building blocks like protected vinylglycine **3**^[5] and the synthetic routes to novel NAAG-analogs which are transition state analogs of peptide bond hydrolysis and will thus be useful for tumor imaging using cancer specific proteases like PSMA.

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[2] W.D. Heston, *Urologe A* **1996**, *35*, 400.

[3] P. Misra, V. Humblet, N. Pannier, W. Maison, J. V. Frangioni, *J. Nucl. Med.* **2007**, *48*, 1379.

[4] J. Zhou, J. H. Neale, M. G. Pomper, A. P. Kozikowski, *Nat. Rev. Drug Discov.* **2005**, *4*, 1015.

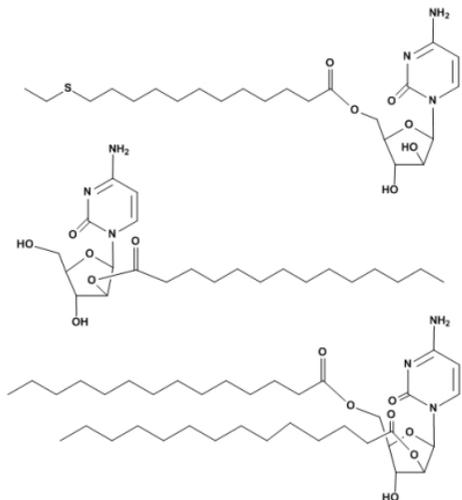
[5] C.-H. Küchenthal, W. Maison, *Amino Acids* **2010**, *in press*.

MEDI 49

Synthesis and anticancer activity of fatty acid derivatives of cytarabine

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Cytarabine is predominately used against acute myelogenous leukemia and non-Hodgkin's lymphoma. Cytarabine is a polar nucleoside and continuous intravenous infusion is required to maintain constant plasma levels in 8 to 24 hours. Liposomal cytarabine was approved by the FDA for the treatment of lymphomatous meningitis. Lipophilic fatty acyl derivatives of cytarabine were synthesized to improve cellular permeability. Furthermore, intracellular hydrolysis of the conjugate may result in the slow release of cytarabine, possibly increasing the compound duration of action. Multistep protection and deprotection reactions of hydroxyl and amino groups and conjugation with fatty acids (i.e., myristic acid and 12-thioethyldodecanoic acid) was used to synthesize five fatty acyl derivatives of cytarabine, including 5'-O-substituted, 2'-O-substituted, and 2',5'-disubstituted derivatives



. 2',5'-Dimyristoyl derivative was found to inhibit the growth of CCRF-CEM cells by approximately 47% at concentration of 10 μ M. Further optimization will be used to generate lead compounds with optimal anti-cancer activity and cellular uptake.

MEDI 50

Application of *in silico* design and high-throughput chemistry platform in the lead optimization of selective and potent mutant-B-RAF inhibitors

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Woburn Ma 01801, United States (2) Department of Preclinical Development and Clinical Pharmacology, ArQule, Inc, Woburn Ma 01801, United States (3) Department of Molecular Oncology, ArQule, Inc., Woburn Ma. 01801, United States

The B-RAF^{V600E} mutation is present in 70% of B-RAF-mutated melanoma tumors. The same mutation also accounts for more than 50% of B-RAF mutations in thyroid carcinomas. We considered targeting B-RAF^{V600E} to be a rational therapeutic goal and undertook a program to identify selective, bio-available small molecule inhibitors suitable for development as drugs to treat patients with B-RAF^{V600E}-driven tumors. Herein, we describe an application of *in silico* prediction and high throughput chemistry to ArQule's B-RAF kinase inhibitor program. Manipulating chemical structure to improve physico-chemical properties is a key step in the drug discovery process and we describe how we applied the introduction of heteroaromatic groups to our lead series to improve solubility and ADME properties while maintaining enzymatic and cellular potency. The compounds were synthesized in parallel and evaluated for *in vitro* mutant-B-RAF inhibition, cellular p-Erk inhibition, as well as solubility and *in vitro* ADME properties.

MEDI 51

Discovery and optimization of a potent and selective triazolopyridinone series of c-Met inhibitors

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Deregulation of the receptor tyrosine kinase c-Met has been implicated in several human cancers and is an attractive target for small molecule drug discovery. We have previously shown that nitrogen- or oxygen-linked quinoline or naphthyridine triazolopyridazines are potent inhibitors of c-Met. Herein, we report the discovery of a structurally diverse series of carbon-linked quinoline triazolopyridinones, which demonstrate nanomolar inhibition of c-Met kinase activity. This novel series of inhibitors exhibits favorable pharmacokinetics and displays potent inhibition of HGF-mediated c-Met phosphorylation in a mouse liver pharmacodynamic model.

MEDI 52

Discovery of water soluble *N*,2-dimethyl-*N*-substituted phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amines as antimetabolic agents that circumvent taxol resistance

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Antimetabolic agents are classified as microtubule stabilizers such as the taxanes, or destabilizers such as the *Vinca* alkaloids and colchicine. These agents inhibit microtubule dynamics. The taxanes are clinically useful antimetabolic agents for the treatment of breast, lung, ovarian, head and neck and bladder cancers among others. Although the taxanes are arguably some of the most valuable chemotherapeutic agents available today, intrinsic and acquired drug resistance and a lack of water solubility limit their anticancer actions. The identification of new antimetabolic agents that overcome taxane resistance mechanisms could provide significant clinical advantages in the treatment of cancer.

We have discovered a series of *N*,2-dimethyl-*N*-substituted phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amines as novel antimetabolic agents. These compounds were originally synthesized as RTK inhibitors. However they showed potent inhibitory activity against both tumor cell growth and microtubule polymerization. In addition, these compounds showed potent inhibition against resistance tumor cells that over express either Pgp or β III tubulin the two most clinically relevant resistance mechanisms for taxol and *Vinca* alkaloids. The design, synthesis and discovery of tumor cell inhibitory activities of these compounds will be presented and discussed.

MEDI 53

Discovery of substituted pyrrolo[2,3-*d*]pyrimidines as water soluble antitubulin antitumor agents

Aleem Gangjee⁽¹⁾, gangjee@duq.edu, 600 Forbes Ave., 451 Mellon Hall, Pittsburgh PA 15282, United States ; **Lu Lin**⁽¹⁾; Susan L Mooberry⁽²⁾; Ernest Hamel⁽³⁾. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh PA 15282, United States (2) Cancer Therapy and Research Center, University of Texas Health Science Center San Antonio, San Antonio TX 78229-3900, United States (3) National Cancer Institute-Frederick, Frederick MD 21702-1201, United States

Compound **1** and its *N*-methylated analog **2** were initially designed and synthesized as RTK inhibitors. No RTK inhibition was observed on evaluation.

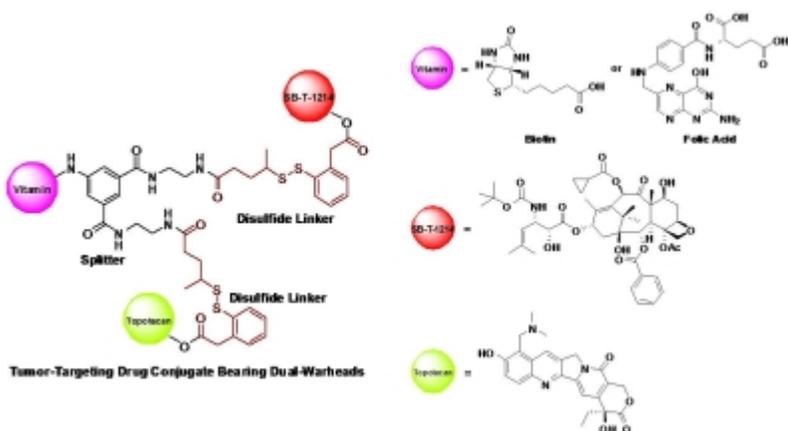
However, compound **2** afforded GI₅₀s of 2 or 3 digit nanomolar inhibitory activities against 52 of the NCI cancer cell lines. A Compare Analysis of the results revealed the best correlation with the antitubulin, antimetabolic, anticancer agents (vinblastine, paclitaxel, maytansine, rhizoxin, vincristine). Further evaluation showed that compound **2** is a colchicine site tubulin inhibitor and is active against tumor cells regardless of p-glycoprotein or β -III tubulin status of the tumor cell. These are two of the most clinically relevant resistance mechanism against antimetabolic agents. In addition, **2** as its HCl salt is highly water soluble. The synthesis, mechanism of action and remarkable biological activities of compound **2** will be presented.

MEDI 54

Novel tumor-targeting anticancer drug conjugate bearing a taxoid and a topotecan

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A novel tumor-targeting drug conjugate bearing dual-warheads was designed and synthesized utilizing biotin or folic acid as a tumor-targeting module. The warheads chosen were SB-T-1214, a 2nd-generation taxoid that inhibits microtubule depolymerization, and topotecan, a camptothecin analog that inhibits DNA topoisomerase I. Both warheads show a greater potency in various cancer cell lines compared to their parent compounds. It is reasonable to assume that the dual mechanism of action makes the drug conjugate highly efficacious. Furthermore, the presence of a vitamin increases tumor-specificity of the drug conjugate, as cancer cells overexpress vitamin receptors. Based on the published studies on single-warhead conjugates from this laboratory, the drug conjugate should be specifically delivered to cancer cells and internalized *via* receptor-mediated endocytosis. Then, the drug moieties should be released in their active form through the self-immolation of disulfide linkers triggered by the presence of a cellular thiol to target microtubules (SB-T-1214) and topoisomerase I (topotecan). The synthesis and biological evaluation of novel tumor-targeting drug conjugates bearing dual-warheads will be presented.



MEDI 55

Synthesis and biological evaluation of novel carbocycle-containing combretastatin A-4 analogs

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Combretastatin A-4 was isolated by Pettit from the African willow tree *Combretum caffrum* in 1982. The natural product shows promising cytotoxicity against a wide range of human cancer cell lines and derivatives are currently used in clinical studies.

SAR-studies revealed that the substitution pattern on both aromatic rings of the highly oxygenated stilbene derivative and the geometry of the *cis*-double bond is of crucial importance for biological activity.

Goal of our studies is to increase the *in vivo* activity of combretastatin by replacing the physiologically unstable *cis*-double bond with carbocycles of different ring sizes thus maintaining the overall polarity and simultaneously preventing the system to undergo *cis-trans* isomerization.

Derivatives containing carbocycles with different ring sizes have been prepared and these novel compounds were found to express extremely high levels of activity in the nanomolar range. Syntheses, docking studies, and evaluation of biological activity against human cancer cell lines are discussed.

MEDI 56

Design of potent guanase inhibitors based on azepinomycin skeleton

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Cancerous cells require a large nucleotide pool, which led to an increasing amount of research on the enzymes involved in nucleotide biosynthesis.

Guanine deaminase is an important enzyme in nucleotide metabolism. There have

been reports of abnormally high levels of serum guanase activity in patients with liver diseases, multiple sclerosis, in cancerous kidney and breast cancer tissue cells. These observations suggest that a potent guanase inhibitor is necessary for exploring the biochemical mechanisms of the above metabolic disorders and to understand the specific physiological role played by guanase. Such studies are anticipated to pave the way for discovery of novel therapeutics in effectively treating these disorders. Azepinomycin is a known, naturally occurring inhibitor of the enzyme. As a step forward in designing potent guanase inhibitors, we report here our synthetic strategies to access azepinomycin and its analogues, along with our biochemical investigations to assess their K_i values.

MEDI 57

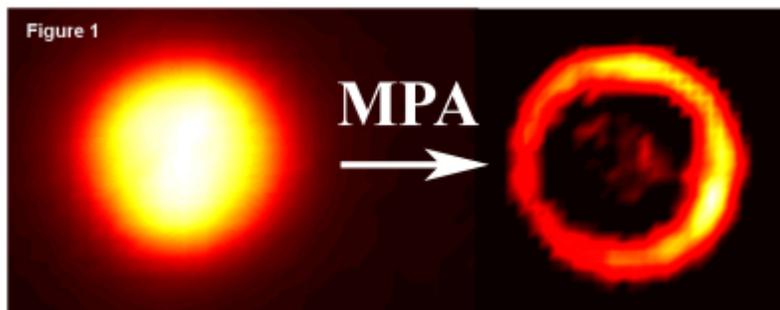
Blocking the nuclear translocation of signal transducer and activator of transcription 3 (STAT3) protein via membrane anchorage

Miriam Avadisian⁽¹⁾, *miriam.avadisian@utoronto.ca*, 3359 Mississauga Rd N, Mississauga Ontario L5L1C6, Canada ; **Steven Fletcher**⁽¹⁾; **Baoxu Liu**⁽¹⁾; **Wei Xu**⁽²⁾; **Pei Bin Yue**⁽³⁾; **Aaron D Schimmer**⁽²⁾; **James Turkson**⁽³⁾; **Claudiu Gradinaru**⁽¹⁾; **Patrick T Gunning**^{*⁽¹⁾}. (1) Department of Chemical and Physical Sciences, University of Toronto, Mississauga Ontario L5C1C9, Canada (2) Department of Hematology and Oncology, Princess Margaret Hospital, Toronto Ontario M5G 2M9, Canada (3) Department of Molecular Biology and Microbiology, University of Central Florida, Orlando Florida 32826, United States

Signal Transducer and Activator of Transcription 3 (STAT3) is an oncogenic signaling protein that promotes cancer through the relaying of extracellular signals to the nucleus where it promotes the transcription of genes controlling cancer cell growth, survival and angiogenesis. We reasoned that inhibition of nuclear translocation could be accomplished through small-molecule mediated protein-membrane anchorage (MPA). Thus, we synthesized a proof-of-principle probe incorporating a cholesterol anchor coupled to a STAT3 binding sequence,

pYLPQTV.

Preliminary studies in liposome models have demonstrated the nature of our inhibitors to sequester STAT3 protein to the plasma membrane (Figure 1). Whole cells treated with protein-membrane anchors showed significant suppression of nuclear residing STAT3. This project represents an innovative new drug modality for the inhibition STAT3 function by suppressing its cellular motility.



MEDI 58

Development of PET and SPECT radiotracers for the imaging of cancers overexpressing the ErbB family of growth factor receptors

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Patients presenting subclasses of cancers that overexpress EGFR or HER2, two members of the ErbB family of growth factor receptors, have poorer prognoses, with higher risks of disease recurrence and metastatic events. Despite FDA approval of small molecule EGFR/HER2 inhibitors, the widespread use of these therapeutics has been hampered by an inability to identify subpopulations sensitive to anti-EGFR/HER2 therapy.

This project addresses this issue through the design and synthesis of PET and SPECT imaging agents specific to these subclasses of cancer, by ligating the characteristic 4-anilinoquinazoline inhibitor scaffold to a linker bearing an appropriate radioisotope. The modular synthetic approach employed produces a more readily optimized series of

molecular probes, while strategic placement of the imaging modality in solvent-accessible space minimizes the negative effect of its presence on the binding of the radiotracer in the active sites of the receptors. Supported by DOE Award ER647823.

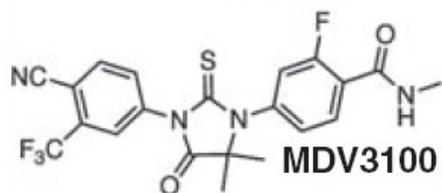
MEDI 59

Development of a second-generation antiandrogen for treatment of castration-resistant prostate cancer (CRPC)

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Prostate cancer is the most common non-skin cancer in the United States and the third most common cancer worldwide. More than 1 million men in the United States have prostate cancer. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that continues to grow despite all standard-of-care hormonal (anti-androgen) therapies. Patients with castration-resistant (also known as hormone-refractory) prostate cancer have few treatment options and a poor prognosis.

We carried out a structure-activity relationship study on a series of thiohydantoin which led to the discovery of MDV3100 as the clinical candidate for the treatment of CRPC. Also we utilized various models of CRPC and provided evidence that MDV3100's novel mechanism of action is unlike that of the leading anti-androgen therapy bicalutamide. Currently MDV3100 is being evaluated in Phase 3 clinical trials worldwide.



MEDI 60

Targeting the interaction of mixed lineage leukemia 1 (MLL1) and wd repeat domain 5 (WDR5) for new anticancer drug design

Hacer Karatas⁽¹⁾⁽²⁾⁽³⁾, hkaratas@umich.edu, 1500 E. Medical Center Dr., Ann Arbor MI, United States ; **Elizabeth Townsend**⁽⁴⁾; **Denzil Bernard**⁽²⁾⁽³⁾; **Yali Dou**⁽⁴⁾; **Shaomeng Wang**⁽¹⁾⁽²⁾⁽³⁾⁽⁵⁾. (1) Medicinal Chemistry, University of Michigan, Ann Arbor MI, United States (2) Internal Medicine, University of Michigan, Ann Arbor MI, United States (3) Comprehensive Cancer Center, University of Michigan, Ann Arbor MI, United States (4) Pathology, University of Michigan, Ann Arbor MI, United States (5) Department of Chemistry, University of Michigan, Ann Arbor MI, United States

United States (5) Pharmacology, University of Michigan, Ann Arbor MI, United States

MLL1, one of the H3K4 methyltransferase, is highly deregulated in cancer and inhibiting MLL1 activity could be a novel approach in cancer therapy. MLL1 functions in a core complex with WDR5, RbBP5 and Ash2L. The interaction between WDR5 and MLL1 is required for the complex integrity and catalytic activity of MLL1. Therefore, targeting MLL1-WDR5 interaction can effectively inhibit MLL1 function. In our study, we determined that -CO-ARA-NH- is the minimal motif in MLL1 for WDR5 binding and the carbonyl at the N-terminal of this tripeptidic motif is the key reason for higher affinity of MLL1 peptides to WDR5 compared to Histone 3 peptides. We further demonstrated that two intramolecular hydrogen bonds formed in this motif are required for high affinity binding of MLL1 peptides. Finally, we identified a series of peptidomimetics with low nM binding affinity to WDR5, which could be used for the design of peptidomimetic and small molecule inhibitors of MLL1.

MEDI 60

Targeting the interaction of mixed lineage leukemia 1 (MLL1) and wd repeat domain 5 (WDR5) for new anticancer drug design

Hacer Karatas⁽¹⁾⁽²⁾⁽³⁾, hkaratas@umich.edu, 1500 E. Medical Center Dr., Ann Arbor MI, United States ; **Elizabeth Townsend**⁽⁴⁾; **Denzil Bernard**⁽²⁾⁽³⁾; **Yali Dou**⁽⁴⁾; **Shaomeng Wang**⁽¹⁾⁽²⁾⁽³⁾⁽⁵⁾. (1) Medicinal Chemistry, University of Michigan, Ann Arbor MI, United States (2) Internal Medicine, University of Michigan, Ann Arbor MI, United States (3) Comprehensive Cancer Center, University of Michigan, Ann Arbor MI, United States (4) Pathology, University of Michigan, Ann Arbor MI, United States (5) Pharmacology, University of Michigan, Ann Arbor MI, United States

MLL1, one of the H3K4 methyltransferase, is highly deregulated in cancer and inhibiting MLL1 activity could be a novel approach in cancer therapy. MLL1 functions in a core complex with WDR5, RbBP5 and Ash2L. The interaction between WDR5 and MLL1 is required for the complex integrity and catalytic activity of MLL1. Therefore, targeting MLL1-WDR5 interaction can effectively inhibit MLL1 function. In our study, we determined that -CO-ARA-NH- is the minimal motif in MLL1 for WDR5 binding and the carbonyl at the N-terminal of this tripeptidic motif is the key reason for higher affinity of MLL1 peptides to WDR5 compared to Histone 3 peptides. We further demonstrated that two intramolecular hydrogen bonds formed in this motif are required for high affinity binding of MLL1 peptides. Finally, we identified a series of peptidomimetics with low nM binding affinity to WDR5, which could be used for the design of peptidomimetic and small molecule inhibitors of MLL1.

MEDI 61

Rational design and evaluation of small molecule DNA ligase inhibitors as potential cancer chemotherapeutics

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Based on the crystal structure of human DNA ligase I complexed with nicked DNA, computer aided drug design was used to identify compounds that were predicted to bind to and inhibit the enzyme.

Experimental

screening was carried out using two different DNA ligation assays, yielding a series of active compounds with different specificities for the three human DNA ligases (I, III, and IV). Cell proliferation studies were carried out on a variety of normal and cancer cell lines; several compounds are cytotoxic alone, or are effective at subtoxic doses in combination with DNA damaging agents. Two compounds that inhibit both Ligase I and Ligase III have been shown to kill imatinib resistant chronic myeloid leukemia cells with the BCR-ABL mutation. *In vivo* pharmacokinetic and efficacy studies with these compounds are being carried out in mice. Additional derivatives have been synthesized and screened in order to optimize activity, stability, and solubility.

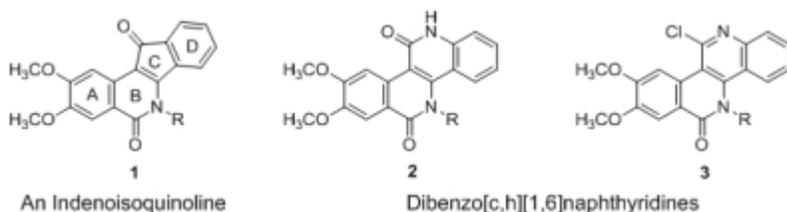
MEDI 62

Design, synthesis and evaluation of dibenzo[c,h][1,6]naphthyridines as Top1 inhibitors and potential anticancer agents

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Indenoisoquinoline topoisomerase I (Top1) inhibitors represent a novel class of potential anticancer agents. Modifications of indenoisoquinoline A, B and D rings

have been extensively studied in order to optimize Top1 inhibitory activity and cytotoxicity. To improve understanding of the forces that stabilize drug-Top1-DNA ternary complexes, the five-membered C-ring of indenoisoquinoline **1** was substituted with a new six-membered fragment of dibenzo[*c,h*][1,6]naphthyridines **2** and **3**. The designed dibenzo[*c,h*][1,6]naphthyridines were prepared by a novel synthetic route and tested for Top1 inhibition.



MEDI 63

Design and synthesis of ezrin inhibitors for metastatic osteosarcoma

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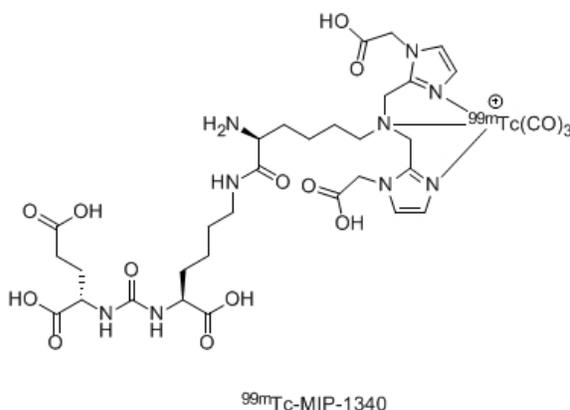
Although extensive research has identified numerous molecular scaffolds aimed at the identification and treatment of osteosarcoma, the metastatic phenotype remains a critical therapeutic target. Ezrin, a cytoskeletal protein and component of the FERM protein complex is vital to various cellular functions, including cell motility, cellular proliferation and apoptosis. However, its contribution to these activities also links ezrin to both tumor progression and metastasis. In human studies, 43.7% of high-grade human osteosarcoma tumor samples were positive for ezrin while low-grade osteosarcoma had 0% ezrin immunoreactivity. With surface plasmon resonance technology, we have identified a ligand for ezrin, which inhibits cell migration in a metastatic osteosarcoma cell line. Herein, we detail a structure activity relationship in efforts toward targeting ezrin for the prevention of cancer metastasis.

MEDI 64

Small molecule prostate specific membrane antigen inhibitors with Re/Tc for the diagnosis and staging of prostate cancer

Genliang Lu⁽¹⁾, glu@molecularinsight.com, 160 Second Street, Cambridge MA 02142, United States ; Kevin P Maresca⁽¹⁾; Shawn M Hillier⁽¹⁾; John C Marquis⁽¹⁾; Craig N Zimmerman⁽¹⁾; William C Eckelman⁽¹⁾; John L Joyal⁽¹⁾; John W Babich⁽¹⁾.
(1) Molecular Insight Pharmaceuticals, Cambridge MA 02142, United States

Prostate specific membrane antigen (PSMA) is recognized as an attractive target for imaging and potentially treating metastatic prostate cancer. A series of novel ^{99m}Tc/Re labeled radiopharmaceuticals were synthesized by attaching single amino acid chelators to the Glu-Urea-Lys and Glu-Urea-Glu pharmacophores. The *in vitro* affinities of the Re-complexes were determined using PSMA expressing LNCaP cells. IC₅₀ values ranged from 1.4 nM to 4,280 nM. A linker between the chelator and the Glu-Urea-Lys or Glu-Urea-Glu binding domain was required for high affinity binding. The conjugates with the carboxylic acid substituted imidazole chelators bis(1H-imidazole)diacetic acid and bis(1H-imidazole)tetraacetic acid were among the most potent compounds. Tissue distribution of one compound, ^{99m}Tc-MIP-1340 (IC₅₀ = 18 nM), in nude mice bearing LNCaP tumors achieved >12% ID/g with tumor:blood >20:1 and tumor:muscle >40:1 at 1 h. These inhibitors are currently being investigated for the potential use in the imaging of prostate cancer.

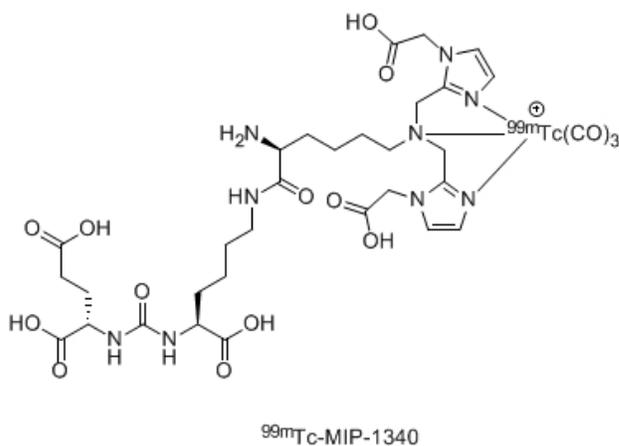


MEDI 64

Small molecule prostate specific membrane antigen inhibitors with Re/Tc for the diagnosis and staging of prostate cancer

Genliang Lu⁽¹⁾, glu@molecularinsight.com, 160 Second Street, Cambridge MA 02142, United States ; Kevin P Maresca⁽¹⁾; Shawn M Hillier⁽¹⁾; John C Marquis⁽¹⁾; Craig N Zimmerman⁽¹⁾; William C Eckelman⁽¹⁾; John L Joyal⁽¹⁾; John W Babich⁽¹⁾.
(1) Molecular Insight Pharmaceuticals, Cambridge MA 02142, United States

Prostate specific membrane antigen (PSMA) is recognized as an attractive target for imaging and potentially treating metastatic prostate cancer. A series of novel $^{99m}\text{Tc}/\text{Re}$ labeled radiopharmaceuticals were synthesized by attaching single amino acid chelators to the Glu-Urea-Lys and Glu-Urea-Glu pharmacophores. The *in vitro* affinities of the Re-complexes were determined using PSMA expressing LNCaP cells. IC_{50} values ranged from 1.4 nM to 4,280 nM. A linker between the chelator and the Glu-Urea-Lys or Glu-Urea-Glu binding domain was required for high affinity binding. The conjugates with the carboxylic acid substituted imidazole chelators bis(1H-imidazole)diacetic acid and bis(1H-imidazole)tetraacetic acid were among the most potent compounds. Tissue distribution of one compound, ^{99m}Tc -MIP-1340 (IC_{50} = 18 nM), in nude mice bearing LNCaP tumors achieved >12% ID/g with tumor:blood >20:1 and tumor:muscle >40:1 at 1 h. These inhibitors are currently being investigated for the potential use in the imaging of prostate cancer.



MEDI 65

Structure-based design, synthesis, and evaluation of a new class of potent Bcl-2/Bcl-X_L inhibitors

Haibin Zhou⁽¹⁾, haibinz@umich.edu, 3120 CCGC, 1500 E. Medical Ctr. Dr., Ann Arbor Michigan 48109, United States ; Jianfang Chen⁽¹⁾; Angelo Aguilar⁽¹⁾; Xin Cong⁽¹⁾; Liu Liu⁽¹⁾; Longchuan Bai⁽¹⁾; Donna McEachern⁽¹⁾; Chao-Yie Yang⁽¹⁾; Han Yi⁽¹⁾; Jennifer Meagher⁽²⁾; Jeanne A. Stuckey⁽²⁾; Xiaoqin Li⁽³⁾; Duxin Sun⁽³⁾; Shaomeng Wang⁽¹⁾. (1) Comprehensive Cancer Center and Department of Internal Medicine, University of Michigan, Ann Arbor Michigan 48109, United States (2) Life Sciences Institute, University of Michigan, Ann Arbor Michigan 48109, United States (3) Department of Pharmaceutical Science, College of Pharmacy, University of Michigan, Ann Arbor Michigan 48109, United States

The anti-apoptotic Bcl-2 proteins have been considered as attractive cancer therapeutic targets. The design, development of highly potent and specific small-

molecule inhibitors of these proteins is a very challenging task in medicinal chemistry since it is involved in targeting protein-protein interaction. We report the structure-based design and synthesis and evaluation of a new class of highly potent and specific Bcl-2/Bcl-X_L inhibitors. Our most potent compounds bind to bcl-2/Bcl-X_L with low nanomolar affinities. They are highly effective in induction of cell death in cancer cell lines that depend upon Bcl-2/Bcl-x_L for survival. The design, synthesis and evaluation for this new class of compounds will be described.

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MEDI 66

Novel VEGFR2 inhibitors: Pyridylmethylthio derivatives with intramolecular nonbonded S-O interaction

Hisashi Tajima⁽¹⁾⁽²⁾, hisashi.tajima@santen.co.jp, 8916-16, Takayama-cho, Ikoma Nara 630-0101, Japan ; Takahiro Honda⁽¹⁾⁽²⁾; Kenji Kawashima⁽¹⁾; Yoshimasa Sasabuchi⁽¹⁾; Minoru Yamamoto⁽¹⁾⁽²⁾; Masakazu Ban⁽¹⁾⁽²⁾; Kazuyoshi Okamoto⁽¹⁾; Kenji Inoue⁽¹⁾; Takaaki Inaba⁽¹⁾; Yuriko Takeno⁽¹⁾; Hiroyuki Aono⁽¹⁾⁽²⁾; Takashi Tsuboi⁽¹⁾; Asaka Tonouchi⁽¹⁾. (1) Research and Development Center, Santen Pharmaceutical Co., Ltd., Ikoma Nara 630-0101, Japan (2) Graduate

*School of Materials Sciences, Nara Institute of Science and Technology, Ikoma
Nara 630-0101, Japan*

Angiogenesis is closely related to the proliferation or metastasis of cancer, and also the pathogenesis and the progression of rheumatoid arthritis and age-related macular degeneration. The pathway of signal transduction through vascular endothelial growth factor (VEGF) plays a very important role in pathological angiogenesis. We previously reported that 4-pyridylmethylthio derivatives **1** were potent VEGFR2 inhibitors and they had a similar conformation to PTK787 (**2**) by their intramolecular nonbonded S-O interaction. Although these derivatives showed activities *in vitro* and efficacies in various animal disease models *in vivo*, they also inhibited CYP which caused drug-drug interaction. To improve the CYP inhibition, we investigated the syntheses and biological evaluations of various derivatives. In this meeting, we will report the detailed optimization of the derivatives and the result of animal disease models.

MEDI 67

Design, synthesis and evaluation of Smac mimetics as selective cIAP-1 and cIAP-2 inhibitors

Haiying Sun⁽¹⁾, haiyings@med.umich.edu, Comprehensive Cancer Center Room 3110, 1500 E Medicinal Center Dr., Ann Arbor MI 48103, United States ; Jianfeng Lu⁽¹⁾; Liu Liu⁽¹⁾; Chao-Yie Yang⁽¹⁾; Han Yi⁽¹⁾; Shaomeng Wang⁽¹⁾. (1) Department of Internal Medicine and Comprehensive Cancer Center, University of Michigan, Ann Arbor MI 48103, United States

Based upon a small molecular Smac mimetic SM-337, a series of novel Smac mimetics with high affinities and selectivity for cIAP-1 and -2 over XIAP were designed, synthesized and evaluated. While the most selective compounds bind to cIAP-1 and cIAP-2 with only slightly less potent binding affinities as SM-337, they are over 1000 times less potent than SM-337 in binding to XIAP. Corresponding to their potent binding affinities to cIAP-1, they potently induce degradation of cIAP-1 in western blot analysis using MBA-MD-231 cell line. More importantly, these compounds are only slightly less potent than SM-337 in cell growth inhibition assay and their cellular activities correlate very well with their abilities for inducing the degradation of cIAP-1 and -2. Taking together, our data suggest that these Smac mimetics inhibit cell growth mainly through antagonizing cIAP-1 and -2, but not XIAP.

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MEDI 68

DNA methyltransferase inhibitors: Molecular modeling and virtual screening

Jose L Medina-Franco⁽¹⁾, jmedina@tpims.org, 11350 SW Village Parkway, Port St. Lucie FL 34987, United States ; Narender Singh⁽¹⁾; Fabian Lopez-Vallejo⁽¹⁾; Dirk Kuck⁽²⁾; Frank Lyko⁽²⁾; Alfonso Dueñas-Gonzalez⁽³⁾; Gianluca Sbardella⁽⁴⁾. (1) Torrey Pines Institute for Molecular Studies, Port St Lucie FL 34987, United States (2) Deutsches Krebsforschungszentrum, Heidelberg 69120, Germany (3) Instituto Nacional de Cancerologia, Mexico City 14080, Mexico (4) Università degli Studi di Salerno, Fisciano (SA) 84084, Italy

The DNA methyltransferase (DNMT) enzyme family represents one of the most promising targets for the development of novel anticancer drugs. Using an homology model of the catalytic domain of human DNMT1 we report herein molecular modeling studies of several small-molecule DNMT1 inhibitors including hydralazine, procaine, procainamide [Singh, N. et al. *ChemMedChem* 2009, 4, 792] and procaine analogues [Castellano, S. et al. *J. Med. Chem.* 2008, 51, 2321]. The docking models suggest key interactions between the inhibitors and the binding pocket that can be exploited in structure-based design. We also present our findings of docking-based virtual screening of large compound databases for novel DNMT1 inhibitors [e.g., Kuck, D. et al. *Bioorg. Med. Chem.* 2010, 18, 822].

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MEDI 69

Apoptosis triggers targeting selectively resistant tumours

Estelle GENOUX⁽¹⁾, estelle.genoux@laposte.net, 470, rue de la Chimie Bât E Andre Rassat, Saint Martin d[apos]Hères Rhône Alpes 38400, France ; Doriane LORENDEAU⁽²⁾; Hélène CORTAY⁽²⁾; Attilio DI PIETRO⁽²⁾; Ahcène BOUMENDJEL⁽¹⁾. (1) Department of Medicinal Chemistry UMR 5063 - University of Grenoble, Grenoble, France (2) Institut de Biologie et Chimie des Protéines UMR 5086 - University of Lyon, Lyon, France

Resistance of tumours to structurally-unrelated anticancer drugs is a common clinical problem that limits the curative potential of chemotherapy in clinical oncology. The present study was carried out to develop drug candidates targeting selectively cancer cells within a tumour, which are chemoresistant through overexpression of the ABC transporter Multidrug Resistance Protein 1 (MRP1). The investigated molecules are apoptosis-triggers by inducing fast and massive cellular glutathione extrusion mediated by MRP1. Newly-designed molecules are investigated among flavonoids (Figure 1) and evaluated through in vitro and in vivo studies.

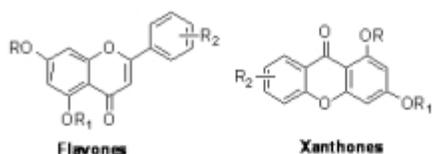


Figure 1 : General structures of synthesized-flavonoids : flavones and xanthenes

MEDI 70

2-Aryl-benzimidazole-4-carboxamides as novel SIRT1 activators

Jeremy S Disch⁽¹⁾, jdisch@sirtrispharma.com, 200 Technology Square, Suite 300, Cambridge MA 02139, United States ; **Chi B Vu**⁽¹⁾; **Lauren McPherson**⁽¹⁾; **Pui Yee Ng**⁽¹⁾; **Jean E. Bemis**⁽¹⁾; **David P. Carney**⁽¹⁾; **Amy V. Lynch**⁽¹⁾; **Christine Loh**⁽¹⁾; **Scott Ribich**⁽¹⁾; **Peggy Romero**⁽¹⁾; **Jesse J. Smith**⁽¹⁾; **Jeffrey Song**⁽¹⁾; **David J. Gagne**⁽¹⁾; **Angela Cote**⁽¹⁾; **Meghan Davis**⁽¹⁾; **Elden Lainez**⁽¹⁾; **Robert B. Perni**⁽¹⁾. (1) Department of Chemistry, Sirtris a GSK company, Cambridge MA 02139, United States

SIRT1, an NAD⁺-dependent protein deacetylase, has been shown to play a role in metabolic homeostasis, inflammation and mitochondrial biogenesis. Transgenic mice over-expressing SIRT1 had improved metabolic function; lower insulin, cholesterol and fasted blood glucose compared to their control littermates. Therefore, small molecule activators of SIRT1 could potentially be beneficial therapeutics in Type 2 diabetes (T2D) and inflammation. Previously we have reported on several series of SIRT1 activators (imidazo[1,2-*b*]thiazoles, oxazole[4,5-*b*]pyridines and thiazolo[5,4-*b*]pyridines). In this paper, we describe the synthesis, structure activity relationships and cellular activity of a distinct new class of 4-substituted benzimidazoles as SIRT1 activators. A representative analog is also shown to have oral anti-diabetic activity in the genetic *ob/ob* mouse model of diabetes.

MEDI 71

Synthesis and SAR of tricyclic isoquinoline derivatives as HCV NS3 protease inhibitors

Jie Chen⁽¹⁾, Jie.Chen@bms.com, 5 Research Parkway, Wallingford CT 06492, United States ; **Li-Qiang Sun**⁽¹⁾; **Fei Yu**⁽¹⁾; **Guangzhi Zhai**⁽¹⁾; **Dennis Hernandez**⁽¹⁾;

Amy K Sheaffer⁽¹⁾; Jacques Friborg⁽¹⁾; Diana Barry⁽¹⁾; Heather Mulherin⁽¹⁾; Min S Lee⁽¹⁾; Fiona McPhee⁽¹⁾; Jay O Knipe⁽¹⁾; Kathy Mosure⁽¹⁾; Nicholas A Meanwell⁽¹⁾; Paul M Scola⁽¹⁾. (1) Research and Development, Bristol-Myers Squibb, Wallingford CT 06492, United States

Hepatitis C virus (HCV) infects approximately 200 million people worldwide and 4 to 5 million cases in the United States. HCV is one of the most common causes of liver disease and has emerged as a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplants. The current standard of care for HCV chronically infected patients is a combination of pegylated interferon- α and ribavirin, neither of which are specific antiviral agents, that exhibits limited efficacy and significant side effects. Therefore, there is a clear unmet medical need to develop HCV specific antiviral agents. The HCV NS3/4A protease is essential for viral replication and this target for anti-HCV therapy has been validated in clinical trials. As part of a continuing effort toward lead optimization, we have designed and synthesized a series of tricyclic isoquinoline derivatives as HCV NS3 protease inhibitors. Details of the preparation and SAR will be described.

MEDI 72

In vitro and in vivo biological annotation of a novel B-RAF inhibitor amenable for clinical evaluation against B-RAF(V600E)-harboring human tumors

Yanbin Liu⁽¹⁾, yliu@arqule.com, 19 Presidential Way, Woburn MA 01801, United States ; **Jean-Marc Lapierre**⁽¹⁾, jmlapierre@arqule.com, 19 Presidential Way, Woburn MA 01801, United States ; **Chang-Rung Chen**⁽²⁾; **Jeff Szwaya**⁽²⁾; **Erin Chiesa**⁽³⁾; **Cathy Bull**⁽³⁾; **Edward Chang**⁽⁴⁾; **Carol Waghorne**⁽⁴⁾; **Jianmin Mao**⁽⁵⁾; **Deirdre Lowe**⁽⁵⁾; **Khanh Nguyen**⁽¹⁾; **Erika Volckova**⁽¹⁾; **Yunxia Wang**⁽⁶⁾; **Terence Hall**⁽⁶⁾; **Ron Savage**⁽⁶⁾; **Dennis France**⁽²⁾; **Mark A. Ashwell**⁽¹⁾. (1) Department of Chemistry, ArQule Inc., Woburn MA 01801, United States (2) Department of Molecular Oncology, ArQule Inc., Woburn MA 01801, United States (3) Department of In vivo Pharmacology, ArQule Inc., Woburn MA 01801, United States (4) Department of Biomarker Research, ArQule Inc., Woburn MA 01801, United States (5) Department of Pharmaceutical Development, ArQule Inc., Woburn MA 01801, United States (6) Department of Preclinical Development & Clinical Pharmacology, ArQule Inc., Woburn MA 01801, United States

An activating somatic mutation in B-RAF kinase (V600E) is found in approximately 70% of melanomas, 50% of papillary thyroid cancers and 10% of colon cancers, fueling interest in B-RAF (V600E) as a therapeutic target for cancer treatment. We have previously described a novel class of RAF inhibitors with initial pre-clinical profiling. This compound class has been optimized for solubility, ADME properties and oral bio-availability resulting in ARQ 736, being selected as a candidate to advance into clinical testing. ARQ 736 is a potent and

extremely selective kinase inhibitor, with only 11 of 272 human kinases being inhibited within 100-fold of the IC₅₀ against B-RAF. ARQ 736 was found to be inactive against vascular endothelial growth factor receptor 2 (VEGFR2 or KDR). In cellular pharmacodynamic assays, ARQ 736 inhibited the MAPK pathway potently in a rapid and durable fashion. *In vivo* acute pharmacodynamic, efficacy and PK data will be presented.

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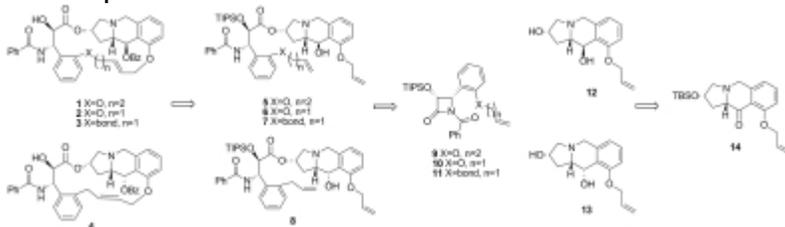
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MEDI 73

Design and synthesis of simplified paclitaxel analogs based on the T-taxol bioactive conformation

Jielu Zhao⁽¹⁾, zhao05@vt.edu, 12000 Cardinal Ct Apt B, Blacksburg VA 24060, United States ; **Susan Bane**⁽²⁾; **James P. Snyder**⁽³⁾; **Haipeng Hu**⁽³⁾; **David G. I. Kingston**⁽¹⁾; **Kamalika Mukherjee**⁽²⁾. (1) Department of Chemistry, Virginia Polytechnic Institute & State University, Blacksburg VA 24061, United States (2) Department of Chemistry, State University of New York at Binghamton, Binghamton NY 13902, United States (3) Department of Chemistry, Emory University, Atlanta GA 30322, United States

The simplified paclitaxel analogs **1-4** have been designed as compounds which should bind to tubulin, based on their similarity to the T-taxol conformation. The target compounds were synthesized by Grubbs' metatheses of compounds **5-8**, which were prepared by coupling β -lactams **9-11** with alcohols **12** and **13**. Compounds **12** and **13** were formed by reduction of the intermediate **14**, which was constructed by coupling a *cis*-4-hydroxyproline derivative with 3-(allyloxy)-2-iodobenzaldehyde. The syntheses of **1-4** together with their biological data will be presented.



MEDI 74

Discovery of novel 2,4,6-trisubstituted pyrimidine and pyridine based SIRT1 activators

Karsten J. Koppetsch⁽¹⁾, kkoppetsch@sirtrispharma.com, 200 Technology Square, Suite 300, Cambridge MA 02139, United States ; **Christopher J. Oalman**⁽¹⁾; **Bruce Szczepankiewicz**⁽¹⁾; **Chi B. Vu**⁽¹⁾; **Giovanna Gualtieri**⁽¹⁾; **Rebecca L. Casaubon**⁽¹⁾; **Jeremy S. Disch**⁽¹⁾; **Amy V. Lynch**⁽¹⁾; **Jeff Song**⁽¹⁾; **David J. Gagne**⁽¹⁾; **Angela Cote**⁽¹⁾; **Meghan Davis**⁽¹⁾; **Elden Lainez**⁽¹⁾; **Robert B. Perni**⁽¹⁾. (1) Sirtris, A GSK Company, Cambridge MA 02139, United States

SIRT1, an NAD⁺-dependent protein deacetylase, has been implicated as a key modulator in pathways downstream of calorie restriction that produce beneficial effects on metabolic parameters such as glucose and insulin homeostasis. Activation of SIRT1 has been shown to modulate insulin resistance, increase mitochondrial content and prolong survival in lower organisms and in mice on a high fat diet. We have identified novel small molecule activators of SIRT1 and here we present the SAR of pyridine and pyrimidine based analogs.

MEDI 75

Discovery of a new class of selective Chk1 "diazacarbazoles"

Joy Drobnick⁽¹⁾, drobnick.joy@gene.com, 1 DNA Way, South San Francisco CA 94080, United States ; Brent Appleton⁽¹⁾; Lorraine Axford⁽²⁾; Maureen Beresini⁽¹⁾; Brenda Burton⁽²⁾; Huifen Chen⁽¹⁾; David Clark⁽²⁾; Kevin Clark⁽¹⁾; Peter Crackett⁽²⁾; Charles Ellwood⁽²⁾; Emanuela Gancia⁽²⁾; Arunima Ganguli⁽²⁾; Matthew Gill⁽²⁾; Jennie Goldstein⁽²⁾; Simon Goodacre⁽²⁾; Joanne Hewitt⁽²⁾; David Hurst⁽²⁾; Sam Kintz⁽¹⁾; Peter Lockey⁽²⁾; Joe Lyssikatos⁽¹⁾; Sarah Major⁽²⁾; Calum McLeod⁽²⁾; David McNair⁽²⁾; Guillaume Medard⁽²⁾; Raman Narukulla⁽²⁾; Richard Newman⁽²⁾; Steve Sideris⁽¹⁾; Chris Weismann⁽¹⁾; Hazel Hunt⁽²⁾; Karen Williams⁽²⁾; Shiva Malek⁽¹⁾; Lewis Gazzard⁽¹⁾. (1) Department of Medicinal Chemistry, Genentech CA, United States (2) Argenta, United Kingdom

Checkpoint kinase 1 (Chk1) is a key mediator in the DNA damage-induced checkpoint network. Inhibiting this serine/threonine protein kinase can preferentially potentiate the efficacy of DNA-damaging agents against various tumors making Chk1 an attractive therapeutic target for cancer treatment. A high-throughput screening campaign led to identification of the diarylpyrazines as a promising lead series, providing micromolar activity against Chk1. Structure-based design around these leads led to the discovery of the diazacarbazole series of potent Chk1 inhibitors. One of the main challenges we initially faced was improving selectivity versus both kinases and non-kinases, in particular acetylcholinesterase (AChE). The structure-based evolution of this novel scaffold, together with efforts to circumvent AChE activity, will be presented.

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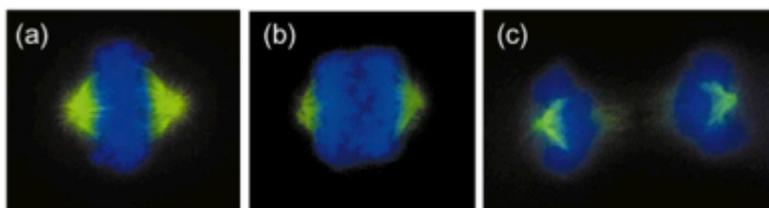
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MEDI 76

Phthalazinone pyrazoles as potent, selective and orally bio-available inhibitors of Aurora-A kinase

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The Aurora kinases (consisting of Aurora A, B and C) are a family of serine/threonine kinases believed to play a key role in the protein phosphorylation events that are essential for the completion of essential mitotic events. Aurora A localizes predominantly to the centrosomes (Figure 1) and is highly expressed in many tumor types. Human tumor cell lines depleted of Aurora A transcripts arrest in mitosis and leads to apoptosis of tumor cells



A novel series of low molecular weight inhibitors of Aurora A Kinase were identified. Optimisation of this inhibitor series was carried out culminating in the identification of a highly potent advanced lead series with a good pharmacokinetic profile that confers growth inhibition to tumor cells.

MEDI 77

Synthesis of novel osteogenic oxysterol activators of the Hedgehog signaling pathway

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Traditional orthopedic medicine treatment procedures for spinal fusion and non-union fractures have relied on osteogenic biologics that while successful in promoting new bone formation are restricted in clinical use due to safety and cost. To date, there are no anabolic small molecules approved for spinal fusions or non-union bone fractures. Recently, several naturally-occurring oxysterols were shown to play a critical role during the differentiation of pluripotent mesenchymal stem cells to osteoblasts through activation of the Hedgehog signaling pathway. Subsequent studies established the efficacy of specific oxysterols in stimulating bone formation in vivo. In search of new anabolic bone agents, we examined novel oxysterols in several cell lines for up-regulation of Hedgehog target genes and increased expression of osteogenic markers. Our efforts in the chemical synthesis and biological evaluation of these compounds will be presented.

MEDI 78

Putative exosite targeting for optimization of 4EGI-1, a PPI inhibitor and a potent anti-cancer agent

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Inhibition of a protein-protein interaction between eIF4E and eIF4G by a small molecule prevents the formation of the eIF4F complex, a rate limiting step in the translation initiation cascade that plays a critical role in the control of cell growth and malignant transformation. We have identified 4EGI-1 as a potent small molecule inhibitor of eIF4E/eIF4G interaction and demonstrated its anti-cancer activity in vitro and in animal models of human cancer. 4EGI-1 competes with peptide sequences derived from eIF4G and 4E-BP that bind to a hot spot on eIF4E. Targeting putative exosites on eIF4E by charged and hydrophobic moieties extending from 4EGI-1 presents one approach for lead optimization that may contribute to higher binding affinity and specificity. Herein, we report the synthesis of a series of exosite targeting 4EGI-1 analogs and their in vitro activities in translation initiation specific assays.

MEDI 79

Structure-based computational design of selective, small molecule PRMT5 inhibitors for experimental therapeutics of cancer: Protein modeling, virtual screening and lead validation

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Protein Arginine methyltransferases (PRMTs) are epigenetic enzymes that perform post-translational modification of histone proteins and thus contribute to transcriptional repression. Recent investigations have shown that PRMT5 is overexpressed in a variety of cancer cells. The objective of our study is to discover inhibitors for this enzyme class and thus, to develop drugs capable of targeting PRMT5 overexpression in aggressive hematologic and solid tumors.

We employed structure-based *in silico* drug design methods together with *in vitro* experiments to identify candidate compounds to inhibit PRMT5 enzyme activity. A virtual screening of ChemBridge CNS-Set™ library was carried out with PRMT5 model. Out of the eight compounds tested for bioactivity, three were capable of inhibiting H4R3Me2 arginine methylation. One appeared to demonstrate the best efficacy in reducing the proliferation of the U1242 astrocytoma cell line. A dose response was also observed with cellular proliferation and the degree of H4R3 methylation.

MEDI 80

***In vitro* and *in vivo* studies on the effectiveness of free drug and nanoparticle encapsulated silver carbene complexes on H460 lung cancer**

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Approximately 30% of all diagnosed cancer is specific to the lung. Currently the mortality rate of patients afflicted with this disease stands at greater than 85%. The aim of this study was to evaluate the effectiveness of silver carbenes on NCI-H460, a non small cell lung cancer. MTT assays were conducted to determine IC₅₀ values of both the free drugs and drugs encapsulated in nanoparticles. Compounds that showed the lower IC₅₀ values were then used in the treatment of an orthotopic mouse model. BALB/c nude mice

were implanted intrabronchially with NCI-H460 and then aerosol delivered daily for up to 36 days. Tumor sizes were then compared with controls to determine the compounds effectiveness *in vivo*.

MEDI 81

Design, synthesis, and pharmacological evaluation of multireceptor modulating agents as potential atypical antipsychotics

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Atypical antipsychotic drugs have fewer extrapyramidal side effects (EPS) than neuroleptics largely due to their lower affinity to dopamine D₂ receptors, and their ability to modulate serotonin receptor subtypes. Haloperidol is an effective neuroleptic with EPS attributed in part to its quaternary pyridinium (BCPP⁺) and 3-(4-Fluorobenzoyl) propionic acid (FBPA) metabolites. In this study, we designed and synthesized haloperidol analogues with altered butyrophenone and arylocycloalkylamines to resist biotransformation to these metabolites, and with activity at D₂ and 5HT receptors. The structures were confirmed by NMR spectra and elemental analysis. Binding assays and pharmacological evaluations indicate that several target compounds displayed clozapine-like binding affinity, while a homopiperazine congener has an affinity profile at DA and 5HT receptor subtypes consistent with those of atypical antipsychotics. The design, synthesis and the pharmacological evaluations would be presented.

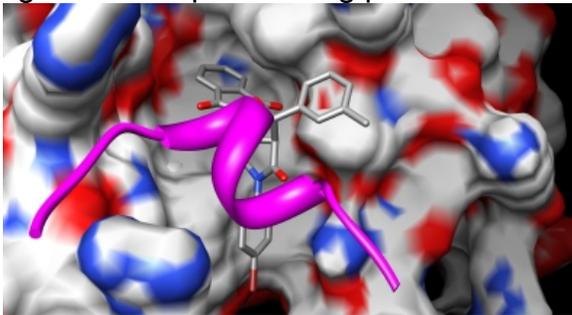
MEDI 82

Selective small molecules targeting G-protein interactions to combat cancer metastasis

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Heterotrimeric G proteins act as molecular switches that modulate numerous cellular signaling pathways. G protein signaling is initiated and mediated by the binding of guanine nucleotide Exchange Factors (GEFs) to inactive G-proteins which accelerates the rate of exchange of GDP for GTP. G-alpha proteins have

been demonstrated to enhance Akt activation, remodel the actin cytoskeleton, and mediate cell migration, making them a desirable pharmacological target for inhibiting cancer metastasis. A GDP-selective G-alpha i binding peptide, KB-752, has previously been demonstrated to enhance spontaneous nucleotide exchange of G-alpha i subunits. Several specific contacts between a conserved TWXE/DFL and Galphai1 have been shown to be critical for nucleotide exchange. An intramolecular hydrogen bonding network within the alpha-helical TWXE/DFL motif involving threonine 4 (T4) and aspartate 7 (D7) serve to orient both tryptophan (W5) and phenylalanine (F8) toward the G alpha binding face of the peptide, burying W5 within a hydrophobic pocket formed by F215, L249, and I253 of Galphai1, while F8 likewise resides within a hydrophobic environment established by W211, I212, and F215 of Galphai1. Here, we present the key structural differences within the G alpha proteins and their implications on the specificity of interactions. Using the nucleotide bound G-alpha models generated; we performed in silico screening against a database of approximately five million commercially available small organic molecules and selected top ligand for each binding partner. A docked pose of KB-peptide and top ranking small molecular ligand in G-alpha binding pocket is illustrated in the figure.



These molecules were structurally and functionally diverse from the G-protein ligands designed and tested till date. The selective targeting G-protein interactions identified in the study would not only lead to novel anti-cancer drugs but could also provide chemical probes for in vivo and in vitro studies to determine the biochemical mechanisms involved in cancer metastasis.

MEDI 83

Synthetic strategies for developing multivalent nitric oxide donors

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Nitric oxide (NO) is a multifaceted bioregulatory agent. Diazeniumdiolate prodrugs are efficient sources of NO, and have significant biological applications. We are developing methods for generating multivalent prodrugs (those containing two or more diazeniumdiolate groups per prodrug molecule) with the aim of improving efficacy and selectivity of action on the part of these NO donors. Amongst several strategies, *bis*-amines were transformed to *bis*-diazeniumdiolate anions, which were further converted to their O^2 -protected derivatives. These *bis*-prodrugs could release up to 4 moles of NO. In another approach, the carboxylic acid group of diazeniumdiolated proline or sarcosine was coupled with diamines like ethylenediamine and lysine. Another set of bivalent diazeniumdiolates was prepared by 'Click reaction' of *bis*-azides with suitably functionalized terminal alkyne prodrugs. The ruthenium carbene-catalyzed cross metathesis reaction was also utilized to develop multivalent NO-donors. This poster will elaborate on our efforts in developing novel multivalent NO-releasing drug candidates.

MEDI 84

Synthesis of carbon-11-labeled casimiroin analogs as new potential PET agents for imaging of quinone reductase 2 and aromatase expression in cancer

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The enzymes quinone reductase 2 (QR2) and aromatase are associated with a number of neurological diseases such as Parkinson's disease and schizophrenia, and cancer diseases such as breast cancer. Recently a series of carimiroin analogues has been developed by Maiti et al. as new QR2 and aromatase inhibitors, potential chemopreventive or chemotherapeutic agents. QR2 and aromatase provide attractive targets for the development of both therapeutic agents for use in cancer treatment and diagnostic agents for use in the biomedical imaging technique positron emission tomography (PET). This study was designed to develop carbon-11-labeled carimiroin analogues as new PET agents for imaging of enzymes QR2 and aromatase expression in cancer. Carimiroin (6-methoxy-9-methyl-[1,3]dioxolo[4,5-*h*]quinolin-8(9*H*)-one) and its precursor 6-hydroxy-9-methyl-[1,3]dioxolo[4,5-*h*]quinolin-8(9*H*)-one, carimiroin analogue 5,6,8-trimethoxy-1,4-dimethylquinolin-2(1*H*)-one and its precursor 5,6,8-trimethoxy-4-methylquinolin-2(1*H*)-one, and carimiroin analogues 8-methoxy-1,4-dimethylquinolin-2(1*H*)-one, 6,8-dimethoxy-1,4-dimethylquinolin-2(1*H*)-one, 5,8-dimethoxy-1,4-dimethylquinolin-2(1*H*)-one and their precursors 8-methoxy-4-methylquinolin-2(1*H*)-one, 6,8-dimethoxy-4-methylquinolin-2(1*H*)-one, 5,8-dimethoxy-4-methylquinolin-2(1*H*)-one, were synthesized from the starting materials 2,3-dihydroxybenzoic acid, 2,4,5-trimethoxybenzoic acid, and 2-

methoxyaniline, 2,4-dimethoxyaniline, 2,5-dimethoxyaniline, respectively, in multiple steps with moderate to excellent yields. The target tracers, [¹¹C]carimiroin (6-[¹¹C]methoxy-9-methyl-[1,3]dioxolo[4,5-*h*]quinolin-8(9*H*)-one) and carbon-11-labeled carimiroin analogues 5,6,8-trimethoxy-1-[¹¹C]methyl-4-methylquinolin-2(1*H*)-one, 8-methoxy-1-[¹¹C]methyl-4-methylquinolin-2(1*H*)-one, 6,8-dimethoxy-1-[¹¹C]methyl-4-methylquinolin-2(1*H*)-one, and 5,8-dimethoxy-1-[¹¹C]methyl-4-methylquinolin-2(1*H*)-one, were prepared from their corresponding precursors with [¹¹C]methyl triflate ([¹¹C]CH₃OTf) under basic conditions (NaH) through *N*-[¹¹C]methylation and isolated by semi-preparative HPLC method in 40-50% radiochemical yields decay corrected to end of bombardment (EOB), based on [¹¹C]CO₂, and 111-185 GBq/μmol specific activity at the end of synthesis (EOS).

MEDI 85

Property based optimization of lactam based histone deacetylase (HDAC) inhibitors

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Histone deacetylase(HDAC) and histone acetyltransferase(HAT) involved chromatin remodelling and epigenetic gene expression. HDACs are associated with carcinogenesis and have been considered as promising targets for anti-cancer chemotherapy. HDAC inhibitors, are developed, showed inhibition of several tumor growth and cell differentiation. Recently, SAHA(Zolinza, Vorinostat, 2006) and depsipeptide (Istodax, Romidepsin, 2009) are approved US FDA for treatment of cutaneous T-cell lymphoma(CTCL).

We have designed and prepared the series of novel δ-lactam based HDAC inhibitors and have evaluated their anti-proliferative activities *in vitro* and *in vivo* levels. Among these HDAC inhibitors, KBH-A118 revealed that it showed the potent biological and pharmacological profiles for an anti-cancer agent. The pharmacokinetic profiles, however, showed the low profiles. We here report optimization process to improve microsomal stability by introducing para- and meta- substituent on aromatic ring and reducing carbon chain length. The designed analogues were also *in silico* using pre-ADME program for the efficient discovery.

MEDI 86

Discovery of potent imidazo[1,2-*a*]pyrazine Aurora kinase inhibitors

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Aurora kinases are required for orderly progression of cells through mitosis. Inhibition of these kinases by siRNA or small molecule inhibitors results in aberrant endoreduplication and cell death. The synthesis and structure activity relationships (SAR) of novel, potent imidazo[1,2-a]pyrazine-based Aurora kinase inhibitors are described. The X-ray crystal structure of an imidazo[1,2-a]pyrazine Aurora inhibitor is disclosed. Compound **25** was identified as good lead compound with an attractive *in vitro* DMPK profile.

MEDI 87

Design, synthesis and biological evaluation of pemetrexed(PMX) homologs for folate receptor targeting multiple enzyme antifolates

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The two major hurdles in cancer chemotherapy are the inability of the chemotherapeutic agent to selectively target tumor cells resulting in toxicity and tumor cell resistance common to mono-targeted therapy. The multiple enzyme targeted anticancer drug pemetrexed (PMX) suffers from dose-limiting toxicity due to its transport by reduced folate carrier (RFC) which is ubiquitously expressed in normal cells. We recently reported a series of 6-substituted pyrrolo[2,3-d]pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC₅₀ values. GARFTase was confirmed as the target enzyme and no DHFR or TS inhibitory activity was found for these compounds. In an attempt to determine if increasing the side chain length of PMX (5-regioisomers of our 6-substituted compounds) would maintain the multitarget attributes of PMX and provide the selectivity of FR over RFC of our 6-substituted compounds, we designed and synthesized a series of classical 5-substituted pyrrolo[2,3-d]pyrimidines. The synthesis and evaluation of these compounds as substrates for folate transporters RFC, FR α , FR β and PCFT (proton coupled folate transporter) and as potent inhibitors of TS (thymidylate synthase), DHFR

(dihydrofolate reductase) and GARFTase (glycinamide ribonucleotide formyl transferase) will be presented.

MEDI 88

Design, synthesis, and testing of orthoamido diphenylamines as inhibitors of MEK5

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The mitogen activated protein kinase (MAPK) pathways mediate appropriate intracellular responses to extracellular events. The phosphorylation of unique isoforms of ERK

by its matched MEK is one of the most specific events in the signaling cascade. The kinase MEK5 is activated by

mitogens and is up regulated in specific tumor types including breast and prostate

cancers. A series of orthoamido

diphenylamines were designed using a MEK5 homology model, synthesized, and assayed for inhibition of MEK5 mediated phosphorylation of ERK5.

MEDI 89

2-Desamino and 2-methyl-6-substituted pyrrolo[2,3-d]pyrimidine classical antifolates as selective folate receptor substrates, glycinamide ribonucleotide formyltransferase inhibitors and antitumor agents

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The important role of reduced folates in one-carbon transfer reactions has made folate metabolism an attractive target in cancer chemotherapy for decades.

Clinically used antifolates enter cells via folate uptake systems, such as reduced folate carrier (RFC), folate receptors (FRs), and proton-coupled folate transporter (PCFT). Toxicity of clinically used antifolates is due to their lack of selectivity for tumor cells, since these antifolates are transported by RFC which occurs in normal as well as tumor cells. FR is usually not expressed in normal cells. However, FR is expressed in some tumor cells, such as ovarian, breast etc. Thus specific FR targeted agents that also possess cytotoxic activity without transport by RFC circumvent the major toxicities of currently used antifolates that all use RFC for transport. The synthesis and biological activity of the 2-desamino and 2-methyl-6-substituted pyrrolo[2,3-*d*]pyrimidine antifolates were designed to evaluate the importance of the 2-amino group for transport by RFC, FR, and /or PCFT as well as for inhibition of folate metabolizing enzymes. This report will present the design, synthesis and evaluation of the title compounds including a two digit nanomolar IC₅₀ against KB tumor cells in culture.

MEDI 90

Synthesis and SAR of diaminopyrimidines as c-Met inhibitors

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The HGF-c-Met signaling axis is an important paracrine mediator of epithelial-mesenchymal cell interactions involving the regulation of multiple cellular activities including cell motility, mitogenesis, morphogenesis and angiogenesis. Dysregulation of c-Met signaling (e.g., overexpression or increased activation) is associated with the development of a wide range of tumor types; thus, inhibiting the HGF-c-Met pathway is predicted to lead to anti-tumor effects in many cancers. Elaboration of a 2-arylamino-pyrimidine scaffold led to a series of potent c-Met inhibitors bearing a C4-2-amino-N-methylbenzamide group. Specifically, a series of C2-aminobenzazepine and benzazepinone analogs demonstrated potent inhibition of c-Met in enzymatic and cellular assays. Kinase selectivity could be tuned by varying the nature of the alkyl group on the benzazepine or benzazepinone nitrogen.

MEDI 91

Identification of potential proteins targets of quercetin inhibition of HSP-70 induction with a biotin-quercetin photoaffinity agent

Rongsheng E Wang⁽¹⁾, rwang@artsci.wustl.edu, Campus Box 1134, 1 brookings drive, St Louis MO 63130, United States ; Clayton R Hunt⁽²⁾; John Stephen

Taylor⁽¹⁾. (1) Department of chemistry, Washington University in St Louis, St Louis MO 63130, United States (2) Department of Cancer Biology, Washington University Medical School, St Louis MO 63108, United States

Heat shock protein 70 (HSP70) is a chaperone that mediates intra-cellular protein folding and thereby protects cells from environmental stress. Tumor and cancer cells that over express HSP70 are found to be multidrug resistant and thermo tolerant, which diminish the effectiveness of radio-sensitization therapy and chemotherapy. Among small molecule inhibitors, various quercetin derivatives were previously found by us to be potential anti-HSP70 drug candidates, though their true protein targets remain unclear. To determine their possible targets, we developed a synthetic route to a biotin-quercetin conjugate (BioQ) as a photoaffinity protein pull down probe. We found that proteins could be photocrosslinked to BioQ with a known quercetin binding protein and from cells. Through LC-MS/MS-Mascot proteomic analysis, identification of target proteins and specific crosslinking sites has been achieved that could lead to the rational design of better inhibitors.

MEDI 91

Identification of potential proteins targets of quercetin inhibition of HSP-70 induction with a biotin-quercetin photoaffinity agent

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MEDI 92

Development of polyamides as gene inhibitors of heat shock protein 70 expression

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Chemical inhibitors of heat shock protein 70 (HSP70) induction have great potential in antitumor applications such as radiosensitization and chemotherapy. While our attempts to use antisense agents to inhibit HSP70 expression failed, we show that pyrrole-imidazole polyamides can bind effectively to the heat shock promoter and interfere with binding of heat shock transcription factor 1 and subsequent expression of HSP70. Linear polyamides of different designs were synthesized by solid-phase synthesis and their binding affinities to the heat shock element were evaluated by Dnase I footprinting. Their ability to block heat shock factor 1 binding was demonstrated by an *in vitro* gel shift assay and the most effective polyamide was shown to decrease HSP70 expression to 55% of its normal level in Jurkat cells by western blot assay.

MEDI 93

Rational design of disubstituted triazole conjugated acridines with high selectivity for the human parallel telomeric quadruplex

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A large number of ligands have been reported to inhibit telomere maintenance by their effective stabilisation of quadruplex DNA.

We have demonstrated with docking studies, that carefully designed disubstituted triazole conjugated acridines bind with high selectivity to a human quadruplex DNA sequence, but not to the c-kit quadruplexes or to duplex DNA. Their synthesis has been achieved using click-chemistry; variations in the side chains lengths as well as in the nature of the terminating bases have been investigated for SAR.

The two most potent ligands have been evaluated for quadruplex selectivity by a FRET-based binding and competition assay. Circular dichroism studies have been carried out as a proof of concept experiment, to support structural information. Both lead compounds show effects on a panel of cancer cell lines

but not on a normal fibroblast cell line and one in particular has been shown to inhibit telomerase enzyme activity.

MEDI 93

Rational design of disubstituted triazole conjugated acridines with high selectivity for the human parallel telomeric quadruplex

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A large number of ligands have been reported to inhibit telomere maintenance by their effective stabilisation of quadruplex DNA.

We have demonstrated with docking studies, that carefully designed disubstituted triazole conjugated acridines bind with high selectivity to a human quadruplex DNA sequence, but not to the c-kit quadruplexes or to duplex DNA. Their synthesis has been achieved using click-chemistry; variations in the side chains lengths as well as in the nature of the terminating bases have been investigated for SAR.

The two most potent ligands have been evaluated for quadruplex selectivity by a FRET-based binding and competition assay. Circular dichroism studies have been carried out as a proof of concept experiment, to support structural information. Both lead compounds show effects on a panel of cancer cell lines but not on a normal fibroblast cell line and one in particular has been shown to inhibit telomerase enzyme activity.

MEDI 94

Synthesis and characterization of rigidified 4EGI-1 mimetics that block protein-protein interaction, inhibit translation initiation, and have anticancer activity

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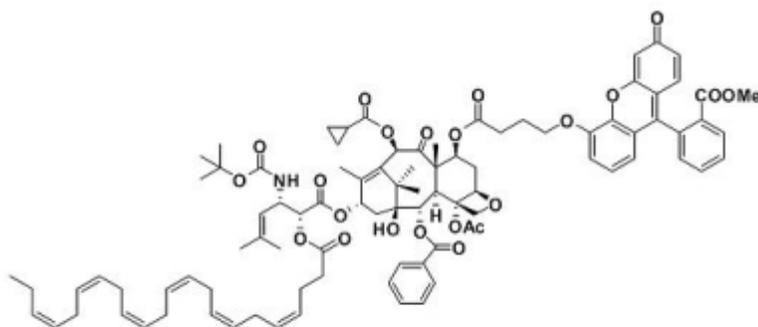
Inhibition of translation initiation is recognized as a novel paradigm for targeting cancer cells *in vitro* and *in vivo*. We have identified a small molecule 4EGI-1 as an inhibitor of translation initiation and an efficacious anti-cancer agent in xenograft animal models of human cancer. It disrupts a protein-protein interaction between eIF4E, a cap-mRNA binding protein, and eIF4G, a scaffolding protein, blocking the formation of the critical eIF4F complex and affects preferentially translation of mRNAs that regulate expression of genes involved in cell growth, proliferation, differentiation and apoptosis. In an effort to avoid the potential *cis-trans* isomerization around the hydrazone moiety we have designed, synthesized and tested rigidified 4EGI-1 mimetics locked in either Z- or E-configuration. We will report on our efforts to develop 4EGI-1 mimetics in which the 2-hydrazono-3-phenylpropanoic acid substructure was replaced with mimetics such as 1-phenylpiperidine-2-carboxylic acid, tetrahydroisoquinoline-3-carboxylic acid and indazole-3-carboxylic acid scaffolds.

MEDI 95

Novel fluorescently labeled omega-3 fatty acid-taxoid conjugates

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It has been shown that certain polyunsaturated fatty acids (PUFAs), especially omega-3 fatty acids, are readily taken up by tumors cells as biochemical precursors. This observation has led to the study on a range of anticancer-PUFA conjugates with substantially higher antitumor activities than their corresponding free states, while also providing lower systemic toxicity. We linked omega-3 PUFAs to highly potent 2nd-generation taxoids, which have exhibited remarkable efficacy *in-vivo* against several paclitaxel-resistant tumor xenografts in mice. However, despite this progress, investigation into the selectivity of omega-3 PUFAs for particular cancer cell types has not been studied in detail. Therefore, we synthesized novel fluorescently labeled omega-3 PUFAs and omega-3 PUFA-taxoid conjugates as probes for this investigation, utilizing confocal fluorescence microscopy as well as flow cytometry. The synthesis and the use of these probes as molecular tools to investigate their cancer cell selectivity will be discussed.



DHA-SB-T-1214-Fluorescein

MEDI 96

Discovery of TAK-700, a naphthylmethylimidazole derivative, as a highly selective, orally active 17, 20 lyase inhibitor for prostate cancer

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As endogenous androgens produced in the adrenal gland and possibly prostate cancer cells themselves have been recently recognized to play an important role in progression of castration-resistant prostate cancer, the key enzyme involved in their biosynthesis, 17, 20 lyase, can be considered as a therapeutic target to delay prostate cancer progression. In our research on novel nonsteroidal 17, 20 lyase inhibitors, we developed *de novo* designs based on the enzyme's substrate, 17 α -hydroxypregnenolone. Amongst several designed compounds, the naphthylmethylimidazole derivative was identified as a promising lead compound for further development. Optimization of the functional groups on the naphthylmethylimidazole scaffold led to the discovery of TAK-700 as a highly selective and orally active 17, 20 lyase inhibitor. The androgen synthesis inhibitor TAK-700 was selected as a clinical candidate and phase II evaluation of TAK-700 is currently ongoing. The details of design, synthesis, and biological activities of the naphthylmethylimidazole derivatives will be presented.

MEDI 96

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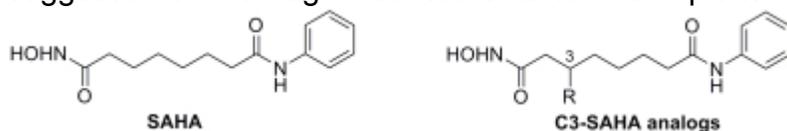
MEDI 97

Structural requirements of histone deacetylase (HDAC) inhibitors: Suberoyl anilide hydroxamic acid (SAHA) analogs modified at the C3 position

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HDAC proteins are targets for drug design towards the treatment of cancers. Several HDAC inhibitors, such as SAHA, are in or have cleared clinical trials and have emerged as anti-cancer drugs. We synthesized several libraries of small molecule HDAC inhibitors based on SAHA to understand the structural requirements of inhibitory potency. SAHA analogs functionalized at the C3 position (C3-SAHA analogs) near the metal binding hydroxamic acid displayed decreased inhibitory activity compared to SAHA. The most potent compound

contained a methyl group at the C3 position and displayed 3.9-fold decreased activity. Interestingly, the ethyl-substituted analog displayed 12-fold selectivity for HDAC6 over HDAC3. The potency and selectivity of the C3-SAHA analogs suggest that linker region substituents can be exploited in future drug design.



MEDI 98

Antagonism of the Bak–Bcl-xL complex by α -helix mimetics of varying curvatures

Steven Fletcher⁽¹⁾, sfletche@rx.umaryland.edu, 20 Penn Street, HSFII, Room 633, Baltimore MD 21201, United States . (1) Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore MD 21201, United States

Protein–protein interactions remain a daunting target for small molecules due to their large interfacial areas and often non-contiguous contact points. Nevertheless, considerable success in this area has been achieved through mimicry of the key α -helical domains found at the protein–protein interface. In particular, an oligoamide-foldamer strategy, with *ortho*-substituted alkoxy pyridine repeating subunits, identified low micromolar inhibitors of the Bak–Bcl-xL protein–protein interaction, an important anti-cancer target, through effective mimicry of the Bak BH3 α -helical peptide. Due to the pre-organizing, bifurcated hydrogen-bonds between the inter-subunit amide NH and the ether oxygen and pyridine nitrogen of adjacent subunits, the scaffold backbone adopts a curved structure. In an iterative strategy, the pyridine rings have been replaced with benzene rings to reduce the degree and location of curvature of the α -helix mimetic scaffold, and the impact of these structural modifications will be related to the antagonism of the Bak–Bcl-xL complex.

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MEDI 99

Anticancer properties of gold(I)-N-heterocyclic carbene complexes and their silver(I) precursors

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Several silver(I)-N-heterocyclic carbene (NHC) complexes were synthesized with varying atoms at the 4- and 5-positions of the imidazolyl ring. The corresponding gold(I)-NHC complexes were generated by silver transmetalation. The anticancer properties of these complexes were explored.

MEDI 100

Development of small molecule protein lysine methyltransferase G9a inhibitors

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Protein lysine methyltransferase (PKMT) G9a, a H3K9 methyltransferase, is over expressed in human cancers and knockdown of G9a inhibits cancer cell growth. Despite evidence that PKMTs play an important role in the development of various human diseases, only a handful of PKMT inhibitors have been reported. Thus, high quality small molecule PKMT inhibitors are needed to serve as research tools for studying the biological function of PKMTs. SAR exploration of the 2,4-diamino-6,7-dimethoxyquinazoline template led to the discovery of UNC0224 as a potent and selective inhibitor of G9a. The first cocrystal structure of G9a with a small molecule inhibitor (UNC0224) was obtained, enabling structure-based design of novel PKMT inhibitors. Structural insights led to the optimization of the 7-dimethylaminopropoxy side chain, resulting in the discovery of the most potent G9a inhibitor so far, UNC0321. The SAR exploration leading to the discovery of UNC0321 and other potent PKMT inhibitors will be presented.

MEDI 101

From isothiazole to thiophene and thiazole: A bioisosteric approach to the discovery of potent imidazo[1,2-a]pyrazines as Aurora kinase inhibitors

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The Aurora kinases are serine/threonine kinases that regulate key mitotic events and are emerging as attractive targets for anti-cancer drug development. Our continued effort towards development of the imidazo[1,2-a]pyrazine scaffold as Aurora kinase inhibitors is described. Bioisosteric approach was applied to optimize the 8-position of the scaffold. The synthesis and structure-activity relationships (SAR) will be discussed.

MEDI 102

SAR of various Aurora selective chemotypes

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Glaser⁽¹⁾; Terry J Magoc⁽¹⁾; kent D Stewart⁽¹⁾; Paul Tapang⁽¹⁾; Ru-Qi Wei⁽¹⁾; Michael Michaelides⁽¹⁾. (1) R47J, Abbott Laboratories, Abbott Park IL 60064, United States

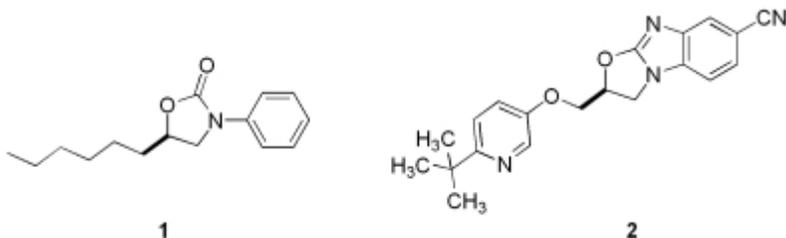
Aurora kinases consisting of Aurora A, Aurora B and Aurora C play critical roles during mitosis in chromosome segregation and cell division. Aurora Kinases are over-expressed in a variety of human tumors and increased expression correlates with advanced clinical progression in several tumor types. The inhibition of Aurora kinases is regarded as a promising approach for the development of anticancer drugs. We have designed and developed several structurally unique ATP-competitive templates, aminobenzoisoxazole, aminoindazole, aminoisothiazole and pyrrolotriazine for Aurora kinase inhibition. The synthesis, SARs, *in vitro* and *in vivo* activities of these novel inhibitors will be discussed.

MEDI 103

Development of oxazolidinone and oxazolobenzimidazole positive allosteric modulators for the treatment of Schizophrenia

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(1) Department of Medicinal Chemistry, Merck & Co., Inc., West Point Pennsylvania 19486, United States (2) Psychiatry Research, Merck & Co., Inc., West Point Pennsylvania 19486, United States (3) Department of In Vitro Sciences, Merck & Co., Inc., West Point Pennsylvania 19486, United States (4) Department of Central Pharmacology, Merck & Co., Inc., West Point Pennsylvania 19486, United States (5) Department of Drug Metabolism, Merck & Co., Inc., West Point Pennsylvania 19486, United States (6) Department of Automated Biotechnology, Merck & Co., Inc., West Point Pennsylvania 19486, United States

Herein we present the synthesis and development of positive allosteric modulators of mGluR2 designed for the treatment of schizophrenia. An N-aryl oxazolidinone HTS hit **1** was optimized to potent and selective oxazolobenzimidazole mGluR2 potentiator leads. SAR trends initially explored around the oxazolidinone hit were successfully transferred to the more potent, constrained oxazolobenzimidazole series. Metabolite identification was used to guide PK optimization and eventually led to the discovery of an oxazolobenzimidazole **2** that was shown to be orally bioavailable, brain penetrant, and efficacious in a preclinical model predictive of antipsychotic effects.



MEDI 104

2-Substituted benzimidazoles as metabotropic glutamate receptor-2 positive allosteric modulators: A hit to lead evaluation

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Modulation of the mGlu₂ receptor has recently been recognized as a mechanism for the treatment of neurodegenerative and neuropsychiatric disorders. A potential advantage of targeting a potentiator rather than a classical orthosteric agonist is mitigation of receptor desensitization from chronic dosing of an agonist. In addition, the allosteric binding sites on glutamate receptors within a group might be sufficiently different as to make subgroup selectivity potentially easier to achieve than for an orthosteric ligand.

A medium-throughput screening campaign of Lundbeck's compound collection identified the known antihistamine clemizole as a hit, with moderate functional efficacy and low glutamate potentiation in a calcium efflux assay. In order to explore the potential of this hit a systematic structure-activity relationship study was undertaken. The objective was to increase the functional efficacy explore chemical tractability and CNS exposure.

MEDI 105

Structure activity relationship studies of 4-(((3S,6S)-6-benzhydryltetrahydro-2H-pyran-3-yl)amino)methylphenol and its analogs: Development of novel triple uptake inhibitors as new generation antidepressants

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Selective and non-selective monoamine uptake inhibitors have been used widely in the treatment of depression. Antidepressants are thought to elicit their therapeutic effects by increasing extraneuronal concentrations of serotonin (5-HT) and norepinephrine (NE). Tricyclic antidepressants developed earlier acted by enhancing both 5-HT and NE transmissions. However, due to their non-specific interactions with multiple central nervous system (CNS) receptors, they exhibited unwanted side effects, which have limited their use in the clinics. Selective serotonin reuptake inhibitors (SSRIs), even though useful in many occasions, exhibits number of side effects including delayed onset of action. 5-HT and NE dual uptake inhibitors (SNRI) have proven to be more efficacious with relatively faster onset of action with reduced undesirable side effects. Recently, triple monoamine uptake inhibitors (TUI) have been implicated in potent antidepressant activity. This is due to the fact that additional dopaminergic component can effectively relieve depression by activating mesocorticolimbic dopaminergic pathways in the reward system. This can act to reduce anhedonia, which is associated with a deficit in dopaminergic transmission and is a central component to a depressive state of mind. In our effort to discover and develop novel molecules for interaction with multiple monoamine transporters, we have developed asymmetric di- and tri-substituted pyran derivatives. Uptake inhibition studies with all three monoamine transporters indicated variety of activities depending upon the nature of substitutions either on the pyran ring or on the N-benzyl moiety. Three different classes of molecules emerged from these studies and they are labeled as SNRI, NRI and TUI. Synthesis and SAR studies will be presented. Supported by MH84888.

MEDI 106

Probing S1' site of caspase-3: A new hope for mechanism based treatment of neurological disorders

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A review of published articles focusing on the S1' site of caspase-3 will be discussed. Although there are many pathways for the treatment of neurological disorders, but recent advances have shown that inhibitors both peptide and non-peptide based, binding specifically with S1' site of caspase-3, not only suppresses the activity of enzyme but also control selectivity over other

caspases. We and others have identified templates from which novel, potent, and selective small molecule antagonists of caspase-3 can be synthesized. This breakthrough holds the promise of being a big step forward in the treatment of Alzheimer's disease, Parkinson's disease, Stroke and other neurological disorders.

MEDI 107

SAR evaluation of fused heterocyclic quinolone carboxylic acid M₁ positive allosteric modulators

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The treatment of the neurodegenerative effects of Alzheimer's disease (AD) continues to be an important unmet medical need. One method to address this issue is through the activation of the M₁ muscarinic receptor. Non-selective muscarinic agonists have previously exhibited positive cognitive behavioral effects in AD patients; however, cholinergic adverse events, generally attributed to activation of the M₂ to M₅ sub-types, have restricted their use. A way to circumvent this selectivity issue is to identify compounds that would target an allosteric site on the M₁ receptor. We have previously reported the quinolone carboxylic acid BQCA as a highly selective M₁ positive allosteric modulator with good pharmacokinetic and in vivo properties. This presentation will discuss replacement of a biphenyl linkage leading to fused heterocycles such as naphthalene that are highly potent and CNS penetrant M₁ positive allosteric modulators.

MEDI 108

New aryl sulfonamides compounds as potent and selective 5-HT₆ receptor ligands

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Alzheimer's disease (AD) is a neurological condition characterized by a progressive decline in cognitive performance accompanied by behavioral and psychological syndromes. 5-hydroxytryptamine₆ (5-HT₆) receptor with its exclusively expression in CNS areas associated with learning and memory makes it a viable target for treating cognitive dysfunction. Blockade of 5-HT₆ receptors leads to improvement of cognitive performance in a wide variety of learning and memory paradigms.

Using a classical medicinal chemistry and scaffold hopping approach, a new series of compounds based on aryl sulfonamide scaffold have been identified. The compounds are highly potent (K_i = 0.5 to 15 nM) and selective over the several CNS relevant receptors. The lead compound is orally active in preclinical model of cognition like NORT and Water Maze at lower doses. Details on the synthesis, SAR, *in-vitro*, Pharmacokinetic and *in vivo* data will be discussed in the poster.

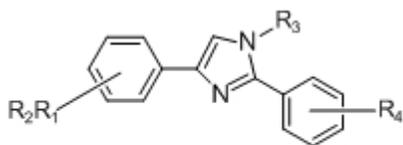
MEDI 109

Structure-activity relationships of 2,4-diphenyl-1H-imidazole analogs as CB2 receptor agonists for the treatment of chronic pain

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Cannabinoid receptors, a member of the superfamily of G protein-coupled receptor, mediate many of the CNS effects of Δ^9 -tetrahydrocannabinol (THC), the active component of marijuana. Up to now, the two cannabinoid receptors, CB1 and CB2, have been cloned and characterized. Although both receptors and their ligands have been implicated in pain perception, CB1 is expressed predominantly in the brain and its activation is linked to the CNS side effects. In contrast, CB2 is mainly found in the peripheral sensory afferent and spinal cord. Therefore selective CB2 agonists have potential to retain analgesic efficacy without the adverse effects associated with the CB1 receptors, such as catalepsy, ataxia, sedation, and undesired psychotropic effects.

After high-throughput screening of our chemical library, compounds with 2,4-diphenyl-1H-imidazole skeleton were identified to show high CB2 affinity and good selectivity against CB1. In this poster, we will present syntheses and structure activity relationships of a series of 2,4-diphenyl-1H-imidazole analogs (1). The biological data of some key compounds will be presented.



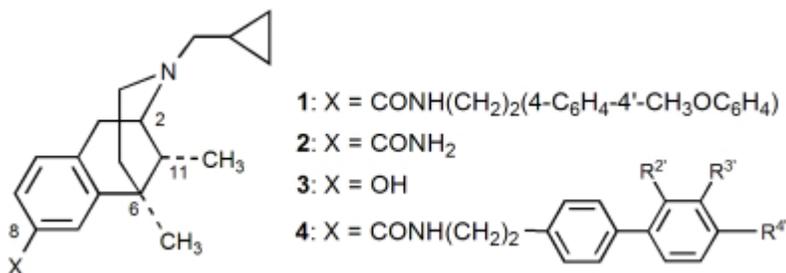
2,4-Diphenyl-1H-imidazole analogs (1)

MEDI 110

High affinity ligands for opioid receptors in the picomolar K_i range: N-(2-[1,1'-biphenyl]-4-ylethyl) analogs of 8-CAC

Mark P. Wentland⁽¹⁾, wentmp@rpi.edu, 110 8th Sreet, Troy NY 12180, United States ; **Jean M. Bidlack**⁽²⁾; **Dana J. Cohen**⁽²⁾; **Joseph M. Gargano**⁽¹⁾; **Xiangna Jia**⁽¹⁾; **Sunjin Jo**⁽¹⁾; **Melissa A. VanAlstine**⁽¹⁾. (1) Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy NY 12180, United States (2) Department of Pharmacology and Physiology, University of Rochester, Rochester NY 14642, United States

In order to further explore the SAR of our racemic lead opioid **1**, we have prepared and characterized the opioid receptor binding properties of analogues (**4**) having a variety of substituents in the distal phenyl ring. Compound **1** [K_i = 0.084 nM (mu)] is the N-[2-(4'-methoxy[1,1'-biphenyl]-4-yl)ethyl]-analogue of 8-carboxamidocyclazocine (8-CAC, **2**), a long-acting derivative in vivo of the well-known phenolic-OH-containing opioid cyclazocine (**3**). Binding affinities for the mu opioid receptor in the single-digit picomolar range were observed for the optically active (2*R*,6*R*,11*R*) 4'-OH [K_i = 4.9 pM (mu)] and 4'-NH₂ [K_i = 2.6 pM (mu)] derivatives as well as the racemic 3',4'-OCH₂O [K_i = 1.6 pM (mu)] and 4'-CHO [K_i = 2.0 pM (mu)] analogues. Our current understanding of the SAR will be described. (Supported by NIDA grants R01-DA012180 and K05-DA00360)



MEDI 111

Novel series of CB2 selective antagonists for the treatment of autoimmune disorders: Synthesis, functional evaluation and ligand-steered modeling

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The cannabinoid receptor CB2 has emerged as a new target for the treatment of pain without the CB1 mediated psychotropic side effects. Emerging evidence suggests that CB2 receptor blockage is a promising therapeutic approach for more effective treatment of autoimmune disorders. Two series of novel cannabinoid modulators have been synthesized using two different heterocyclic scaffolds. In vitro binding and functional assays were used to identify highly potent and selective CB2 agonists and antagonists. Fluorescent ligands were prepared based on the new analogs. More importantly, we were able to shift from CB2 agonist to CB2 antagonist functional activity by using a "chemical switch". Using the ligand-steered homology modeling method two models for CB2 were developed. The models successfully rationalized the structure-activity relationship data and predicted binding modes for both series of compounds. Details about the synthesis, CB1 and CB2 receptors structure-activity relationships, will be presented.

MEDI 112

7-Hydroxy-benzopyran-4-one derivatives: Discovery and structure-activity relationships of PPAR α and - γ (PPAR α and γ) dual agonists

Navnath Gavande⁽¹⁾, *nsgavande@hotmail.com, 902, 71-75 Regent street, Chippendale, Sydney NSW 2008, Australia* ; **Azadeh Matin**⁽¹⁾; **Moon S Kim**⁽¹⁾; **Noeris K Salam**⁽¹⁾; **Jane R Hanrahan**⁽¹⁾; **Rebecca H Roubin**⁽¹⁾; **David E Hibbs**⁽¹⁾. (1) *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The University of Sydney, Sydney NSW 2006, Australia*

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that function as ligand activated transcription factors regulating the expression of specific genes. Three PPAR isoforms are known to date, PPAR-alpha, gamma and delta/beta. PPAR-alpha is mainly found in liver, kidney, heart, muscle and adipose tissue and plays a critical role in fatty acid oxidation and lipoprotein metabolism. PPAR-gamma is predominately expressed in adipose tissue, macrophages, monocytes and intestinal cells, as well as, skeletal muscle and endothelium. The significant role of PPAR-gamma in lipid metabolism, adipogenesis, glucose homeostasis and insulin sensitization is well documented. Herein, we wish to present design, synthesis and *in vitro* bio-evaluation of a novel class of potential dual PPAR-alpha and -gamma agonists discovered

through a structure-driven design paradigm. A highly promising class of dual PPAR-alpha and -gamma agonists, 7-hydroxy-benzopyran-4 one that are structurally distinct from fibrates and TZDs, has been discovered. Novel lead PPAR ligands were identified from 'natraceuticals' and synthetic analogues. In total, 77 molecules including chalcones, flavones, flavanones, isoflavones and pyrazole derivatives were screened and structure activity relationship studies of the dual agonists undertaken.

MEDI 113

Synthesis and structure-activity relationships of 3-aminopyridazine derivatives of γ -aminobutyric acid acting as GABA_C (ρ) antagonists

Navnath Gavande⁽¹⁾, nsgavande@hotmail.com, 902, 71-75 Regent street, Chippendale, Sydney NSW 2008, Australia ; *Graham AR Johnston*⁽²⁾; *Jane R Hanrahan*⁽¹⁾; *Mary Chebib*⁽¹⁾. (1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The University of Sydney, Sydney NSW 2006, Australia (2) Department of Pharmacology, The University of Sydney, Sydney NSW 2006, Australia

γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and is essential for the overall balance between neuronal excitation and inhibition. GABA influences neurons via three major classes of receptors which are grouped on the basis of their subunit composition, gating properties and pharmacological profiles: GABA_A, GABA_B, and GABA_C (GABA ρ) receptors. The GABA rho receptor (GABA_C) is a homomeric ligand-gated chloride channel. Antagonists at these receptors improve learning and memory, and reduce the onset of myopia in animal models. The distinct anatomical areas of the central nervous system where the GABA rho receptor is located and its low expression levels compared to other subunits deem this receptor a strong target for developing agents that can improve learning and memory with a reduced risk of side-effects. Various 3-aminopyridazine derivatives which are extended analogues of γ -aminobutyric acid (GABA) act as a competitive GABA_A receptor antagonists. Specifically, gabazine (SR-95531) has showed high specificity and potency towards GABA_A receptors. Herein, we wish to present synthesis and structure-activity relationships of a series of 3-aminopyridazine derivatives of γ -aminobutyric acid (GABA) acting as GABA_C (ρ) antagonists. The pharmacophore design and synthesis of 3-aminopyridazine derivatives of GABA along with their in vitro bio-evaluation as GABA_C receptor antagonists will be presented.

MEDI 114

Design, synthesis and pharmacological evaluation of fluorescent GABA_C probes for receptor visualization and localization studies

Navnath Gavande⁽¹⁾, *nsgavande@hotmail.com*, 902, 71-75 Regent street, Chippendale, Sydney NSW 2008, Australia ; **Graham AR Johnston**⁽²⁾; **Jane R Hanrahan**⁽¹⁾; **Mary Chebib**⁽¹⁾. (1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The University of Sydney, Sydney NSW 2006, Australia (2) Department of Pharmacology, The University of Sydney, Sydney NSW 2006, Australia

Analogues of GABA have been investigated as potential drugs for the treatment of various disorders that have been implicated with GABA such as epilepsy, anxiety, depression and memory-related disorders associated with Alzheimer's disease and Schizophrenia. The GABA_C rho subunit forms a homomeric ligand-gated chloride channel. Antagonists at these receptors improve learning and memory, and reduce the onset of myopia in animal models. The distinct anatomical areas of the central nervous system where the GABA_C (rho) receptor is located and its low expression levels compared to other subunits deem this receptor a strong target for developing agents that can improve learning and memory with a reduced risk of side-effects.

The main aim of our study is to develop selective GABA_C receptor fluorescent probes without the drawbacks associated with radioligand studies, such as health and safety concerns, and the need for large numbers of cells with high receptor expression. To date, no labelled (either radioactive or fluorescent) GABA_C selective ligands have been developed as markers for visualization and localization of GABA_C receptor.

In this study, the fluorescent probes were designed based on the selective high-affinity antagonist 4-(aminocyclopent-1-enyl)-alkylphosphinic acid. A number of probes were synthesised incorporating various spacer linkages and fluorophores either at the amino terminal or the phosphinic acid ends. Potency and selectivity of the fluorescent probes were evaluated using 2-electrode voltage clamp methods on recombinant GABA receptors expressed in *Xenopus* oocytes.

Pharmacological studies showed that the probes synthesized have reasonable antagonist potency for GABA rho receptors with optimal activity when the linkers were 4-6 carbons long.

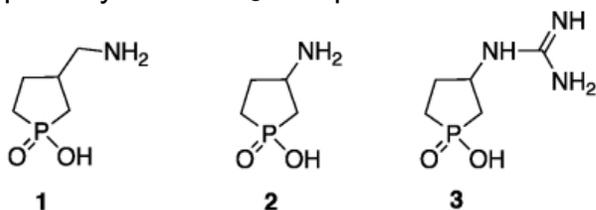
MEDI 115

Design, synthesis, and pharmacological evaluation of novel, selective γ -aminobutyric acid ρ (GABA_C) receptor antagonists

Navnath Gavande⁽¹⁾, *nsgavande@hotmail.com*, 902, 71-75 Regent street, Chippendale, Sydney NSW 2008, Australia ; **Kenneth Mewett**⁽²⁾; **Graham AR Johnston**⁽²⁾; **Jane R Hanrahan**⁽¹⁾; **Mary Chebib**⁽¹⁾. (1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The University of Sydney,

Sydney NSW 2006, Australia (2) Department of Pharmacology, The University of Sydney, Sydney NSW 2006, Australia

γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and is essential for the overall balance between neuronal excitation and inhibition. GABA influences neurons via three major classes of receptors which are grouped on the basis of their subunit composition, gating properties and pharmacological profiles: GABA_A, GABA_B, and GABA_C (GABA ρ) receptors. The GABA rho receptor (GABA_C) is a homomeric ligand-gated chloride channel. Antagonists at these receptors improve learning and memory, and reduce the onset of myopia in animal models. The distinct anatomical areas of the central nervous system where the GABA rho receptor is located and its low expression levels compared to other subunits deem this receptor a strong target for developing agents that can improve learning and memory with a reduced risk of side-effects. The synthesis of novel cyclic phosphinic acid analogues of GABA (**1**, **2** and **3**) and their activity as selective GABA_C receptor antagonists will be presented. The activity of these compounds has been investigated at the three major GABA receptor subtypes, and cyclic guanidino phosphinic acid (**3**) scaffold showed excellent selectivity and potency at GABA_C receptors.



MEDI 116

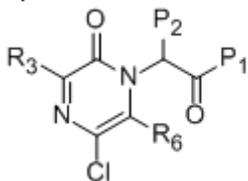
Hepatitis C protease inhibitors based on 2(1H)-pyrazinones

Anna Karin Belfrage⁽¹⁾, AnnaKarin.Belfrage@orgfarm.uu.se, Box 574, Uppsala 751 23, Sweden ; **Pernilla Örtqvist**⁽¹⁾; **Mats Larhed**⁽¹⁾; **U. Helena Danielson**⁽²⁾; **Anja Sandström**⁽¹⁾; **Johan Gising**⁽¹⁾. (1) Department of Organic Pharmaceutical Chemistry, Medicinal Chemistry, Uppsala SE-751 23, Sweden (2) Biochemistry and Organic Chemistry, Uppsala SE-751 24, Sweden

Protease inhibitors based on substituted pyrazinones have proved to function as non-peptidic β -strand conformation inducers. Consequently, these heterocyclic systems are interesting from a medicinal chemistry point of view. Molecular modelling of HCV NS3 protease inhibitors suggested that the space occupied by the P2 side chain could be reached by the substituent in position six on the P3-pyrazinone.

We have previously reported a rapid microwave method for synthesis of *N*-1, C-6-disubstituted 3,5-dichloro-2(1*H*)-pyrazinones¹ which enables the introduction of

a variety of substituents in crucial positions. We herein present our further optimization of these pyrazinone based inhibitors.



(1) Gising, J., *et al. Org. Biomol. Chem.*, **2009**, 7, 2809-2815.

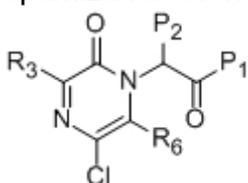
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MEDI 117

Synthesis and SAR studies on novel heteroaryl fused tetracyclic indole-diamide compounds: Potent allosteric inhibitors of the hepatitis C virus NS5B polymerase enzyme

Min Ding⁽¹⁾, min.ding@bms.com, 5 Research Parkway, Wallingford CT 06033, United States ; **Feng He**⁽¹⁾; **Xiaofan Zheng**⁽¹⁾; **Thomas W Hudyma**⁽¹⁾; **Michael A Poss**⁽²⁾; **John F Kadow**⁽¹⁾; **Karen L Rigat**⁽¹⁾; **Ying-Kai Wang**⁽¹⁾; **Robert Fridell**⁽¹⁾;

Dike Qiu⁽¹⁾; Susan B Roberts⁽¹⁾; Min Gao⁽¹⁾; Robert G Gentles⁽¹⁾; Mengping Liu⁽¹⁾; Stacey Boss⁽¹⁾. (1) Research and Development, Bristol-Myers Squibb Company, Wallingford CT 06492, United States (2) Research and Development, Bristol-Myers Squibb Company, Lawrenceville NJ 08540, United States

Hepatitis C Virus (HCV) currently infects about 180 million people globally and frequently results in serious and often fatal liver disease. Current standard of care [peglyated interferon α and ribavirin] provides limited efficacy against the most common HCV genotypes (1a/1b) and is associated with significant adverse side-effects. HCV RNA-dependent RNA polymerase (NS5B) is essential for viral replication and no mammalian counterpart has been identified. Correspondingly, it has been considered an attractive target for drug development. Several orthosteric and allosteric NS5B inhibitors have been reported and recent clinical data on both inhibitor classes have validated HCV NS5B as a viable target for HCV therapy. Presented here are our initial investigations on a series of highly potent, bridged indole-diamide allosteric NS5B inhibitors. For example, (2*E*)-3-(4-(((1-(((13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-pyrido[3',2':5,6][1,4]diazepino[1,7-*a*]indol-10-yl)carbonyl)amino)cyclopentyl)carbonyl)amino)phenyl)acrylic acid displays potent replicon activities (EC₅₀ 1a/1b = 14 / 11 nM). The synthetic methodology used to access these novel compounds and exploratory SAR studies are presented.

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MEDI 118

Synthesis and biological evaluation of the selective inverse agonist PWZ-029 for alpha 5 Bzr/GABA_aergic receptor subtypes: This ligand enhances cognition in rhesus monkeys

Sundari K Rallapalli⁽¹⁾, sundari@uwm.edu, 3210, N. Cramer Street, Milwaukee WI 53211, United States ; *Casey Moran*⁽²⁾; *James K Rowlett*⁽²⁾; *James M Cook*⁽¹⁾.
(1) Chemistry and Biochemistry, University of Wisconsin, Milwaukee WI 53211, United States (2) Harvard Medical School, New England Primate Research Center, Southborough MA 01772, United States

GABA_A/BzR chloride ion channels comprise the major inhibitory neurotransmitter system in the CNS. This central role carries with it a direct influence on many diseases of the CNS. Inverse agonists acting at alpha 5 subunits containing GABA_A receptors are thought to act as cognitive enhancers while eliminating unwanted side effects associated with non-selective compounds. The novel alpha 5 selective inverse agonist PWZ-029 was evaluated as a cognitive enhancer in rhesus monkeys in the CANTAB paradigm. This ligand had the ability to reverse cholinergic deficits in performance induced by the antimuscarinic scopolamine under mixed trial conditions. In the ORD task, PWZ-029 showed only a modest trend for enhancement of performance, but when task difficulty was increased by testing with difficult trials only, PWZ-029 robustly increased performance. This enhancement was reversed by administration of the alpha 5 GABA (A) subtype selective antagonist Xli-093 and this antagonism in turn was reversed by increasing the dose of PWZ-029. In addition, PWZ-029 enhanced performance in the DNMS task using the 10 minute delay with distracters. This ligand also exhibited anxiolytic activity in some primates and was an orally active anticonvulsant in rats. The synthesis and biological activity of this inverse agonist will be discussed in regard to drug development for treatment of age-associated memory impairment and Alzheimer's disease.

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Sundari K Rallapalli⁽¹⁾, sundari@uwm.edu, 3210, N. Cramer Street, Milwaukee WI 53211, United States ; Casey Moran⁽²⁾; James K Rowlett⁽²⁾; James M Cook⁽¹⁾.
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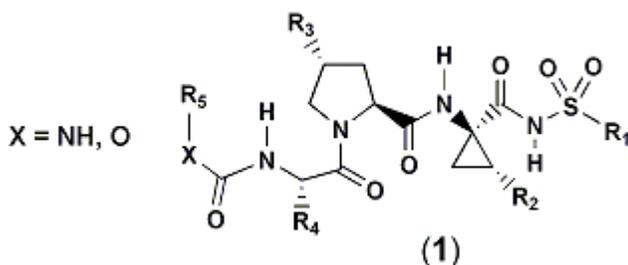
MEDI 119

Highly potent inhibitors of HCV NS3 protease

Brian Venables⁽¹⁾, brian.venables@bms.com, 5 Research Parkway, Wallingford Connecticut 06492-1996, United States ; Ny Sin⁽¹⁾; Alan Wang⁽¹⁾; Li-Qiang Sun⁽¹⁾; Dennis Hernandez⁽²⁾; Amy Sheaffer⁽²⁾; Min Lee⁽²⁾; Diana Barry⁽²⁾; Jacques Friborg⁽²⁾; Fei Yu⁽²⁾; Jay Knipe⁽³⁾; Jason Sandquist⁽³⁾; Andrew C Good⁽⁴⁾; Fiona Mcphee⁽²⁾; Nicholas A Meanwell⁽¹⁾; Paul M Scola⁽¹⁾. (1) Department of Chemistry, Bristol-Myers Squibb, Wallingford Connecticut 06492, United States (2) Department of Virology, Bristol-Myers Squibb, Wallingford Connecticut 06492, United States (3) Department of Metabolism and Pharmacokinetics, Discovery Support, Bristol-Myers Squibb, Wallingford Connecticut 06492, United States (4) Department of CADD, Bristol-Myers Squibb, Wallingford Connecticut 06492, United States

Approximately 180 million people worldwide are estimated to be infected with hepatitis C virus (HCV), a small, enveloped, positive strand RNA virus that infects the liver. HCV is a major cause of chronic liver diseases such as cirrhosis and hepatocellular carcinoma. The current standard of care combination of peg-

interferon alpha and ribavirin is only moderately effective in treating the disease and is associated with several undesired side effects which can often lead to discontinuation of treatment. In an effort to address these issues by providing potent and effective antiviral agents, we have discovered a series of novel tripeptidic inhibitors of the HCV NS3 serine protease. These molecules potentially inhibit this essential protein in the viral life cycle in both an *in vitro* biochemical assay and a replicon-based screen. This presentation will focus on chemical variations of the P3 and P4 subregions of these inhibitors, with emphasis on structure-activity relationships and optimization of potency against the protease. Urea and carbamate variants will be evaluated in the context of optimization of intrinsic and replicon potencies and ADME properties.



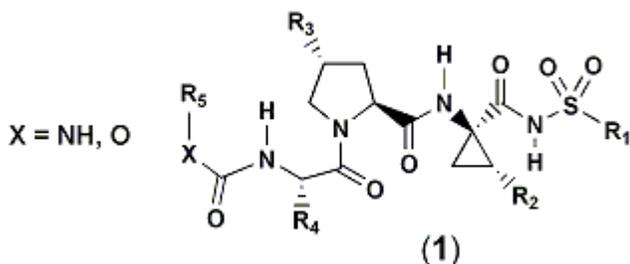
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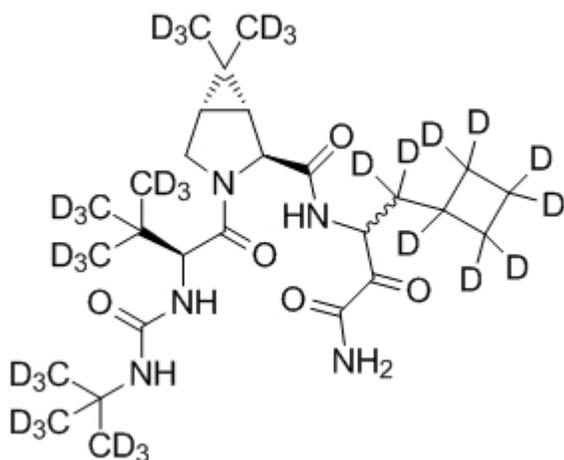
inhibit this essential protein in the viral life cycle in both an *in vitro* biochemical assay and a replicon-based screen. This presentation will focus on chemical variations of the P3 and P4 subregions of these inhibitors, with emphasis on structure-activity relationships and optimization of potency against the protease. Urea and carbamate variants will be evaluated in the context of optimization of intrinsic and replicon potencies and ADME properties.



MEDI 120

Design and synthesis of deuterated boceprevir analogs with enhanced pharmacokinetic properties

Adam J. Morgan⁽¹⁾, amorgan@concertpharma.com, 99 Hayden Ave., Suite 500, Lexington Massachusetts 02421, United States ; **Craig E. Masse**⁽¹⁾; **Sophia Nguyen**⁽¹⁾; **Vinita Uttamsingh**⁽¹⁾; **Roger Tung**⁽¹⁾; **Scott Harbeson**⁽¹⁾. (1) Concert Pharmaceuticals, Inc., Lexington Massachusetts 02421, United States



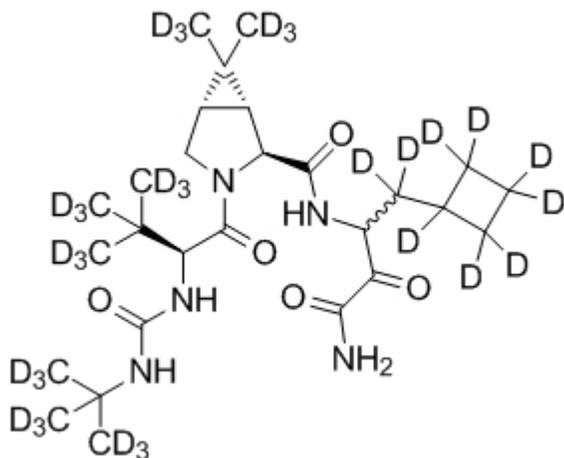
The HCV protease inhibitors comprise an emerging class of anti-infectives, in many cases exhibiting dramatic viral responses in the clinic when administered with peginterferon and ribavirin. Our investigation of deuterated analogs of boceprevir, one of the most advanced compounds in this class, has led to the identification of multiple novel agents with enhanced pharmacokinetic properties.

The design and synthesis of these lead compounds employing routes amenable to precise deuterium incorporation will be presented along with corresponding *in vitro* pharmacokinetic data.

MEDI 120

Design and synthesis of deuterated boceprevir analogs with enhanced pharmacokinetic properties

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The HCV protease inhibitors comprise an emerging class of anti-infectives, in many cases exhibiting dramatic viral responses in the clinic when administered with peginterferon and ribavirin. Our investigation of deuterated analogs of boceprevir, one of the most advanced compounds in this class, has led to the identification of multiple novel agents with enhanced pharmacokinetic properties. The design and synthesis of these lead compounds employing routes amenable to precise deuterium incorporation will be presented along with corresponding *in vitro* pharmacokinetic data.

MEDI 121

Rational design, virtual screening, synthesis and biological activity of donepezil-based new acetylcholinesterase inhibitors

Silpi Datta⁽¹⁾, silpi.datta@umb.edu, 100 Morrissey Blvd, Boston MA 02125, United States ; **Dmitry Borkin**⁽¹⁾; **Aleksandra Rudnitskaya**⁽¹⁾; **Marianna Torok**⁽¹⁾; **Bela Torok**⁽¹⁾. (1) Department of Chemistry, University of Massachusetts Boston, Boston MA 02125, United States

One of the most prevalent types of neurodegenerative disorders in the aging population is Alzheimer's disease (AD), which is characterized by memory loss and other cognitive impairments. Pathological studies relate this disease to formation of extracellular plaques and cholinergic system abnormalities. Symptomatic treatments of AD till date are mostly focused on improving the cholinergic function mainly by inhibition of acetylcholinesterase (AChE). AChE inhibitors act by preventing the hydrolysis of the acetylcholine by AChE. Recent studies that reported the possible role of AChE in A β self-assembly have generated a renewed interest in AChE inhibitors. In the present study we have used extended computational docking to map the binding of the well known inhibitor, donepezil to AChE. Strategic modifications were carried out on three distinguished motifs of the core structure using structural requirements and physical properties from our previous AChE structure-activity relationship studies. Various combinations of these parts were subjected to an extended computational docking that provided promising results thereby leading to the successful synthesis of a series of potent inhibitor lead compounds. The potency of the molecules was assessed by Ellman's in vitro spectrophotometric method.

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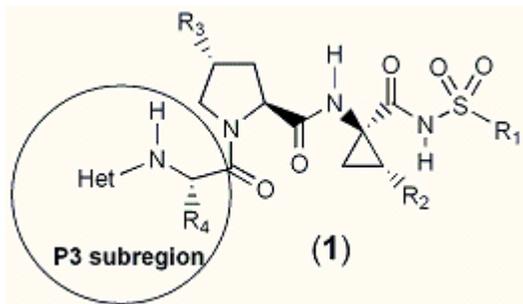
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MEDI 122

Application of small heterocyclic P3 caps in HCV NS3 protease inhibitors

Ny Sin⁽¹⁾, *ny.sin@bms.com*, 5 Research Parkway, Wallingford CT 06492, United States ; **Brian L. Venables**⁽¹⁾; **Li-Qiang Sun**⁽¹⁾; **Alan X. Wang**⁽¹⁾; **Sing-Yuen Sit**⁽¹⁾; **Yan Chen**⁽¹⁾; **Jie Chen**⁽¹⁾; **Ying Han**⁽¹⁾; **Andrew C. Good**⁽²⁾; **Jacques Friborg**⁽³⁾; **Diana Barry**⁽³⁾; **Fei Yu**⁽³⁾; **Dennis Hernandez**⁽³⁾; **Amy Sheaffer**⁽³⁾; **Jay Knipe**⁽⁴⁾; **Fiona McPhee**⁽³⁾; **Nicholas A. Meanwell**⁽¹⁾; **Paul M. Scola**⁽¹⁾. (1) Department of Chemistry, Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States (2) Department of Computer-Aided Drug Design, Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States (3) Department of Virology, Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States (4) Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States

The hepatitis C virus (HCV) is a small enveloped positive strand RNA virus that infects the liver. There are approximately 180 million people infected worldwide making it the leading cause of chronic liver disease. Complications from the disease include cirrhosis and hepatocellular carcinoma. Currently, the approved treatment for HCV is a combination of pegylated interferon alpha (peg-IFN α) and ribavirin. However, this therapy is only moderately effective and is associated with a range of side effects that can be of sufficient severity to cause discontinuation of treatment. Therefore, there is a clear unmet medical need for the development of new, effective therapeutics for the treatment of HCV infection. In our continuing study of acylsulfonamide-containing tripeptides (**1**) as HCV NS3 serine protease inhibitors, we have discovered a series of compounds containing small heterocyclic P3 caps which provide excellent virological profile. This presentation will describe our progress in employing small heterocycles such as aminopyridines, aminopyrimidines and aminothiazoles in an effort to modulate and enhance the physical and PK properties of our HCV NS3 protease inhibitors.

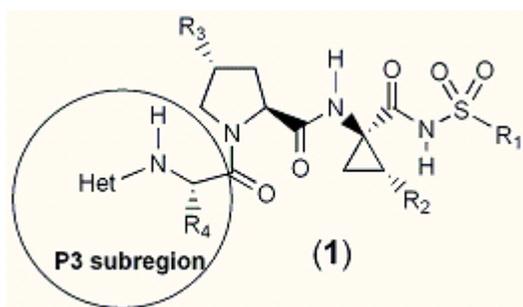


MEDI 122

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MEDI 123

Cyclic phosphate prodrugs of 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside analogs as inhibitors of HCV NS5B polymerase

P. Ganapati Reddy⁽¹⁾, pgreddy@pharmasset.com, 303A College Road East, Princeton NJ 08540, United States ; Donghui Bao⁽¹⁾; Wonsuk Chang⁽¹⁾; Byoung-Kwon Chun⁽¹⁾; Jinfa Du⁽¹⁾; Dhanapalan Nagarathnam⁽¹⁾; Suguna Rachakonda⁽¹⁾; Bruce S. Ross⁽¹⁾; Hai-Ren Zhang⁽¹⁾; Shalini Bansal⁽¹⁾; Christine L. Espiritu⁽¹⁾; Meg Keilman⁽¹⁾; Angela M. Lam⁽¹⁾; Congrong Niu⁽¹⁾; Holly M. Steuer⁽¹⁾; Phillip A. Furman⁽¹⁾; Michael J. Otto⁽¹⁾; Michael J. Sofia⁽¹⁾. (1) Pharmasset, Inc., Princeton NJ 08540, United States

An estimated 180 million people worldwide are infected with the hepatitis C virus (HCV). The current standard of care for HCV infection, the combination of pegylated interferon- α and ribavirin, provides less than 50% response rates among patients infected with the most prevalent genotype 1 virus. There is an urgent medical need for more effective and well tolerated anti-HCV agents to treat HCV infections across all genotypes. We have shown that nucleoside/tide analogs with 2'-F-2'-C-methyl substitution represent an important class of HCV NS5B polymerase inhibitors with broad genotype coverage. Nucleoside derivatives need to be phosphorylated to their corresponding active triphosphate by host cellular kinases before they can bind to the HCV NS5B polymerase resulting in chain termination. However, many nucleoside analogs are poor substrates for nucleoside kinases responsible for the first phosphorylation step. Here, we report the synthesis and *in vitro* anti-HCV activity of a novel class of cyclic phosphate prodrugs of 2'-deoxy-2'-F-2'-C-methyl nucleoside monophosphate. Our structure activity relationship studies led to PSI-352938, which is efficiently converted to the active triphosphate in human hepatocytes. On the basis of favorable *in vitro* and *in vivo* efficacy and tolerability, PSI-352938 was selected for further development. PSI-352938 is currently in phase I human clinical trials. In this presentation we will disclose the synthesis, SAR, and preclinical *in vitro* data supporting the nomination of cyclic phosphate prodrugs of 2'-deoxy-2'-F-2'-C-methyl nucleoside class for clinical development.

MEDI 123

Cyclic phosphate prodrugs of 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside analogs as inhibitors of HCV NS5B polymerase

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MEDI 124

Discovery of PSI-353661: A novel purine nucleotide prodrug with improved *in vitro* potency for the treatment of HCV infection

Wonsuk Chang⁽¹⁾, -, 303A College Road East, Princeton NJ 08540, United States ; Donghui Bao⁽¹⁾; Byoung-Kwon Chun⁽¹⁾; Dhanapalan Nagarathnam⁽¹⁾; Suguna Rachakonda⁽¹⁾; P. Ganapati Reddy⁽¹⁾; Bruce S. Ross⁽¹⁾; Hai-Ren Zhang⁽¹⁾; Shalini Bansal⁽¹⁾; Christine L. Espiritu⁽¹⁾; Meg Keilman⁽¹⁾; Angela M. Lam⁽¹⁾; Congrong Niu⁽¹⁾; Holly M. Steuer⁽¹⁾; Phillip A. Furman⁽¹⁾; Michael J. Otto⁽¹⁾; Michael J. Sofia⁽¹⁾. (1) Pharmasset, Inc., Princeton NJ 08540, United States

Hepatitis C virus afflicts more than 180 million people worldwide. In the United States alone, approximately four million people are infected, with 25,000 to 40,000 new cases reported annually. The current standard of care for chronic HCV infection, PEG-IFN α and ribavirin, demonstrates limited sustained virologic response (SVR) rates (only about 50% for genotype 1 patients) and various undesirable side effects. Consequently, there is a clear unmet need to discover new direct acting antivirals (DAA) to effectively and safely treat chronic HCV infection. Anti-HCV nucleoside/tide analogs have conserved activity across genotypes and a higher barrier to resistance selection than most other classes of DAA. PSI-353661 is a novel purine nucleotide analog which has demonstrated *in vitro* potent activity against HCV, broad genotype coverage and equipotent activity against both the wild type and the known S282T nucleoside/tide resistant virus. PSI-353661 is currently in preclinical development for HCV. The structure activity relationships and drug discovery process that led to the selection of this candidate will be discussed.

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MEDI 125

Synthesis of novel, fluorinated P1 NS3 protease inhibitors of HCV

Yan Chen⁽¹⁾, yan.chen@bms.com, 5 research pkway, Wallingford CT 06492, United States ; SY Sit⁽¹⁾; Jie Chen⁽¹⁾; Li-Qiang Sun⁽¹⁾; Stanley V D'Andrea⁽¹⁾; Zhizhen Zheng⁽¹⁾; Alan X Wang⁽¹⁾; Sheldon Hiebert⁽¹⁾; Mike Bowsher⁽¹⁾; Anthony Cocuzza⁽¹⁾; Qian Zhao⁽¹⁾; Donna Bilder⁽¹⁾; Ny Sin⁽¹⁾; Brian L Venables⁽¹⁾; David Carini⁽¹⁾; Barry Johnson⁽¹⁾; Eric Mull⁽¹⁾; Dennis Hernandez⁽²⁾; Amy K Sheaffer⁽²⁾; Heather Mulherin⁽²⁾; Fei Yu⁽²⁾; Jay O Knipe⁽³⁾; Kathy Mosure⁽³⁾; Andrew C Good⁽³⁾; Ramkumar Rajamani⁽³⁾; Herbert Klei⁽³⁾; Jacques Friborg⁽²⁾; Vinod Arora⁽³⁾; Yue-Zhong Shu⁽³⁾; Xiaohua Huang⁽³⁾; L Levesque⁽³⁾; Danshi Li⁽³⁾; J Zhu⁽³⁾; S. Adam⁽³⁾; Fiona McPhee⁽²⁾; Nicholas Meanwell⁽¹⁾; Paul M Scola⁽¹⁾. (1) Department of chemistry, Bristol-Myers Squibb Company, Wallingford CT 06492, United States (2) Department of virology,, Bristol-Myers Squibb Company, Wallinford CT 06492, United States (3) Department of research and development, Bristol-Myers Squibb company, Wallingford CT 06492, United States

Abstract - Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV). This virus 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 HCV is a combination of pegylated interferon and ribavirin. The main objective with these biologics, and synthetic antiviral agents is to achieve a sustained elimination of HCV RNA from the blood. Unfortunately, current SOC demonstrates a wide range of undesirable side effects in all sub-groups of patients and limited efficacy in genotype 1 patients (<50%). Therefore 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 efforts in modifying this region of the molecule which resulted in the identification of novel and very potent inhibitors.

MEDI 126

Synthesis and SAR studies on highly potent, novel, N,1-C2- phenyl-bridged 2-phenyl-indole-6-carboxamide based hepatitis C virus NS5B inhibitors

Xiaofan Zheng⁽¹⁾, xiaofan.zheng@bms.com, 5 Research Parkway, Wallingford CT 06492, United States ; Thomas W Hudyma⁽¹⁾; Min Ding⁽¹⁾; Feng He⁽¹⁾; Michael A Poss⁽¹⁾; John F Kadow⁽¹⁾; Chong-Hwan Chang⁽¹⁾; changhong wan⁽¹⁾; Mark R Witmer⁽¹⁾; Paul Morin⁽¹⁾; Daniel M Camac⁽¹⁾; Steven Sheriff⁽¹⁾; Brett R Beno⁽¹⁾; Karen Rigat⁽¹⁾; Ying-Kai Wang⁽¹⁾; Robert Fridell⁽¹⁾; Julie Lemm⁽¹⁾; Dike Qiu⁽¹⁾; Susan B Roberts⁽¹⁾; Min Gao⁽¹⁾; Jay Knipe⁽¹⁾; Robert G Gentles⁽¹⁾; Pengping Liu⁽¹⁾; Stacey Voss⁽¹⁾. (1) Bristol-Myers Squibb Research and Development, 5 Research Parkway CT 06492, United States

Hepatitis C Virus (HCV) infection affects approximately 180 million people world wide and frequently results in serious or fatal liver disease. The current standard of care [peglyated interferona and ribavirin] provides limited efficacy against common HCV genotypes (1a/1b) and is associated with significant adverse side-effects. HCV RNA-dependent RNA polymerase (NS5B) is an attractive target for drug development as it is required for viral replication and no mammalian counterpart exists. In this current work we present initial SAR studies on a series of N,1-C2-phenyl bridged 2-arylindole based NS5B inhibitors. The introduction of bridging elements results in the generation of a number of novel indole ring systems that provide additional vectors for advancement of these series of highly potent NS5B inhibitors. The binding mode and PK profiles of select examples such as, (2E)-3-(4-(((1-(((13-cyclohexyl-6,7-dihydroindolo[1,2-d][1,4]benzoxazepin-10-yl)carbonyl)amino)cyclopentyl)carbonyl)amino)phenyl) acrylic acid [EC₅₀ =10 nmol: %F = 5 to 18], are presented.

MEDI 127

Isoquinoline tripeptides as HCV NS3 protease inhibitors

Zhizhen Barbara Zheng⁽¹⁾, zhizhen.zheng@bms.com, 5 Research Parkway, Wallingford CT 06492, United States ; Alan Xiangdong Wang⁽¹⁾; David Carini⁽¹⁾; Anthony Cocuzza⁽¹⁾; Sheldon Hiebert⁽¹⁾; Michael Bowsher⁽¹⁾; Yan Chen⁽¹⁾; Sing-Yuen Sit⁽¹⁾; Li-Qiang Sun⁽¹⁾; Fiona Mcphee⁽¹⁾; Jacques Friborg⁽¹⁾; Diana Barry⁽¹⁾; Fei Yu⁽¹⁾; Dennis Hernandez⁽¹⁾; Jay Knipe⁽¹⁾; Ramkumar Rajaman⁽¹⁾; Herbert Klei⁽¹⁾; Alicia Ng⁽¹⁾; Baoqing Ma⁽¹⁾; Qi Gao⁽¹⁾; Nicholas A Meanwell⁽¹⁾; Paul M Scola⁽¹⁾; Stanley D'Andrea⁽¹⁾. (1) Research & Development, Bristol-Myers Squibb, Wallingford CT 06492, United States

Infection with hepatitis C virus (HCV) has reached pandemic levels with approximately 4 million people in the U.S. and 3% of the world's population carrying the virus. Current standard of care for HCV infection is a combination of pegylated interferon- α and ribavirin. However, patients infected with HCV genotype 1 respond poorly to this therapy which is also associated with poorly tolerated side effects. The HCV NS3 protease is essential for viral replication and has been validated as a therapeutic target in clinical trials. We describe herein the design, synthesis, and SAR of acyclic isoquinoline tripeptides as HCV NS3 protease inhibitors. These inhibitors contain novel P1 moieties including cyclopropanes substituted with fluorinated or oxygenated sidechains. These compounds have demonstrated sub-10 nM potencies in both biochemical and whole cell replicon screens.

MEDI 128

SAR and mode of binding studies on a series of N-benzyl-4-heteroaryl-1-(phenylsulfonyl)piperazine-2-carboxamides: Potent inhibitors of the polymerase enzyme (NS5B) of the hepatitis C virus

Robert G Gentles⁽¹⁾, gentlesr@gmail.com, 52 High Hill Rd, Wallingford CT 06492, United States ; Min Ding⁽¹⁾; Xiaofan Zheng⁽¹⁾; Louis Chupak⁽¹⁾; Michael A Poss⁽¹⁾; Chong-Hwan Chang⁽¹⁾; Changhong Wan⁽¹⁾; Mark R Witmer⁽¹⁾; Paul Morin⁽¹⁾; Daniel M Camac⁽¹⁾; Steven Sheriff⁽¹⁾; Brett R Beno⁽¹⁾; Karen Rigat⁽¹⁾; Susan B Roberts⁽¹⁾; Min Gao⁽¹⁾; John F Kadow⁽¹⁾; Julie Lemm⁽¹⁾; Stacey Voss⁽¹⁾; Mengping Liu⁽¹⁾; Lenore Pelosi⁽¹⁾; Ying-Kai Wang⁽¹⁾. (1) Research and Development, Bristol Myers Squibb Co, Wallingford CT 06492, United States

Hepatitis C virus (HCV) infection is a pressing medical problem: approximately 180 million people are affected globally. Patients with the disease often progress to develop fibrosis and cirrhosis, the sequelae of which include liver failure, portal hypertension and hepatocellular carcinoma. Current standard of care involves extended treatment (48 weeks) with pegylated interferon and ribavirin (Peg-IFN/RBV). This regime is associated with a poor response rate with only 40–50% of patients infected with genotype 1 HCV able to achieve a sustained viral response (SVR). Correspondingly, a number of companies are attempting to

develop specifically targeted antiviral therapies for HCV (STAT-C). Described herein is our initial optimization of (+/-) N-benzyl-4-heteroaryl-1-(phenylsulfonyl)piperazine-2-carboxamide (**1**), an HTS hit identified in an NS5B polymerase screen. This effort resulted in the identification of (R)-N-sec-butyl-6-((R)-3-(4-(trifluoromethoxy)benzylcarbamoyl)-4-(4-(trifluoromethoxy)phenylsulfonyl) piperazin-1-yl)pyridazine-3-carboxamide (**2**) that displayed potent replicon activities against HCV genotypes 1a and 1b (EC₅₀ 1a/1b = 99 / 7 nM).

MEDI 129

Development of novel carbohydrate binding agents: A new class of potent antiviral therapeutics

Paul C Trippier⁽¹⁾, trippierp@cardiff.ac.uk, Redwood Building, King Edward VII Avenue, Cardiff South Glamorgan CF10 3NB, United Kingdom ; Jan Balzarini⁽²⁾; Chris McGuigan⁽¹⁾. (1) Welsh School of Pharmacy, University of Cardiff, Cardiff CF10 3NB, United Kingdom (2) Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven B-3000, Belgium

HIV contains a highly glycosylated envelope with high mannose-type glycan content. Such carbohydrate assemblies play a pivotal role in viral infectivity and escape from the immune system.

Exposure of HIV to mannose-selective carbohydrate binding agents (CBA) provides a novel approach to anti-viral chemotherapy. Selectivity is achieved through the virtual absence of a1,2-mannose oligomers on the mammalian cell surface's and high density on the viral envelope.

Such compounds display two distinct modes of action; binding of mannose residues on the gp120 cell surface protein of HIV blocks the carbohydrate termini and triggers a conformational change in the protein, thus inhibiting the viron from entering its target cells; secondly, development of drug resistance through deletion of glycan residue's on the envelope glycoprotein, generating highly immunogenic epitopes which may stimulate an immunological response from the host.

We

describe herein the design, synthesis and evaluation of mannose-specific carbohydrate binding agents as potential antiviral compounds.

MEDI 129

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We

describe herein the design, synthesis and evaluation of mannose-specific carbohydrate binding agents as potential antiviral compounds.

MEDI 130

Synthesis and HIV-1 integrase inhibitory activity of C2-C-linked heterocyclic-5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides

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The HIV-1 integrase enzyme, one of three virus-encoded enzymes, plays an important role in retroviral replication. After reverse transcription into a double stranded DNA, the integrase, as part of a pre-integration complex, migrates into the nucleus and proceeds to insert the viral genome into the host chromosome via a multi-step process. The two enzymatic steps in this insertion process are cleavage and strand transfer. Although interrupting either of these steps could, in

principle, lead to inhibition of viral replication, compounds that inhibit the strand transfer reaction were found to exhibit antiviral activity, leading to FDA approval of the strand transfer inhibitor, Isentress®. A systematic SAR survey of C2-substitutents led to the identification of furan and pyran derivatives as optimal moieties for combining antiviral potency and good animal pharmacokinetic profiles. In this study, we disclose the synthesis, antiviral activity and pharmacokinetic properties of C2-C-linked heterocyclic-5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides as novel strand transfer inhibitors.

MEDI 130

Synthesis and HIV-1 integrase inhibitory activity of C2-C-linked heterocyclic-5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides

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MEDI 131

Design, synthesis and HIV-1 integrase inhibitory activity associated with spirocycle-fused 5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides

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Zheng⁽¹⁾; Nicholas A Meanwell⁽¹⁾; Mark Krystal⁽¹⁾; Michael A Walker⁽¹⁾. (1) Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States

5-Hydroxy-6-oxo-dihydropyrimidine-4-carboxylic acid derivatives are densely functionalized small molecules with promising biological activities. We and others have recognized the presence of the diketoacid pharmacophore embedded into these molecules, an essential requirement for inhibitors of the strand transfer step catalyzed by the HIV-1 integrase enzyme. Consequently, we investigated the dihydropyrimidines-4-carboxamides as potential HIV-1 integrase inhibitors. During the course of this investigation, we discovered that compounds in which the dihydropyrimidine core is perpendicular to the plane of the C2-cyclic-substituent exhibited good biological activity and pharmacokinetic properties in preclinical species. We took advantage of this key finding by designing a series of spirocyclic dihydropyrimidines. In this presentation, we disclose the synthesis, antiviral activity and pharmacokinetic properties of spirocycle-fused 5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides as inhibitors of HIV-1 integrase.

MEDI 131

Design, synthesis and HIV-1 integrase inhibitory activity associated with spirocycle-fused 5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides

B. Narasimhulu Naidu⁽¹⁾, b.narasimhulunaidu@bms.com, 5 Research Parkway, Wallingford CT 06492, United States ; Margaret E Sorenson⁽¹⁾; John D Matiskella⁽¹⁾; Yasutsugu Ueda⁽¹⁾; Sagarika Bollini⁽¹⁾; Ira Dicker⁽¹⁾; Helen Higley⁽¹⁾; Zeyu Lin⁽¹⁾; Dedong Wu⁽¹⁾; Lori Pajor⁽¹⁾; Dawn D Parker⁽¹⁾; Brian Terry⁽¹⁾; Ming Zheng⁽¹⁾; Nicholas A Meanwell⁽¹⁾; Mark Krystal⁽¹⁾; Michael A Walker⁽¹⁾. (1) Bristol-Myers Squibb Research and Development, Wallingford CT 06492, United States

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MEDI 132

Synthesis and evaluation of novel phosphoramidates of acyclic nucleosides in the bypass of the first phosphorylation step mediated by the thymidine kinase

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Acyclovir is an antiviral guanine derivative used in the treatment of HSV and VZV infection. The mechanism of action involves phosphorylation, which is mediated by a herpes virus-specified thymidine kinase (TK).

Several acyclovir prodrugs proved inhibitory against herpes virus infections, including a TK-deficient virus strain. These data revealed that the compounds efficiently released the monophosphate of acyclovir in the virus-infected human HEL lung fibroblasts. Interestingly, some of the compounds showed anti-HIV activity, indicating that the prodrug also released acyclovir monophosphate in HIV-infected human CEM lymphocyte cells¹. The acyclovir phosphoramidate approach might be interesting to be further investigated to treat HIV/HSV-infected individuals.

In this work, we applied the ProTide² approach to the synthesis of novel phosphoramidates of acyclic nucleosides. The synthesized compounds were evaluated for their antiviral activity against HSV-1, HSV-2 and thymidine kinase deficient HSV-1, and against HIV-1 (III_B) and HIV-2 (ROD).

1. Lisco, A.; Vanpouille, C. et al., *Cell Host & Microbe* **2008**, 4, 260-270.

2. Cahard, D.; McGuigan, C. et al., J., *Mini Rev. Med. Chem.* **2004**, 4, 371-381.

MEDI 133

Study of C2-N-linked heterocyclic pyrimidin-6-oxa-5-hydroxy-4-carboxamide derivatives as HIV integrase inhibitors

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The HIV-1 Integrase enzyme catalyzes the insertion of the viral DNA into the host cellular genome, a process that is required for viral replication. The diketo acid pharmacophore has been shown to possess inhibitory activity against the HIV-1 Integrase enzyme, which translates into antiretroviral activity in cell culture. The presence of an embedded diketo acid metal (Mg^{2+}) binding pharmacophore in pyrimidin-6-oxa-5-hydroxy-4-carboxylic acid derivatives has led to the investigation of benzyl carboxamides as potential HIV Integrase inhibitors. We examined a variety of C2-N-linked heterocyclic carboxamides and found that the C2-piperidine derivatives had excellent potency and pharmacokinetic properties. In this study, the synthesis and structure-activity relationship of C2-N-linked heterocyclic pyrimidin-6-oxa-5-hydroxy-4-carboxamides will be described.

MEDI 134

Design, synthesis and SAR study of novel spiro aza-pyrimidinone HIV integrase inhibitors

chen li⁽¹⁾, chen.li@bms.com, 5 research parkway, wallingford CT 06492, United States ; Michael A. Walker⁽¹⁾; Yasutsugu Ueda⁽¹⁾; John Matiskella⁽¹⁾; Zeyu Lin⁽²⁾; Ira Dicker⁽²⁾; Himadri Samanta⁽²⁾; Brian Terry⁽²⁾; Helen Higley⁽²⁾; Sagarika Bollini⁽²⁾; Mark Krystal⁽²⁾; Nicholas A. Meanwell⁽¹⁾. (1) virology medicinal chemistry, Bristol-Myers Squibb, wallingford connecticut 06492, United States (2) virology, Bristol-Myers Squibb, wallingford CT 06492, United States

HIV integrase is an enzyme responsible for the integration of reverse-transcribed viral DNA into the host cell DNA, a step that is essential for viral replication. HIV integrase inhibitors have proven to be an efficacious new addition to current HAART therapy. In this presentation, we report our efforts towards the discovery of N-(4-fluorobenzyl)-3'-hydroxy-4'-oxo-4',6',7',8'-tetrahydrospiro[cyclobutane-1,9'-pyrazino[1,2-a]pyrimidine]-2'-carboxamide as a new class of HIV integrase inhibitor. Structural modifications at the N-position were made in order to examine effects on inhibitory potency, and SAR studies showed that a variety of groups can be introduced there that maintain activity against the HIV integrase enzyme. Details of the synthesis and properties of these analogs will be presented.

MEDI 135

Discovery and preclinical evaluation of the HIV integrase inhibitor BMS-727740

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Narasimhulu Naidu⁽¹⁾; Margaret Sorenson⁽¹⁾; Roger Remillard⁽²⁾; Alain Martel⁽²⁾; Yasutsuga Ueda⁽¹⁾; Timothy Connolly⁽¹⁾; Jonathon Weiss⁽¹⁾; Chen Li⁽¹⁾; Ashok Trehan⁽³⁾; Henry Wong⁽³⁾; Zeyu Lin⁽⁴⁾; Ira Dicker⁽⁴⁾; Himadri Samanta⁽⁴⁾; Brian Terry⁽⁴⁾; Helen Scarnati⁽⁴⁾; Carol Deminie⁽⁴⁾; Sagariki Bollini⁽⁴⁾; Ming Zheng⁽⁵⁾; Anjaneya Chimalakonda⁽⁵⁾; Lori Pajor⁽⁵⁾; Thoma Philip⁽⁶⁾; Dawn Parker⁽⁷⁾; Mark Krystal⁽⁴⁾; Nicholas A Meanwell⁽¹⁾. (1) Department of Virology Medicinal Chemistry, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (2) Department of Medicinal Chemistry, Bristol-Myers Squibb, Candiac Montreal, Canada (3) Department of Chemical Synthesis, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (4) Department of Virology, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (5) Department of MAP, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (6) Department of Biotransformation, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (7) Department of Pharmaceuticals, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States

The HIV-Integrase inhibitor BMS-707035 was advanced into Phase I clinical trials due to its highly potent activity against HIV in cell culture and exceptional pre-clinical PK in rat, dog and monkey. Despite its high intrinsic activity, BMS-707035 exhibited high binding to human serum albumin and low aqueous solubility. In an effort to overcome these undesirable physiochemical properties, a number of structural modifications were explored. Examination of 5-membered ring heterocycles attached to the *ortho*-position of the benzylamide portion of the molecule yielded an unexpected SAR trend which resulted in improvements to solubility and lowering of protein binding. An *N*-linked, 5-methyl triazole attached to the *ortho*-site arose as the optimal substituent and the resulting compound, BMS-727740, was advanced as a clinical candidate for further studies

MEDI 135

Discovery and preclinical evaluation of the HIV integrase inhibitor BMS-727740

Michael A Walker⁽¹⁾, michael.a.walker@bms.com, 5 Research Pkwy, Wallingford Connecticut 06422, United States; Jacques Banville⁽²⁾; B Narasimhulu Naidu⁽¹⁾; Margaret Sorenson⁽¹⁾; Roger Remillard⁽²⁾; Alain Martel⁽²⁾; Yasutsuga Ueda⁽¹⁾; Timothy Connolly⁽¹⁾; Jonathon Weiss⁽¹⁾; Chen Li⁽¹⁾; Ashok Trehan⁽³⁾; Henry Wong⁽³⁾; Zeyu Lin⁽⁴⁾; Ira Dicker⁽⁴⁾; Himadri Samanta⁽⁴⁾; Brian Terry⁽⁴⁾; Helen Scarnati⁽⁴⁾; Carol Deminie⁽⁴⁾; Sagariki Bollini⁽⁴⁾; Ming Zheng⁽⁵⁾; Anjaneya Chimalakonda⁽⁵⁾; Lori Pajor⁽⁵⁾; Thoma Philip⁽⁶⁾; Dawn Parker⁽⁷⁾; Mark Krystal⁽⁴⁾; Nicholas A Meanwell⁽¹⁾. (1) Department of Virology Medicinal Chemistry, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (2) Department of Medicinal Chemistry, Bristol-Myers Squibb, Candiac Montreal, Canada (3) Department of Chemical Synthesis, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (4) Department of Virology, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (5) Department of

MAP, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (6) Department of Biotransformation, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States (7) Department of Pharmaceuticals, Bristol-Myers Squibb, Wallingford Connecticut 06422, United States

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MEDI 136

Towards the synthesis of novel boronates as potential HIV-1 protease inhibitors

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Drug discovery for HIV/AIDS has resulted in many life-saving therapies, making a great impact on modern medicine. Even though new therapies are available many drugs are highly susceptible to resistance development, have poor bioavailability, and cause several side effects. Consequently, there is an urgent need for the development of new inhibitory compounds with, increased resistance profiles, higher bioavailability, and decreased toxicity. We are synthesizing novel boronates that were designed as compounds with potential dual-mode, both competitive and associative, inhibitory action. Recent studies have demonstrated that boron-modified inhibitors have a higher affinity for the protease than their corresponding non-boronated analogs. Furthermore, these boron-modified structures were inhibitory to an HIV-1 protease variant that is resistant to several HIV-1 protease inhibitors. A library of both straight chain and cyclic boronates are being synthesized. The cyclic boronates, due to their structural rigidity, are expected to be better inhibitors than the straight chain compounds.

MEDI 137

Novel spirocyclobutyl- and spirocyclooxetanyl-pyrimidin-6-oxa-5-hydroxy-4-carboxybenzylamides as potent HIV-1 integrase inhibitors

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HIV-1 integrase, the enzyme critical for insertion of viral DNA into the host cell genome, has been the subject of intense investigation for controlling HIV infection. Diketo acids are believed to bind to a complex of integrase and the cleaved viral LTR in a manner competitive with the host target DNA to inhibit the strand transfer step. Recently, we incorporated essential elements of the diketo acid motif into a pyrimidinone-carboxamide template, along with additional structural elements to provide for improvements in potency and pharmacokinetic (PK) parameters. Several extremely potent integrase inhibitors arose out of this investigation, which focused on a spirocyclobutyl-tricyclic template, including one compound considered for advanced study. Further, we incorporated an oxygen atom, forming a spirocyclooxetane, in an effort to decrease lipophilicity and improve intrinsic enzyme inhibitory activity, while decreasing protein binding. The synthesis, antiviral activity and PK properties of selected analogs will be disclosed in this presentation.

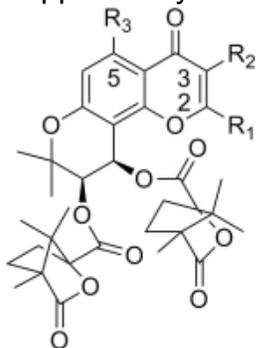
MEDI 138

Design, synthesis and structure-activity relationships of novel dicamphanoyl-2',2'-dimethyldihydropyranochromone (DCP) analogs as potent anti-HIV agents

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Novel DCP derivatives were designed and synthesized to explore anti-HIV SAR of dihydropyranochromones. Compounds **1-4** exhibited not only potent anti-HIV activity against HIV_{NL4-3} with EC₅₀: 0.036-0.14 μM, but also twofold higher potency than the lead 2EDCP (EC₅₀:0.11 μM) against drug-resistant HIV_{RTMDR-1} (EC₅₀:0.049 μM and 0.054 μM for **1** and **2**), suggesting that appropriate alkyl

groups at position-5 and electronic/hydrogen-bonding effects derived from the substitutions at positions-2 and -3 may play a role in enhancing anti-HIV activity. Supported by AI033066 (NIAID).



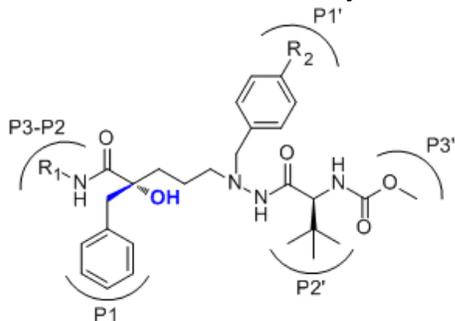
- 2EDCP** $R_1 = \text{CH}_2\text{CH}_3$, $R_2=R_3=\text{H}$
1 $R_1 = R_3 = \text{CH}_3$, $R_2 = \text{H}$
2 $R_1 = \text{CH}_2\text{CH}_3$, $R_2 = \text{H}$, $R_3 = \text{CH}_3$
3 $R_1 = \text{CN}$, $R_2 = \text{CH}_3$, $R_3 = \text{H}$
4 $R_1 = \text{CH}_2\text{CH}_3$, $R_2 = \text{NH}_2$, $R_3 = \text{H}$

MEDI 139

HIV-1 protease inhibitors with a tertiary-alcohol-containing transition-state mimic and various P2/P1' substituents

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We have previously reported promising HIV-1 protease inhibitors (PIs) using a shielded tertiary alcohol as the transition state mimic.¹ Despite a slightly unsymmetrical binding arrangement of the tertiary alcohol to the two catalytically active aspartic acid residues in the enzyme highly potent inhibitors were obtained. Thus, we decided to further elaborate this class of inhibitors by replacing the P2-indanol moiety previously used with the aim to improve the pharmacokinetic profile. We herein present a new series of HIV-1 PIs with varied P2 groups and show successful replacement of the P2-indanol moiety with retained inhibition activity on both enzyme and cell.



(1) Wu, X., *et al. J. Med. Chem.* **2008**, 51, 1053-1057.

MEDI 140

Design and synthesis of novel isatin derivatives as potent anti-HIV agents

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Design and synthesis of novel isatin derivatives as potent anti-HIV agents

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The Human Immunodeficiency Virus, HIV, a serious factor behind CNS infections, has been observed to cross the blood brain barrier (BBB), and hence the brain has been designated as a sanctuary for viral propagation. The integrity of the BBB has significant implications for antiretroviral therapy. In the absence of effective antiretroviral therapies that cross the BBB, the brain may serve as a site for constant reseeding by HIV. The present-day HAART for AIDS selectively inhibits viral replication in the peripheral tissues to a greater extent than in the CNS, which allows the brain to serve as a sanctuary for HIV.

It is assumed that drugs containing isatin moiety, may have affinity with endogenous isatin present in the brain and thus, could be of great therapeutic value. On the basis of this hypothesis, 13 novel isatin derivatives have been designed and synthesized. A pharmacophore distance map of the known NNRTIs and these molecules has been created using DS 2.5 software and it has been found that the molecules comply with the specification of the pharmacophore distance map.

5-Chloro-2-[2-methyl-4-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoin-dole-1,3-dione; 5-chloro-2-[2-methyl-4-(2-oxo-5-trifluoromethoxy-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoindole-1,3-dione; 5-chloro-2-[2-methyl-4-(5-methyl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoindole-1,3-dione; 5-chloro-2-[2-methyl-4-[5-nitro-1-(4-nitro-benzenesulfonyl)-2-oxo-1,2-dihydro-indol-3-ylideneamino]-phen-yl]-isoindole-1,3-dione; 5-chloro-2-[4-(1-methanesulfonyl-5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-2-methyl-phenyl]-isoindole-1,3-dione ; 5-chloro-2-[2-methyl-4-(2-oxo-1-trifluoromethanesulfonyl-5-trifluoromethoxy-1,2-dihydro-indol-3-ylideneam-ino)-phenyl]-isoindole-1,3-dione ; 5-chloro-2-[4-(1-methanesulfonyl-2-oxo-5-

trifluoromethoxy-1,2-dihydro-indol-3-ylideneamino)-2-methyl-phenyl]-isoindole-1,3-dione ; 5-chloro-2-[2-methyl-4-[1-(4-nitro-benzenesulfonyl)-2-oxo-5-trifluoromethoxy-1,2-dihydro-indol-3-ylideneamino]-phenyl]-isoindole-1,3-dione ; 2-[4-(1-Benzyl-5-nitro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-2-methyl-phenyl]-5-chloro-isoindole-1,3-dione; 5-chloro-2-[2-methyl-4-(5-nitro-2-oxo-1-prop-2-ynyl-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoindole-1,3-dione ; 5-chloro-2-[2-methyl-4-(5-nitro-2-oxo-1-propyl-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoindole-1,3-dione; 5-chloro-2-[2-methyl-4-(2-oxo-1-prop-2-ynyl-5-trifluoromethoxy-1,2-dihydro-indol-3-ylideneamino)-phenyl]-isoindole-1,3-dione and 2-[4-(1-benzyl-2-oxo-5-trifluoromethoxy-1,2-dihydro-indol-3-ylideneamino)-2-methyl-phenyl]-5-chloro-isoindole-1,3-dione have been synthesized and characterized using various chromatographic and spectroscopic techniques. The anti-HIV screening of the compounds is under progress.

MEDI 141

Small molecules to target *Mycobacterium tuberculosis* 1-Deoxy-D-xylulose-5-phosphate reducto-isomerase (MtbDxr)

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is one of the deadliest infectious diseases. Emergence of drug resistant strains of Mtb and co-infection with HIV has made TB both difficult and expensive to treat. New TB therapies are needed to shorten treatment and be effective against all strains and metabolic states of the organism. Development of inhibitors of 1-deoxy-D-xylulose-5-phosphate reducto-isomerase (Dxr), an essential enzyme for Mtb, is a novel approach toward the development of a new TB chemotherapy. Natural product fosmidomycin inhibits Dxr and kills other organisms reliant on this enzyme. Interestingly, fosmidomycin is not effective against Mtb. We present lipophilic prodrugs of fosmidomycin that kill Mtb. The goals of our work are to rationally design inhibitors that will specifically inhibit Mtb Dxr and to synthesize prodrugs of these molecules to enhance cell penetration. The biological and synthetic results of this work will be described.

MEDI 142

Synthesis and in silico studies of altered DNA substrates as HIV RT inhibitors

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Synthesis and *in silico* studies of altered DNA substrates as HIV-RT inhibitors

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The etiological agent of Acquired Immune Deficiency Syndrome (AIDS)- an immunocompromised condition, is Human Immunodeficiency Virus (HIV). Like all other retroviruses, HIV type 1 contains the multifunctional enzyme Reverse Transcriptase (RT). HIV-1 RT is essential for conversion of viral ssRNA into a linear dsDNA, a provirus which gets integrated into the host genome and produces new virion particles through transcription followed by translation.

HIV-1 RT is an important target for developing chemotherapeutic agents against HIV/AIDS. There are two different types of HIV-1 RT inhibitors- Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). Acyclonucleosides act as nucleoside reverse transcriptase inhibitors (NRTIs) against HIV. The NRTIs target the active site that lies at the floor of DNA binding cleft and render the enzyme inactive by incorporating itself into the growing chain and acts as a terminator of chain elongation by inhibiting addition of incoming nucleotides.

We have developed several acyclonucleosides of uracil base bearing modifications at N-3. These molecules are 3-benzoyl-1-(4-hydroxy-but-2-ynyl)-uracil, 3-benzyl-1-(4-hydroxybut- 2-ynyl)-uracil, 3-sulphonyl-1-(4-hydroxy-but-2-ynyl)-uracil and their triphosphates. These molecules were designed on the basis of extensive literature survey and *in silico* studies using DS 2.5 software and following Lipinski's rule of five. The docking of molecules with HIV-RT has shown very encouraging results. The molecules formed 3-10 H-bonds with Gln44, Lys46, Lys65, Arg72, Asp110, Asp113, Gln151, Pro217, Asp185, His221 and Lys223 present in the active dNTP site and showed no violation of Lipinski's rule.

Thus, the SAR studies have shown that presence of carbonyl group and sulphonyl group at N-3 position in the molecules enhances their interaction with enzyme. So, acyclonucleosides of uracil with modification at N-3 have shown potential as probable lead molecules against HIV-RT. The molecules are under

biological screening under *in vitro* conditions.

MEDI 143

Synthesis of new antimalarial bi-drug molecules

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Malaria is caused by protozoan parasites of the *Plasmodium falciparum* kind and is responsible for 1.2 to 2.7 million deaths every year. Research of new antimalarial chemotherapy has become urgent because of parasite resistance to classical drugs. In the literature, it appears that enantioselective pharmacomodulations of mefloquine are not fully explored. Although the racemic mixture is used for therapy, the mefloquine *R* enantiomer is supposed to be the most active form and side effects (brain damage) may essentially come from the *S* enantiomer.¹

A new way to overcome these aforementioned issues is to use a bi-drug strategy in order to simultaneously reach two targets.

We decided to synthesize new mefloquine asymmetric bi-drug derivatives incorporating an antimalarial quinolinol to inhibit the formation of *Plasmodium* b-hematin and an iron(III) chelator to trap the iron necessary to the parasite survival.

1. Shepherd, R. WO98/39003, 1998.

MEDI 144

Motualevic acid analogs: Synthesis, antimicrobial activity, and structure–activity relationship (SAR) studies

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Infectious diseases are one of the foremost causes of death worldwide, thus increased the consumption of antibiotic drugs tremendously. As a consequence of this many bacteria developed resistance against most of these drugs, and the existing drugs are becoming less effective. To overcome this problem, there is an imperative need for the development of new antibiotics that function with unique mechanism-of-actions, which do not succumb to the resistance mechanisms of existing antibacterial agents. Recently, we have reported on the isolation,

structural elucidation and antibacterial properties of motualevic acids (MA) A-E, which are the glycyyl conjugates of related terminal dibromo fatty acids; from *Siliquariaspongia* sp. To further explore the SAR, we have synthesized the MA-A and its analogs that feature the shortened fatty acid chain length and also various amino acid conjugates and were tested against four bacterial strains namely, SA, MRSA, EF and VRE in agar disk diffusion and microbroth dilution assays. In the process we discovered the potent anti-bacterial agents, which were more or equally active than the natural product MA acid A. In general, more hydrophobic amino acid conjugates and a QAC found to be more potent antibiotics, inhibiting the growth of tested bacterial strains at loadings ranging from 2-12 µg/disk. Few of these analogs were not cytotoxic, up to 100 µg/mL, to the human colo-rectal cancer cell line HCT-116 or to a healthy mammalian cell line, BSC-1 where as QAC was selectively cytotoxic towards HCT-116 with an IC₅₀ of 18.3±5.4 µg/mL, but was not cytotoxic towards BSC-1.

MEDI 145

New bicyclic peptidomimetic inhibitors of secreted aspartic proteinase 2 (SAP2) for the treatment of drug-resistant *Candida albicans* infections

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Candida albicans is a fungal pathogen that causes severe mucosal and systemic infections, especially in immunodeficient individuals. The need for new drugs is escalating due to both the widespread occurrence of mucosal infections caused by *Candida*, and the development of drug-resistance. Secreted Aspartic Proteinases (SAPs) appear to be a main virulence factor of this fungus, therefore these enzymes offer a target for drug intervention in infections. The screening of a library of peptidomimetics toward SAP2 of *Candida albicans* allowed us to identify two compounds with in vitro inhibitory potency comparable to pepstatin A. Moreover, in an experimental model of vaginal candidiasis, the two compounds were as active as a therapeutic dose of fluconazole, and this activity was fully preserved when the challenger was a fluconazole-resistant strain of the fungus. The synthesis, SAR, and binding mode of these SAP2 inhibitors by ligand-protein docking studies will be presented.

MEDI 146

Quinolonimines as novel antimalarial leads

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Cytochrome *bc*₁, from the mitochondrial electron transport chain, is one attractive and validated drug target, for which few efficient inhibitors are known today [1]. Clopidol is a known *bc*₁ complex inhibitor and has been taken as a lead for optimization [2]. Based in the 4(1*H*)-pyridone scaffold we recently designed and synthesized potential isosters containing the pyridin-4-amines core [3]. Now we report the synthesis of related quinolin-4-amines. These were obtained in good or excellent yields and their activity found to be in the low or sub-micromolar range against *P. falciparum* W2 strain. A docking study was also carried out to predict the major interactions of the ligand with the binding pocket. SAR will be discussed.

[1] Rodrigues, T. *et al.*, *Curr Med Chem* **2010**, *17*, 929-956; [2] Yeates, C. L. *et al.*, *J Med Chem* **2008**, *51*, 2845-2852; [3] Rodrigues, T. *et al.*, *Bioorg Med Chem Lett* **2009**, *19*, 3476-3480

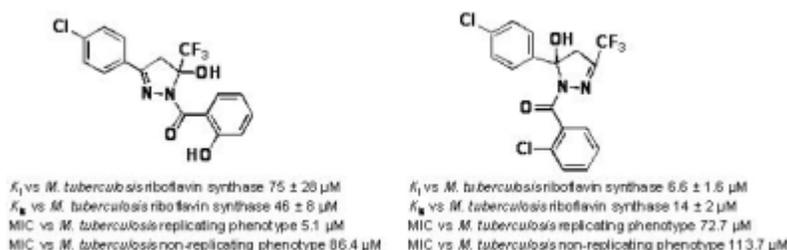
MEDI 147

Discovery and development of the covalent hydrates of trifluoromethylated pyrazoles as riboflavin synthase inhibitors with antitubercular activity

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Lumazine synthase and riboflavin synthase catalyze the last two steps in the biosynthesis of riboflavin, a vitamin that is involved in many critical biochemical reactions that are essential for maintenance of life. The inhibition of these enzymes represents a very specific strategy for antibiotic drug design, because the targets are not present in human or animal hosts. A high-throughput screening (HTS) hit compound displayed moderate inhibition of *Mycobacterium tuberculosis* and *Escherichia coli* riboflavin synthases, and moderate antibiotic activity against both *M. tuberculosis* replicating phenotype and non-replicating

persistent phenotype. Molecular modeling studies suggest that two inhibitor molecules bind in the active site of the enzyme, and that the binding is stabilized by stacking between the benzene rings of two adjacent ligands. The HTS hit compound and its analogues provide the first example of riboflavin synthase inhibitors with antibiotic activity.



MEDI 148

Hybrid compounds targeting both liver and blood stages of malaria parasites

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Malaria eradication requires novel prophylactic and therapeutic approaches targeting the obligatory liver stage and the erythrocyte-infecting parasites. Blocking the transmission of the disease via gametocytocidal activity is also a much desirable goal. Existing drugs are active in only one or two stages of the parasite's life cycle. Primaquine, a 8-aminoquinoline, is the only clinically available antimalarial active against the *Plasmodium* liver-stages (including *P. vivax* hypnozoites) and the gametocytes of all *Plasmodia* strains, but is weakly active against the blood stages of infection. Artemisinin and related analogues are potent blood-schizontocidals and reasonable gametocytocidals, but their effect in the liver stage of infection is less clear. We now report the development of hybrid molecules encompassing 8-aminoquinoline and artemisinin-based pharmacophores to convey activity against both the liver stage and the blood stage of the parasite. The synthesis, *in vitro* blood- and liver-stage screening and *in vivo* evaluation on the liver-stage will be presented.

MEDI 149

Synthesis and antiviral activity of a second generation of measles virus RNA-dependent RNA polymerase activity inhibitors

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We previously described a non-nucleoside Measles Virus (MV) RNA-dependent RNA polymerase (RdRp) complex inhibitor. In an effort to develop more water soluble derivatives, a new series of compounds were designed and synthesized. Substitution at the 2-position of piperidine gave analogs with retained activity. Chirality at the 2-position was found to have little effect on antiviral activity. Additionally, a new series of compounds where the piperidine ring was replaced with a phenyl or substituted phenyl was discovered and found to have comparable activity. Both the 2-substituted piperidine and the phenyl series of compounds have improved water solubility compared to the lead compound. Efforts are underway to study the bioavailability of these new compounds to find a suitable candidate for efficacy studies. Introduction of a photoaffinity label on the phenyl series provided an analog with antiviral activity. These analog will be utilized for studying the secondary structure of the target protein.

MEDI 150

Design and synthesis of a sixteen million member DNA-encoded library (DEL) and discovery of potent *Mycobacterium tuberculosis* (Mtb) InhA inhibitors

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Encoded library technology (ELT) provides a new tool for the identification of small molecules that bind to protein targets of pharmaceutical interest. To date, the majority of DNA-encoded libraries (DELs) reported by our research team have incorporated planar aryl and heteroaryl scaffolds as the core structure. Herein we describe the design and synthesis of a DEL based on twenty two aliphatic scaffolds which are elaborated with a diverse set of reactants to generate a sixteen million member DEL. Selection of this DEL against *Mycobacterium tuberculosis* (Mtb) InhA has led to a series of novel, potent inhibitors that display antimicrobial activity.

MEDI 151

Cell-based optimization of imidazolopiperazines as new antimalarials

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Drug resistance is a significant problem for most of the currently marketed drugs used to treat malaria – a disease affecting 250 million people annually and claiming at least one million lives per year. Many artemisinin-based combination therapies are now in late stage clinical trials. However, these drug combinations rely on artemisinin, the last antimalarial option without reported clinical resistance. New drug entities for malaria are in urgent need. Here we report our effort to develop novel antimalarials from a cell-based screening strategy. The starting point is one of the hits from our HTS of more than 2 million compounds. This novel imidazolopiperazine scaffold was optimized using an erythrocyte-based *Plasmodium falciparum* proliferation assay. SAR for this series of compounds will be disclosed, focusing on optimization of cellular potency against wild-type and drug-resistant parasites and improvement of physicochemical and pharmacokinetic properties. The most advanced compounds in this series show good potency *in vitro* and excellent efficacy in a *Plasmodium berghei in vivo* mouse model.

MEDI 152

Modeling trypanosomal TOR kinase domains: Implications for the design of anti-parasitic drugs

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Trypanosomiasis and leishmaniases are parasitic diseases caused by several species of trypanosomes impacting more than 22 million people every year, primarily in the developing world. These diseases can be fatal if untreated, but current therapeutic interventions are unsatisfactory, all with limited efficacy or life-threatening side effects. The mammalian kinase target of rapamycin (mTOR), has demonstrated importance in the area of cancer therapies and immunology. The trypanosomal homologues of TOR (TrypTORs) have also been reported to

be promising targets for control of trypanosomiasis, providing an opportunity to repurpose the extensive knowledge in human mTOR medicinal chemistry towards the development of TrypTOR inhibitors. Comparative models are reported of the kinase domains for several different TrypTORs. Ligand binding residues, computationally predicted by THEMATICS and POOL, together with docking studies of derivatives of "hit" compounds, provide computational guidance for TrypTOR inhibitor design.

MEDI 153

High-speed synthesis of 3,6-disubstituted pyrazolo[1,5-a]pyrimidines applied to bone morphogenetic protein signaling inhibitors

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In the SAR study of dorsomorphin, an inhibitor of SMAD 1/5/8 phosphorylation by BMP type 1 receptors ALK2, 3, and 6, high-speed synthesis using MW reactions was developed for the preparation of pyrazolo[1,5-a]pyrimidine derivatives. This MW-assisted route has been used to prepare the lead compound LDN-193189 on gram-scale. Application of high-speed chemistry in the SAR study and in scale-up greatly increased the efficiency and lowered costs.

MEDI 153

High-speed synthesis of 3,6-disubstituted pyrazolo[1,5-a]pyrimidines applied to bone morphogenetic protein signaling inhibitors

Ji-Feng Liu⁽¹⁾, jliu@aberjona.com, 100 Cummings Center, STE 242F, Beverly MA 01915, United States ; Gregory D. Cuny⁽²⁾; Paul B. Yu⁽³⁾⁽⁴⁾; Xuechao Xing⁽²⁾; Kenneth D. Bloch⁽³⁾⁽⁴⁾; Randall T. Peterson⁽⁴⁾. (1) Aberjona Laboratories, Inc., Beverly MA 01915, United States (2) Laboratory for Drug Discovery in

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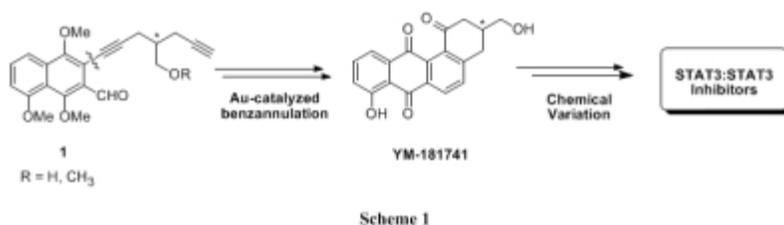
In the SAR study of dorsomorphin, an inhibitor of SMAD 1/5/8 phosphorylation by BMP type 1 receptors ALK2, 3, and 6, high-speed synthesis using MW reactions was developed for the preparation of pyrazolo[1,5-a]pyrimidine derivatives. This MW-assisted route has been used to prepare the lead compound LDN-193189 on gram-scale. Application of high-speed chemistry in the SAR study and in scale-up greatly increased the efficiency and lowered costs.

MEDI 154

Total synthesis of YM-181741 for the preparation of natural product-like STAT3:STAT3 inhibitors

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Inhibition of the STAT3:STAT3 protein interaction is an attractive approach for cancer therapy as it can lead to suppression of tumour cell growth and apoptosis. Racemic ochromycinone (STA-21) is one of the few known small-molecule STAT3:STAT3 inhibitors. Our synthetic efforts have focused on the preparation of the natural product YM-181741 which possesses at least three points for chemical variation to prepare libraries of potential STAT3:STAT3 inhibitors. The synthesis of YM-181741 has been carried out employing an approach based on a Au(III)-catalyzed intramolecular [4+2] benzannulation reaction (Scheme 1). The synthesis of the racemic precursor **1** has been achieved employing a facile and efficient route that offers a high degree of flexibility to modify the scaffold at different stages of its synthesis. The asymmetric synthesis of YM-181741 has also been investigated *via* the enantioselective preparation of the diyne fragment. Both of these synthetic approaches will be presented.



MEDI 155

Tetrapodal Stat3 inhibitors offer potent disruption of Stat3 in vitro and in whole cell assays

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Signal transducer and activator of transcription 3 (Stat3) protein is an oncogenic transcription factor that exhibits aberrant functioning in many human cancers. Constitutive Stat3 activation causes over-expression of anti-apoptosis proteins and makes cancer cells resistant to natural apoptotic processes. Disrupting Stat3 signalling presents an avenue for anticancer therapy as many cancers depend on elevated levels of Stat3 activity.

Starting from S3I-201, a non-phosphorylated Stat3 inhibitor, an extensive SAR has identified a series of molecules that more potently bind to Stat3's SH2 domain. In particular, we have developed a focused set of tetrapodal inhibitors that optimally access the phosphopeptide binding region of Stat3's SH2 domain. Lead analogs show a 20-fold improvement over S3I-201 with *in vitro* and whole cell IC₅₀ values as low as 1 μ M. To the best of our knowledge, these highly promising molecules are amongst the most potent small molecule, non-phosphorylated Stat3 inhibitors to date.

MEDI 156

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

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Deshattiwar⁽²⁾; Somnath Halder⁽¹⁾; Dattatraya C. Desai⁽¹⁾; Jayesh Mudgal⁽²⁾; Mini Dhiman⁽¹⁾; Aslam U. Burhan⁽²⁾; Ankur Sharma⁽²⁾; Nauzer P. Dubash⁽¹⁾; Naveen K. Mangu⁽¹⁾; Milan Dutta⁽¹⁾; Gajanan Thakre⁽¹⁾; Santosh Goud⁽¹⁾; Dnyaneshwar Pacharne⁽¹⁾; Lokesh Babu⁽¹⁾; Shubhada Deshpande⁽¹⁾; Vijaya Nadar⁽¹⁾; Somesh Sharma⁽²⁾. (1) Medicinal Chemistry Division, PIRAMAL LIFE SCIENCES LIMITED, Nirlon Complex, Goregaon East, Mumbai Maharashtra State 400063, India (2) Pharmacology Department, PIRAMAL LIFE SCIENCES LIMITED, Nirlon Complex, Goregaon East, Mumbai Maharashtra State 400063, India

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

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

MEDI 157

Inhibition of CuZnSOD by low MW natural products

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We have found a class of low molecular weight natural products inhibits bovine CuZnSOD and have characterized the pH and concentration dependence of the reaction. We report the SAR for inhibition by related molecules. At high pH, deprotonation of an active site residue leads to a second step that irreversibly inactivates the enzyme. We describe how aggregation of inhibitors competes with their inhibitory activities.

MEDI 158

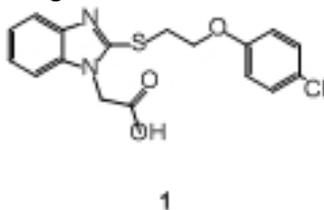
Thiobenzimidazole-1-acetic acids as CRTH2 antagonists

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The human chemoattractant receptor-homologous molecule expressed on T-helper

2 cells (hCRTH2), a member of the G-protein coupled receptor family, is expressed on eosinophils, basophils, and T-helper 2 lymphocytes. Upon its activation by prostaglandin D2 (PGD2) it plays a role in the chemotactic recruitment of granulocytes and Th2 cells to inflammation sites. Therefore, CRTH2 antagonists are expected to be valuable for the treatment of inflammatory disorders (1)(2).

High-throughput screening of our in-house compound collection for hCRTH2 antagonists by means of a FLIPR assay provided thiobenzimidazole-1-acetic acid **1** as a hit, antagonizing the hCRTH2 receptor in the micromolar range.



A straightforward synthetic route to analogues of **1** has been devised and a detailed structure activity relationship (SAR) could be established. In addition, pharmacokinetic results will be presented.

(1) Kostenis, E.; Ulven, T. *Trends Mol. Med.* **2006**, *12*, 148-158.

(2) Pettipher, R. et al *Nat. Rev. Drug Discovery* **2007**, *6*, 313-325.

MEDI 159

Development of SH2 domain proteomimetics as potent disruptors of oncogenic Stat3:Stat3 dimerization

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We report the design and development of coordination complex SH2 domain proteomimetics that can replicate the phosphotyrosine binding function of key SH2 domains native to the human cell. Specifically, we have designed Stat3-SH2 domain proteomimetics to disrupt the oncogenic Stat3-Stat3 protein complex in human tumor cells.

Select compounds exhibited promising activity against Stat3-dependant cancer cell lines, including single digit micromolar activity against breast cancer tumors. This work represents the first example of a functional SH2 domain proteomimetic and the first disruption of a clinically-important oncogenic protein-protein interaction using a non-classical mechanism where a phosphorylated residue, and not its cognate binding pocket, is targeted. This presentation will focus on the synthesis and biological evaluation of select inhibitors, as well as the development of complex proteomimetics capable of achieving selectivity for Stat3 amongst other STAT isoforms.

MEDI 160

1,3,6-substituted-4-aminopyrazolopyrimidines, new potent inhibitors for phospholipase D

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Phospholipase D (PLD) enzymes generate phosphatidic acid (PA) from phospholipid substrates. Human PLD is a drug target to modulate cancer cell invasiveness. PLD from *S. chromofuscus* has high homology with human PLD1 and GPI-PLD and is activated

on its binding with PA. Structure-activity-relationships of 1,3,6-substituted-4-aminopyrazolopyrimidines for the inhibition of PLD enzymes were studied. A variety of substituted inhibitors based on the 4-aminopyrazolopyrimidine core structure were synthesized. The inhibitors were synthesized in four steps starting from acyl chloride and malononitrile. The first three steps were carried out in a one pot manner to get pyrazoles in moderate yields (50-60%). The intermediate was refluxed with a primary amide to get the final product in quantitative yields. The inhibitors exhibited very

good activity (in nanomolar range) for the inhibition of PLD enzymes in the pH stat assay. The exogenous (*in vitro*) inhibition is 5-50 fold more potent than previously reported inhibitors to mammalian PLD.

MEDI 161

Development of potent and selective MMP inhibitors with a triazole zinc binding group

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Matrix Metalloproteases (MMPs) are zinc-dependent endopeptidases that are involved in the tissue and vascular remodeling associated with many physiological and pathological processes. As such, these enzymes are potential drug targets for a variety of diseases including osteoarthritis, rheumatoid arthritis, macular degeneration and cancer. MMP inhibitors often derive potency by incorporating a functional group that binds the catalytic zinc atom at the active site. Common zinc binding groups (ZBG's) like hydroxamates, carboxylates and thiols, while potency enhancing, often impart undesirable *in vivo* properties that have hampered the clinical advance of these classes of inhibitors. Herein we describe the potency, selectivity and pharmacokinetics of a novel series of MMP inhibitors containing a triazole zinc binding group. The advantages of this ZBG strategy over existing ZBG strategies will be discussed.

MEDI 162

Reduction of hERG activity in (4,5,6,7-tetrahydro-1H-indazolyl)ethanamines, a novel series of potent and selective S1P1 selective agonists

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Agonism of the S1P1 receptor has recently been identified as a novel mechanism of action for immunosuppression and diseases such as transplant rejection, multiple sclerosis or other autoimmune conditions could be treated with a selective S1P1 agonist. Gilenia (Fingolimod, FTY720 from Novartis) is a novel immunomodulator that has recently been pre-registered at the FDA for the oral treatment of multiple sclerosis (MS). It has been established that FTY720 acts *via*

its phosphorylated form, FTY720-P, which is a potent agonist of four out of the five sphingosine-1-phosphate (S1P) G-protein coupled receptors. Several companies, however, have direct (ie., non-prodrug) and selective S1P1 agonists under clinical evaluation in this competitive field.

Literature analysis in conjunction with an homology model of the S1P1 receptor lead us to the identification of (4,5,6,7-tetrahydro-1*H*-indazolyl)ethanamines, as potent and selective S1P1 agonists with an impressive in vivo activity. These compounds, however, have also been found to be active in hERG channels and as such, they could induce QTc-interval prolongation and its related undesired cardiac effects.

Herein we describe the different chemical approaches used to reduce this hERG activity while keeping potency selectivity and good pharmacokinetic profile.

MEDI 163

Structure-activity relationship studies of sphingosine kinase inhibitors

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Sphingosine kinase

(SphK), an enzyme that rapidly phosphorylates sphingosine (Sph) to form sphingosine-1-phosphate (S1P), is overexpressed in a variety of tumor types. Sph and its precursor, ceramide promote apoptosis while S1P promotes survival and cell proliferation. The dynamic balance between S1P and Sph/ceramide is regulated by SphK which makes it an attractive target for anticancer drugs. However,

the lack of selective inhibitors of SphK and the scarcity of isoenzyme-selective inhibitors leaves a lot to be done in this research area. We have synthesized a library of SphK inhibitors and discovered subtype selective inhibitors with K_i of 9 μ M. We are currently investigating the structure-activity relationship studies of these inhibitors by exploring different regions of the pharmacophore.

MEDI 164

Amido-1,3,4-thiadiazole derivatives as novel S1P1 selective agonists: From an HTS hit to a sub-nanomolar, orally active advanced lead

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Godessart⁽¹⁾; Gema Tarrasón⁽¹⁾; Teresa Domenech⁽¹⁾; Dolors Vilella⁽¹⁾; Clara Armengol⁽¹⁾; Mònica Córdoba⁽¹⁾; Mar Sabaté⁽¹⁾; Daniel Casals⁽¹⁾; Maria Domínguez⁽¹⁾; Nuria Aguilar⁽¹⁾. (1) Almirall Research Center, Almirall S.A., Sant Feliu de Llobregat Barcelona 08980, Spain

Sphingosine 1-phosphate receptor agonists, like fingolimod (Novartis), are emerging as a novel class of oral immunosuppressants. These compounds act by blocking the exit of lymphocytes from secondary lymph nodes back to blood during the immunosurveillance process. This causes a significant reduction in the number of lymphocytes in blood (lymphopenia) and prevents autoreactive lymphocytes to reach and destroy the target tissues in autoimmune diseases. Among the 5 existing S1P receptors, the subtype S1P1 is the responsible for the lymphopenic effect of these compounds.

Fingolimod had shown *in vivo* activity in several models of immune-mediated diseases in rodents. The compound was, later on, found to be a prodrug that, after phosphorylation, is converted into an agonist of four S1P receptors, namely S1P1, S1P3, S1P4 and S1P5. The efficacy of fingolimod has been confirmed in phase 3 clinical trials in patients with multiple sclerosis. Several pharmaceutical companies are currently developing direct agonists (i.e., they do not require phosphorylation to be active), that are selective for the S1P1 receptor, with the aim of improving safety.

In this Poster, we shall describe the discovery of amido-1,3,4-thiadiazoles as a novel structural class of potent and selective direct S1P1 agonists. From a weakly-active HTS hit, using conformational analysis and competitor SAR in conjunction with a homology model of the S1P1, we optimised *in vitro* activity and selectivity, while maintaining drug-like properties. Rapid *in vivo* PK-PD evaluation was carried out in an oral rat lymphopenia model; key compounds were further profiled by oral dosing in an experimental model of multiple sclerosis in rats. This hypothesis-driven cycle resulted in a sub-nanomolar advanced lead, with exceptional selectivity for S1P1 over S1P3. The full SAR evolution and full pharmacological profiling of this compound will be described in detail.

MEDI 165

Structure-based design of potent, conformationally constrained, cell-permeable STAT3 inhibitors

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STAT3, the signal transducer and activator of transcription 3, is a transcription factor that transmits signals directly from cell surface receptors to the nucleus. Persistent activation of STAT3 signaling has been demonstrated to contribute directly to oncogenesis by stimulating cell proliferation and preventing apoptosis in human cancer cells. Activation of STAT3 not only provides a growth advantage to tumor cells, allowing their accumulation, but also confers resistance to conventional therapies that rely on apoptotic machinery to eliminate tumor cells. STAT3 is thus an attractive cancer therapeutic target.

Herein we report the structure-based design, synthesis and evaluation of a new class of conformationally constrained peptidomimetic inhibitors of STAT3. Our efforts have produced a set of compounds that bind to STAT3 with high affinities. Furthermore, by incorporating a long hydrocarbon chain into one STAT3 ligand to improve cell-permeability, we have successfully obtained a potent and cell-permeable STAT3 inhibitor.

MEDI 166

Structure and activity relationships of tartrate-based TACE inhibitors

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The syntheses and structure activity relationships of the tartrate-based TACE inhibitors are discussed. The optimization of both the prime and non-prime sites led to compounds with picomolar activity. Several analogs demonstrated good rat pharmacokinetics.

MEDI 167

New nNOS PDZ domain ligands and their biological evaluation

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PDZ domains are small protein-protein interaction modules that bind free C-terminal peptides or internal protein regions. Although PDZ domains share a common three-dimensional structure, they differ in their binding specificities. Interactions involving PDZ domains may be the target of novel drugs for important disease states.

PSD95 recruits nNOS to the NMDA receptor, providing Ca²⁺-mediated nNOS activation adjacent to the NMDA-receptor-mediated Ca²⁺ influx. The over stimulation of the NMDA receptors has been related to several neurodegenerative diseases. Disrupting the PSD95/nNOS interface likely provides fewer side effects than targeting the PSD95/NMDA receptor interface or the NMDA receptor itself.

The nNOS PDZ domain participates in the above interactions. New nNOS PDZ domain ligands aimed at interfering with the formation of the ternary complex have been synthesized on solid phase. These inhibitors were also bound to molecular transporters to allow cellular internalization. The affinity for the nNOS PDZ domain has been established.

MEDI 168

Synthesis of a series of nonpeptidic thiochromanone-based thiosemicarbazone analogs as inhibitors of cathepsin L

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Cathepsin L is an attractive target for drug design due to the important role that it plays in a variety of diseases including SARS, arthritis, and tumor invasion and metastasis. A series of 1,1-dioxo-1-thiochromanone thiosemicarbazone and 1-thiochromanone thiosemicarbazone analogues were designed, synthesized, and evaluated for their inhibitory activity against both cathepsin L and cathepsin B. The majority of the functionalized thiochromanone analogues were prepared utilizing a polyphosphoric acid mediated ring closing reaction. Condensation of the resultant ketone moiety with thiosemicarbazide afforded the requisite thiosemicarbazone derivatives in good yield. The corresponding 1,1-dioxo

analogues were prepared in an analogous fashion with an oxidation step added prior to formation of the thiosemicarbazone moiety. Each of the compounds were evaluated for their ability to inhibit the cysteine proteases cathepsin L and cathepsin B. The most active compounds in the series demonstrate IC₅₀ values in the low nanomolar range. In general, the thiochromanone series of compounds show better inhibition towards cathepsin L as compared to their 1,1-dioxo counterparts. The most active compounds were selective in terms of their ability to inhibit cathepsin L versus cathepsin B.

MEDI 169

Thiosemicarbazone derivatives of functionalized tetralone, indanone, chromanone, and 2,3-dihydroquinolinone scaffolds as inhibitors of cathepsins L and B

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Cathepsins are lysosomal cysteine proteases belonging to the papain family of enzymes. This class of enzymes function primarily as intracellular proteases that are responsible for protein turnover. Upregulation and mislocalization of the cathepsins have been associated with certain types of cancer. Increased extracellular activity of the cathepsins in cancer cells facilitates extracellular matrix and basal membrane degradation, which aids in tumor metastasis. The thiosemicarbazone functional group is known to interact with the active site of many cysteine proteases. The discovery of a potent thiochromanone thiosemicarbazone inhibitor of cathepsin L has led to interest in the tetralone, indanone, chromanone, and 2,3-dihydroquinolinone molecular templates. A series of thiosemicarbazone derivatives of these functionalized scaffolds has been prepared utilizing a variety of synthetic strategies. Details regarding the molecular design and synthesis of these compounds along with preliminary data on their ability to function as inhibitors of cathepsins L and B will be presented.

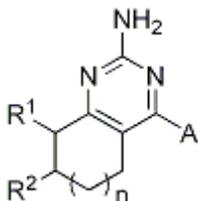
MEDI 170

Rigidified 2-aminopyrimidines as histamine H₄ receptor antagonists: Effects of substitution about the rigidifying ring

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Novel histamine H₄ receptor (H₄R) antagonists containing the 2-aminopyrimidine motif are described.



MEDI 171

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

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We report the synthesis of 3-alkylsulfonylmethyl cyclohexylaminobenzamides (**3**) as

CCR2 inhibitors for the potential treatment of inflammatory diseases. The *in vitro* structure-activity relationships of **3** are described. A number of the alkylsulfone-derived compounds display low-nanomolar binding IC₅₀s for CCR2.



MEDI 172

Synthesis and development of multimeric molecules to mimic the pro-apoptotic ligand TRAIL, a member of the TNF superfamily

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The tumor necrosis factor related apoptosis inducing ligand (TRAIL) is a member of the TNF superfamily that can bind to two apoptosis inducing receptors, namely DR4 and DR5. Initiation of apoptosis by TRAIL requires receptor oligomerization on the cell membrane. This is documented by crystallographic studies of TRAIL/DR5 complexes, which reveal a homotrimeric ligand binding to three copies of the receptor. Experimental studies have shown that TRAIL can trigger apoptosis in tumor cells while sparing normal ones. These results provided the basis to the clinical development of new anticancer approaches based on signaling by TRAIL. Recently, small apoptogenic peptides that bind to DR5 have been reported (Angell *et al.*, 2005). In the present study, we synthesized and used these sequences to systematically study the effect of peptide multimerization (dimerization, trimerization, anchoring point) on DR5 binding and selective DR5-mediated death induction *in vitro* and *in vivo* (Pavet *et al.*, 2010).

MEDI 173

Utilizing a pharmacophore model for the development of potent small molecule inhibitors of STAT3 function

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Signal Transducer and Activator of Transcription 3 (Stat3) is a regulatory protein implicated in the anti-apoptotic behaviour of many human cancers. Small molecule knockdown of aberrant Stat3 activity in cancer cells is an effective molecularly targeted method of killing compromised cells. Numerous investigations indicate that small molecule inhibitors can disrupt the transcriptionally active Stat3-Stat3 homo-dimer and selectively halt cancer cell progression. Given the relative importance of STAT3's SH2 domain in

dimerization, we have developed a pharmacophore model via docking analysis of recognized Stat3-SH2 domain inhibitors. Our pharmacophore describes a hetero-tri-substituted scaffold projecting functionality into the three main sub-pockets of STAT3's SH2 domain. Thus, we elected to utilize 2,6,9-trisubstituted aminopurines as a platform for optimal functional group projection. We will present the promising *in vitro* and *in vivo* results derived from our pharmacophore model investigations.

MEDI 174

Design and synthesis of substituted 6-arylquinazolin-4-amines as potent and selective inhibitors of members of the CLK and DYRK kinase families

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Modulation of protein kinases using small molecule inhibitors is a powerful tool to control numerous aspects of cell function and offers the potential for management of various diseases. Among the kinases reported to alter the function of the spliceosome, a protein complex that removes intron sequences from genes, is the cdc2-like kinase (CLK) family. The CLK family contains four isoforms (1-4) that are capable of auto-phosphorylation and phosphorylation of exogenous proteins. These proteins have been implicated in the regulation of mRNA splicing. Herein, we report a new class of 6-arylquinazolin-4-amines with nanomolar potency against CLK1 and CLK4. Several of our molecular probes show high selectivity for one isoform. In addition to CLK potency, several of our lead compounds have high potency and selectivity against similar kinases, DYRK1A and DYRK1B, which are thought to be implicated in the causes of Down's Syndrome and early onset Alzheimer's disease.

MEDI 175

Design, synthesis and structure-activity relationships of potent B-RAF inhibitors

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B-RAF has been identified as a critical initiator and promoter of malignancy, and B-RAF mutations lead to constitutive activation of the kinase. Studies have found that mutations are present in 70% of melanomas, 50% of papillary thyroid cancers, 10% of colorectal cancers and a smaller number of others cancers including early ovarian cancer. Therefore, V600E mutant B-RAF is considered an important target for cancer therapy. From the preliminary SAR derived for the imidazo-oxazole/thiazole chemical class, SAR refinement led to the discovery of very potent mut-B-RAF inhibitors. The design, synthesis and biological properties will be discussed.

MEDI 176

Discovery of pyrazol-3-yl and thiazol-2-yl amino pyrazines as novel JAK2 inhibitors

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Following the discovery of disease linkage between JAK2 mutations and myeloproliferative neoplasms we embraced the identification of selective JAK2 inhibitors to ameliorate such diseases. As part of our efforts we have recently reported several series as JAK2 ATP-competitive inhibitors including the pyrazol-3-ylamino pyrazine series. In this poster we are describing the design, synthesis and biological evaluation of this series. Furthermore the ADME properties of lead compounds along with their *in vivo* evaluation will be reported.

Finally, the identification of thiazol-2-yl amine as an isosteric replacement for pyrazol-3-yl amine in the pyrazine series will be reported. Subsequently the rationale, synthesis and biological evaluation of a thiazol-2-ylpyrimidine-2,4-diamine series derived from the initial pyrazine series will be reported, along with the *in vivo* evaluation of the lead compounds.

MEDI 177

Utilization of 1,3,5-triazine as a pyrimidine surrogate for the evaluation of PDK1 inhibitors

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Shuster⁽¹⁾; Charles Blackledge⁽¹⁾; Seth Grant⁽¹⁾; Art Shu⁽¹⁾; Chris Becker⁽¹⁾; Sridhar Rabindran⁽¹⁾; Christine Gardiner⁽¹⁾; Hong Xiang⁽¹⁾. (1) Signal Transduction DPU, Oncology R & D, GlaxoSmithKline, Collegeville PA 19426, United States

Phosphoinositide-dependent protein kinase-1 (PDK1) is a key regulator of the PI3K pathway, and inhibitors of PDK1 are thought to present a potential class of anti-cancer agents. A series of 6-(indazol-6-yl)-2,4-pyrimidinediamines that are both potent and selective for PDK1 has been discovered. Though the synthesis of these compounds was fairly straightforward, a more flexible route was sought to explore different combinations of the 4- and 6-positions of the pyrimidine core. A 1,3,5-triazine scaffold, which offered synthetic benefits due to its reactive compatibility, symmetry and availability of the triazine starting material, was therefore proposed as a pyrimidine surrogate. The synthesis, SAR, and physical property results of these 1,3,5-triazine-based PDK1 inhibitors will be presented.

MEDI 178

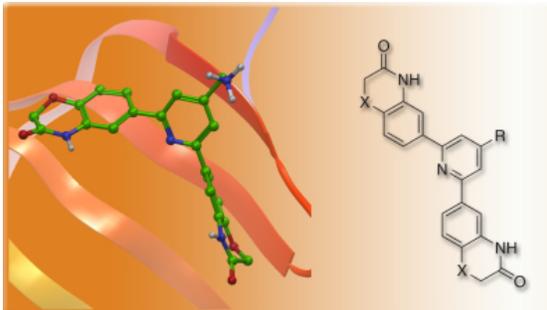
WITHDRAWN

MEDI 179

Structure-based discovery and optimization of a novel protein kinase B (AKT) inhibitor

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Protein kinase B is an attractive therapeutic target in anticancer drug development. Herein we report the findings of virtual screening for novel inhibitors of AKT-2 using sequential docking. The cascade docking approach led to the identification of a low micromolar AKT-2 inhibitor with a novel scaffold [*Bioorg. Med. Chem. Lett.* **2009**, *19*, 4634]. A structure-based design strategy towards the optimization of this hit is also discussed. The newly designed molecules have high predicted affinity for AKT-2; are synthetically accessible and are contained within the kinase-relevant property space.



MEDI 180

Design and synthesis of a novel, potent, and selective class of type II p38 inhibitors

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We had previously reported our work in identifying a class of novel, potent and selective urea-based p38 inhibitors. Guided by our computational fragment-based drug discovery technology, we were able to design type II inhibitors that lack the typical hinge binding portion, common for many reported p38 compounds. In an attempt to modulate the physical properties of the initial urea compounds, we explored in parallel a new class of p38a inhibitors. Our strategy was to constrain the urea and amide motifs of the urea series into 6-5 fused ring systems. Synthesized compounds in this novel class showed good kinase and cell potency, and they were very selective for p38a. In addition, many analogs of this type exhibited good oral bioavailability profile. X-ray structures confirmed that the constrained molecules also bind to p38 in a type II binding mode, having no contact with the hinge.

MEDI 181

Development of a gene family targeted workflow for the identification of inhibitors of kinase targets

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We have developed an efficient workflow for evaluating library ideas and translating the best ideas into products. The process consists of an initial phase in which ideas from medicinal chemists are rapidly evaluated. Ideas chosen based on this assessment are then progressed to detailed design and synthesis, applying an integrated, iterative process to insure the best possible products are produced. We have applied this approach towards the synthesis of kinase targeted libraries. Results based on sampling and screening of the libraries, show a 25% hit rate against selected kinase targets. A retrospective analysis was performed to evaluate the methods used, as well as comparing the approximations made for the rapid initial assessment with the more detailed results from the full design work. The workflow described is applicable to any biologically relevant target or gene family for which novel small molecule modulators are desired.

MEDI 182

Novel approaches to CDK2 modulation: Hit identification, characterization, and optimization

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Cell growth and differentiation is a highly controlled process which, when lost, can lead to aberrant cell function, potentially resulting in disease. Multiple cellular signals can stimulate growth, differentiation, and apoptosis. A key mechanism for regulating these processes involves the cell cycle. Progression through the eukaryotic cell cycle is controlled by the cyclin dependent kinase (CDK) family. Uncontrolled regulation of the cell cycle pathway is thought to be a source of human cancers and inhibition of unregulated CDK activity by small molecule inhibitors should be beneficial in the treatment of cancer.

Most CDK2 research efforts have focused on screening the active active CDK2/Cyclin A complex for direct kinase inhibition. With the intent of finding new modes of inhibition we describe a new strategy of screening inactive CDK2 in the absence of Cyclin A in order to find direct binders which may modulate protein-

protein interactions (i.e. cyclin binding), inhibit phosphorylation of CDK2, or identify non-ATP competitive inhibitors. By utilizing the AS/MS-based ALIS technology, a high-throughput screening campaign using basal CDK2 succeeded in identifying an initial hit series which only binds to CDK2 in the absence of Cyclin A. Optimization of the initial hit utilized several affinity-based assays, including a Fluorescence Polarization (FP) Assay; Isothermal Titration Calorimetry (ITC) and Temperature-dependent Circular Dichroism (TDCD). The formation of a complex of the inhibitor with the CDK2 basal form has been confirmed with a co-crystal structure. The inhibition of binding between CDK2 and Cyclin A has also been demonstrated. This process of screening and binding profiling may serve as an example for future kinase programs and offer alternatives to traditional approaches.

MEDI 183

Design, synthesis and *in vitro* characterization of phosphate pro-drugs of mutant-B-RAF inhibitors

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Raf kinases are effectors in the Ras / Raf / MEK / ERK signaling pathway which are important modulators of cell proliferation, differentiation, survival and angiogenesis. The activating V600E mutation of B-RAF is found in 70% of melanomas and 50% of thyroid carcinomas and therefore has emerged as a key target for treatment of malignant melanomas. Our extensive lead optimization efforts of the imidazo-oxazole chemical class led to several potent and selective mutant-B-RAF inhibitors. A different strategy to improve physico-chemical and pharmacokinetic properties was developed. We initiated a discovery effort toward the identification of a suitable pro-moiety that would confer increased solubility to our lead compounds and stable formulation. We will describe the design, synthesis and characterization of several pro-drugs, highlighting the effect on solubility and stability.

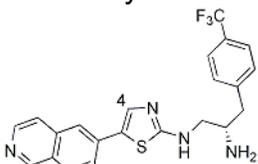
MEDI 184

Design and synthesis of 4-substituted thiazoles as AKT inhibitors

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Huang⁽¹⁾; Bruce Han⁽¹⁾; Erich Wohlhieter⁽¹⁾; John Allen⁽¹⁾; Shiwen Zhang⁽²⁾; Julie Lofgren⁽²⁾; Xiaoling Zhang⁽²⁾; Daniel Freeman⁽²⁾; James Bready⁽³⁾; Carl Davis⁽³⁾; Chris Fotsch⁽¹⁾; Randall Hungate⁽¹⁾; Richard Kendall⁽²⁾. (1) Department of Chemistry Research & Discovery, Amgen Inc., Thousand Oaks CA 91320-1799, United States (2) Department of Oncology, Amgen Inc., Thousand Oaks CA 91320-1799, United States (3) Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks CA 91320-1799, United States

AKT/PKB kinases represent a central node in signal transduction pathways that are important for cellular transformation and tumor progression. Constitutive activation of AKT has been observed in a large proportion of human malignancies and can result from gain-of-function mutations of PI3K and AKT, amplification of receptor tyrosine kinase HER2, and loss-of-function mutations of the tumor suppressor PTEN,. Inhibition of enhanced AKT activity would induce apoptosis and suppress tumor progression. We have reported a novel, potent AKT inhibitor **1** (Zeng et. al BMCL 2010, 20, 1559). In an effort to improve selectivity, pharmacokinetic profile while retaining potency against AKT, we studied the effect of adding additional substituents at the C-4 position of thiazole core. Herein, we describe the synthesis and structure-activity relationships of a series of 4-substituted thiazoles, which led to the identification of potent, selective and orally available AKT inhibitors.



1

AKT1 IC₅₀ = 4.9 nM
AKT2 IC₅₀ = 28.1 nM
PKA IC₅₀ = 59.4 nM
CDK2 IC₅₀ = 12.4 nM

MEDI 185

Design and synthesis of novel heterocyclic scaffolds as protein kinase inhibitor

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Deregulation of kinase activity is often responsible for tumorigenesis. To date, tremendous effort has been invested in the discovery of small molecule kinase inhibitors for the treatment of cancer and other diseases. Based the kinases' X-ray crystal structures and associated molecular modeling studies, our investigation has led to the design and synthesis of novel heterocycles as

potential serine/threonine or tyrosine kinase inhibitors. These compounds contain a core heterocyclic scaffold with hydrogen bond acceptor/donor properties known to be important for the binding of small molecule to the ATP binding pocket of protein kinase. We have developed efficient methodologies for the syntheses of this new compound series. Representative compounds in this series have shown selective inhibitory effect on the growth of renal cancer carcinoma cells (UO31) and human breast adenovarcinoma cells (MCF7), which frequently overexpress various growth factor kinases, including the epidermal growth factor receptor (EGFR) family members (EGFR, Her1/2 in human), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), etc. The Structure-Activity Relationship (SAR) studies are in progress to facilitate further development of this new compound class. Results of this study will be presented.

MEDI 186

Discovery of orally bioavailable Aurora kinase inhibitors

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Aurora kinases are required for orderly progression of cells through mitosis. Small molecule inhibition of these kinases results in aberrant endoreduplication and cell death. Optimization of the imidazo[1,2-a]pyrazine scaffold will be described. Medicinal chemistry efforts lead to the discovery of morpholine-based, orally bioavailable Aurora A/B kinase inhibitors with *in vivo* activity in tumor growth efficacy models.

MEDI 187

Discovery of pyrrolo[2,1-f][1,2,4]triazine C6-ketones as potent, orally active p38 α MAP kinase inhibitors

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The mitogen-activated protein kinase p38 α has been shown to be on the critical path to pro-inflammatory cytokine production (notably TNF- α and IL-1 β). In recent years, biotherapeutic treatments have provided clinical validation for anti-cytokine approaches to treating rheumatoid arthritis, Crohn's disease and psoriasis. Small molecule-based inhibition of p38 α as an alternative approach to block production of these cytokines offers the potential benefits of reduced cost and ease of administration. These aspects, along with the ability to simultaneously affect multiple cytokines and inflammatory mediators, have stimulated continued efforts to develop safe, potent and orally active p38 α inhibitors. Pyrrolo[2,1-*f*][1,2,4]triazine based analogs incorporating aryl and heteroaryl ketones at the C6 position have been prepared leading to potent inhibitors of p38 α . The structure-activity relationships, pharmacokinetic properties, activity in a pharmacodynamic model and efficacy in a rodent model of rheumatoid arthritis will be presented.

MEDI 188

Discovery of 2-aminophenyl quinazolines as potent and selective PDK1 inhibitors

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PDK1 (3-phosphoinositide-dependent protein kinase 1) is a key signaling mediator in the frequently mutated PI3K (phosphoinositide 3-kinase) oncogenic pathway and implicated with growth and survival of many cancers. Inhibitors of PDK1 are believed to have potential as anticancer agents. In recent years, small molecule PDK1 inhibitors are being developed within the pharmaceutical industry.

2-Aminophenyl quinazolines were first identified as weak PDK1 inhibitors in our high throughput screening. Here we wish to describe the use of iterative structure-guided design to improve the potency of initial screening hits and how co-crystal structure analyses of anti-targets allowed us to improve the selectivity of these inhibitors. Structure activity relationship of the series and in vitro/in vivo profile of the representative compound will be discussed.

MEDI 189

SAR of a new series of Stearoyl-CoA desaturase inhibitors

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Obesity and type II diabetes are two of the major health problems found in Western countries and new medicines targeting novel mechanisms are urgently needed. Stearoyl-CoA desaturase (SCD) is one of the major enzymes involved in the lipogenic pathway. Studies in rodents have shown that inhibition, mutation or deletion of SCD has effects on fat utilization and storage, improvement in insulin sensitivity, resistant to diet-induced obesity, reduction of adiposity and plasma levels triglycerides. Therefore, SCD represents an attractive target and its inhibition could lead to the discovery of novel treatments for obesity, type-2 diabetes and related metabolic disorders. Recently, we have disclosed the discovery of **MF-152**¹ and **MF-438**² for assay development and proof-of-concept studies. As a continued effort to identify SCD inhibitors with improved adverse effect profiles, SAR and results on a structurally diverse series of SCD inhibitors will be disclosed.

¹ Li, C.S.; Belair, L.; Guay, J.; Murgasva, R.; Sturkenboom, W.; Ramtohum, Y. K.; Zhang, L.; Huang, Z.; *Bioorg. & Med. Chem. Lett.*, **19**, **2009**, 5214.

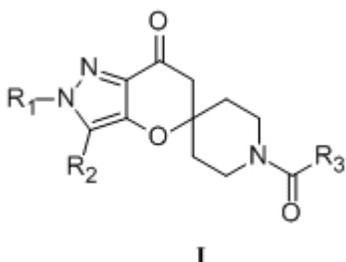
² Léger, S.; Black, C. W.; Deschenes, D.; Dolman, S.; Falguyret, J.-P.; Gagnon, M.; Guiral, S.; Huang, Z.; Guay, J.; Leblanc, Y.; Li, C.-S.; Massé, F.; Oballa, R.; Zhang, L.; *Bioorg. & Med. Chem. Lett.*, **20**, **2010**, 499.

MEDI 190

Synthesis of pyrazolospiroketone ACC inhibitors

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In recent years, acetyl CoA carboxylase (ACC) inhibitors have emerged as novel targets for the treatment of type II diabetes mellitus (T2DM). ACC is a key metabolic switch which regulates lipogenesis and fatty oxidation. To this end, we have identified a series of pyrazolospiroketones **I** as potent ACC inhibitors. Herein, we describe an efficient and scalable route to these compounds.



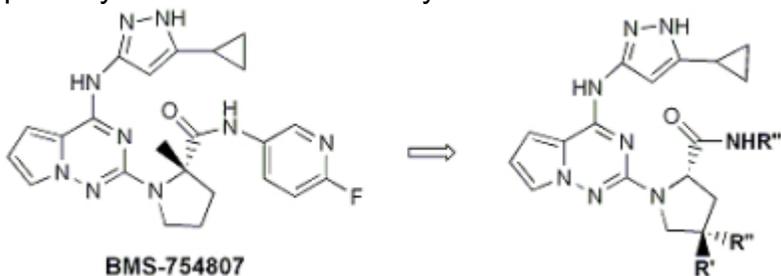
MEDI 191

Discovery of a potent small molecule inhibitor of IGF-1R

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Inhibition of IGF-1R signaling results in blockade of two important pathways for tumor growth: The RAS/Raf/MAP Kinase, pathway primarily responsible for mitogenesis, and the PI-3 kinase pathway which has an anti-apoptotic role. Epidemiological studies have also highlighted the importance of IGF-1R in key tumor types by correlating elevated IGF-I levels with increased risk of developing colon, breast, prostate, and lung tumors. Recently, several inhibitors of IGF-1R

have entered the clinic including OSI-906, Figitumumab (CP-751,871) and BMS-754807. This work is focused on identifying a back up candidate for the clinical candidate BMS-754807. Our efforts were focused on improvements in the potency and metabolic stability of BMS-754807.



MEDI 192

Novel dual agonists of the GPR40 and PPAR γ receptors

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Abstract: Type 2 diabetes is a complex disease characterized by two main deficiencies, namely progressive decline in insulin secretion in pancreatic β -cells and insulin resistance in glucose-utilizing tissues.

Fatty acids are involved in signaling nutrient status to both types of tissues. In β -cells, fatty acids potentiate glucose-stimulated insulin secretion via activation of the GPR40 receptor mostly expressed in those cells. Fatty acids are also involved in adipocyte differentiation and gene transcription via their activation of the nuclear receptor PPAR γ . PPAR γ is the target of the thiazolidinedione class of antidiabetic agents, which reduce insulin resistance peripherally. Molecules capable of simultaneously activating GPR40 and PPAR γ should in principle display higher levels of efficacy compared to molecules aimed at single targets, via the targeting of both T2D deficiencies. We hereby report results of our ongoing efforts aimed at identifying dual GPR40/PPAR γ agonists, which so far resulted in the identification of several dual agonists. Preliminary structure-activity relationships of novel dual and selective agonists will be presented.

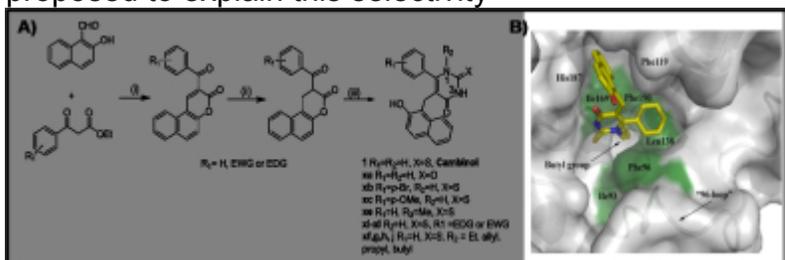
MEDI 193

Novel cambinol analogs as sirtuin inhibitors: Synthesis, biological evaluation and rationalisation of activity

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Sirtuins are a group of NAD⁺-dependent protein deacetylases. Two sirtuin members, SIRT1 and SIRT2 are known to regulate p53 activity by deacetylating this protein. Due to their ability to decrease p53 function, inhibition of SIRT1 and 2 represents a target for cancer treatment.

Cambinol **1** is a moderate and non-selective inhibitor of SIRT1 and SIRT2 showing antitumor activity in preclinical models. We showed that different *N*-1 alkyl substituents (**1e-j**) led to an increase in activity against SIRT2, with **1j** being the most potent SIRT2 inhibitor (IC₅₀ = 1.0 μM). Hydrophobic interactions between the *N*1-aliphatic substituent and a previously unoccupied lipophilic channel around Phe96, Leu138 and Ile169 in the SIRT2 active site were proposed to explain this selectivity



In a second generation of studies we aimed to further explore the SAR associated with these new potent and selective SIRT2 inhibitors. The results of these new studies will be presented.

MEDI 194

Metabolism-guided design of amino alcohol acids as orally active, short-acting calcium-sensing receptor antagonists

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Li⁽¹⁾; Tristan S Maurer⁽¹⁾; Constantin Neagu⁽¹⁾; Vishwas M Paralkar⁽¹⁾; David A Price⁽¹⁾; Keith A Riccardi⁽¹⁾; John Sagal⁽¹⁾; Samantha Spath⁽¹⁾; Ingrid A Stock⁽¹⁾.
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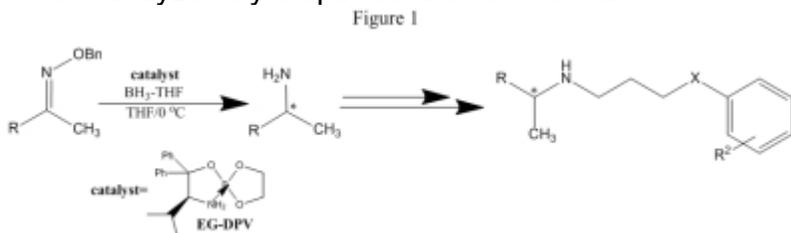
Calcium-sensing receptor (CaSR) antagonists that induce pulsatile elevations in parathyroid hormone (PTH) levels are known to produce significant bone effects with potential for treatment of Osteoporosis. In the CaSR antagonist program at Pfizer, orally active, short-acting amino alcohol acids were identified as promising candidates *via* a metabolism-guided strategy. These agents possess the metabolically labile thiomethyl functionality that provides the desired clearance while delivering a pharmacologically inactive sulfoxide metabolite. Herein, we describe our efforts leading to the identification of these candidates.

MEDI 195

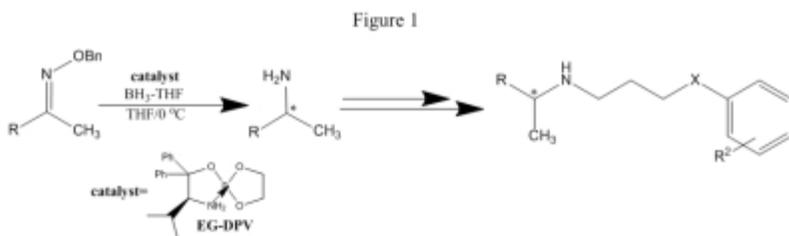
Synthesis of possible calcimimetic derivatives from enantiopure primary amines

Sandraliz Espinosa-Diaz⁽¹⁾, sandrespid@hotmail.com, 100 Carr. 908, Humacao, PR 00791-4300, Puerto Rico ; **Jaime L. Alvarez**⁽¹⁾, jaimelillo@hotmail.com, 100 Carr. 908, Humacao PR 00791-4300, Puerto Rico ; **Kiara M. Santiago**⁽¹⁾, kiara.santiago2@upr.edu, 100 Carr. 908, Humacao PR 00792-4300, Puerto Rico . (1) Department of Chemistry, University of Puerto Rico at Humacao, Humacao Puerto Rico 00792, Puerto Rico

Optically pure amines have been used as chiral building blocks for the synthesis of a variety of biologically active compounds. The asymmetric reduction of oxime ether catalyzed by a spiroborate ester/borane



was developed in our laboratory to afford enantiopure primary amines. Employing only 10% of the catalyst derivative from diphenyl valinol and ethylene glycol (EG-DPV) we obtained the corresponding primary amines in good yields and excellent enantioselectivity (> 95% ee). Calcimimetics are new drugs whose name reflects their major action: to mimic the effect of calcium on calcium receptors. Calcimimetics have the potential to control hyperparathyroidism. A new approach for the synthesis of some novel class calcimimetic analogs has been developed

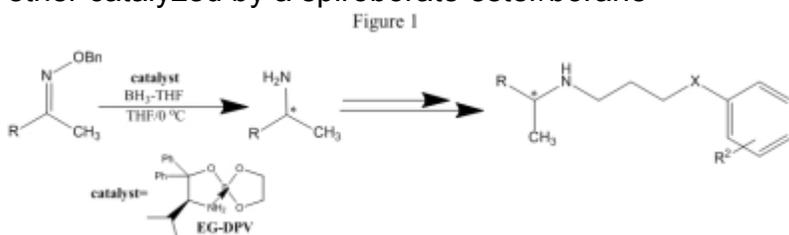


MEDI 195

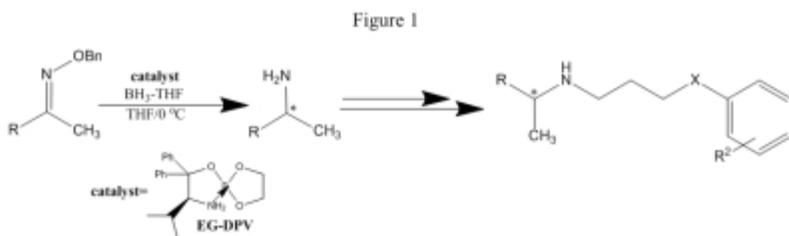
Synthesis of possible calcimimetic derivatives from enantiopure primary amines

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MEDI 196

Discovery of TAK-875: A potent, selective, and orally bioavailable GPR40 agonist

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GPR40, a G protein-coupled receptor predominantly expressed in pancreatic β -cells, mediates enhancement of glucose-stimulated insulin secretion by free fatty acids. A potent and selective GPR40 agonist may prove to be a safe and effective anti-diabetic drug with little or no risk of hypoglycemia. Initial efforts based on ligand-based drug design identified benzyloxyphenylpropanoic acids as a promising lead series. Cyclization of the phenylpropanoic acid moiety of lead compound produced fused phenylalkanoic acids with favorable in vitro agonist activities and pharmacokinetic profiles. Further optimization led to the discovery of TAK-875, a dihydrobenzofuran derivative as a potent, selective, and orally bioavailable GPR40 agonist. The design, synthesis, structure-activity relationship, in vivo animal studies, and molecular modeling study will be presented.

MEDI 197

Investigation of functionally liver selective glucokinase activators

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Type 2 diabetes is a polygenic disease affecting 200 million people worldwide and which is expected to reach epidemic levels within the next decade.

Activators of Glucokinase, a high K_m hexokinase, are currently under investigation by a number of pharmaceutical companies, however only a few have reached early clinical evaluation. A GK activator can potentially decrease glucose levels via improving glucose stimulated insulin secretion from the pancreas and/or decreasing levels of uncontrolled gluconeogenesis in the liver. The increased potential for hypoglycemia by affecting insulin levels via the pancreatic beta cell, led us to pursue a strategy to generate liver selective agents.

In this paper, the synthesis, SAR and pharmacological evaluation of a series of sulfonamide based glucokinase activators will be described. This culminated in the discovery of a functionally liver selective molecule, which normalized glucose levels in diabetic mice, without affecting pancreatic insulin levels, thereby reducing the risk of hypoglycemia.

MEDI 198

Glucokinase activators with improved physicochemical properties and off target effects

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Type 2 diabetes is a polygenic disease affecting 200 million people worldwide and which is expected to reach epidemic levels within the next decade.

Activators of Glucokinase, a high K_m hexokinase, present in key glucose metabolising tissues are currently under investigation by a

number of pharmaceutical companies, however only a few have reached early clinical evaluation.

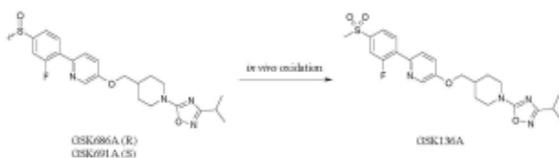
In previous disclosures, we have reported a series of potent, functionally liver selective, sulfonamide based glucokinase activators. As part of our continued efforts towards optimization of this scaffold, we hereby detail synthesis and SAR around a series of compounds with both improved physicochemical parameters and off target effects. This culminated in the discovery of a potent, water soluble glucokinase activator with reduced off target effects which normalized blood glucose levels in diabetic animals.

MEDI 199

Investigation of chiral sulfoxide GPR119 agonists for type 2 diabetes

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A series of potent biaryl GPR119 agonists exemplified by GSK136A was discovered with the aid of our Drug Rings Database. This series possessed poor aqueous solubility and, in turn, mediocre oral exposure in rodents, which resulted in low efficacy in a rat IVGTT model. Sulfoxides of GSK136A were prepared in racemic fashion, and then separated to provide chiral sulfoxides. These sulfoxides, resulted in improved exposure of GSK136A and better efficacy in our animal model than when GSK136A was dosed separately.

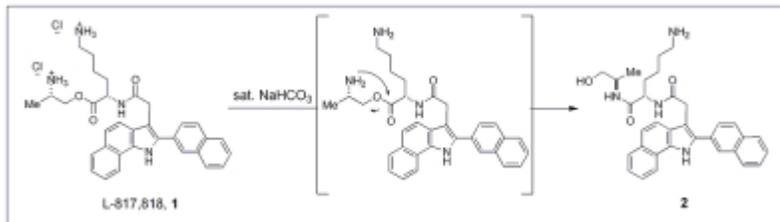


MEDI 200

Rearrangement of the SSTR5 agonist L-817,818 under physiological conditions affords an alternate SSTR5 agonist that elevates plasma glucose excursion during OGTT

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Somatostatin plays an important role in the regulation of endocrine secretion via five distinct receptors (SSTR1-5), and recent evidence implicates SSTR5 in the contributory control of glucose-stimulated insulin release from the endocrine pancreas. The commercially available ester derivative **1** (L-817,818)



has been reported as a selective, non-peptidyl SSTR5 agonist.¹ We show herein that **1** re-arranges under both basic and neutral experimental or assay conditions to afford the corresponding amide derivative **2**, as confirmed by both HPLC and ¹H NMR studies. Compound **2** is a potent and selective SSTR5 agonist in its own right, with activity against the human, mouse, rat and dog SSTR5 receptors. Administration of the compound in both rat and mouse oral glucose tolerance test (OGTT) experiments leads to an increase in blood glucose excursion, and the effect is entirely ablated in the SSTR5^{-/-} mouse strain.

1. Rohrer et al., *Science*, **1998**, 282, 737.

MEDI 201

Design, synthesis and evaluation of novel (4-piperidiny)-piperazine class as acetyl-CoA carboxylase 1/2 non-selective inhibitors

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Acetyl-CoA carboxylases (ACCs), the rate limiting enzymes in de novo lipid synthesis, play important roles in modulating energy metabolism. The inhibition of ACC has demonstrated promising therapeutic potential for treating obesity and type 2 diabetes mellitus in transgenic mice and preclinical animal models. We have recently reported the identification of (4-piperidiny)-piperazine core as a new platform for non-selective ACC1/2 inhibitor and its structure-activity relationship. The subsequent structural modifications resulted in a series of potent ACC inhibitors. The synthesis, SAR, and biological profiles of the (4-piperidiny)-piperazine class of ACC 1/2 non-selective inhibitors will be presented.

MEDI 202

Discovery of O-spiroketal C-arylglucosides as novel and selective sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes

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Inhibition of sodium-dependent glucose cotransporter 2 (SGLT2) has been proposed as a novel therapeutic approach to treat type 2 diabetes. In our efforts to find novel inhibitors of SGLT2, we generated a 3D pharmacophore model based on the superposition of known inhibitors. A search of the Cambridge Structural Database using the pharmacophore model as a query led to the discovery of an O-spiroketal C-arylglucoside scaffold. Computational modeling and chemical examination resulted in the identification of the clinical candidate CSG452. Process of the scaffold exploration, synthetic methods and the *in vitro* and *in vivo* profiles of select compounds will be described.

MEDI 203

Synthesis and evaluation of a series of piperazinyropyridines as GPR119 agonists

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GPR119 is a recently discovered GPCR expressed in pancreatic islets and gastrointestinal (GI) tract. It has been reported that small molecule GPR119 agonists promote incretin release and nutrient-stimulated insulin secretion, thus contributing to lowering plasma glucose levels during oral glucose tolerance tests (OGTTs). Furthermore, some GPR119 agonists have been reported to slow gastric emptying, reduce food intake and promote weight loss. We synthesized a series of 2, 5-disubstituted pyridines containing piperazines with the general structure (**1**), and screened these compounds against human GPR119 receptor. Through SAR analysis, compounds containing 2-alkylsulfonylpiperazinyl-5-alkoxy pyridines were discovered and found to be potent agonists of the human GPR119 receptor. One of the most potent compounds (**2**) in this series, with the structure shown below, showed an EC₅₀ = 0.09 μM. The *in vitro* potency and

efficacy of this series of compounds against human GPR119 receptor are detailed in this poster.

MEDI 204

Structure-based Virtual Screening for the discovery of potential P2Y₁₄ receptor ligands

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P2Y₁₄ is a purinergic receptor belonging to the superfamily of G-protein couple receptors (GPCRs). The development of novel ligands, especially antagonists, would be helpful to better understand not only the physiological role of P2Y₁₄ but also the activation mechanism and the structural aspects of ligand binding of this receptor. Our previously published 3D model P2Y₁₄, obtained by means of homology modeling based on the crystal structure of A₂A and optimized in presence of UDP sugar-derivatives, has been used for further computational studies on our target. Some site-directed mutagenesis experiments were suggested to corroborate the binding modes of P2Y₁₄ agonists and the involvement of some critical residues in the interactions between receptor and ligands. Using the optimized binding pocket of P2Y₁₄ we also performed a Structure-based Virtual Screening of a large compound library with the goal of identifying new hits, agonists and antagonists, with high selectivity and potency on our target.

MEDI 205

Exploring structural scaffolds as a strategy to design selective ligands

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Designing ligands that are specific towards a receptor is central in the development of ligand selectivity. One approach is via functional group modifications, while another is by directing the functional moieties, in the three-dimensional space, to selectively fit in particular binding pockets. Towards the second goal, here we employed molecular dynamics (MD) simulations as well as quantum mechanics (QM) calculations to determine their feasibility in

reproducing observed experimental product formation in two potential scaffold sources: three stereochemically-related peptides and three regioisomerically-related derivatized C₆₀ fullerene bis-adducts. 20-ns explicit-solvent MD simulations were performed for the peptides followed by restrained QM calculations at the B3LYP/PCM/cc-pVTZ//HF/6-31G* level with implicit water, while for the fullerenes the B3LYP/PCM/6-31G**/B3LYP/3-21G* level with implicit toluene was utilized. We correctly predict the cyclization tendencies of two of the peptides, while for the fullerenes the experimentally observed bis-adducts predominate.

MEDI 206

WITHDRAWN

MEDI 207

Art of crystallization and application of single crystal X-ray diffraction to support solid-state characterization of pharmaceuticals

Nancy Tsou⁽¹⁾, nancy_tsou@merck.com, P. O. Box 2000, Rahway NJ 07065, United States ; Arlene Mckeown⁽¹⁾; Richard Ball⁽¹⁾; Michael McNevin⁽¹⁾; Courtney Maguire⁽¹⁾; Alex Chen⁽²⁾; Annette Bak⁽¹⁾. (1) Phase Definition and Material Science, Pharmaceutical Research, Merck Sharp & Dohme Corp., Rahway NJ 07065, United States (2) Center for Material Science and Engineering, Merck Sharp & Dohme Corp., Rahway NJ 07065, United States

Single crystal x-ray crystallography (SCXRD) is often referred to as the gold standard for characterization of crystalline material. Within the pharmaceutical industry, SCXRD plays a large role in helping to address lead optimization and modeling questions in drug discovery, and also helps to define the physical properties of active pharmaceutical ingredients (APIs) in drug development. Moreover, SC-XRD plays an important role for filing and intellectual property protection.

The work described herein details the use of small molecule SCXRD to support solid-state characterization at Merck Sharp & Dohme Corp. The general approaches to obtaining diffraction quality crystals for successful structure determination are also discussed. Several case studies will be presented : 1) determination of the absolute stereochemistry/structure connectivity of complex small molecules to help identify lead candidates in drug discovery, 2) determination of the structures of API polymorphic forms to help select the optimal form for drug development, and 3) determination of a novel API co-crystal structure.

MEDI 208

Estrogen receptor antagonist-functionalized gold nanoparticles for breast cancer drug delivery and imaging systems

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Developing a drug delivery system that targets a specific cancer constitutes a major challenge in medicine. Herein, we report the results of our initial study in which we use therapeutic drug-target hybrids and multifunctional gold nanoparticles (AuNPs) of estrogen receptor (ER) antagonist-functionalized with cytotoxic drug, to treat breast cancer cells.

Tamoxifen,

a common drug for treating ER(+) breast cancer was used as a standard. The initial *in vitro* data indicated that both Tamoxifen (Tam) and Doxorubicin (Doxo) modified with heterobifunctional linkers, inhibit the proliferation of both ER α (+) MCF-7, and ER α (-) MDA-MB-231; in contrast our modified steroidal

ER antagonists showed slow inhibition as of 17 β -estradiol in both cell lines. These studies suggest that the modified ER antagonists and cytotoxic drugs can be used in bioconjugation for multidrug system (Figure 1). In addition, AuNPs functionalized with the both ER antagonists and cytotoxicity drugs demonstrated increased intracellular uptake and drug potency (IC₅₀) when compared with either 17 β -estradiol or Tamoxifen.

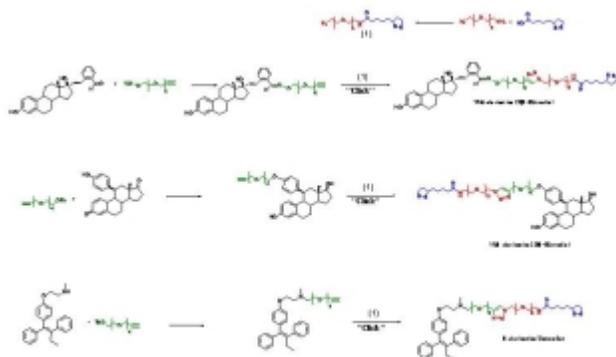


Figure 1: Synthetic modification of ER antagonist and Tamoxifen

Our approach in making functionalized AuNPs is to use an initial primer, an azido lipoamide on AuNPs, which serves to activate the surface toward its complementary

derivative (Figure 2). Different variations of 17 β -estradiol moiety are then ligated to the primed AuNPs via “Click” chemistry. Our preliminary data suggest that the AuNPs surface can be coated with a mixture of primers that have different terminal groups. Therefore, multiple targeting moieties can be appended in a modular and chemo-orthogonal manner. Optimization of this strategy would lead to the development of a versatile platform technology for multi-functional AuNPs drug delivery and imaging systems.

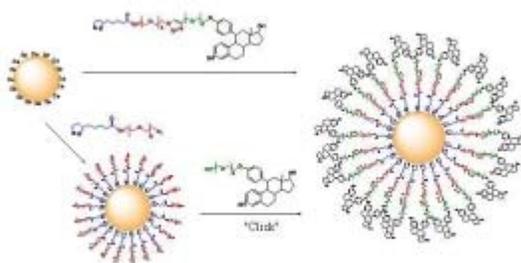


Figure 2: A representative scheme for ER antagonist functionalized AuNPs-top down and convergent methods

MEDI 209

Bipolar biphenyl proteomimetics as estrogen receptor α and androgen receptor coactivator binding inhibitors

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It has been shown that inhibiting the binding of coactivator proteins to nuclear receptors can decrease the cell proliferation that leads to tumor growth in many cancers. Coactivator proteins bind to nuclear receptors through a conserved LXXLL (FXXLF) motif and a charge clamp provided by polar residues flanking the coactivator binding domain (CBD). We have previously described the synthesis of a proteomimetic scaffold consisting of a bipolar biphenyl core substituted at the 3 and 3' positions with hydrophobic side chains capable of inhibiting coactivator binding to estrogen receptor alpha. Here we report the biological evaluation of a larger compound library that varies the

identity of the hydrophobic substituents as well as the polar termini which support the ability of these compounds to compete for the CBD of both estrogen receptor α and androgen receptor.

MEDI 210

Identification of a novel series of [2.2.1]-oxabicyclo lactam-based androgen receptor antagonists

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The development and progression of carcinoma of the prostate is known to be dependent on androgens and the signaling which results from their ligation to the androgen receptor (AR). Though current therapies show good initial response rates, a large percentage of patients will progress to castration resistant prostate cancer. Though palliative treatments are available, there are few treatments for this unmet medical need. The identification of small molecule AR antagonists that are more effective than current therapies has been an ongoing goal for our lab. A novel series of [2.2.1]-oxabicyclo lactam-based compounds were identified as potent antagonists of the AR. Iterative drug design was performed

leading to compounds which demonstrated *in vivo* efficacy upon oral dosing in the CWR-22 human prostate tumor xenograft model. This presentation will cover the SAR of this series of AR antagonists.

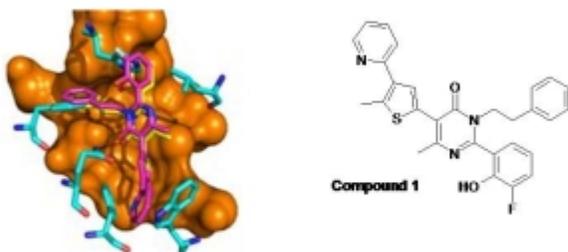
MEDI 211

Development and application of the pharmacophore model of pregnane X receptor

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Robert Marquis⁽¹⁾. (1) Immuno-Inflammation, GlaxoSmithKline, Collegeville PA 19426, United States (2) Computational Chemistry, GlaxoSmithKline, Collegeville PA 19426, United States (3) Structural Biology, GlaxoSmithKline, RTP NC 27711, United States

PXR is a nuclear receptor that is responsible for inducing the expression of CYP3A4, an enzyme known to metabolize >50% of marketed drugs. Therefore, compounds with PXR liability may potentially lead to drug-drug interactions. As such, it is requisite to address this issue prior to selection of preclinical candidate. Our efforts to overcome PXR liability were successful in identifying multiple analogs with lower induction potential which ultimately delivered a lead analog (1). We have also had successfully co-crystallized multiple analogs with the ligand binding domain of h-PXR which extended our understanding of the binding mode of analogs.



The poster highlights the description of how pharmacophore model was generated, its utility, and how it compares to the reported understanding of the binding pocket. It will also illustrate general characteristics of PXR agonists and highlight molecular properties which may reduce affinity towards this promiscuous receptor. The key learnings from our efforts can be applied to other programs that may encounter similar concerns.

MEDI 212

Synthesis and evaluation of fluorinated β 1-adrenoreceptor selective ligands

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Guaraldi⁽¹⁾; Jennifer McDonald⁽¹⁾; Mikhail Kagan⁽¹⁾; Simon Robinson⁽¹⁾; David Casebier⁽¹⁾. (1) Research and Development, Lantheus Medical Imaging, North Billerica MA 01862, United States

The β_1 - and β_2 -adrenoreceptors (AR) play an important role in the regulation of heart function, where variability in the number or ratio of β -ARs has been allied with diverse stages of disease. In the specific case of heart failure, reports have confirmed that down-regulation of β_1 -AR density may predict left ventricular dysfunction and therefore serve as a leading indicator of clinical progression. Despite this considerable opportunity to improve both risk assessment and modern patient management, no clinically relevant conjugates exist for the diagnostic imaging of cardiac β_1 -ARs.

In this presentation, we will describe an extensive series of fluorinated β_1 -AR selective antagonists useful for the tomographic imaging of cardiac β_1 -ARs. Noteworthy among the highlighted conjugates are several derivatives of ICI 89,406, that preserve useful levels of potency and selectivity (IC_{50} : 0.04-0.25 nM; β_1/β_2 : 65-448). Translation of select constructs into ^{18}F -labeled congeners and consequent in vivo performance will also be revealed

MEDI 213

Tetra-aryl cyclobutanes as direct inhibitors of the nuclear receptor/coactivator interaction

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In a continued effort to develop novel therapeutics for the management of hormone receptor-driven cancers, we have developed a set of 1,3-biphenyl-2,4-bipyrimidynyl-cyclobutanes that directly disrupt the interaction between the estrogen and androgen receptors and their coactivators. These compounds differ from traditional nuclear hormone receptor antagonists in that they bind to the surface of the receptors, as opposed to an internal hydrophobic pocket, and are active even in the presence of an agonist ligand. The cyclobutanes are active in both in vitro (time-resolved FRET) and cell-based (luciferase reporter gene) assays, and bind with affinities ranging from submicromolar to low micromolar. These preliminary results suggest that compounds with this mechanism of action may prove efficacious in the treatment of hormone-refractory breast and prostate cancers.

MEDI 214

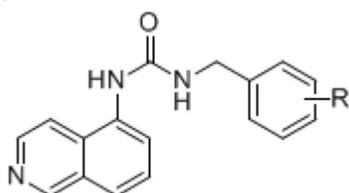
WITHDRAWN

MEDI 215

Design, synthesis, and evaluation of isoquinoline urea derivatives of A-425619 as TRPV1 antagonists

Neha A Gujarati⁽¹⁾, *neha.gujarati06@stjohns.edu*, 301 St. Albert Hall, 8000 Utopia Parkway, Queens NY 11439, United States ; **Bradley J. Undem**⁽²⁾; **Vijaya L Korlipara**⁽¹⁾. (1) Department of Pharmaceutical Sciences, St. John's University, Queens NY 11439, United States (2) Asthma and Allergy Center, Johns Hopkins, Baltimore MD 21224, United States

A series of thirteen transient receptor potential vanilloid receptor 1 (TRPV1) antagonists derived from A-425619 (hTRPV1 IC₅₀ = 4nM) was synthesized and tested for TRPV1 antagonist activity in a functional assay using the guinea pig trachea. In addition, molecular modeling studies were carried out on a congeneric series of analogues in order to correlate the biological activity and predicted activity of these analogues. The results of these studies will be presented



R
p-CF₃ (A-425619)
m, *p*-NO₂
o, *m*, *p*-NH₂
o, *m*, *p*-NHCOCH₃
o, *m*, *p*-NCS
p-Cl, *p*-Br

MEDI 216

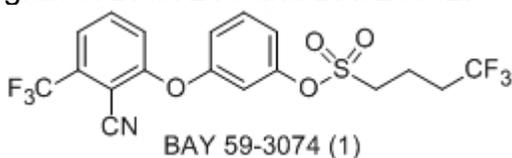
Conformationally constrained analogs of BAY 59-3074, a CB1 cannabinoid receptor partial agonist

Heidi Teng⁽¹⁾, *teng.h@neu.edu*, 360 Huntington Ave, Boston MA 02115, United States ; **Ganesh Thakur**⁽¹⁾; **Alexandros Makriyannis**⁽¹⁾. (1) Center for Drug Discovery, Northeastern University, Boston MA 02115, United States

Two cannabinoid receptors (CB1 and CB2) which belongs to the superfamily of GPCRs play a vital role in multiple physiological functions. CB1 is found primarily in the central nervous system (CNS) and CB2 in the periphery. BAY59-3074(**1**) is a structurally novel high affinity partial agonist of CB1 and is an attractive lead for further optimization. To better understand the conformations optimal for receptor recognition we have designed and synthesized a number of conformationally constrained analogs of **1**. In this work we have identified a novel dibenzofuran series that binds to the cannabinoid receptors and exhibit receptor selectivity. The design, synthesis, computational analysis and biological evaluation of these analogs will be discussed.

Acknowledgment. This work has been supported by National Institutes of Health

grants: DA07215 and DA023142.



MEDI 217

Arylguanidines as analgesic adjuvants: Graphics modeling studies

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Our laboratory has shown that arylguanidines, e.g. *meta*-chlorophenylguanidine (MD-354), acts as an analgesic adjuvant when co-administered with clonidine due, in part, to an α_2 -adrenoceptor (AR) mechanism. MD-354 binds at the low-affinity states of $\alpha_{2A/2B/2C}$ -ARs (K_i =110, 220, 4,700 nM, respectively) and the high-affinity states of $\alpha_{2A/2B/2C}$ -ARs (K_i =825, 25, 140 nM, respectively). Furthermore, functional assays show that MD-354 is a weak partial agonist at α_{2A} -ARs, but an antagonist at $\alpha_{2B/2C}$ -ARs.

To help explain binding and functional activity we generated homology models of $\alpha_{2A/2B/2C}$ -ARs (β_2 -AR template: pdb=2RH1) and performed docking studies (GOLD). For example, binding modes of MD-354 at the α_{2A} -AR active-state model are similar to endogenous ligands, including hydrogen-bond interactions with TM5 serine(s). Although MD-354 lacks this interaction in the inactive-state, the increased affinity could be due to stronger ionic interactions with the conserved aspartate (D3.32) and additional hydrophobic interactions. These findings are consistent with the partial agonist nature of MD-354.

MEDI 218

Novel peptidyl boronic acid based inhibitors of PSA

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United States (2) Department of Pharmacology and Molecular Science, The Johns Hopkins University, School of Medicine, Baltimore MD 21231, United States

Prostate-Specific Antigen (PSA) is a well known serine protease used extensively as a prostate cancer biomarker. High levels of enzymatically active PSA are produced by androgen dependent as well as androgen independent prostate cancers. Even though the expression of PSA is closely related to the cancer progression its role in the cancer pathobiology is not well established. To aid the better understanding of the PSA role in prostate cancer development and the design of new therapeutic agents we have prepared a library of new PSA inhibitors. Based on the PSA specific cleavage map and specific substrates identified earlier in our group we developed peptidyl boronic acid inhibitors. These candidates for targeted inhibition were synthesized and screened for their ability to inhibit PSA.

MEDI 219

Amino aryl sulfonamides as novel and potent 5-HT₆ receptor ligands

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Over the last decade, several research groups have demonstrated the usefulness of 5-HT₆ receptor ligands in the treatment of Alzheimer's disease, Parkinson's disease, Schizophrenia and other neurodegenerative disorders. However, lack of desirable pharmacokinetic properties required for these CNS agents, has greatly hampered the full characterization of functional and physiological usefulness of these molecules. As a part of the ongoing program at Suven Life Sciences Ltd, for the synthesis of selective 5-HT₆ receptor ligands, attempts have been made to optimize the drug-like properties of these compounds by suitably modifying their physicochemical properties, which resulted in a series of potent ligands on a chemically novel skeleton. Herein we report a novel series of potent and selective amino aryl sulfonamides as 5-HT₆ receptor ligands with K_i in the range of 2 to 10 nM. The lead compound was found to be orally active in preclinical models of cognition like NORT and Water Maze. The synthesis, physicochemical properties and the *in-vitro* binding data along with the SAR will be discussed.

MEDI 220

Strategy for conjugation of “clickable” agonists of the A₃ adenosine receptor to polyamidoamine (PAMAM) dendrimers

Dilip K Tosh⁽¹⁾, toshd@niddk.nih.gov, Blg 8; Rm B1A15, Bethesda Maryland 20892, United States ; *Leena S Yoo*⁽²⁾; *Moshe Chinn*⁽³⁾; *Zhan-Guo Gao*⁽⁴⁾; *Kenneth A Jacobson*⁽⁵⁾. (1) Laboratory of Biorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda Maryland 20892, United States (2) Laboratory of Biorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda Maryland 20892, United States (3) Laboratory of Biorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda Maryland 20892, United States (4) Laboratory of Biorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda Maryland 20892, United States (5) Laboratory of Biorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda Maryland 20892, United States

(N)-Methanocarba nucleosides containing bicyclo[3.1.0]hexane, a replacement of the ribose ring system were previously demonstrated selective A₃ adenosine receptor (AR) agonists. Here we modified a series of (N)-methanocarba nucleoside 5'-uronamides to contain dialkyne groups on an extended adenine C2 substituent. The proximal alkyne was intended to promote receptor recognition, and the distal alkyne reacted with azides to form triazole derivatives *via* click cycloaddition. Click chemistry was utilized to couple an octadiynyl A₃AR agonist to azido-containing fluorescent, chemically reactive, biotinylated, and other moieties with retention of selective binding to the A₃AR. The most potent and selective novel compound in the series was a 1-adamantyl derivative (K_i 6.5 nM). The maximal functional effects in inhibition of forskolin-stimulated cAMP were measured, indicating that this class of click adducts varied from partial to full A₃AR agonist compared to other widely used agonists. Thus, this strategy provides a general chemical approach to linking potent and selective A₃AR agonists to reporter groups of diverse structure and to carrier moieties. This strategy is also used to couple the distal alkyne of a 2-octadiynyl nucleoside to an azide-derivatized G4 (fourth-generation) PAMAM dendrimers. A₃AR activation was preserved in these multivalent conjugates, which bound with apparent K_i of 0.1-0.3

nM. They were substituted with nucleoside moieties, solely or in combination with water-solubilizing carboxylic acid groups derived from hexynoic acid. A comparison with various amide-linked dendrimers showed that triazole-linked conjugates displayed selectivity and enhanced A₃AR affinity. Multiple ligands were conjugated to a PAMAM dendrimer containing equiproportioned peripheral azido and amino groups.

A bifunctional conjugate activated both A₃ and P2Y₁₄ receptors with selectivity in comparison to other ARs and P2Y receptors. This is the first example of targeting two different GPCRs with the same dendrimer conjugate, which is intended for activation of heteromeric GPCR aggregates.

MEDI 220

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MEDI 221

Structure-activity relationship of (N)-methanocarba phosphonate analogs of 5'-AMP as cardioprotective agents acting through a cardiac P₂X receptor

Santhosh Kumar Thatikonda⁽¹⁾, thatikondas@niddk.nih.gov, Building 8, Room B1A15, 9000 Rockville Pike, Bethesda Maryland 20892, United States ; Si-Yuan Zhou⁽²⁾; Bhalchandra V Joshi⁽¹⁾⁽³⁾; Ramachandran Balasubramanian⁽¹⁾; Tiehong Yang⁽²⁾; Bruce T Liang⁽²⁾; Kenneth A Jacobson⁽¹⁾. (1) Molecular Recognition Section, National Institutes of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda Maryland 20892, United States (2) Pat and Jim Calhoun Cardiology Center, University of Connecticut Health Center, Farmington Connecticut 06030, United States (3) Nektar Therapeutics, Bethesda Maryland 20892, United States

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 bicyclic ring system

(bicyclo[3.1.0]hexane) in place of ribose, activates this cardioprotective channel. This ring system impedes hydrolysis of the 5'-phosphate in a model compound by its nucleotidase. A more chemically and biologically stable linkage than the phosphate group in MRS2339 has been introduced in the form of the phosphonate groups using Michaelis–Arbuzov and Wittig reactions, which provided

various short chain, saturated or unsaturated long chain phosphonate and short chain methyl phosphonate analogues.

After chronic administration of these phosphonates via a mini-osmotic pump (Alzet), some analogues significantly increased intact heart contractile function in calsequestrin-overexpressing mice (genetic model of heart failure) compared to vehicle-infused mice. Two phosphonates, (1'S,2'R,3'S,4'R,5'S)-4'-(6-amino-2-chloropurin-9-yl)-2',3'-(dihydroxy)-1'-(phosphonomethylene)-bicyclo[3.1.0]hexane,

MRS2775, and its homologue MRS2935, both 5'-saturated, containing a 2-Cl substitution, improved echocardiography-derived fractional shortening (20.25% and 19.26%, respectively, versus 13.78% in controls), while unsaturated 5'-extended phosphonates, all 2-H analogues, and a methylphosphonate were inactive. However, it is worth noting that all these phosphonate analogues were inactive at 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. Thus, chronic administration of nucleotidase-resistant phosphonates conferred a beneficial effect, likely via cardiac P2X receptor activation. Therefore, we have greatly expanded the range of carbocyclic nucleotide analogues that represent potential candidates for the treatment of heart failure.

MEDI 221

Structure-activity relationship of (N)-methanocarba phosphonate analogs of 5'-AMP as cardioprotective agents acting through a cardiac P2X receptor

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Center, University of Connecticut Health Center, Farmington Connecticut 06030, United States (3) Nektar Therapeutics, Bethesda Maryland 20892, United States

Cardiac

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After chronic administration of these phosphonates via a mini-osmotic pump (Alzet), some analogues significantly increased intact heart contractile function in calsequestrin-overexpressing mice (genetic model of heart failure) compared to vehicle-infused mice. Two phosphonates, (1'S,2'R,3'S,4'R,5'S)-4'-(6-amino-2-chloropurin-9-yl)-2',3'-(dihydroxy)-1'-(phosphonomethylene)-bicyclo[3.1.0]hexane,

MRS2775, and its homologue MRS2935, both 5'-saturated, containing a 2-Cl substitution, improved echocardiography-derived fractional shortening (20.25% and 19.26%, respectively, versus 13.78% in controls), while unsaturated 5'-extended phosphonates, all 2-H analogues, and a methylphosphonate were inactive. However, it is worth noting that all these phosphonate analogues were inactive at 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. Thus, chronic administration of nucleotidase-resistant phosphonates conferred a beneficial effect, likely via cardiac P2X receptor activation. Therefore, we have greatly expanded the range of carbocyclic nucleotide analogues that represent potential candidates for the treatment of heart failure.

MEDI 222

Chemical enhancement for skin drug delivery using gemini surfactants

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(1) Ernest Mario School of Pharmacy, Rutgers - The State University of New Jersey, Piscataway NJ 08854, United States (2) Faculty of Pharmacy, University of Coimbra, Piscataway NJ 08854, United States (3) Chemistry Department, University of Coimbra, Coimbra 3004-535, Portugal

The objective of this study was to evaluate the efficacy of different alkylammonium gemini surfactants on the *in vitro* permeation of two model drugs using porcine skin. Lidocaine hydrochloride and caffeine were formulated as a 1% hydroxypropylmethylcellulose hydrogel with a drug content of 2.5 and 1.5% (w/w) respectively. Permeation studies ($n \geq 4$) were conducted in vertical Franz-type diffusion cells, with an area of 0.64 cm^2 , a receptor compartment of 5.1 mL filled with PBS, kept at 37°C under stirring, over 24h. Dermatomed skin pieces were pretreated with 60 mL of 0.16 M of enhancer solution in propylene glycol (Azone, dodecyltrimethylammonium bromide and three C_{12} gemini surfactants) for 1h prior application, in the donor compartment, of drug-loaded hydrogel. MTS assay in human dermal fibroblasts and keratinocytes was performed to assess the cytotoxicity of these compounds.

We observed that the gemini surfactant $\text{G}_{12-10-12}$, was the most effective enhancer for lidocaine hydrochloride, while $\text{G}_{12-2-12}$ showed the highest enhancement for caffeine.

MEDI 223

Development of small molecular weight non-aminoglycosides for compound-induced readthrough of premature termination codons caused by nonsense mutations

Jin-Mo Ku⁽¹⁾, organick@chem.ucla.edu, 607 Charles E. Young Drive East, Los Angeles CA 90095, United States ; Liutao Du⁽²⁾; Robert Damoiseaux⁽³⁾; Hailiang Hu⁽²⁾; Carmen Bertoni⁽⁴⁾; Richard A. Gatti⁽²⁾; Michael E. Jung⁽¹⁾. (1) Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles California 90095, United States (2) Department of Pathology and Laboratory Medicine, The David Geffen School of Medicine at UCLA, Los Angeles California 90095, United States (3) Molecular Shared Screening Resources, California NanoSystems Institute, Los Angeles California 90095, United States (4) Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles California 90095, United States

Large numbers of genetic disorders are caused by nonsense mutations.

Compound-induced readthrough of premature termination codons (PTCs) might be exploited as a potential treatment strategy for these diseases. We have successfully developed a sensitive and quantitative high-throughput screening (HTS) protocol using a protein transcription/translation (PTT)–enzyme linked immunosorbent assay (ELISA), for identifying novel PTC-readthrough

compounds using ataxia-telangiectasia (A-T) as a genetic disease model. We screened 34,000 compounds and identified 12 low molecular weight non-aminoglycosides with potential PTC readthrough activity. From these, two leading compounds consistently induced functional ATM protein in ATM-deficient cells containing disease-causing nonsense mutations, as demonstrated by direct measurement of ATM protein, restored ATM kinase activity, and colony survival assays for cellular radiosensitivity. Furthermore, an SAR (Structure Activity Relationship) study of the lead compounds 13 and 14 gave analogues with increased readthrough activity (figure 1). Finally, we demonstrated that some of compounds showed readthrough activity in a nonsense mutated cell based system.

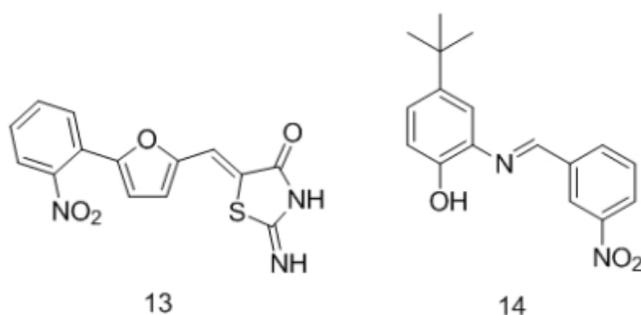


Figure 1.

MEDI 224

Characterizations of diastereoisomers of polyamine analogs with oxime functionalites

Erica Rawls⁽¹⁾, *Rawls.eric@students.mcm.edu*, McM 158, Abilene TX 79697, United States ; *Heather Whitehead*⁽¹⁾; *Jong-Sun Lee*⁽²⁾; *Sung-Kun Kim*⁽²⁾; *Hyunshun Shin*⁽¹⁾. (1) Chemistry and biochemistry, McMurry University, Abilene TX 79697, United States (2) chemistry and biochemistry, Baylor University, Waco TX 76798, United States

Polyamines are a set of aliphatic cationic substances such as putrescine, spermidine, and spermine. Cell growth and cell proliferation are required for a certain level of polyamine in all higher organisms. Since the elevated level of polyamines is expressed in tumor and neoplastic cell lines, the depletion of the polyamine biosynthetic pathway is a promising target for the preventive cancer.

Analogues of polyamines with oxime functionalities are of a great value to be experimented due to hydrogen bonding moieties of different geometrical isomers in interaction with enzymes.

We here present the characterizations of geometrical isomers of ornithine aldoxime derivatives in interaction with ornithine decarboxylase.

MEDI 225

Development and evaluation of a novel radiogallium labeled peptide as a bone imaging agent for PET

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⁶⁸Ga ($T_{1/2} = 68$ min, a generator-produced nuclide) is a great interesting radionuclide for clinical PET. Meanwhile, poly-glutamic acid or poly-aspartic acid has high affinity for hydroxyapatite. In this study, to develop new ⁶⁸Ga labeled bone imaging agents for PET, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was chosen as a chelating site, and Ga-DOTA-conjugated (Asp)₈ peptide (Ga-DOTA-(Asp)₈) was prepared and evaluated with the easy-to-handle ⁶⁷Ga by comparison with ⁶⁷Ga-citrate.

Methods: After DOTA-(Asp)₈ was synthesized by Fmoc-based solid-phase methodology, ⁶⁷Ga-DOTA-(Asp)₈ was prepared by complexation of DOTA-(Asp)₈ with ⁶⁷Ga. Biodistribution experiments for ⁶⁷Ga-labeled compounds were performed in normal mice.

Results: ⁶⁷Ga-DOTA-(Asp)₈ was prepared with a radiochemical purity of over 97 %. In the biodistribution experiments, ⁶⁷Ga-DOTA-(Asp)₈ rapidly and highly accumulated to bone, and was cleared from non-target tissues faster than ⁶⁷Ga-citrate. Consequently, ⁶⁷Ga-DOTA-(Asp)₈ showed a higher bone-to-blood ratio than ⁶⁷Ga-citrate.

Conclusion: ⁶⁷Ga-DOTA-(Asp)₈ holds great potential as a bone imaging agent for PET.

MEDI 226

Fluorescence-labeled celecoxib derivatives as novel pharmacological tools

Andreas P. Lill⁽¹⁾, lill@pharmchem.uni-frankfurt.de, Max-von-Laue-Strasse 9, Frankfurt/Main Hesse 60438, Germany ; **Susanne Schiffmann**⁽²⁾; **Sabine Groesch**⁽²⁾; **Ewgenij Proschak**⁽¹⁾; **Holger Stark**⁽¹⁾. (1) Johann Wolfgang Goethe University, LiFF, Institute of Pharmaceutical Chemistry, Frankfurt/Main 60438, Germany (2) Johann Wolfgang Goethe University, Institute of Clinical Pharmacology, Frankfurt/Main 60596, Germany

Celecoxib,

4-(5-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, a cyclooxygenase-2 (COX-2) selective inhibitor, shows COX-dependent and COX-independent anti-carcinogenic effects, which are far from being understood. It was demonstrated that surprisingly the concentrations necessary for these effects are 20-times lower in *in-vivo* than in *in-vitro* assays, which is potentially due to celecoxib-accumulation in certain cell compartments. With use of fluorescence-labeled celecoxib derivatives, as novel pharmacological tools, the accumulation hypothesis and the interactions of celecoxib and its binding partners within cancer cells can be studied and tested.

Based on structure-activity-relationships and molecular docking-experiments different fluorescence-labeled celecoxib derivatives were designed, synthesized and tested for activity. Celecoxib derivatives were coupled with different dansylated linkers to yield fluorescence-labeled analogues at the position of the former trifluoromethyl group and the former tolyl group.

First experiments showed that these derivatives are still active on COX-2, are able to pass the cell membrane and, upon excitation, can be visualized / localized within the cell.

MEDI 226

Fluorescence-labeled celecoxib derivatives as novel pharmacological tools

Andreas P. Lill⁽¹⁾, lill@pharmchem.uni-frankfurt.de, Max-von-Laue-Strasse 9, Frankfurt/Main Hesse 60438, Germany ; **Susanne Schiffmann**⁽²⁾; **Sabine Groesch**⁽²⁾; **Ewgenij Proschak**⁽¹⁾; **Holger Stark**⁽¹⁾. (1) Johann Wolfgang Goethe University, LiFF, Institute of Pharmaceutical Chemistry, Frankfurt/Main 60438, Germany (2) Johann Wolfgang Goethe University, Institute of Clinical Pharmacology, Frankfurt/Main 60596, Germany

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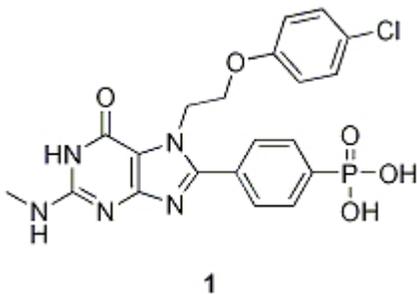
able to pass the cell membrane and, upon excitation, can be visualized / localized within the cell.

MEDI 227

Design and optimization of a potent series of eIF4E inhibitors

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(1) Department of Chemistry Research & Discovery, Amgen Inc., South San Francisco CA 94080, United States (2) Department of Oncology Research, Amgen Inc., South San Francisco CA 94080, United States

eIF4E (eukaryotic initiation factor 4E) plays a central role in cap-dependent translation in eukaryotic cells and is implicated in tumor growth and proliferation. Over-expression of eIF4E is frequently observed in a variety of human tumor types. Thus, a small molecule inhibitor of the eIF4E/mRNA cap interaction was targeted as a potential cancer therapeutic. Through the use of x-ray co-crystallography and molecular modeling we designed a series of potent eIF4E inhibitors derived from the 7-methylguanosine monophosphate (m⁷-GMP) structure. Further structural modification allowed removal of the sugar, phosphate and positive charge without a significant effect upon biochemical potency. These efforts led to compound 1, a potent eIF4E inhibitor (biochemical IC₅₀ = 95 nM).

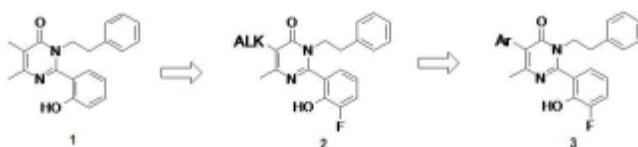


MEDI 228

Discovery of a pyrimidinone-based antagonist of calcium sensing receptor

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



We have explored the SAR and pharmacokinetics of a series of pyrimidinone-based derivatives such as 2-(2-hydroxyphenyl)-5,6-dimethyl-3-(2-phenylethyl)-4(3H)-pyrimidinone (**1**). Analogs related to compound **1** and **2** were shown to have limited oral bioavailability primarily due to rapid liver metabolism. Therefore, efforts to discover compounds with improved potency and pharmacokinetic profiles were undertaken. The structure activity relationships and the developability characterizes of this series of compounds, culminating in the identification of (**3**), will be presented.

MEDI 229

Dimeric modulators of NaC for the treatment of cystic fibrosis

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Excessive

absorption of sodium from the airway surface liquid leads to a thickening of the mucus in the lung of patients with Cystic Fibrosis. This leads to a reduced mucociliary clearance and contributes to the increased risk of respiratory infections. Amiloride, a short acting ENaC blocker, was shown to be beneficial in patients with Cystic Fibrosis in a small pilot study. In the hit to lead phase of our program we

investigated if dimeric, high molecular

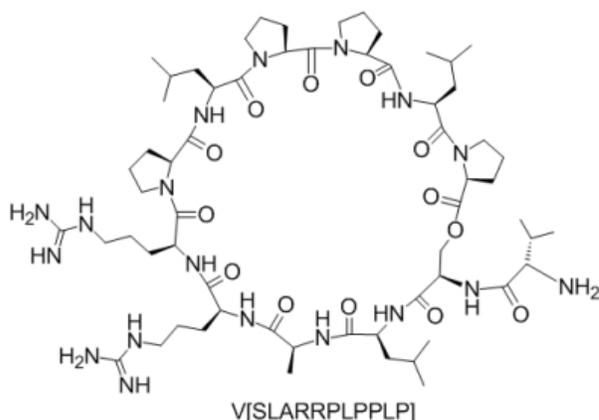
weight, high PSA would have a potential for longer duration of action and less potential for side effects such as hyperkalaemia.

MEDI 230

Conformationally constrained peptides as the Src SH3 domain binding ligands

Rakesh Tiwari⁽¹⁾, *rakeshtiwarisir@gmail.com*, 41 Lower College Road, Kingston RI 02881, United States ; Alex Brown⁽²⁾; Seetha Narramaneni⁽²⁾; Gongqin Sun⁽²⁾; Keykavous Parang⁽¹⁾. (1) Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston RI 02881, United States (2) Department of Cell and Molecular Biology, University of Rhode Island, Kingston RI 02881, United States

Src is a non-receptor tyrosine kinase that is involved in many cellular signaling pathways. The Src SH3 domain regulates Src kinase activity through interactions with proline-rich regions of other proteins. Herein, we report the development of the Src SH3 domain binding ligands by designing conformationally constrained peptides. Previously reported SH3 domain binding ligand linear peptide, Ac-VSLARRPLPPLP (Ac-VSL-12, $K_d = 0.34 \mu\text{M}$), was used as the template. The conformational constraints were introduced through the cyclization between *N*-terminal to *C*-terminal [VSLARRPLPPLP], *N*-terminal to side chain flanking residues (i.e., [β AVS]LARRPLPPLP and [VSLE]RRPLPPLP), and *C*-terminal to side chain V[SLARRPLPPLP]. The peptide V[SLARRPLPPLP]



, which was synthesized through cyclization of C-terminal to the serine side chain displayed a comparable binding affinity ($K_d = 0.35 \mu\text{M}$) towards the Src SH3 domain when compared to Ac-VSL-12. Further optimization of V[SLARRPLPPLP] may be used to generate ligands with higher binding affinity and stability.

MEDI 231

Discovery of novel 4-oxo-2-thioxo-7-quinazoline carboxamides and derivatives as prolyl hydroxylase inhibitors

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Anemia occurs often in cancer patients, particularly those receiving chemotherapy. It is also often seen in the elderly population, patients with renal disease, and in a wide variety of conditions associated with chronic disease. Frequently, the cause of anemia is reduced erythropoietin (EPO) production resulting in attenuation of erythropoiesis. EPO production can be increased by inhibition of prolyl hydroxylases that regulate hypoxia inducible factor (HIF).

A high-throughput screen of the GSK compound collection led to discovery of 4-oxo-2-thioxo-7-quinazolinecarboxamides as a novel series of prolyl hydroxylase inhibitors (PHI). Subsequent hit to lead optimization yielded a number of potent, selective and orally bioavailable PHI lead compounds. In this poster, synthesis, structure-activity relationship (SAR), and some developability parameters of the 4-oxo-2-thioxo-7-quinazoline carboxamides and their derivatives will be described.

MEDI 232

Bisphosphonate analogs of geranyl and farnesyl pyrophosphate as potential inhibitors of prenyl synthases

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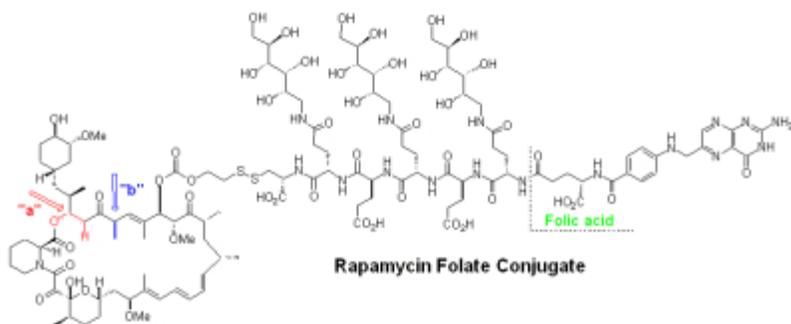
Polyprenyl phosphates play a central role in the biosynthesis of bacterial cell walls. The enzymes that form polyprenyl phosphates utilize farnesyl pyrophosphate as the natural substrate and initiate a series of biosynthetic reactions. As a result prenyl synthases have been investigated as possible therapeutic targets for new antibacterial agents, and the design and synthesis of prenyl synthase inhibitors has attracted considerable interest. We have synthesized a series of bisphosphonate analogs of geranyl and farnesyl pyrophosphates where the terminal isoprene unit was modified to accommodate anthranilate derivatives. The synthesis of these compounds and their in vitro activity against decaprenyl diphosphate synthase (Rv2361c) will be presented.

MEDI 233

Design and synthesis of folate conjugates of Rapamycin and Everolimus

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Rapamycin and Everolimus are well known mTOR inhibitors. Conjugation of these drugs to folic acid will facilitate folate receptor (FR)-mediated targeting to cancer cells and avoid undesirable collateral toxicity to normal cells. The synthesis of such complex water-soluble molecules encounters two major problems; a) ring opening of the macrolactone region *via* β -elimination, and b) epimerization of the methyl group situated in α -position to the carbonyl and allyl moieties. Herein, we describe an efficient conjugation approach involving novel water-soluble spacers and releasable disulfide-based linker system



MEDI 234

Discovery of TAK-438: Synthesis and biological evaluation of novel pyrrole derivatives as potassium-competitive acid blockers (P-CABs)

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Gastric H⁺,K⁺-ATPase of the parietal cell is a final step of acid secretion in the stomach and the target of proton pump inhibitors (PPIs) in a treatment of acid-related diseases. Potassium-competitive acid blockers (P-CABs) inhibit H⁺,K⁺-ATPase in a reversible and K⁺-competitive fashion, and their mode of action in inhibition of gastric acid secretion is quite different from those of PPIs.

In pursuit of P-CABs with a novel structure, we found pyrrole derivatives as a novel lead which show potent H⁺,K⁺-ATPase inhibitory activity. Further optimization aimed for improvement of in vivo potency and reduction of hERG inhibitory activity, mainly by transformation of the functional groups, led to the discovery of TAK-438 as a potent, selective and orally active P-CAB. The details of design, synthesis and biological activities of the pyrrole derivatives will be presented.

MEDI 235

Series of non-covalent inhibitors of the human 20S Proteasome derived from N-β-neopentyl asparagine with unprecedented potency and selectivity

Christopher Blackburn⁽¹⁾, blackburn@mpi.com, 40 Landsdowne St, Cambridge MA 02139, United States ; **Cynthia Barrett**⁽¹⁾; **Nancy Bump**⁽¹⁾; **Frank Bruzzese**⁽¹⁾; **Larry Dick**⁽¹⁾; **Paul Fleming**⁽¹⁾; **Khris Garcia**⁽¹⁾; **Ken Gigstad**⁽¹⁾; **Paul Hales**⁽¹⁾; **Lee**

Herman⁽¹⁾; Matt Jones⁽¹⁾; Jane Liu⁽¹⁾; Darshan Sappal⁽¹⁾; Mike Sintchak⁽¹⁾; Chris Tsu⁽¹⁾; Jonathan Blank⁽¹⁾. (1) Department of Discovery, Millennium Pharmaceuticals, The Takeda Oncology Company, Cambridge MA 02139, United States

A series of potent dipeptide biological probes derived from N- β -neopentyl asparagine was designed and optimized based on X-ray co-crystals with the yeast open gate $\beta 5$ 20S proteasome. These derivatives are completely selective for the $\beta 5$ site over the $\beta 1$ (caspase-like) and $\beta 2$ (trypsin-like) sites of the proteasome, and over a panel of less closely related proteases with the best example showing a 20S $\beta 5$ $IC_{50} = 1.2$ nM. The X-ray structures established the non-covalent binding mode and indicated that the N-neopentyl asparagine residue confers potency by providing a near optimal fit in the S3 specificity binding pocket of the catalytic $\beta 5$ site. These compounds also inhibit the activity of the 26S proteasome in Calu6 cells (Proteasome-GloTM assay), the degradation of the 4xUb-Luc reporter, the activation of NF κ B in response to TNF α , and the proliferation of cancer cells.

MEDI 236

Total synthesis of racemic and natural glyceollin II

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Phytoalexins are a special kind of natural product that are synthesized *de novo* by plants in response to various external insults such as parasitic attacks. Glyceollin I, II and III are major 6a-hydroxypterocarpan phytoalexins produced by Soybean plants. Glyceollin I possesses antifungal, antibacterial, anti-estrogenic and anticancer activities. Our lab has undertaken a multi-step synthesis of glyceollin II to produce it in quantities large enough to test against various cancer cell lines. Important experimental and chemical details will be described during the presentation.

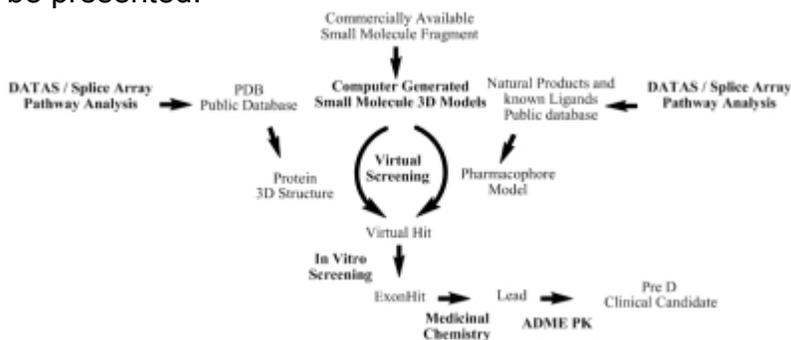
MEDI 237

Genomics guided medicinal chemistry

Eric Beausoleil⁽¹⁾, eric.beausoleil@exonhit.com, 65 Bd Massena, Paris 75013, France ; Thierry Taverne⁽¹⁾; Cédric Chauvignac⁽¹⁾; Bertrand Leblond⁽¹⁾; Diego Pallares⁽²⁾; Mike Brenner⁽³⁾; Matt Pando⁽⁴⁾. (1) Department of Medicinal Chemistry, Exonhit Therapeutics, Paris 75013, France (2) Department of Bioinformatics, Exonhit Therapeutics, Paris 75013, France (3) Department of

Bioinformatics, Exonhit Therapeutics, Gaithersburg MD 20877-2164, United States (4) Exonhit Therapeutics, Paris 75013, France

Alternative splicing is a fundamental process which is responsible for much of the tremendous transcriptome diversity that is derived from a finite number of genomically encoded genes. The alterations in mRNA structure that result can lead to profound effects on protein structure, function and ligand specificity. When deregulated, alternative splicing can also be a driving force for the onset and progression of disease¹. The identification of deregulated gene transcripts using DATASTM and SpliceArrayTM technologies enable various modes of intervention at the molecular level. From a medicinal chemistry perspective the importance of the target at the protein level must also be addressed in terms of druggability, novelty, patentability and fast lead identification strategies. Combining public and proprietary databases with computational chemistry methods, such as molecular docking and pharmacophore based searches, we have developed a unique process that enables the rapid initiation of new medicinal chemistry projects. The overall strategy and the applicability will be presented.



MEDI 238

De-convolution of medicinal citrus products

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The polymethoxyflavones (PMFs) found in citrus peels are a complex family of natural compounds reported to exert a variety of biological effects in vitro and in vivo including anti-tumor, anti-inflammatory, anti-hyperglycemia and anti-hyperlipidemia. There are a few marketed products whose major ingredients are

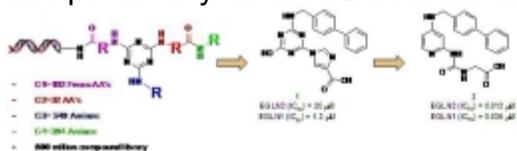
from citrus peel extracts, including both oral and topical preparations. Even though the forms, applied dosages and the therapeutic claims of these products vary, efficacy is supported by both in vitro testing and preclinical and clinical trials. Reliable information on the chemical composition of these products is essential for quality control and to enable consumers to make informed choices regarding use of these products. However, the measurement of the active components in the medicinally used citrus products has been sparsely performed or reported, pure standards are costly to synthesize and the analytical methods are complex. This presentation will describe our methodology for accurate measurement and report our analytical results describing the polymethoxyflavones in citrus peel products.

MEDI 239

Utilization of DNA-encoded libraries for the identification of novel inhibitors of prolyl hydroxylases

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⁽¹⁾ Molecular Discovery Research, GlaxoSmithKline, United States

Encoded Library Technologies (ELT) is an exciting new approach for hit identification within GSK. The technology is able to select affinity binders for molecular targets by screening million to billion member libraries of DNA-tagged molecules. Application of this technology for the inhibition of prolyl hydroxylases led to the discovery of the low micromolar triazine hit **1**. The design of the novel and potent acyclic urea **2** from the initial off-DNA hit **1** will be described.



MEDI 240

Oxyphors R3 and G3 — new phosphorescent probes for tissue oxygen measurements: Synthesis and characterization

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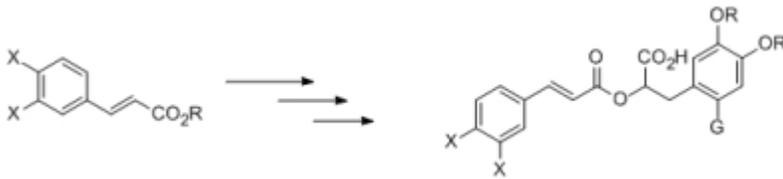
Oxygen levels in biological systems can be measured by the phosphorescent quenching method [1, 2] using probes with controllable quenching parameters and defined bio-distributions. Previously developed probes (Oxyphors R2 and G2) [3] had to be bound to albumin in order to allow sensing in the physiological pO₂ range (0-160 mm Hg). Recently we reported a general approach to the construction of fully dendritically protected phosphorescent probes for oxygen measurements [4], which do not require albumin pre-binding and can operate in any biological aqueous environment. In this paper we present the optimized synthesis and detailed characterization of two new Oxyphors, which enable robust and accurate intravascular and interstitial tissue oxygen measurements, and applicable in high-resolution microscopy and tomography. The phosphorescent cores of the probes comprise Pd-porphyrin (R3) and Pd-tetrabenzoporphyrin (G3) with *meso*-3,5-dicarboxyphenyl substituents. Both chromophores exhibit bright phosphorescence at ambient temperature. The phosphorescent cores are encapsulated into hydrophobic poly(aryl-glycine) dendrimers. To facilitate attachment of the dendrons, the carboxyl anchor points of the porphyrins are extended with flexible 4-aminobutyrate linkages. The peripheral groups of the dendrimers are modified with amino-PEG's (Av. MW 1000), which provide sufficient protection against probe self-aggregation. Photophysical and quenching parameters of the probes were measured under physiological conditions and found to be unaffected by bio-macromolecules. The probes were validated in high-resolution *in vivo* imaging of vascular pO₂ in the brain.

MEDI 241

Synthesis of rosmarinic acid analogs

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Rosmarinic acid is well known for its antioxidant and anti-inflammatory activities. In the context of a program designed to understand how changes in the structure of rosmarinic acid affect its activity, a direct synthesis of rosmarinic acid analogs was needed. A search of the literature indicated that relatively few analogs have been reported. We will describe a convergent approach to rosmarinic acid analogs beginning from cinnamic acid derivatives.



MEDI 242

Overexpression, isolation, and oral delivery of the appetite suppressant peptide PYY

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Injections of peptide tyrosine tyrosine (PYY) have shown positive effects on appetite regulation. With nearly 400 million adults worldwide considered obese, these positive effects have sparked an increased interest in PYY research, including release profiles, receptor targets, and medicinal applications. A major area of interest is oral delivery of PYY that can display clinically relevant outcomes related to weight loss in what would be a highly patient compliant route. The vitamin B₁₂ (B₁₂) pathway has already been successfully used for oral delivery of other peptides including erythropoietin and insulin. We present the overexpression and isolation of a recombinant PYY as well as the synthesis, purification, and characterization of a B₁₂-PYY conjugate with concomitant *in vivo* studies.

MEDI 243

Using haptocorrin and intrinsic factor as oral delivery agents

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Oral delivery of peptides such as erythropoietin and insulin has been successfully achieved by conjugation of these peptides to vitamin B₁₂ (B₁₂), thereby utilizing the dietary uptake pathway for the vitamin. Haptocorrin (HC) and intrinsic factor (IF) are glycoproteins that carry and protect B₁₂ during gastrointestinal passage. Although these proteins serve a critical function in the B₁₂ uptake pathway, up

until now, their use as delivery agents has not directly been explored. Herein, we describe the overexpression and utilization of HC and IF in oral delivery.

MEDI 244

Benzo[d]imidazole/indole inhibitors of coactivator associated arginine methyltransferase 1 (CARM1)

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Protein arginine methyltransferases (PRMTs) are enzymes that catalyze the transfer of methyl groups from S-adenosyl methionine (SAM) to specific arginine residues of proteins. Coactivator Associated Arginine Methyltransferase 1 (CARM1 or PRMT4) has been shown to methylate arginine residues asymmetrically in a wide variety of substrate proteins such as histone H3, p300/CBP, U1C, SAP49, CA150, HuR, HuD and PABP. These events affect chromatin architecture which impacts transcriptional initiation, alternative splicing, mRNA processing and stabilization. CARM1 also plays role in regulating gene expression responsible for inflammation and viral infection. These findings suggest that inhibitors of CARM1 may have utility in treating cancer, inflammation and viral infection.

Synthesis, SAR and *in-vitro* characterization of potent, selective and novel enzo[d]imidazole/indole based inhibitors of Coactivator Associated Arginine Methyltransferase (CARM1) is presented.

MEDI 245

Quadruplex nucleic acids as functional elements and therapeutic targets

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This lecture will discuss the hypothesis that four stranded DNA structures called G-quadruplexes exist in nature and consider whether such motifs are functional. I will present the latest examples of our work on natural G-quadruplexes from the

telomeres at the end of chromosomes, the promoters of protooncogenes and in the RNA of 5'-UTRs. I will discuss the use of biophysical and chemical biology approaches to elucidate G-quadruplexes. I will also provide a perspective on the chemical biology of natural G-quadruplexes and also their potential to act as therapeutic targets.

MEDI 246

Overview of G-quadruplexes, their biological role, and G-quadruplex structures

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G-quadruplex (G4) secondary structures, formed in specific G-rich nucleic acid sequences, have recently been demonstrated as potential regulatory elements. G-quadruplexes can form in regions of biological significance, such as in human telomeres, in promoters regions of growth-related genes, as well as in 5'-UTR regions of mRNA. G-quadruplexes have also emerged as a new class of molecular targets for cancer therapeutics. In my presentation, I will provide an introduction to the G-quadruplex area. I will cover the distribution and function of G4s in the human genome. I will then discuss the structural aspects of G4s that are found naturally. G-quadruplexes can readily form in solution under physiological conditions. G-quadruplexes are globularly folded nucleic acid structures, which are uniquely determined by the primary nucleotide sequences. Significantly, G-quadruplexes exhibit great conformational diversity that not only comes from different folding patterns but also from specific loop conformations, which may provide unique drug binding pocket(s).

MEDI 247

Structure-based design and evaluation of small molecules with selectivity for telomeric quadruplex nucleic acids

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Human telomeres end in 100-200 nt of single-stranded DNA, which can be induced to fold into quadruplex arrangements by appropriate small molecules.

We have shown that certain acridine and naphthalene diimide (ND) derivatives can be potent stabilizers of telomeric G-quadruplexes, whose formation inhibits the function of the oncogenic telomere-maintaining enzyme telomerase.

Crystallographic studies on DNA and RNA telomeric quadruplex-ligand complexes have led to structure-based optimization of side-chain features for the ND series and enhanced quadruplex affinity and selectivity for quadruplex vs duplex DNA. These compounds have potent anti-proliferative activity (IC₅₀ values of ca 20 nM) in a panel of pancreatic and other cancer cell lines together with ca 100-fold lower activity in normal human fibroblasts. Treated cancer cells have decreased telomerase activity and dis-regulation of telomere maintenance. A lead ND compound has now been identified with significant anti-cancer activity in pancreatic cancer xenografts, which concomitantly down-regulates telomerase activity *in vivo*.

MEDI 248

Drug targeting of the c-Myc G-quadruplex and associated proteins to inhibit gene transcription

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The proto-oncogene c-Myc is associated with cellular proliferation and apoptosis and is overexpressed in the majority of cancers. A small molecule approach to modulation of c-Myc expression has been demonstrated in a number of laboratories worldwide. This strategy involves targeting of a secondary DNA structure termed a G-quadruplex, which has been found to be a silencer element in the c-Myc promoter. Nucleolin and NM23-H2 have been recently identified as the proteins that control the cellular formation and resolution of the c-Myc G-quadruplex. Thus, possible approaches to silencing c-Myc gene expression would involve either inhibition of NM23-H2-catalyzed unfolding of the G-quadruplex through stabilization of the c-Myc G-quadruplex or cellular relocalization of nucleolin from the nucleolus, where it is associated with G-quadruplexes on the template strand of rDNA, to the nucleoplasm. In this presentation I will present data that supports silencing of c-Myc gene expression by both of these approaches.

MEDI 249

Free fraction, free drug concentration and *in vitro* to *in vivo* extrapolation- no common consensus on a common problem

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Following absorption into the circulation, drug molecules are either bound to plasma proteins (PPB) and tissues, or free (unbound) to diffuse among the aqueous environment of the body and interact with the therapeutic target. Permeable drugs show similar free drug concentrations, throughout the body. Drugs of lower permeability will see perturbations of the equilibrium across membranes and these effects may be exaggerated by the effects of transporters. The presence or addition of serum proteins to *in vitro* preparations will often decrease the apparent activity of a molecule. The lowering of activity may trigger the belief that to make a successful candidate, it is necessary to reduce PPB. However, whilst free fraction in an *in vitro* experiment directly influences free drug concentration, free fraction *in vivo* (which is now a dynamic situation) does not usually influence free drug concentration: free drug concentration *in vivo* is determined by intrinsic clearance.

MEDI 250

Considerations of protein binding in CNS drug design

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It has been a common strategy to optimize plasma and brain tissue binding in CNS drug design to enhance unbound brain concentration. Theoretical analyses and experimental data demonstrate that unbound brain concentration is not determined by brain tissue binding but by unbound plasma concentration, drug transporters and permeability at the blood-brain barrier. Likewise, unbound plasma concentration is not determined by plasma protein binding but by hepatic clearance for orally dosed compounds. A significant increase in unbound fraction is often due to decrease in compounds' lipophilicity, which in turn often leads to decrease of their hepatic clearance. However, a few fold increase of unbound fraction may not lead to a decrease of their hepatic clearance. Protein binding is an essential parameter to calculate unbound concentration but it should not be optimized independently. Instead clearance should be optimized to enhance *in vivo* unbound concentration.

MEDI 251

Determinants of drug disposition in tumors

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Greater emphasis is being placed on target tissue pharmacokinetics [PKs] and pharmacodynamics [PDs], not only due to the mechanistic insight it provides, but also as a component of revamped drug development paradigms. Such a strategy is of particular importance in the area of anticancer drugs where the target site is the tumor whose architecture and physiological alterations can significantly influence the local PK/PD behavior of drugs. In brain tumors, the impact of anatomic and physiological changes is paramount, and creates a heterogeneous environment that requires careful analyses to assess a drug's PK/PD characteristics. The presentation will review variables that influence anticancer drug disposition in tumors, experimental approaches and the associated caveats that should be considered to clearly interpret PK/PD data obtained in tumor models. In addition, examples of tumor-based PK/PD models will be presented that support new drug development strategies and a means to translate preclinical data to patients.

MEDI 252

Managing plasma protein binding

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The “Free Drug Principle” has proven to be a useful conceptual framework for understanding the role of plasma protein binding in the translation of *in vitro* target modulation into *in vivo* pharmacology. This presentation will focus on plasma protein binding from a medicinal chemist's point of view. The question as to whether one should optimize for free fraction in a drug discovery program will be addressed from several perspectives. Strategies for assessing plasma protein binding and increasing free fraction in highly plasma-protein-bound series will be reviewed. Examples of successful management of plasma protein binding will be discussed.

MEDI 253

Changes in protein binding: When can they be clinically relevant?

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Plasma protein binding is often mentioned as a factor playing a role in pharmacokinetics, pharmacodynamics and drug interactions. However, there are very few clinically relevant examples of changes in drug disposition, or more importantly drug effects, that can be clearly ascribed to changes in plasma protein binding. The idea that a drug displaced from plasma protein would yield an increase in unbound drug concentrations and thereby an increase in drug effects, perhaps producing toxicity, seems to be a simple and obvious mechanism. This talk will explain why changes in protein binding due to drug interactions or to disease states are probably of little clinical relevance. However, differences in protein binding between species can be very important in allometric scaling to predict human outcomes, and must be considered in selecting the initial doses in human trials.

MEDI 254

Discovery of telaprevir

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Telaprevir, a potent, covalent, reversible and slow off-rate inhibitor of the hepatitis C virus NS3•4A protease, an essential protein in HCV replication, is currently being evaluated in Phase 3 clinical trials. A structure-based drug design approach starting from an NS3•4A protease natural substrate was employed to identify a tetrapeptide aldehyde lead that was further optimized based on enzyme affinity, antiviral potency in replicon cells and animal pharmacokinetics, in particular liver exposure. This presentation will summarize the SAR that led to the discovery of telaprevir, as well as the biological data and animal pharmacokinetics supporting its further development.

MEDI 255

Novel noncovalent inhibitors of the HCV serine protease

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The quest to develop direct acting antiviral agents to treat hepatitis C virus (HCV) infections has continued for 20 years. One of the first HCV antiviral targets exploited in drug discovery was the serine protease of the NS3 protein. A feature of the NS3 protease is the observation of N-terminal product inhibition by C-terminal cleavage product peptides which has led to the development of

inhibitors that gain a significant portion of their enzyme active-site binding energy through ionic interactions with catalytic triad residues. In one class of peptide-based inhibitors, a C-terminal carboxylic acid interacts with residues from the catalytic triad and contributes to potency and specificity. A second class of non-covalent inhibitors are the acyl sulfonamides which bind tightly to the enzyme with high selectivity. Other classes of inhibitors are peptides containing C-terminal electrophilic groups (e.g., α -ketoamides and α -ketoacids) which form a covalent and reversible bond with the hydroxyl group of the catalytic serine. The interactions of the carboxylate group in the Boehringer Ingelheim inhibitor BI 201335, as well as compounds containing other active site binding groups will be described.

MEDI 256

Discovery of potent HCV inhibitors targeting the NS5A protein

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From a cell-based, high throughput screen, a hit was identified that exhibited an EC₅₀ of 0.57 μ M in a HCV 1b replicon assay and for which resistance mapped to the NS5A protein. During an initial SAR investigation, it became apparent that minor dimeric derivatives of the parental compounds contributed to the antiviral activity. This observation, along with the preliminary understanding of the SAR, allowed the design of a novel stilbene-based lead that was 2300-fold more potent than the initial hit. Subsequent iterative optimization of potency and ADME properties culminated in the discovery of the highly potent analog BMS-790052 (1a/1b EC₅₀ = 50 pM / 9 pM), currently in Phase II studies as an add-on to standard of care. Notable aspects of the lead identification effort, *in vitro* cell-based studies that corroborated NS5A as the likely target, and early clinical results will be discussed.

MEDI 257

HCV NS4A antagonists

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NS4A is a 52 amino acid protein that serves as a cofactor of NS3 protease and is essential for the formation of replicase complex. A series of aminothiazoles that function as antagonists of NS4A protein were identified. Aminothiazoles disrupt the formation of functional replicase complex, and lead to inhibition of HCV replication. The biology of aminothiazoles as HCV inhibitors, and the structure-activity relationship for inhibition HCV RNA replication will be presented.

MEDI 258

Benzofuran inhibitors of HCV NS5b polymerase: An in-depth look at SAR and pre-clinical characteristics that let to the advancement of HCV-796 into human clinical studies

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As of February 2010, more than 10 specific Hepatitis-C (HCV) drugs are in Phase-II clinical development, including 7 inhibitors of HCV NS5b RNA dependent RNA polymerase. Two inhibitors of NS3 protease, viz. Telaprevir and Boceprevir are in Phase-III. First clinical trials involving combinations of polymerase and protease inhibitors in exclusion of current standard of care pegylated alpha-interferon and ribavirin has begun. A specific antiviral therapy against HCV is likely to emerge very soon. Of particular interest to HCV researchers is benzofuran polymerase inhibitor HCV-796. Unlike many early non-nucleoside inhibitors of HCV polymerase which bind at surface allosteric sites, HCV-796 binds near the encircled active site in the palm region of the enzyme. It is the first non-nucleoside inhibitor of HCV RNA polymerase to have demonstrated clinical proof-of-concept. It is also reported to be the most potent inhibitor of HCV replication *in vitro* among compounds advanced to the clinic. The medicinal chemistry effort towards the discovery of HCV-796 involved rapid parallel optimization of ADME/PK and enzyme/replicon activities. An in-depth look at design, synthesis, SAR and unique features of HCV-796 will be described.

MEDI 259

Discovery and development of 2'-F-2'-C-methyl nucleosides and nucleotides for the treatment of HCV

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Hepatitis C is a global health problem with over 170 million individuals infected with the hepatitis C virus (HCV). Infection with HCV is known to lead to chronic liver disease, cirrhosis and eventually hepatocellular carcinoma. Our search for direct acting antiviral agents to treat HCV has led to the discovery of several potent and selective nucleoside/tide inhibitors of the HCV NS5B polymerase. These inhibitors, RG7128 and PSI-7851/PSI-7977, are based on the unique 2'-F-2'-C-methyl class of nucleos(t)ides. RG7128, a cytidine derivative, has demonstrated potent clinical efficacy in genotype 1,2,3 and 4 patients and is currently in Phase IIb clinical study. PSI-7977 is the single isomer of the uridine phosphoramidate prodrug PSI-7851 which has demonstrated clinical efficacy and an acceptable safety profile in genotype 1 patients. PSI-7977 is currently in a Phase II clinical study in combination with interferon and ribavirin standard of care. The discovery and current status of clinical development of these nucleos(t)ides will be presented.

MEDI 260

Principles of protein-protein interactions: What is the preferred way for proteins to interact?

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Proteins are the working horse of the cellular machinery. They are responsible for diverse functions ranging from molecular motors to signaling. The broad recognition of their involvement in all cellular processes has led to efforts to predict their functions from sequences, and if available, from their structures. A practical way to predict protein function is through identification of the binding partners. Since the vast majority of protein chores in living cells are mediated by protein-protein interactions, if the function of at least one of the components with which the protein interacts is identified, it is expected to facilitate its functional and pathway assignment. Through the network of protein-protein interactions, we can map cellular pathways and their intricate cross-connectivity. Since two protein partners cannot simultaneously bind at the same (or overlapping) site, discovery of the ways in which proteins associate should assist in inferring their dynamic regulation. Identification of protein-protein interactions is at the heart of functional genomics. The talk will describe our recent work in this direction and the implications for the design of small molecule modulators of protein-protein interactions through allosteric effects.

MEDI 261

Synthesis and evaluation of libraries designed to modulate protein-protein and protein-DNA interactions

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A summary of studies leading to the design and evaluation of compound libraries to comprehensively interrogate protein-protein and protein-DNA interactions will be presented.

MEDI 262

Protein-protein interaction inhibitors of transcription factors and kinases

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According to current thinking, only one in seven human proteins can be targeted by small organic molecules. However, since most biological processes are carried out by protein complexes, small-molecule modulators of specific protein-protein interactions have the potential to expand the spectrum of druggable protein families. In support of this notion, we have demonstrated that dimeric transcription factors can be efficiently and selectively inhibited by small molecules that interfere with the protein-protein interactions required for their activity. Examples will be provided for the transcription factors STAT3, STAT5, and c-Myc.

Moreover, small-molecule inhibitors of protein-protein interactions can provide alternative methods by which to interfere with the function of established small-molecule targets, such as protein kinases. In collaboration with the group of Prof. Klaus Strebhardt (University of Frankfurt, Germany), we have provided proof-of-principle that the serine/threonine kinase Plk1 can be inhibited by small molecules which do not target its ATP binding pocket, but instead inhibit the protein-protein interactions required for correct intracellular localization of the enzyme. The discovery and characterization of the inhibitors will be presented.

MEDI 263

Drugging the undruggable using stapled peptides

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Only a small fraction of all human proteins are targetable by the two well-established classes of drugs, namely small molecules and biologicals. The target range of small molecules is limited to the ~10% of human proteins having a hydrophobic pocket, while the target range of biologicals is limited to the ~10% of human proteins that are resident in the outer cell membrane or are secreted. Our laboratory has been developing a new class of potential therapeutic agents -- hydrocarbon-stapled peptides -- that combine the versatile target-recognition abilities of biologicals with the ability of small molecules to access intracellular targets. Progress on the development of stapled peptides targeting a variety of "undruggable" human proteins will be reviewed in this talk.

MEDI 264

Small molecule inhibitors of protein-protein interactions: Targeting Bcl-2 family proteins to treat cancer

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Blocks in apoptotic signaling are a common requirement for oncogenesis, tumor maintenance and chemoresistance. Dynamic binding interactions between the pro-apoptotic and anti-apoptotic Bcl-2 family members control commitment to cell death. Anti-apoptotic Bcl-2 family members (e.g. Bcl-2, Bcl-x_L, Mcl-1) that promote survival of cancer cells are attractive drug targets for anticancer therapy. Unlike traditional small molecule drug targets that involve small enzyme binding pockets, the Bcl-2 family proteins function through large, hydrophobic protein-protein interactions (PPIs) that have traditionally been thought of as undruggable. Using NMR fragment-based screening and structure-based drug design, we have developed small molecules that bind with high affinity ($K_i < 1 \text{ nM}$) to multiple anti-apoptotic Bcl-2 family proteins. The orally active Bcl-2/Bcl-x_L dual inhibitor, ABT-263, is currently being evaluated in Phase 1/2 clinical trials in lymphoid malignancies and solid tumors. Challenges associated with the design of small molecule PPI inhibitors and some lessons learned will be discussed.

MEDI 265

JANUVIA® and beyond: Selective dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes

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Dipeptidyl peptidase IV (DPP-4), a proline selective serine dipeptidase, is responsible for the N-terminal inactivation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), incretin hormones that evoke glucose dependent secretion of insulin and inhibition of glucagon release. Inhibitors of DPP-4 have been shown to increase circulating levels of GLP-1 and GIP, both in animal models and in the clinic, resulting in improved glucose tolerance. Thus, DPP-4 inhibitors represent a new therapy for type 2 diabetes. Early α -amino acid-derived inhibitors that were not selective over related family members, in particular DPP-8 and DPP-9, induced profound toxicities in preclinical species. SAR studies in a β -amino amide series led to the discovery of JANUVIA® (sitagliptin phosphate), a highly selective DPP-4 inhibitor that was very well tolerated in pre-clinical toxicity studies and in human clinical trials. In addition, using different approaches, three preclinical candidates were identified as potential back-up compounds to sitagliptin. With the approval of JANUVIA® in more than 80 countries including the US, Europe and Japan, a new treatment is now available for patients with type 2 diabetes.

MEDI 266

Bioorganic studies on recognition of soluble amyloid oligomers using small molecules

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Soluble oligomers of amyloid peptides have long been implicated as one of the main species responsible for the occurrence and progression of Alzheimer's disease. Recognition of these oligomers using small molecule-based probes is of interest from fundamental and practical points of view.

We have recently identified several natural and synthetic scaffolds that could efficiently recognize distinct secondary structure conformations of various amyloidogenic peptides. Specifically, macrolide antibiotics, such as amphotericin B, could serve as a circular dichroism spectroscopic probe to monitor conformational transitions of amyloid peptides; triazole-functionalized bodipy dyes could be used as sensitive fluorescence probes to differentiate between unordered and ordered conformations of amyloidogenic species. Details on the synthesis and small molecule-amyloid peptide interactions will be presented.

MEDI 267

Application of aminoglycoside-N-acetyltransferases in the development of novel N-acylated aminoglycoside antibiotics

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Aminoglycosides are broad-spectrum antibiotics that have enjoyed decades of widespread clinical use, but evolutionarily driven bacterial resistance, as well as inherent toxicity, has compromised their clinical use. One way bacteria evade aminoglycosides is by expressing aminoglycoside-modifying enzymes such as aminoglycoside N-acetyltransferases (AACs). However, there have also been many reports of N-acylated aminoglycosides demonstrating equal or improved activity as well as abrogated toxicity. We have reported a methodology that utilizes AACs and unnatural acyl-CoA analogues to chemoenzymatically generate mono-N-acylated as well as homo- and hetero-di-N-acylated aminoglycosides in quantities sufficient to screen each analogs' antibacterial potential. This presentation will focus on the development of methodology that allows us to efficiently screen libraries of chemoenzymatically generated analogues. Our method allows us to rapidly generate and qualitatively screen diverse aminoglycoside analogs in order to determine which compounds justify investigation on a larger scale.

MEDI 268

Designing attenuated Michael acceptors as experimental redox chemotherapeutics targeting skin cancer

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Altered redox regulation in cancer cells represents a chemical vulnerability that can be targeted by small-molecule redox modulators that have shown therapeutic promise in animal xenograft models and clinical trials. Based on the emerging role of pro-oxidant therapeutics in anti-cancer intervention, we hypothesized that drug-like molecules containing a reactive Michael acceptor pharmacophore with attenuated electrophilicity may be developed into experimental redox chemotherapeutics. Using gene expression array analysis and luciferase-based transcriptional reporter profiling (Nrf2, NFkappaB) of the

cellular electrophilic stress response we identified Michael acceptor pharmacophores that impart anti-cancer activity at doses devoid of systemic toxicity. 2,6-dichlorophenolindophenol (DCPIP) was identified as a glutathione-directed Michael acceptor targeting metastatic A375 melanoma in vivo. Proteomic identification of molecular targets in melanoma modulated by Michael adduction is ongoing. Moreover, cinnamaldehyde-derived Nrf2 activators are now in preclinical development for skin cancer chemoprevention. (Support: NIH (R01CA122484); ACS, predoctoral fellowship (CC), Division of Medicinal Chemistry, sponsored by Novartis).

MEDI 269

Small molecule glycosaminoglycan mimics

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Heparan sulfate (HS) is a polyanionic glycosaminoglycan found on mammalian cell surfaces. Numerous physiological processes and pathogenic microorganisms employ protein-HS binding interactions for endogenous and infectious activities, respectively. There are many potential therapeutic applications for compounds that bind and block HS-binding proteins. Development of such compounds has traditionally focused on optimizing the degree and spatial orientation of anionic substituents on a scaffold, to mimic HS, but their utility is diminished by non-specific interactions with many positively-charged proteins. Previous work in our lab has replaced anionic *N*-sulfo groups on heparin with non-anionic *N*-arylacyl groups; these derivatives possess increased affinity for select HS-binding proteins. The work presented here advances these findings by introducing *N*-arylacyl groups onto smaller, structurally-defined oligosaccharide scaffolds, to create novel small molecule lead structures that selectively bind HS-binding proteins. Screening these compounds against known heparin-binding proteins demonstrates the *N*-arylacyl groups are essential in promoting binding contacts.

MEDI 270

Discovery of a pharmacophore for inhibition of poly(ADP-ribose) glycohydrolase

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The metabolism of ADP-ribose polymers, mediated by poly(ADP-ribose) polymerases (PARPs) and poly(ADP-ribose) glycohydrolase (PARG), is involved in maintenance of genomic integrity. PARP-1 has emerged as a promising therapeutic target with several PARP inhibitors in clinical evaluation. While a precise coordination between PARP and PARG activity is required for function, evaluation of the therapeutic potential of PARG has been limited by the lack of potent, selective and bioavailable PARG inhibitors. We have identified compounds that inhibit PARG with IC50 values in the micromolar range. Interestingly, these compounds also inhibit PARP-1, indicating homology in the active sites of PARG and PARP-1 and raising interesting questions concerning the selectivity of existing PARP inhibitors. This has led to the discovery of a unique pharmacophore required for PARG inhibition. We report here the synthesis and characterization of a series of analogs and examine their potency and selectivity for PARG inhibition. (Support: NIH (CA23994); ACS, predoctoral fellowship, Division of Medicinal Chemistry, sponsored by Amgen).

MEDI 271

Exploring Alphanaphthoflavone heterotropic allosteric regulation of Cytochrome P450 3A4

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Cytochrome P450 (CYP) enzymes facilitate the oxidation of xenobiotic compounds, contributing significantly to their pharmacokinetics. One isoform in particular, Cytochrome P450 3A4 (CYP3A4), is thought to be responsible for over 50% of oxidative drug metabolism because of high expression levels in the gut and the liver and a high level of substrate promiscuity. CYP3A4 *in vitro* allosterism remains unexplained from a mechanistic standpoint and complicates *in vitro* to *in vivo* scaling. Using the archetypal allosteric effector molecule alphanaphthoflavone (ANF) we report the kinetic parameters for the sequential de-ethylation of fluorescent substrate Nile Red (NR) to its mono and di des-ethyl metabolites M1 and M2. ANF increases Vmax for NR metabolism to both products while the Km is not significantly affected. ANF also decreases uncoupling at the point of peroxide production, indicating that increased coupling in the P450 cycle is a probable mechanism for the observed heterotropic allosteric activation.

MEDI 272

Rational design of Tubastatin A: An immunosuppressant HDAC6 inhibitor with unprecedented selectivity

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Protein function is regulated by the enzymatic addition and removal of acetyl groups at specific lysine residues. Lysine deacetylation is catalyzed by histone deacetylase (HDAC) enzymes and HDAC inhibitors have been aggressively pursued as potential therapeutics. Eleven isoforms are found in the HDAC family, each with unique functions and tissue distribution. Due to the potential toxicities and unwanted off-target effects of nonselective HDAC inhibitors, isoform selective inhibitors may provide greater therapeutic benefit and can also be used as chemical probes. Using protein homology modeling techniques, unique structural regions at the HDAC6 active site were identified and small molecules were designed to target these regions. This approach resulted in the creation of tricyclic hydroxamic acids with HDAC6 IC₅₀ values in the low nanomolar range with over 3000 fold selectivity versus other HDAC isoforms, far more selective than other inhibitors of HDAC6. These compounds were designed to be highly drug-like with simple syntheses that allow for easy scale-up and rapid generation of analogs. One inhibitor from this series, Tubastatin A, is a potent immunosuppressant in in vivo models of autoimmune disease. In vitro and in vivo results establish the superior biological profile of Tubastatin A.

MEDI 273

Evaluation of a direct procaspase activating compound in pet dogs with lymphoma

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Many cancers that respond poorly to conventional chemotherapies harbor deficiencies in the apoptotic machinery. As such, therapies that are capable of re-activating apoptosis, even in cells with defective apoptotic pathways may be effective therapies for clinical use. In 2006, a small molecule that enhances the catalytic activity of procaspase-3 and induces its auto-activation to caspase-3 was reported. This compound, called **PAC-1**, induces apoptosis in cancer cells in culture and exhibits antitumor activity in murine xenograft models. Further analysis demonstrated that **PAC-1** activates procaspase-3 through relief of zinc-mediated inhibition. As a first-in-class activator of procaspases, the evaluation of this class of compounds in clinical models is important to validate the therapeutic potential of procaspase activating compounds in general. Herein we report the

evaluation of **PAC-1** in mice and dogs, the resulting dose-limiting toxicity, the design and synthesis of a **PAC-1** derivative and the evaluation of this derivative in pet dogs with lymphoma. The safety, pharmacokinetics and efficacy of this strategy were assessed and further clinical studies are underway.

MEDI 274

Heterocyclization in cyanobactin biosynthesis

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Cyanobactins are a large class of macrocyclic compounds found widely among free-living and symbiotic cyanobacteria. These compounds are initially synthesized as a ribosomal precursor peptide, which is then modified post-translationally via heterocyclization, prenylation, oxidation, and finally N-to-C macrocyclization. Many gene clusters that produce these compounds are known, and some in vitro studies have examined their biosynthesis. Recent advances made in defining the mechanism and regioselectivity of heterocyclase enzymes will be described. Additionally, several experiments concerning the enzymatic synthesis of several unnatural analogues will be presented.

MEDI 275

Discovery of novel BACE1 inhibitors for the treatment of Alzheimer's disease

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A neuropathological hallmark of Alzheimer's disease (AD) is the presence of β -amyloid (Ab)-containing neuritic plaques. Ab is produced by proteolytic cleavage of the amyloid precursor protein (APP) by the aspartyl protease β -secretase (BACE1), followed by cleavage of the APP C-terminal fragment by γ -secretase. Because accumulation of $A\beta$ peptides is implicated in AD pathogenesis, inhibition of BACE1 is a potential disease-modifying approach for the treatment of AD. However the development of brain penetrant BACE1 inhibitors has proven to be a difficult challenge.

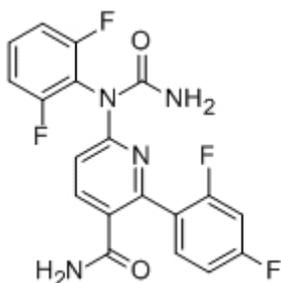
In efforts to address this challenge, we have applied structure-based drug design to discover two structurally distinct series of BACE1 inhibitors. In one approach, a series of inhibitors based on the classical hydroxyethylamine transition state isostere was investigated. Prompted by the poor in vivo properties of these inhibitors, we pursued a second approach utilizing fragment-based screening.

Screening of a fragment library by NMR against BACE1 resulted in identification of a series of low MW, low affinity isothioureas that bound to the BACE1 active site catalytic aspartic acids. Unique hydrogen bonding interactions between the isothiourea and the catalytic diad of BACE1 were revealed by X-ray crystallography, which led to the conception of a novel cyclic acylguanidine aspartyl protease inhibitor design. Optimization of prototype cyclic acylguanidine ligands guided by structure-based design resulting in potent, orally bioavailable and brain-penetrant BACE1 inhibitors will be described.

MEDI 276

Development of a scalable process for p38 inhibitor VX-702

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Form control and chemical stability are challenging issues for a process chemist during early stage drug development. This lecture will discuss the route selection and process development strategy to manufacture VX-702, a p38 MAPK inhibitor. The ultimate synthesis is practical, safe and requires no chromatographic purification. The process for preparing the most thermodynamically stable polymorph was refined after new forms were uncovered late in development and kinetic and thermodynamic controls were introduced to the crystallization process.

MEDI 277

Continuing process development for existing HIV/AIDS drugs: Improving access to medicines in the developing world

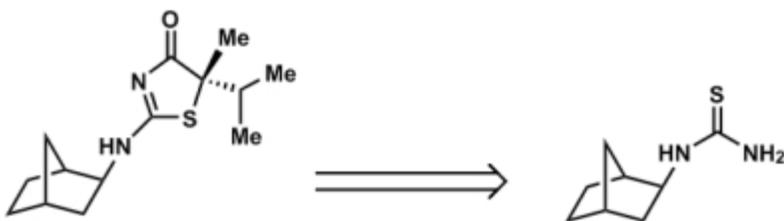
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The WHO estimates that 20 million people are infected with the HIV virus in the developing world, but only 3 million patients are currently receiving anti-retroviral treatment. The cost of medications puts increasing strain on aid budgets for increasing the number of patients receiving treatment; a sustainable supply of lower-cost drug products is crucial to improving access to medicines. The entry of new manufacturers into the market facilitates introduction of newly improved manufacturing processes. Process improvement can then drive price competition while maintaining a sustainable marketplace. The Clinton Health Access Initiative conducts and supports research into improved manufacturing processes, including investigation of routes to drugs like Tenofovir Disoproxyl Fumarate. A number of these process improvements will be reported.

MEDI 278

Discovery and development of scalable routes to prepare AMG-221

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AMG 221 is a potent inhibitor of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) discovered in our laboratories. Inspired by its challenging structure, several synthetic approaches have been developed to prepare AMG 221 in quantities required for pharmaceutical development. Routes to the core norbornyl fragment as well as construction of the chiral thiazolinone will be discussed in terms of their utility for both short-term clinical and long term commercial needs.

MEDI 279

Development of a scaleable process for the production of a small molecule clinical candidate

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A scaleable process to a promising clinical candidate is described. Experiments to understand the formation of impurities, define the key parameters for efficient scale up, and additional process optimizations discussed.

MEDI 280

Catalytic asymmetric reactions in the synthesis of complex drug targets

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The design and development of practical asymmetric syntheses of complex drug substances represents a critically important activity within Process Research. A case study which highlights the discovery and development of catalytic, asymmetric reactions toward the synthesis of drug candidates will be discussed. The presentation will focus on the definition of synthetic strategies and development of novel synthetic methodologies that are generally useful to synthetic chemists.

MEDI 281

Combination strategies to treat obesity: Overview of peripheral and central pathways modulating energy homeostasis

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Obesity rates in adults have increased from 15% in 1962 to over 30% in 2006 and beyond. The same trend has been observed in children and adolescents, where rates in the 1960s were approximately 5% and have increased to 15% in the current decade. Since there is considerable evidence that obesity increases the risk of both metabolic and cardiovascular disease and that weight loss can significantly reduce this risk, the importance of safe therapeutics in this area is widely recognized. Although the biology of energy balance is extremely complex, the strategies to reduce adiposity and body weight appear deceptively simple: either reduce energy absorption or increase energy expenditure. Both approaches, however, are tightly modulated by multiple “redundant” systems designed to maintain energy homeostasis. Therefore, most research groups focused on treating obesity have adopted the strategy of developing agents representing multiple mechanisms which can be utilized for combination therapeutics. Since the field of combination therapeutics in obesity is relatively new, the choice of mechanisms of action (MOA) for combination is still quite

empirical. This seminar will attempt to provide a rational framework for combination strategies by examining the major peripheral and central nervous system pathways known to regulate energy absorption and expenditure.

MEDI 282

Discovery of Lorcaserin: A selective 5-HT_{2C} receptor agonist for the treatment of obesity

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This presentation highlights the strategies, progress and challenges of the Arena 5-HT_{2C} drug discovery program along the path to the discovery and development of lorcaserin.

MEDI 283

MCH R1 antagonists: Problems and solutions

Donald L Hertzog⁽¹⁾; **Michael J Bishop**⁽¹⁾; **Kamal A Al-Barazanji**⁽²⁾; **Kevin K Barvian**⁽¹⁾; **Eric Bigham**⁽¹⁾; **Christy S Britt**⁽²⁾; **David L Carlton**⁽³⁾; **Andrew J Carpenter**⁽¹⁾; **Joel P Cooper**⁽¹⁾; **Dulce M Garrido**⁽¹⁾; **Aaron S Goetz**⁽²⁾; **Gary M Green**⁽¹⁾; **Mary K Grizzle**⁽²⁾; **Yu C Guo**⁽¹⁾; **Anthony L Handlon**⁽¹⁾; **Clifton E Hyman**⁽¹⁾; **Diane M Ignar**⁽²⁾; **Daniel G Lang**⁽²⁾; **Ronda O Morgan**⁽⁴⁾; **Andrew J Peat**⁽¹⁾; **Gregory E Peckham**⁽¹⁾; **Amy J Reisinger**⁽²⁾; **Jason D Speake**⁽¹⁾; **William R Swain**⁽¹⁾; **Francis X Tavares**⁽¹⁾; **Huiqiang Zhou**⁽¹⁾. (1) Department of Medicinal Chemistry, GlaxoSmithKline, Research Triangle Park North Carolina 27709, United States (2) Department of Biology, GlaxoSmithKline, Research Triangle Park NC 27709, United States (3) Department of Pharmaceutical Development, GlaxoSmithKline, Research Triangle Park NC 27709, United States (4) Department of DMPK, GlaxoSmithKline, Research Triangle Park NC 27709, United States

Melanin-concentrating hormone (MCH) is a 19 amino acid peptide that is a key mediator in the regulation of energy balance and body weight in rodents. The effects of MCH on body weight appear to be mediated by MCH receptor 1 (MCH R1). Thus, MCH R1 antagonists are potentially useful agents for the treatment of obesity. Initial optimization studies led to the potent tool compound GW803430 which demonstrated significant weight loss in animal models of obesity but which suffered from an unacceptable hERG profile for further development. Additional optimization identified GW856464, a potent MCH R1 antagonist that was progressed into clinical studies for the treatment of obesity. A series of prodrugs was made to address the potential liabilities in the ADME profile of GW856464.

Two of the prodrugs showed superior ADME profiles to GW856464 and one was selected for preclinical evaluation as a potential clinical candidate.

MEDI 284

Discovery of S-2367 (velneperit): A potent and selective NPY Y5 antagonist for the treatment of obesity

Takayuki Okuno⁽¹⁾; **Hideyuki Takenaka**⁽¹⁾; **Yasunori Aoyama**⁽¹⁾; **Yasuhiko Kanda**⁽¹⁾; **Yutaka Yoshida**⁽¹⁾; **Tetsuo Okada**⁽¹⁾; **Hiroshi Hashizume**⁽¹⁾; **Masahiro Sakagami**⁽¹⁾; **Takuji Nakatani**⁽¹⁾; **Kazunari Hattori**⁽¹⁾; **Teruhisa Ichihashi**⁽¹⁾; **Takayoshi Yoshikawa**⁽¹⁾; **Hideo Yukioka**⁽¹⁾; **Kohji Hanasaki**⁽¹⁾; **Yasuyuki Kawanishi**⁽¹⁾. (1) *Discovery Research Laboratories, Shionogi & CO., Ltd, 12-4, Sagisu 5-chome, Fukushima-ku Osaka 553-0002, Japan*

Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter that is widely distributed in the mammalian central and peripheral nervous systems. So far five distinct subtypes of G protein-coupled NPY receptors, Y1, Y2, Y4, Y5, and y6, are known. Among them, the Y5 receptor subtype is thought to play a role in meal initiation and the regulation of energy balance. Therefore, antagonist of NPY Y5 receptor is considered to have a potential as an anti-obesity drug.

In this presentation, we will describe how we successfully found a novel, potent and selective orally available NPY Y5 antagonist, S-2367 (Velneperit), starting from the HTS hit, benzanilide analogue. During the lead optimization stage, the PK profile was improved by introducing less lipophilic amine fragment to give an orally available Y5 antagonist, which was found to be effective in reducing weight in DIO mice model. S-2367 is now under clinical trial, and was already proved to be well tolerated and have a significant effect on the weight loss in Phase II clinical trial, suggesting a potential of promising anti-obesity drug. The early clinical profile of S-2367 will be also describe.

MEDI 285

Anti-obesity potential of SGLT2 inhibitors in development for treatment of diabetes

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The focus will be the discovery, synthesis and characterization of the C-aryl glucoside-derived renal sodium-dependent glucose cotransporter-2 (SGLT2) inhibitors. The SAR evolution from O-glucoside to the C-glucoside derived SGLT2 inhibitors will be reviewed. Efficacy of these agents with particular emphasis on that achieved with dapagliflozin in both diabetic and anti-obesity

animal models will be discussed. Selected correlations with clinical findings will be presented.



MEDI 286

Discovery of pramlintide and peptide approaches to treating obesity

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Gut-, islet-, and adipocyte-derived peptide and protein neurohormones play key roles in glucose and body weight regulation. Pramlintide, a synthetic analog of human amylin, reduces postprandial glucose excursions by suppressing inappropriately elevated postprandial glucagon secretion and by slowing gastric emptying. Pramlintide has also been shown to reduce body weight in Type 2 diabetes patients and obese subjects. We have postulated that amylin acts in concert with other peptide neurohormones to leverage integrated physiological mechanisms for weight control and glucoregulation. The promise of highly effective combinatorial peptide hormone therapy has been borne out in pre-clinical studies. Clinical evidence to support the concept of an integrated neurohormonal therapy for obesity was recently obtained in overweight/obese humans where combination treatment with pramlintide and the leptin analog metreleptin elicited greater weight loss than did either agent alone. The synergistic effects of these peptides and their analogs may provide innovative treatment prospects for obesity.

MEDI 287

Isoquinucline-based GlyT1 inhibitors for schizophrenia: Discovery, optimization, synthesis, and in vivo pharmacology

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*William M. Potts⁽¹⁾; Gennady Smaggin⁽¹⁾; Dekun Song⁽¹⁾; Simon Sydserff⁽¹⁾; Mark Sylvester⁽¹⁾; Gaochao Tian⁽¹⁾; Jeffrey G. Varnes⁽¹⁾; Chris A. Veale⁽¹⁾; Xia Wang⁽¹⁾; Dan Widzowski⁽¹⁾; Dee Wilkins⁽¹⁾; Michael Wood⁽¹⁾; Hui Xiong⁽¹⁾; Steven Zukin⁽¹⁾.
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We explored chemical modifications around compounds related to SSR504734 (2-chloro-N-[(S)-phenyl[(2S)-piperidin-2-yl] methyl]-3-trifluoromethyl benzamide with the aim of rapidly and efficiently discovering chemotypes with high solubility, low lipophilicity, and low clearance.

The core amide, the basic piperidine, and the benzamide were systematically investigated. Computational analysis suggested that the methine position of the piperidine might be particularly metabolically labile. This drove optimization efforts leading to the identification of the isoquinuclidine basic region. Next, we explored the benzamide region using a Hammett-type linear free energy analysis by preparing a focused set of analogs and correlating the results with a various types of substituent constants. This led to the development of a predictive QSAR model based on the Fujita ortho steric parameter. The resulting optimized compounds had in vitro potency of less than IC₅₀ 5 nM.

We describe synthesis, structures and the properties of the optimized compounds in several in vivo animal models of antipsychotic efficacy and cognitive enhancement. In particular, these compounds elevated glycine levels in the CSF and were potently active in rodent novel object recognition, conditioned avoidance response, and reversal of MK801-induced elevation of locomotor activity models.

MEDI 288

From fragment-based lead generation to 2-aminoquinolines as potent beta-secretase inhibitors that are efficacious in vivo

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Alzheimer's disease (AD) is a progressive, neurodegenerative disorder and the leading cause of dementia in the elderly. Aggregation of the β -amyloid peptide ($A\beta$) in the brains of AD patients is believed to be a key pathogenic event. $A\beta$ is produced via sequential proteolysis from amyloid precursor protein (APP) by β -secretase (BACE1) and γ -secretase. BACE1 is responsible for the initial cleavage of the APP and is believed to be the rate limiting step in $A\beta$ production. Thus, the development of BACE inhibitors to lower $A\beta$ peptide formation represents an attractive therapeutic approach for the treatment of AD. Using a fragment-based lead generation approach, 2-aminoquinoline was identified 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 coupled with in-vitro assays has resulted in subnanomolar 2-aminoquinoline derived BACE1 inhibitors. Further optimization on physicochemical properties required for CNS penetration led to potent BACE1 inhibitors that lower CSF $A\beta$ levels in rat.

MEDI 289

From discovery to clinic: GSK962040, the first oral, small molecule motilin receptor agonist for treatment of conditions associated with impaired gastric motility

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Motilin is a 22-amino acid peptide hormone involved in regulating gastric and upper-intestinal motility. In the interdigestive phase, motilin promotes the migrating motor complex and in the fed state, motilin and other motilin receptor agonists, such as the antibiotic erythromycin, promote increased gastric motility. Impaired gastric motility is a characteristic of gastroparesis patients, subsets of functional dyspepsia patients and intensive care patients with enteral feeding intolerance. Erythromycin is often used 'off-label' to treat this condition but it possesses a combination of undesirable properties. From identification of a small molecule HTS hit through lead optimisation, we will describe the challenges in balancing acceptable potency and efficacy at both the recombinant motilin receptor and in a therapeutically relevant native tissue preparation, with physicochemical and ADME properties suitable for further development. The outcome of Phase I clinical trials, including the effects on gastric emptying in human volunteers, will also be described.

MEDI 290

Discovery of BMS-582949, a clinical p38a MAP kinase inhibitor for the treatment of inflammatory diseases

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The p38a MAP kinase plays a crucial role in regulating the biosynthesis of many inflammatory cytokines including TNF- α and IL-1, and has been extensively studied as a promising molecular target for the treatment of inflammatory diseases. In this presentation, we will describe for the first time the discovery and characterization of BMS-582949, a highly selective p38a MAP kinase inhibitor that is currently in phase II clinical trials for the treatment of rheumatoid arthritis. A key to its discovery was the rational use of an N-cyclopropyl benzamide moiety, whereby we envisioned that the cyclopropyl group would enhance the hydrogen bonding ability of the benzamide NH due to its sp² character, in contrast to alkyl and related cycloalkyl groups. Results from Phase I clinical trials will also be presented.

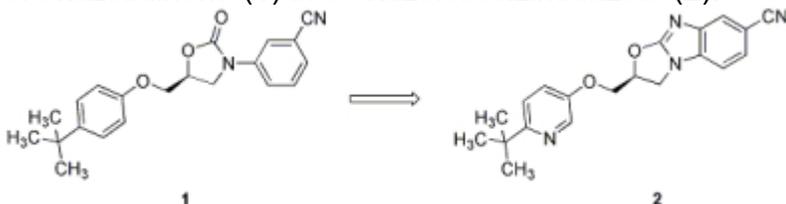
MEDI 291

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 approach for the

treatment of schizophrenia. Clinical validation of this approach was achieved in a Phase II study in schizophrenic patients with orthosteric mGluR2/3 agonist LY404039. Alternatively, positive allosteric modulators (potentiators) of mGluR2 may offer advantages over orthosteric mGluR2/3 agonists as a result of their unique mode of action and selectivity. Herein we describe the lead optimization of oxazolidinone (**1**) into oxazolobenzimidazole (**2**).



MEDI 292

Substituted biaryl pyrazoles as sodium channel blockers for the treatment of neuropathic pain

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Neuropathic pain arises from the injury to the peripheral or central nervous system and causes persistent debilitating pain long after the initial injury is healed. Blockade of the voltage gated sodium channel offers a viable option for treatment of neuropathic pain. Of the several existing sodium channel blockers, the lack of potency and the off-target activity limits their usefulness for treatment of neuropathic pain. In our search for sodium channel blockers lacking many of these side effects, we recently discovered a series of low molecular weight substituted biaryl pyrazole carboxamides that are potent, selective and show excellent efficacy in the rodent models of neuropathic pain. The structure-activity relationships and biological data for this class of sodium channel blockers will be described in this presentation.

MEDI 293

Molecular pathogenesis and therapy of myeloproliferative neoplasms

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The discovery of the JAK2V617F mutation in human myeloproliferative neoplasms (MPN) provided important insight into the molecular pathogenesis of polycythemia vera (PV), essential thrombocythemia, and primary myelofibrosis (PMF), and suggests that activation of JAK2 signaling is an important pathogenetic event in PV, ET, and PMF. Subsequently genomic screens have identified somatic mutations in JAK2V617F-negative PV (JAK2 exon 12 mutations) and in JAK2V617F-negative ET and PMF (MPLW515L/K mutations) that serve to underscore the role of JAK-STAT signaling in these neoplasms. We and others have investigated the efficacy of JAK2 inhibitors in preclinical and clinical studies, and can demonstrate that JAK2 inhibitor therapy ameliorates disease-related sequelae in MPN model systems. The current status of JAK2 inhibitor development, and the development of additional targeted therapies for MPN patients, will be discussed.

MEDI 294

Identification of AZD1480 as a novel JAK2 inhibitor

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The modulation of the JAK2/STAT pathway has sparked interest in our laboratories after the discovery of a single somatic mutation harbored in the pseudo kinase domain of JAK2 protein. The V617F mutation leads to the constitutive activation of the mutated JAK2 protein and downstream signaling to the STATs in the absence of cytokine stimulation. The aberrant STAT activation is linked to the pathogenicity of the myeloproliferative neoplasms such as PV, ET and IMF and other cancers.

Here we report the optimization of a pyrazol-4-ylamino pyrimidine series that resulted in the identification of AZD1480 a potent ATP-competitive inhibitor with a K_i of 0.26 nM. AZD1480 demonstrated good selectivity against JAK3 and a panel of 82 kinases chosen as representatives of the kinome diversity. The compound displayed further selectivity for JAK2 when tested in a panel of Ba/F3 cell lines driven by the catalytic domain of JAK1, JAK2, JAK3 and TYK2 fused to the oligomerization domain of TEL.

AZD1480 exhibits good ADME properties and in vivo activity in pre-clinical species and has progressed to Phase I clinical trials for IMF.

MEDI 295

Discovery of CYT387: A potent and selective dual inhibitor of JAK1 and JAK2

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CYT387 is a novel and potent inhibitor of JAK1 and JAK2, with excellent selectivity against a panel of over 150 kinases. CYT387 is an orally bioavailable small molecule that binds competitively to the ATP binding site, confirmed by the X-ray crystal structure of the JAK2 kinase domain in complex with CYT387. The compound blocks JAK2-driven cellular proliferation of both cell lines and primary cells from patients with myeloproliferative neoplasms (MPNs), as well as inhibiting downstream signalling events including phosphorylation of STAT3, STAT5 and, in a pathway dependent manner, ERK1/2. CYT387 is efficacious in vivo in a number of JAK2 driven processes, including a mouse model of MPNs. Together the data indicate that CYT387 is an appropriate candidate for clinical evaluation as a treatment of MPNs, and a Phase I/II trial has been initiated. The utility of CYT387 in the treatment of particular cancers will also be discussed.

MEDI 296

Discovery of polycyclic azaindoles and deazapurines as potent JAK2 inhibitors

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The synthesis and characterization of novel polycyclic azaindole and deazapurine based derivatives is disclosed along with their binding to the JAK2 enzyme. SAR studies, which led to the discovery of a series of potent JAK2 kinase inhibitors, and the ability of one such compound to block the EPO/JAK2 signaling cascade in vitro and in rodent models is discussed.

MEDI 297

Discovery of INCB018424: A potent and selective JAK1/JAK2 inhibitor for the treatment of myeloproliferative neoplasms

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Dysregulation of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway is a hallmark for the myeloproliferative neoplasms (MPNs) polycythemia vera, essential thrombocythemia, and primary myelofibrosis. This presentation will describe the discovery of the JAK1 / JAK2 selective inhibitor INCB018424 as our clinical candidate currently in phase III clinical trials for the treatment of myelofibrosis.

MEDI 298

Opioid receptors: Past, present, and future

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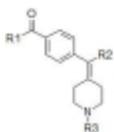
The opium poppy, *Papaver somniferum*, is one of several plants which have profoundly affected human history. For centuries, it has provided an unmatched medicine for the relief of pain. More than 30 alkaloids have been identified in opium and among the most relevant are morphine and codeine. These alkaloids are important for modern medicine as an analgesic and cough suppressant, respectively. Morphine and related opioids exert their major pharmacological effects by interacting with opioid receptors in the central nervous system. Three types of opioid receptors mu (MOP), delta (DOP), and kappa (KOP) have been identified and each has a role in the mediation of pain. As a consequence of target drug design and synthetic efforts, we have achieved a better understanding of the pharmacology, biochemistry, and biology of opioid receptors. Moreover, these efforts have opened new avenues for chemical investigation. This talk will briefly review our current understanding of opioid receptors and highlight their potential as a drug target.

MEDI 299

Strategies employed and outcomes of the multiparameter optimization of 4-piperidin-4-ylidenemethyl-benzamides as potent and selective δ -opioid receptor agonists

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The optimization of a series of 4-piperidin-4-ylidenemethyl-benzamides that possess potent activity at the δ opioid receptor and good selectivity over the μ and κ opioid receptors was undertaken. The three key sites of exploration included the amide substitution (R1), various aryls on the olefin (R2) and substitution on the piperidine nitrogen (R3). Simultaneous strategies to improve the metabolic clearance, reduce the cardiac risk in terms of increasing selectivity over hERG, and reduce Pgp mediated efflux whilst maintaining potency were employed. Utilization of predicted properties facilitated the optimization of this series to obtain overall desirable properties for a CNS drug.



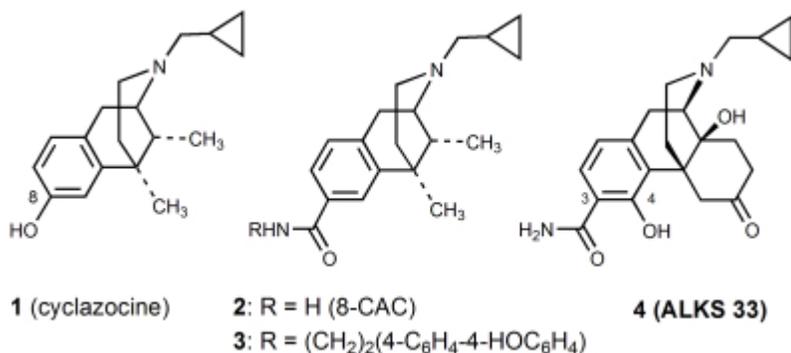
MEDI 300

Discovery of carboxamide bioisosteres of the phenolic-OH of opioids

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In hopes of identifying novel bioisosteric replacements for the phenolic-OH of cyclazocine (**1**) and related opioids, we previously reported the synthesis and biological properties of 8-carboxamido-cyclazocine (8-CAC; **2**). 8-CAC displays very high affinity for opioid receptors and has a 15 hour duration of action (vs. 2 hr for **1**) in a mouse antinociception model. The syntheses, structure-activity relationships and pharmacophore hypotheses of this new series of carboxamido-substituted opioids will be reviewed including the design and characterization of novel second generation compounds, namely the highly potent N-biphenylethyl 8-CAC analogue **3** [$K_i = 0.0056$ nM (μ)] and the 4-hydroxy analogue **4** (ALKS 33) [$K_i = 0.052$ nM (μ)] of 3-desoxy-3-carboxamidonaltrexone. Clinical data for ALKS 33 will also be discussed. Primary funding is provided from the National Institute on Drug Abuse (NIH grants R01 DA012180 and K05-DA00360).



MEDI 301

Discovery and characterization of a new kappa selective opioid receptor antagonist

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Emerging evidence indicates a potential role for Kappa Opioid Receptors as a pharmacological target for such disease states as anxiety, depression, and alcohol dependence. Reports from this laboratory have recently disclosed biarylether-carboxamides as a novel scaffold for opioid receptor antagonist activity. Further investigation of this scaffold has led to the discovery of a Kappa Opioid Receptor selective antagonist. This compound shows greater than 27 fold higher affinity for Kappa receptors, than for Mu or Delta Opioid receptors. This new kappa antagonist also shows in vivo antagonist activity indicative of favorable brain penetration and CNS activity. Utility in preclinical models of anxiety, depression and alcohol dependence will be presented.

MEDI 302

Potential of opioid receptor antagonists to manage L-DOPA-induced dyskinesia in Parkinson's disease

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Parkinson's disease (PD) is a debilitating condition characterized, in part, by the degenerative decline in motor function. Motor symptoms can be restored with L-DOPA, dopamine replacement therapy. For many PD patients, however, prolonged administration of L-DOPA causes disabling dyskinesias. There are no approved therapeutics to treat of dyskinesias. There are reports in the literature suggesting that opioid antagonists may alleviate L-DOPA-induced dyskinesia (LID). Historical data will be reviewed along with recent data from our laboratories investigating selective mu-opioid receptor antagonists as a potential treatment for LID.

MEDI 303

Multifunctional antioxidants for the treatment of age-related eye diseases

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Cataract is the worldwide leading cause of vision loss, while age-related macular degeneration is the leading cause of blindness in people over 60 years of age in

the United States. Although the initiating factors for the development of these age-related ocular diseases remain unknown, common biochemical risk factors in both of these diseases include: 1) an age-dependent increase in the presence of reactive oxygen species (ROS) in the lens and retina; 2) an age-dependent increase in Fe and Cu in the lens and retina; and 3) an age-dependent decrease in cellular antioxidant defenses. Since both antioxidants and chelating agents have been reported to experimentally delay the progression of these diseases in animal models, a series of novel analogs of N,N-dimethyl-4-(pyrimidin-2-yl)-piperazine-1-sulfonamide possessing either a free radical scavenger group, chelating groups, or both (multifunctional) have been synthesized. These orally active compounds readily accumulate in the lens and neural retina in the rat. The effect of these compounds on cataract and retinal induced changes will be discussed.

MEDI 304

Aldose reductase inhibitors for the treatment of diabetic cataracts and retinopathy

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Animal models have been invaluable in elucidating the causes and treatment of ocular complications associated with diabetes mellitus (DM). Lesions associated with DM include altered corneal wound healing, delayed pupil function response, sugar cataract formation, and retinopathy. All of these lesions have been linked to the aldose reductase catalyzed formation of sorbitol and their onset and progression are dose-dependently ameliorated with aldose reductase inhibitors (ARIs). While the clinical use of these inhibitors is controversial, efficacy against the development of diabetic retinopathy and cataracts has clearly been demonstrated in the dog. The development of the topical ARI formulation KinostatTM for the veterinary market will be discussed along with the clinical results of a randomized, prospective, double-masked placebo control pilot study conducted with 40 dogs newly diagnosed with DM and with no or minimal lens changes.

MEDI 305

KDR kinase inhibitors for retinal disease: The design and investigation of small molecules for topical and intravitreal dosing

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Age-related macular degeneration (AMD) is a disease of the macula and is the most common cause of blindness in individuals over 50 years of age. Biologic therapies that neutralize VEGF and prevent signaling through VEGFR2 and other VEGF receptors have shown clinical utility in the treatment of AMD. Small molecule inhibitors of the VEGF pathway may provide advantages if they can provide more convenient and less frequent methods of administration. This talk will present our approaches to designing and investigating KDR kinase inhibitors for topical and intravitreal dosing.

MEDI 306

Recent investigations of prostaglandin receptor agonist analogs as novel ocular hypotensive agents in glaucoma management

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Glaucoma is an asymptomatic disease that if left untreated can eventually lead to blindness. It affects ~66.6 million people worldwide predominantly at >40 years of age. Elevated intraocular pressure (IOP) is considered a major contributor to the events that lead to a slow progression of glaucoma and the eventual loss of sight. For years medical treatment was accomplished with topical drugs, such as b-adrenergics, b-blockers and CAIs, that reduced aqueous humor (AH) production. Drawbacks to these classes of drugs are multiple high dosing daily, compliance, various adverse events and concern that overzealous inhibition of AH formation risks long-term damage to the eye.

The other alternative to controlling IOP in the eye is facilitation of AH outflow, which has always been desired since the physiological defect in glaucoma is increased resistance to AH outflow. Prostaglandin FP-receptor agonists have emerged as the newest class of IOP lowering agents which potently lower IOP and enhance AH outflow. Besides their superior potency a significant attribute of these drugs is their q.d low dose. They are not, however, completely devoid of side effects. FP-receptor agonist research has also yielded discovery of a novel class of prostanoid-like compounds called "prostamides" which have no significant activity at prostanoid receptors but are highly potent IOP lowering agents. More recent reports on prostanoid research indicate that analogs of agonists specific for other PG receptors such as DP and EP are being investigated as IOP lowering agents.

MEDI 307

Discovery and in vitro SAR of AR-12286, a potent kinase inhibitor for the treatment of glaucoma

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From an initial a collection of 6-aminoisoquinoline amides, AR-11236 (100 nM in the porcine trabecular meshwork cellular assay) was found, but it lacked appreciable solubility in PBS and was inactive in vivo. SAR analysis indicated 4 molecular regions that could be optimized. Moving or removing the adjacent aromatic ring from the amine improved water solubility, but decreased potency. Molecules in the AR-11771 series were soluble but not potent (1.7 mmHg decrease at 1%). Finally, moving the aliphatic or aromatic ring of AR-12080 to the alpha position resulted in molecules that were both soluble and potent. Hydrolytic stability of the initial leads was also poor. The stability of these compounds was enhanced by adding alkyl groups to the amine, as exemplified by AR-12162. The clinical candidate, AR-12286, possesses the optimized elements described above, as well as a superior in vivo profile. In summary, a series of potent and hydrolytically-stable molecules was developed that reversibly alter cell shape in porcine and human trabecular meshwork cell lines and are nanomolar inhibitors of Rho kinase. AR-12286 was chosen as a clinical candidate for the treatment of glaucoma.

MEDI 308

Development of Rho kinase inhibitors for the treatment of glaucoma

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Rho Kinase (ROCK) is an AGC kinase family member whose activation results in phosphorylation of many substrates that have effects on cell contraction, regulation of the cytoskeleton, and regulation of microtubules. In this study we set up biochemical and cell-based assays which were used to support medicinal chemistry efforts designed to develop highly potent selective ROCK inhibitors which had drug metabolism and pharmacokinetic (DMPK) properties designed for rapid clearance and poor oral bioavailability, and showed in vivo efficacy in

animal models of glaucoma. Nanomolar ROCK II inhibitors from three structural classes of compounds (benzodioxane amides, ureas, and tetrahydroisoquinolines) which had > 1000-fold selectivity over PKA and had broad kinase selectivity were developed. Furthermore, these compounds were shown to be efficacious in an elevated IOP rat model as well as in a rabbit IOP model.

MEDI 309

Palomid 529, a dual TORC1/TORC2 inhibitor of the PI3K/Akt/mTOR pathway as a therapeutic approach to ocular diseases of retinal neovascularization

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The concept behind the Palomid small molecule drugs came from an observation that at least part of the anti-angiogenic activity of anti-estrogens was off target. In a variety of experimental approaches, anti-estrogens could be shown to exert anti-angiogenic activity in the absence of functional estrogen receptors. If one could tease out this off target activity, one might be able to first identify a new class of anti-angiogenic agents and second create an anti-angiogenic agent which did not have a steroidal backbone hence not be capable of inducing toxicity through estrogen agonist activity, one common side effect of anti-estrogen therapy. This off target activity was isolated by first creating novel, non-steroidal estrogen agonists by computational design, re-designing such agonists to be antagonists (“anti-estrogens”) through computational design and then screening out any analogs which bound or signaled through estrogen receptors alpha or beta but still retain anti-angiogenic activity. Palomid 529 (P529) was created by de novo computational design, medicinal chemistry and in vitro/in vivo screening of three generations of novel small molecule analogs. After exhaustive biological evaluation, P529 was shown to be an allosteric inhibitor of the PI3K/Akt/mTOR pathway functioning by the dissociation the TORC1 and TORC2 complexes. At least 20 pro-angiogenic cytokines have been shown to initiate aberrant ocular angiogenesis in diseases such as age-related macular degeneration or diabetic retinopathy. P529 inhibits angiogenic signaling and transcriptional control by inhibition of pro-angiogenic cytokines and HIF-1a, respectively. P529 also inhibits retinal and subretinal vascularization in the oxygen-induced retinopathy model (diabetic retinopathy model), the laser-induced retinopathy model (age-related macular degeneration, AMD, model) and retinal scarring (fibrosis) in a rabbit model of retinal detachment. In rabbit intravitreal and subconjunctival pharmacokinetic and biodistribution studies, P529 travels from vitreous or conjunctiva to tissues relevant for initiation of angiogenesis, the choroid and retina. With a single dose, P529 resides in the eye as long as 6 months at levels expected to show biologic activity. This, and other work, has led to the initiation of a Phase I human study to examine the effect of

P529 in AMD, “A Phase I Open-Label Study to Investigate the Safety, Tolerability and Pharmacokinetic Profile of Single Intravitreal and Subconjunctival Doses of Palomid 529 in Patients with Advanced Neovascular Age-Related Macular Degeneration”. This presentation will describe work used to create the Palomid series of small molecule drugs along with in vitro, in vivo animal studies and human Phase I data to support activity of P529 in age-related macular degeneration.

MEDI 310

Activation of the serotonin 5-HT1A receptor protects the retina from severe photo-oxidative stress

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Serotonin 1A (5-HT1A) agonists are used to treat anxiety and are neuroprotective in models of ischemia, traumatic brain injury and excitotoxicity. Experimentally induced oxidative damage to the retina has been used as a surrogate model for AMD. We have evaluated the efficacy of 5-HT1A agonists to protect the retina from severe photo-oxidative damage.

In the Blue Light model of retinal degeneration, rats exposed to light develop retinal degeneration that can be quantified by functional (electroretinogram, ERG) and structural (light microscopy) measurements. Protective effects of AL-8309A, 8-OH DPAT and buspirone were assessed in albino rats following the subcutaneous administration of doses ranging between 0.1 and 30 mg/kg. Additional experiments were performed to determine whether activation of the 5-HT1A receptor is required for protection, how rapidly 5-HT1A mediated retinoprotective mechanisms are activated and duration of this activity, and if topical ocular dosing is a viable route of drug administration.

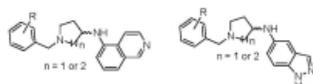
5-HT1A agonists, including AL-8309A, demonstrated potent and complete functional and structural protection. This protection was inhibited by treatment with a 5-HT1A antagonist, WAY 100635, confirming the requirement for activating the 5-HT1A receptor in initiating this survival pathway. 5-HT1A mediated retinoprotective mechanisms were activated quickly, AL-8309A prevented photo-oxidative damage when dosed immediately before light exposure and protection persisted for 48 hours. Topical ocular dosing with AL-8309B provided significant protection in this photo-oxidative induced retinopathy model. Based on these studies, AL-8309B may have utility in treating retinal degeneration.

MEDI 311

Rho kinase inhibitors: A potential new treatment for glaucoma

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Inhibition of Rho-associated Coiled Kinase (ROCK) is known to cause changes of cell morphology in smooth muscle cells. Pharmaceutical companies have attempted to use Rho Kinase inhibitors for the treatment of many diseases such as asthma, cancer, hypertension, stroke, erectile dysfunction (ED), and now glaucoma. Inspire began developing a treatment for glaucoma via cyto-skeletal modification of the trabecular meshwork cells in the eye. Exploration of two molecular series led to potent inhibitors of both Rho Kinase isozymes, ROCK I and ROCK II. These inhibitors were then optimized for topical ophthalmic delivery. Models were developed to study *in vitro* cell morphology changes as well as *in vivo* PK properties (rabbit), ocular tolerability (rabbit), and ocular toxicity (rabbit). These models, in conjunction with a monkey intraocular pressure model (IOP) were used to select a suitable clinical candidate.



MEDI 312

Epigenetic reprogramming of cancer cells by targeting DNA methylation dynamics

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DNA methylation is mediated by the transfer of a methyl group to the 5th position of cytosine bases and has been implicated in the silencing of gene expression and transposable elements. DNA methylation is a dynamic epigenetic mark that changes extensively during the life cycle of cells. This suggests that cells can be dynamically epigenetically reprogrammed in response to different stimuli. The proteins and pathways responsible for this reprogramming are just beginning to be understood. We have recently described a DNA demethylase enzyme complex that minimally consists of: a cytosine deaminase enzyme, a glycosylase and a DNA repair protein. It is clear that dynamic changes in DNA methylation are essential for the development and progression of many human cancers and represents a novel strategy to target cancer. We are actively pursuing approaches to discover new agents that target DNA methylation dynamics and epigenetically reprogram cancer cells.

MEDI 313

Modulating the epigenetic code readout in transcription

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Site-specific post-translational modifications of the chromosomal DNA-packing histones including acetylation, methylation and phosphorylation induced by physiological and environmental stimuli play an important role in epigenetic control of gene transcription. These modifications function to recruit chromatin-remodeling complexes and transcription machineries to specific gene promoter sites for transcriptional activation or silencing. However, how such modifications work in concert with positive or negative cooperativity to regulate distinct nuclear activities has remained elusive. Given the complexity of transcriptional regulation, small molecules designed to modulate selectively epigenetic interactions hold great promise towards better understanding of the basic epigenetic mechanisms as well as discovery and validation of new epigenetic therapeutic targets. In this talk, I will present our recent structural and functional analyses of new molecular

mechanisms concerning gene transcription mediated by chromatin modifications, and target-guided rational ligand design. I will also discuss functional implications of the basic principles of molecular recognition in gene transcription, as well as new possibilities in epigenetic therapies.

MEDI 314

Discovery of epigenetic chemical probes

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The Structural Genomics Consortium (SGC) has embarked on a four-year project to discover chemical probes for epigenetic targets. Epigenetic signaling is responsible for the control of gene expression through the regulation of chromatin packing. At the molecular level this is accomplished by proteins which catalyze methylation/demethylation and acetylation/deacetylation of histone tails. In addition, a large family of proteins recognizes or “reads” the epigenetic “marks”. In order to understand the role of these proteins in diseases, potent, selective inhibitors of these processes are highly desired. A variety of strategies is being employed to discover epigenetic chemical probes, including HTS and structure-based design. An example of how compounds are chemically optimized and characterized in biochemical and epigenetic assays is presented.

MEDI 315

Structure and mechanism guided identification of histone demethylase inhibitors

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Human Fe(II) and 2-oxoglutarate dependent oxygenases have roles including collagen biosynthesis, fatty acid metabolism, DNA repair, and hypoxic sensing. They have also emerged as the largest family of identified histone demethylases with several examples being linked to diseases. The lecture will review current knowledge on the inhibition of 2OG oxygenases with a focus on the application of biophysical knowledge for the development of selective inhibitors of the histone modifying enzymes.

We thank the Wellcome Trust, BBSRC and European Union for funding.

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MEDI 316

Discovery of chemical probes for protein lysine methyltransferase G9a

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Protein lysine methyltransferase (PKMT) G9a, which catalyzes di-methylation of H3K9 and p53 K373, is over expressed in human cancers. Knockdown of G9a inhibits cancer cell growth and the di-methylation of p53 K373 results in the inactivation of p53. As part of our efforts to create multiple high quality chemical probes for PKMTs, we carried out SAR exploration of the 2,4-diamino-6,7-dimethoxyquinazoline template that led to the discovery of UNC0224 as a potent and selective G9a inhibitor. A high resolution X-ray crystal structure of the G9a-UNC0224 complex, the first co-crystal structure of G9a with a small molecule inhibitor, was obtained. Based on the structural insights revealed by this co-crystal structure, optimization of the 7-dimethylaminopropoxy side chain of UNC0224 resulted in the discovery of UNC0321 (Morrison $K_i = 58$ pM), the most

potent G9a inhibitor to date. Progress toward developing cellularly active chemical probes will also be presented.

MEDI 317

Identification of potent and selective small molecule inhibitors of the BET family bromodomains demonstrate the tractability of a new class of epigenetic targets for drug discovery

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Epigenetic mechanisms of gene regulation have a profound role in normal development and disease processes. An integral part of this mechanism occurs through lysine acetylation of histone tails which are recognised by bromodomains. While the biological characterisation of many bromodomain containing proteins has advanced considerably, the therapeutic tractability of this protein family is undemonstrated. This presentation will describes the discovery and molecular characterisation of potent (nM) small molecule inhibitors that disrupt the function of the BET family of bromodomains (Brd2, 3, 4). Using a combination of phenotypic screening, chemoproteomics, biophysical and structural studies we reveal for the first time that the protein-protein interactions between bromodomains and chromatin can be antagonised effectively by selective small molecules that bind at the acetylated lysine recognition pocket. The implications of this discovery for this epigenetic reader class and other reader proteins, previously considered intractable, will be described.

MEDI 318

Asymmetric synthesis of the estrogen receptor β ligand,

S-2,3-bis(*p*-hydroxyphenyl)propionitrile (S-DPN)

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Agonists that show a high selectivity for estrogen receptor beta (ER β) are of interest as probes to study the biology of the two ER subtypes, ER α and ER β , and for potential therapeutic applications. We have recently described 2,3-bis(4-hydroxyphenyl)propionitrile (DPN), which exhibits a 170-fold greater relative potency for ER β in transcription assays. Unlike other ER β selective ligands, DPN exists as a racemate, and only recently has it been shown that each enantiomer

exhibits different biological effects in the presence of both receptor isoforms. Thus, to further assess the biological activities of each enantiomer on ER, it is necessary to conduct studies using enantiopure material. Described herein is the first reported asymmetric synthesis of both enantiomers of DPN, relying on an Evans asymmetric alkylation to form the stereocenter and subsequent functional group interconversions to generate the desired nitrile in a concise fashion and without racemization.

MEDI 319

Synthesis and structural optimization of multiple H-bonding region of diarylalkyl (thio)amides as novel TRPV1 antagonists

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The vanilloid receptor-1 (TRPV1 or VR1), a well-characterized member of the transient receptor potential (TRP) family as a ligand-gated non-selective cation channel, has evoked great interest since it was clearly demonstrated as a new target for treatment of various pain states. In particular, recent extensive findings have implied that direct blockade of TRPV1 by its antagonists could be a promising way for the discovery of novel analgesics

Over the recent years, a number of new TRPV1 antagonists have been reported. We have also reported a lot of antagonists such as amide, urea, and thiourea analogs including SC-0030, which exhibit highly potent competitive TRPV1 antagonistic effects, as well as their structure-activity relationship (SAR). As an extension of this project, we have been working on structural optimization of multiple H-bonding region and structure activity relationship of diaryldialkyl amides/thioamides as novel TRPV1 antagonists. In particular, we identified amide and thioamide analogs, of which antagonistic activities were highly enhanced by an incorporation of cyano or vinyl-substituent to the multiple H-bonding region. They exhibited highly potent $^{45}\text{Ca}^{2+}$ uptake inhibiting effects in rat DRG neuron. We will report our recent progress on structural optimization of multiple H-bonding region of diarylalkyl (thio)amide as Novel TRPV1 Antagonist.

MEDI 320

Active-site probes of serine beta-lactamases: Hydrogen-bond analogs of C-6 substituted hydroxymethyl, synthesis, and structure-activity relationships

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The active sites of the class A, C and D beta-lactamases have distinct similarities. Developing acute understanding of interactions in the active site helps develop more active compounds to inhibit a broad range of beta-lactamase enzymes. Using rational design, a series of beta-lactamase inhibitors was synthesized and tested for percent inhibition against a range of beta-lactamases from class A, C and D. In addition, the activity of the inhibitors was tested in synergy with beta-lactam antibiotics against isogenic strains of *E. coli* bearing representative beta-lactamases. The resulting trends help determine the significance of the hydrogen bond beta to C-6 in penicillin sulfone compounds. Our data showed that the homologated hydroxymethyl lost inhibitory activity, hydrogen bonding amines at C-6 are more effective when extended to the gamma position and less bulky C-6 functionality is more active.

MEDI 321

In vitro effects of C-7 aryl fluoroquinolones on DNA gyrase and DNA

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Fluoroquinolones (FQs), broad-spectrum bactericidal antibiotics, exert their effects by inhibiting DNA gyrase and/or topoisomerase IV through the formation of a ternary complex with the enzyme and DNA. Molecular modeling and crosslinking studies with ciprofloxacin-derived derivatives revealed a potential binding pocket on gyrase. Based on this model, we reasoned that C-7 aryl substituents on FQs could potentially fit into a pocket between Arg121 and Tyr122 and increase binding contacts in the quinolone-resistance determining region on gyrase. The effects of aryl groups added to the C-7 end of FQs on activity with FQ-resistant gyrase mutants were examined. Computed properties of the C-7-aryl groups were determined to look for correlations with activity against different gyrase mutants. Lead compounds were identified. *In vitro* assays with DNA revealed that C-7 aryl FQs do not intercalate and unwind DNA like other FQs do. Additional assays with DNA and DNA gyrase were performed to characterize antimutant activity.

MEDI 322

"Trojan horse" strategy: An efficient therapy against multidrug resistance bacteria

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The emergence of antibiotic-resistant bacteria is a major problem for the healthcare system. Indeed, it is reported that about 10 % of hospitalized patients contract a nosocomial infection. Two important mechanisms, among others, are involved in this resistance phenomenon: first, a decreasing permeability of the bacterial membrane towards some antibiotics and second, a low intra-microbial concentration of antibiotics due to bacterial efflux system. Siderophores are bacterial molecules that bind ferric iron extracellularly for transport into the cell and which have been reported to enhance the antibiotic action of drugs, following a "Trojan Horse" strategy.

In order to develop new therapeutic agents against multi-drug resistant bacteria, we decided to work on siderophore-linked antibiotics: an iron(III) chelator linked by a cleavable chemical bond to a known antibiotic. The first part of our work, concerns the synthesis and preliminary biological results of the catecholamides attached to a functionalized multi-amine backbone.

MEDI 323

Polyacetylene natural products as potential antibiotic agents: Total synthesis, biological evaluation, and analog studies

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Recently, linear polyacetylene natural products have demonstrated growth inhibitory activity against the microorganism causative agents for Leishmaniasis and Chagas Disease. The mechanism of action of these compounds and their broader application against other infectious agents remain unknown and warrant further investigation. Our lab has synthesized a collection of these compounds in racemic and enantiomerically enriched form and begun to evaluate their antibiotic potential against various bacterial and fungal pathogens. Some key aspects of our synthesis has been the use of chemoenzymatic methods for the resolution of chiral propargylic alcohol intermediates and the use of copper mediated, *Cadiot-Chodkiewicz* coupling reaction to form the asymmetrical diyne core. Additionally, we have begun to investigate structural changes to the molecules to identify

some preliminary structure-activity relationships. The details of our synthesis and an analysis of our biological data will be discussed.

MEDI 324

Benzothiophenesulfonylamidophosphonates: Novel inhibitors of Class A and C Beta-lactamases

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A series of benzothiophenesulfonylamidophosphonates of formula I, were found to be effective inhibitors of Class A and C beta-lactamases and restored the activity of imipenem against beta-lactamase producing imipenem-resistant strains of pseudomonas. The SAR and synthesis of these novel BLIs will be discussed along with their *in vivo* efficacy in an imipenem-resistant *Pseudomonas aeruginosa* murine infection model.

MEDI 325

Influence of a C-2 thioether moiety on the activity of fluoroquinolone antibiotics

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Fluoroquinolones are broad-spectrum antibacterial agents derived from naphthyridones. The mechanism of action has been shown to rely on formation of a ternary complex between DNA, gyrase/Topoisomerase IV, and fluoroquinolone. Gyrase/TopoIV is the enzyme responsible for unwinding supercoiled DNA. The ternary complex is known to inhibit cellular growth and may lead to rapid cell death by a mechanism resulting in chromosome fragmentation. Fluoroquinolone generations are characterized by structural changes to the core ring system, with

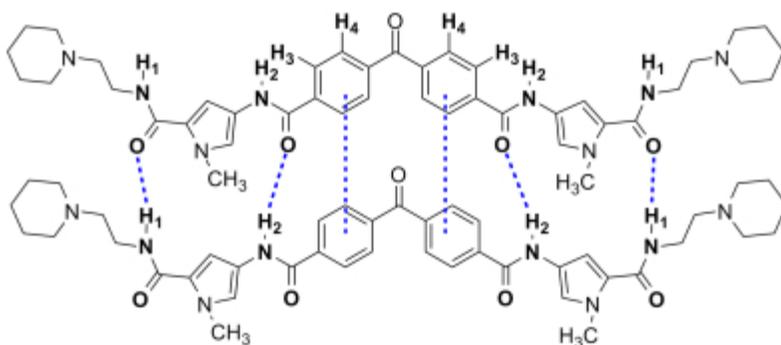
most changes occurring at N-1, C-7, or C-8; Ulifloxacin is among the first to contain a thioether moiety at the C-2 position. Recently studies have shown that different structures have dramatic differences in the rate of and drug concentration required for bacterial killing and antimutant activity despite small differences in MIC. Presented here is an effort towards design, synthesis, and evaluation of fluoroquinolone derivatives to elucidate the structural roles impacting these properties.

MEDI 326

Membrane and self-association studies of benzophenone based antibiotic

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The rapid emergence of pathogenic bacteria that are resistant to common antibiotics is an alarming threat to the healthcare community. Recently our laboratory discovered benzophenone-based membrane targeted antibiotics (BPMTA). The BPMTAs have shown excellent and selective in vitro and in vivo activity against antibiotic resistant Gram-positive microbes such as MRSA, VRE, VISA and VRSA and Gram-negative organisms including *E.coli*. The potent activity of BPMTA was attributed to its function on the bacterial membrane where these agents disrupt the electrochemical gradient of the cell. We hypothesize that BPMTA molecules self-associate in the bacterial membrane through non-covalent interactions (hydrogen bonds and aromatic π - π stacking interactions). Here we present studies that support our hypothesis. The H^1 NMR dilution experiments in $CDCl_3$ solution showed a strong downfield shift for NH_1 and NH_2 protons suggesting self-association of BPMTA through intermolecular hydrogen bonding. Furthermore, a strong upfield shift of H_3 and H_4 aromatic protons indicates that additional energy for this self-association was provided by aromatic π - π stacking interactions from the benzophenones. The concentration dependency of the chemical shifts was probed using self-association model. To investigate the membrane selectivity of BPMTA, we conducted dye release studies using large unilamellar vesicles (LUVs) composed of different lipid concentrations. In conclusion we propose that the BPMTA self-assembles into an oligomeric pore structure in the bacterial membrane and disrupt the electrochemical gradient leading cell death.



self-association of monomers through intermolecular hydrogen bonds (NH1 and NH2) and aromatic pi-pi stacking interactions (H4 and H5)

MEDI 327

Concise synthesis and antibacterial evaluation of 2-hydroxy-1-(indol-3-yl)-4-methylpentan-3-one, a natural product from *Xenorhabdus nematophilus*, and its analogs

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[figure 1]

Treatment of racemic 3-indolyl lactic acid methyl ester with isopropyl magnesium chloride provided the title compound and its isomer, 3-hydroxy-1-(indol-3-yl)-4-methylpentan-2-one. Both enantiomers (>96% ee) of each component were obtained via preparative chiral SFC. In contrast to previous reports, these compounds, as well as their acetate derivatives, were not active or very weakly active (MIC of 40 ug/mL or higher) against 16 bacterial strains, including *Escherichia coli* and *Bacillus subtilis*.

MEDI 328

Discovery of 5-(arenethynyl) monocyclic derivatives as potent inhibitors of native BCR-ABL including the T315I gatekeeper mutant

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The emergence of point mutations in the BCR-ABL kinase domain is a frequent cause of imatinib resistance in patients with chronic myeloid leukemia (CML). In order to overcome resistance, second generation inhibitors including dasatinib and nilotinib have been developed. Despite promising clinical results targeting most mutations, neither compound is effective against T315I which constitutes 15-20% of all clinically observed mutants. Previously, AP24534 was identified as a potent pan-inhibitor of BCR-ABL including the T315I gatekeeper mutation and has advanced into clinical development for the treatment of refractory or resistant CML. In this study, we explored a novel series of monocycles as alternate hinge-binding templates to replace the 6,5-fused imidazopyridazine core of AP24534. Like AP24534, these templates are tethered to pendant hydrophobic diaryl amide substituents *via* an ethynyl linker. Several compounds in this series displayed excellent *in vitro* potency against both native BCR-ABL and BCR-ABL^{T315I}. Notably, a subset of inhibitors exhibited desirable PK and was orally active *in vivo* in resistant BCR-ABL^{T315I} driven tumor CML mouse models.

MEDI 329

Discovery and optimization of potent and selective B-RAF kinase inhibitors

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RAF proteins are members of a family of serine/threonine kinases responsible for the transduction of signals along the conserved mitogen-activated protein kinase (MAPK) cascade, which plays an important role in the regulation of cell growth, differentiation and survival response. Frequency and activating mutations in B-RAF, a member of RAF family, suggest that they have an important role in melanoma and other cancer types. As a single agent or in combination, a potent and selective B-RAF inhibitor could offer a novel therapy to treat cancer. Several drugs acting on RAF or MEK have entered clinical trials. Our initial hit compounds were identified through a kinase selectivity assessment of our most advanced p38 kinase inhibitors. Not surprisingly we found that they were modestly active against C-RAF. Because of the relevance of mut-B-RAF in melanomas and other cancers, we postulated that this chemical class could also generate valuable B-RAF inhibitors. As anticipated, our efforts revealed several low micromolar hits from the fused imidazo-oxazole series. From the identified hits, a systematic screening campaign followed by hit-to-lead activities using

parallel synthesis was carried out. This poster describes the systematic SAR campaign to reveal low nM selective inhibitor of mut-B-RAF kinase.

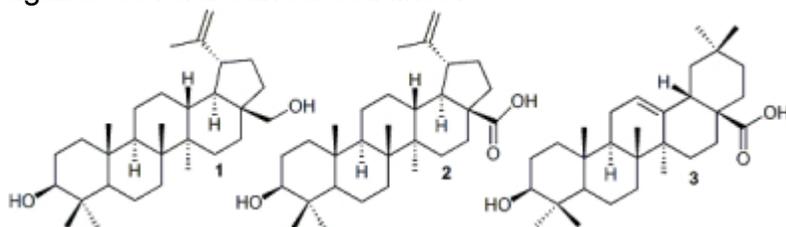
MEDI 330

Novel semisynthetic pentacyclic triterpenoids with cytotoxic activity

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Pentacyclic triterpenoids represent a diverse class of bioactive natural products[1]. Thousands of structures have been reported with hundreds of new derivatives described each year. Both betulin **1**, betulinic acid **2** and oleanolic acid **3** were reported to display several biological effects including anti-inflammatory, antiviral and in particular anticancer [2-8].

Using betulin **1**, betulinic acid **2** and oleanolic acid **3** as starting materials a series of novel derivatives have been synthesized and tested for their cytotoxicity against several cancer cell lines.



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MEDI 331

Aminothiazole analogs as CDK5 inhibitors

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Cyclin dependent

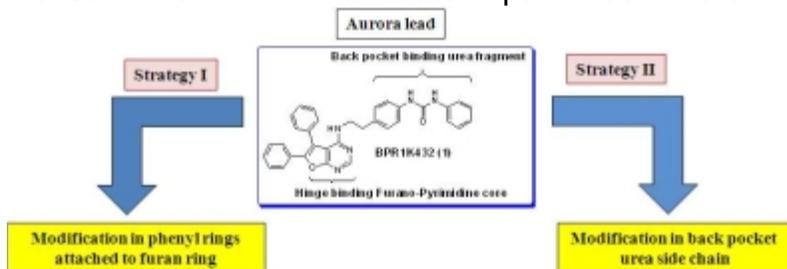
kinase 5 (CDK5) is a proline-directed serine/threonine kinase, which plays an important role in the pathology of Alzheimer's disease (AD). CDK5 has been implicated in hyperphosphorylation of tau protein which contributes to the formation of neurofibrillary tangles (NFTs). It has been proposed that inhibiting CDK5 could be effective anti-Alzheimer therapeutic strategy. Aminothiazoles are a known class of CDK inhibitors in general and of CDK5 in particular. Design, synthesis and enzymatic analysis of new compounds derived from the aminothiazole core will be presented.

MEDI 332

Lead optimization of furanopyrimidine Aurora kinase inhibitors: Development of in vivo active agents in tumor xenograft models

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We have recently identified BPR1K432 (**1**),¹ a potent Aurora kinase A inhibitor (IC_{50} ~50 nM), which possessed anti-proliferative activity in HCT-116 cell line (IC_{50} ~400 nM). However, it was inactive in HCT-116 tumor xenograft nude mouse model. Hence we initiated optimization of the lead **1**.



Structure-activity relationship studies in the urea side chain (Strategy II) and modification in the phenyl rings (Strategy I) were carried out, resulting in the identification of BPR1K724, with improved drug like property and better *in vitro* anti-proliferative activity than the lead **1**. Most importantly, the optimized lead BPR1K724 showed potent *in vivo* anti-tumor efficacy in HCT-116 tumor xenograft nude mouse model. The detailed SAR study leading to the identification of optimized lead BPR1K724 will be disclosed.

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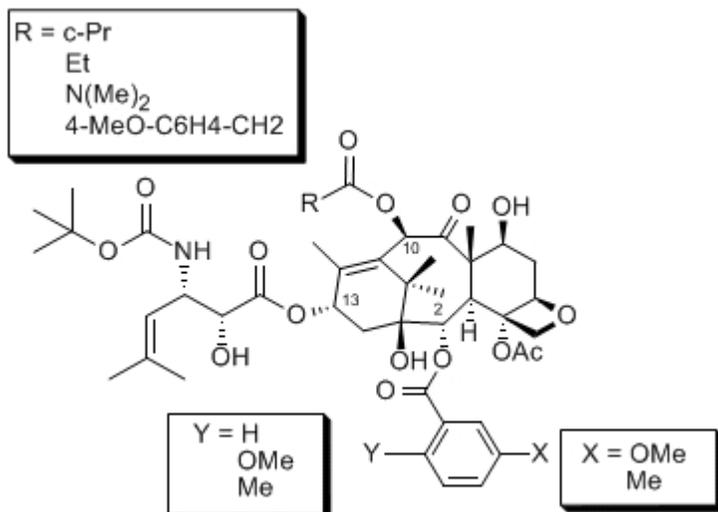
MEDI 333

Synthesis and biological evaluation of novel and highly potent taxoids for tumor-targeted drug delivery

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Paclitaxel and docetaxel are two widely used chemotherapeutic agents for treatment of a number of solid tumors (e.g. breast, ovarian and lung) yet do not show efficacy against drug-resistant tumors due to multi-drug resistance (MDR), point mutation or tubulin isotypes. Several 3rd-generation taxoids were synthesized, which exhibit 2-4 orders of magnitude greater potency against various drug-resistant cancer cell lines compared to paclitaxel and docetaxel. Modifications were systematically made to the substituents on the C-2 benzoyl moiety, the C-10 acyl position and the C-13 side chain. Many of these

compounds possess sub-nanomolar to pico-molar IC₅₀ values against various drug-sensitive and drug-resistant cancer cells, which is necessary for incorporation as cytotoxic agents into effective tumor-targeted delivery systems. The synthesis and biological evaluation of these 3rd-generation taxoids will be presented.

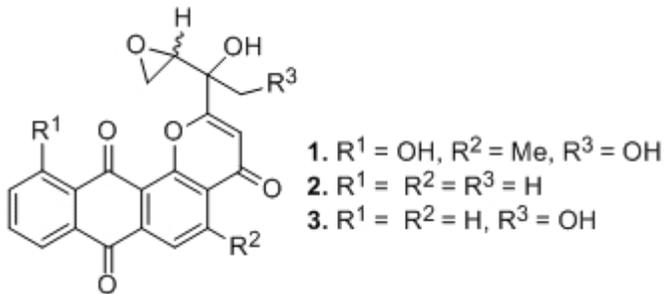


MEDI 334

Anthraquinone-type anticancer compounds: Derivatives of hydramycin (NSC-698410)

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Hydramycin (NSC-698410, **1**) is an anthraquinone-type antitumor agent that has shown broad-spectrum activity against a variety of human-derived cancer cell lines. Among tumors evaluated (lung, colon, melanoma, breast and prostate), GI₅₀'s were <10⁻¹⁰ M in the NCI's 60-cell-line panel. Our objectives were to synthesize and evaluate simplified analogues **2** and **3** that would facilitate synthesis, yet retain potent activities. Antitumor evaluation showed across-the-board GI₅₀'s of ~10⁻⁸–10⁻⁷ M for **2** (NSC-731341, -731342) and **3** (NSC-746372, -746373), with one diastereomer more potent than the other. A total synthesis of the enantiomerically pure **2** and **3** will be discussed.



MEDI 335

Development and optimization of fluorescence polarization and mitochondrial function assays for potent B-Cell Lymphocyte/Leukemia-2 family proteins inhibitors

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The anti-apoptotic B-cell lymphocyte/leukemia-2 (Bcl-2) family proteins can inhibit pro-apoptotic proteins by forming complexes via a conserved Bcl-2 homology 3 (BH3) domain. Designing potent small-molecule inhibitors that target the BH3 domains is a promising strategy for novel drug discovery for cancers.

Here, we report the development and optimization of a novel homogeneous Fluorescence Polarization (FP) assay to determine the binding affinities of potent small-molecule inhibitors to Bcl-2. By choosing fluorescent tracer with higher affinity to proteins, the range of inhibitor potency that can be determined is significantly improved. This result clarifies the widespread misconception that potent tracer should be avoided while screening relatively less potent compounds. We are able to accurately determine the K_i values up to sub-nano molar range. Furthermore, we developed and optimized a mitochondrial function assay to demonstrate the biological functions of the potent inhibitors as inducing Cytochrome c and SMAC release which will cause cell death.

MEDI 336

Antileishmanial activities of new histone deacetylase inhibitors

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Leishmaniasis is caused by parasitic protozoans classified as *Leishmania* species. Only zoonotic *L. infantum* is transmitted in both the eastern and western hemispheres. About two million new cases of human leishmaniasis occur every year in endemic zones. A wide range of adverse reactions are produced by most antileishmaniasis agents, and important resistance phenomena have been described. Thus, there is an increasing interest to using new compounds against leishmaniasis.

Histone acetylation regulates gene transcription in both eukaryotes and prokaryotes. Recent studies have identified roles for histone deacetylases (HDAC) in *Leishmania* species. An investigation with a new HDAC inhibitor, displaying inhibitory activity against *L. infantum*, is introduced. The compounds evaluated have a hydroxamate group in order to mask the HDAC catalytic zinc. The activity was stage specific since *Leishmania* promastigotes *in vitro* growth was not affected. The activity against intracellular amastigotes was similar to pentamidine at concentrations not toxic for mammalian cells.

MEDI 337

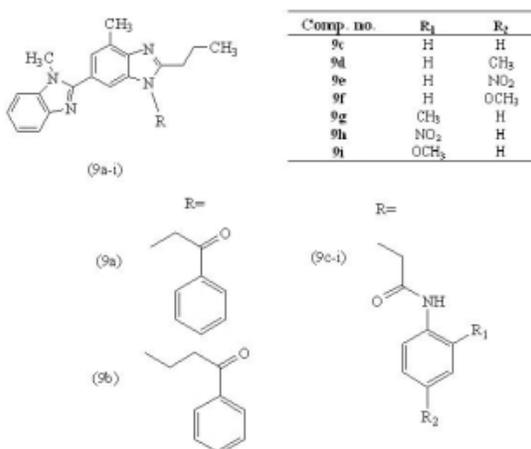
Design, synthesis and screening of novel bis-benzimidazole derivatives as cytotoxic agents

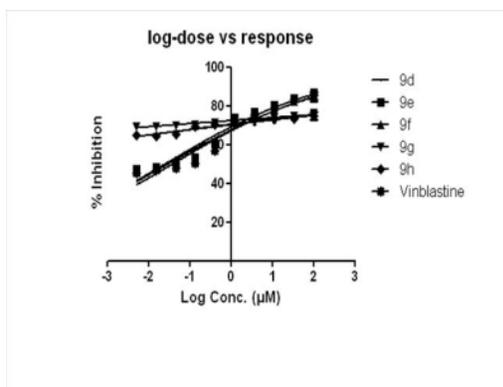
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Bis-benzimidazole, heterocyclic dimers, with acyclic and cyclic spacers, targets the DNA to exhibit their anticancer activity by intercalation and alkylation mechanism. Telmisartan, a bis-benzimidazole dimer, possesses a very good

cytotoxic activity against prostate cancer cell line. Hence, bis-benzimidazole dimer may be used to prepare various compounds that can induce DNA binding, inter strand cross-linking and disrupting cellular processes necessary for cell maintenance and replication in cancer cells. The present study deals with the synthesis of novel bis-benzimidazole derivatives (**9a-i**) from methyl 4-amino-3-methylbenzoate (**1**). All the compounds were characterized using IR, ¹H NMR, MS, elemental analysis and screened for their cytotoxic activity by XTT assay. Results of *in vitro* assay indicated that electron withdrawing substitutions at para position of phenyl ring and increasing lipophilicity of the compound increased the cytotoxic activity. Most active compound in the synthetic series was (**9e**) and demonstrated higher selectivity toward MCF-7 cell line. The IC₅₀ values were 0.025 μM and 0.038 μM for test compound (**9e**) and vinblastin (reference drug), respectively. This indicates compound (**9e**) may possess more potent cytotoxic activity to vinblastine. Hence, we propose that 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)-N-(4-nitrophenyl)acetamide (**9e**) may be used as lead for further development.

Scheme - 1
Schematic representation of novel compounds.





MEDI 338

5a-Carba-b-D-glucopyranose derivatives as novel sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors for the treatment of type 2 diabetes

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Type 2 diabetes mellitus is a progressive metabolic disease characterized by chronic hyperglycemia, and the prevalence has been increasing yearly. Therefore, more effective and safer new drugs for the treatment of type 2 diabetes are strongly desired. Sodium glucose co-transporter 2 (SGLT2) is located in the renal tubules and is responsible for reabsorption of glucose from the renal filtrate. It is a promising molecular target to directly induce glucose excretion into the urine and thus reduce elevated blood glucose concentration in type 2 diabetic patients. SGLT2 inhibitors such as T-1095, sergliflozin and dapagliflozin have been disclosed, one after another, as a potential treatment for type 2 diabetes. Our search for more highly efficient and metabolically more stable SGLT2 inhibitors resulted in the discovery of 5a-carba- β -D-glucopyranose derivatives. The synthesis, SAR and characterization of the compounds will be described.

MEDI 339

Efficient synthesis of pyrazolopyrimidine libraries which exhibit anaplastic lymphoma kinase (ALK) inhibition

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The pyrazolopyrimidine ring system is an important structural scaffold found in numerous biologically active compounds with applications in the development and preparation of drugs for a variety of cancer treatments. Our laboratory was interested in establishing both the parallel chemistry of this interesting class of compounds, and the library accessibility that will serve as tools for important anti-cancer research. Herein, we describe an efficient approach for the parallel synthesis of diversified pyrazolopyrimidines. Starting from easily prepared 2,6-dichloro 4-substituted pyrimidine 5-carbaldehyde, a two step one pot library synthesis with a range of differing 2-substituted amines were synthesized. Compounds within these libraries exhibited activity versus anaplastic lymphoma kinase (ALK) in biochemical assays and showed efficacy in cell lines expressing NMP-ALK.

MEDI 340

Synthesis, biological evaluation and structure-activity relationships of 4-substituted methoxybenzoyl aryl thiazole (SMART) as anticancer agents

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A series of 4-substituted methoxybenzoyl-aryl-thiazoles (SMART) was designed and synthesized in an effort to develop promising anti-cancer agents. We prepared SMART derivatives with modifications of the A, B and C rings and the linkage between the B and C rings. We also designed and synthesized water-soluble SMART analogs by introducing hydrophilic groups into the A ring and generating HCl or sodium salts. The antiproliferative activity of SMART agents against melanoma and prostate cancer cell lines was evaluated and structure-activity relationships were developed. The SMART compounds demonstrated similar activity as paclitaxel and colchicine. The best SMART analogs showed IC₅₀ values around 10 nM against PC-3 and PPC-1 cells as well as broad-spectrum anticancer activity (NCI-60). Preliminary mechanism of action studies indicated that these compounds exert their anticancer activity through inhibition of tubulin polymerization. Synthesis, SAR and biological evaluation of the SMART agents will be presented.

MEDI 341

Chemoenzymatic approach to the synthesis of bioactive tripeptide mimetics for treatment of cancer

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Tripeptides and tripeptide mimetics are widely investigated due to their biological activity. Among them, an anti-inflammatory agent **1**, an antibiotic **2**, and human rhinovirus 3C protease inhibitors can be found.

Tripeptides with C-terminal aldehyde group are of special interest. Compound **3** (Mg-132) is a potent and selective inhibitor of 20S proteasome, which is often used as a reference in biomedical studies [2].

The results of our studies on the successful combination of multicomponent reactions with enzymatic transformations to the synthesis of bioactive tripeptide mimetics, will be presented [3,4,5].

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MEDI 342

5,5'-Substituted indirubin-3'-oxime derivatives as potent cyclin-dependent kinase inhibitors with anticancer activity

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To enhance the ability of indirubin derivatives to inhibit CDK2/cyclin E, a target of anti-cancer agents, we designed and synthesized a new series of indirubin-3'-oxime derivatives with combined substitutions at the 5 and 5' positions. A molecular docking study predicted the binding of derivatives with OH or halogen substitutions at the 5' position to the ATP binding site of CDK2, revealing the critical interactions that may explain the improved CDK2 inhibitory activity of these derivatives. Among the synthesized derivatives, the 5-nitro-5'-hydroxy analog **3a** and the 5-nitro-5'-fluoro analog **5a** displayed potent inhibitory activity against CDK2, with IC₅₀ values of 1.9 nM and 1.7 nM, respectively. These derivatives also showed anti-proliferative activity against several human cancer cell lines, with IC₅₀ values of 0.2 ~ 3.3 μM. A representative analog, **3a** showed greater than 500-fold selectivity for CDK relative to selected kinase panel, and potent in vivo anti-cancer activity.

MEDI 343

Indirubin derivatives as potent FLT3 inhibitors with anti-proliferative activity of acute myleoid leukemic cells

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Indirubin derivatives were identified as potent FLT3 tyrosine kinase inhibitors with antiproliferative activity at acute myeloid leukemic cell lines, RS4;11 and MV4;11 which express FLT3-WT and FLT3-ITD mutation, respectively. Among several 5 and 5'-substituted indirubin derivatives, 5-fluoro analog, **13** exhibited potent inhibitory activity at FLT3 (IC₅₀ = 15 nM) with more than 100-fold selectivity versus 6 other kinases and potent anti-proliferative effect for MV4;11 cells (IC₅₀ = 72 nM) with 30-fold selectivity versus RS4;11 cells. Cell cycle analysis indicated that compound **13** induced cell cycle arrest at G₀/G₁ phase in MV4;11 cells.

MEDI 344

Synthesis and selective tumor targeting properties of some asymmetric porphyrins

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The significant role played by porphyrins as sensitizers in photodynamic therapy of cancer demands today interdisciplinary studies, involving different approaches of the subject. This work emphasizes the close relationship between synthesis, complex structure analysis and biological studies. The synthesis and characterization (involving UV-Vis, IR, and complex NMR studies) of some AAAA vs. ABBB meso-porphyrinic type structures is presented. Their substituents are chosen so as to balance solubility, high singlet oxygen quantum yield and cell interaction. The presentation deals also with the quest for the luminescent properties of the developed porphyrins, including their efficiency in generating singlet oxygen. All data will be used for better understanding and defining the toxicity and efficiency in killing malignancy following the tests on cultured cells. The effect of the general fluorescent properties of the synthesized compounds on the functionality of some standard cancer cell lines as *Jurkat* and *K562* will be presented.

MEDI 345

Design of potent ATP-competitive MEK1 inhibitors

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The RAS/mitogen-activated protein (MAP) kinase pathway is a critical signal transduction pathway and is frequently activated by mutation in human cancers. MEK is one of the kinases in this signaling cascade. Identification of a MEK inhibitor with a mechanism of action distinct from the non-ATP competitive series

exemplified by Pfizer and Array was a key objective of this work. Screening of our in-house collection of compounds resulted in a novel series of ATP-competitive MEK inhibitors which were readily optimized using ligand and structure-based design. The unique binding mode of the series was elucidated using X-ray crystallography and suggested areas for further potency and selectivity improvements. The initial hit *N*-(2-(piperazin-1-yl)phenyl)-2-(1*H*-pyrazol-4-yl)thiazole-4-carboxamide (**1**) was optimized into a high affinity, potent series to MEK1 with good cell-based activity; resulting in improved inhibitors such as *N*-(2-(4-carbamoyl-4-(methylamino)piperidin-1-yl)-3-fluorophenyl)-2-(1*H*-pyrazol-4-yl)thiazole-4-carboxamide (**2**).

MEDI 346

Exploration of novel benzimidazole core as selective CDK5/p25 inhibitors

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Cyclin-dependent kinase 5 (CDK5) is a proline directed serine/ threonine protein kinase that hyperphosphorylates tau protein at Ser202 or Thr205. Hyperphosphorylated tau has been implicated in the formation of neurofibrillary tangles (NFTs), a contributing factor to the etiology of Alzheimer's disease (AD). Based on a prior X-ray crystal structure of CDK5/p25 with *R*-Roscovitine (1UNL), a series of novel compounds with a benzimidazole core were designed, synthesized and tested as selective inhibitors of CDK5/p25. The design, molecular modeling, synthesis, and biological activities of these compounds will be presented.

MEDI 347

Total synthesis and anticancer activity of novel glycolipid derivatives

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Total synthesis and anticancer activity of several novel derivatives based on glycolipid is presented. A versatile and convergent synthesis was accomplished through stereospecific α -glycosylation, which produced di- and tri-rhamnoside

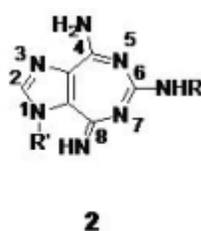
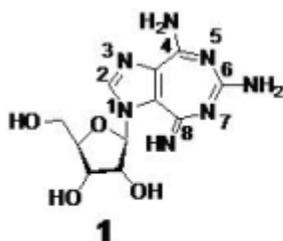
daumone derivatives. Most of the synthetic derivatives possessed potent anticancer activity against human cancer cell lines. Deoxyrhamnose trisaccharides with amide side chains had the most potent anticancer activity among all other known glycolipids, with an effective concentration of 20 nanomolar, which is comparable to that of doxorubicin. Conversely, acyclic and macrocyclic daumone derivatives had drastically decreased anticancer activity. Due to the highly lipophilic nature of the novel glycolipids derivatives, we propose that the observed anticancer activity is due to their potential to inhibit cell differentiation and proliferation via interaction with the membranes of cancer cells.

MEDI 348

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

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



R=C₇-C₁₈ alkyl, C₃-C₄ phenyl
R'=H, PhCH₂, *p*-OMe-PhCH₂, *p*-NO₂PhCH₂

MEDI 349

Discovery and SAR study of antagonists towards both 5-HT_{2C} and 5-HT₆ receptors

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Serotonin receptors are known to be related with central nervous system (CNS) disorders. 5-HT_{2C} receptor antagonists are postulated to be potential drugs for the treatment of anxiety, depression, and other psychiatric disorders. 5-HT₆ receptor antagonists are known to be effective for treatment of cognitive diseases and schizophrenia. Thus, dual 5-HT_{2C} and 5-HT₆ receptor antagonists would be important for synergetically modulating schizophrenia, depression, and anxiety which are induced from Alzheimer's disease.

This presentation will discuss the synthesis and SAR of (piperazin-1-yl-phenyl)-arylsulfonamides which show high binding affinities for both 5-HT_{2C} and 5-HT₆ receptors. Naphthalene-2-sulfonic acid isopropyl-[3-4-methyl-piperazin-1-yl]-phenyl]-amide exhibited high binding affinity towards both 5-HT_{2C} and 5-HT₆ receptors and considerable antagonistic activity for both receptors.

MEDI 350

Facile synthesis of octahydrobenzo[*h*]isoquinolines, a new class of potent and selective D₁ dopamine agonists

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The synthesis of conformationally rigid analogues of dopamine has long been used as a method of identifying ligands that are selective for individual isoforms of dopamine receptors. The octahydrobenzo[*h*]isoquinoline scaffold is a conformationally-restricted phenethylamine that we predicted would have high affinity for D₁-like dopamine receptors. No suitable synthesis of this ring system has been reported in the literature, particularly with the trans ring junction required for optimal binding to the receptor. We currently describe a highly

tractable method for obtaining this framework, and demonstrate that our approach is easily amenable to substitutions at the 5-position. Importantly, we show that the

7,8-dihydroxy-5-phenyl-substituted ligand is an extremely potent, high-affinity, full D₁-like dopamine agonist.

MEDI 351

HPLC study of distribution of two acetylcholinesterase inhibitors: Tacrine and 7-MEOTA after oral administration in rats

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In the present study, some basic pharmacokinetics information about two acetylcholinesterase (AChE; 3.1.1.7) inhibitors, tacrine and its derivate 7-MEOTA were characterized. 7-MEOTA is a potent, centrally active cholinesterase inhibitor with severalfold lower acute toxicity when compared to tacrine. These compounds may be used in therapy of Alzheimer disease.

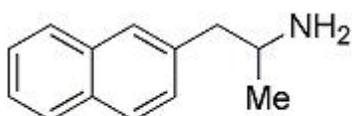
Both tested AChE inhibitors were applied orally in equimolar doses. These doses correspond with therapeutical dose (5 % LD₅₀) of tacrine. Following oral administration of therapeutical doses of tacrine (5.15 mg/kg) and 7-MEOTA (5.01 mg/kg) the basic pharmacokinetics profiles were different. The maximum of tacrine concentration in rat plasma was reached in 30 min giving 176 ± 26 ng/mL. The maximal concentration of 7-MEOTA in rat plasma was observed approximately 15 after application, the measured concentration was more than three-times lower than maximal level of tacrine and matched to 57.8 ± 14.8 ng/mL.

MEDI 352

Monoamine releasers as potential treatments for stimulant addictions

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Monoamine releasers are currently being evaluated as potential agonist medications to treat psychostimulant addictions. However, due to activation of dopamine neurons, agonist medications are often abused. Previous data with universal releaser PAL-287 suggest that serotonin elevations counteract dopamine's reinforcing effects. Therefore, administration of dual dopamine/serotonin releasers could potentially make medications less addictive. A series of PAL-287 analogs and other potential releasers were synthesized and evaluated for dopamine/serotonin release ability with the goal of developing agonist medications for stimulant addictions.



PAL-287

MEDI 353

Structure activity relationship study of BAY 59-3074, a partial agonist of the CB1 cannabinoid receptor

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BAY 59-3074, a partial agonist of CB1 cannabinoid receptor has been shown to have antihyperalgesic and antiallodynic properties. Compounds with this unique template bind to the cannabinoid receptors with good affinities but lacks subtype selectivity and also displays significant binding to other receptors. We have explored the structure activity relationship (SAR) of this template aiming to improve its affinity and receptor subtype selectivity. Structural overlap of BAY 59-3074 and Δ^9 -THC, the key psychoactive constituent of marijuana, suggests possible common pharmacophores. Based on this we extended the well-established SAR of classical cannabinoids to the BAY 59-3074 template. We found that the SAR trends of classical cannabinoids could be successfully extended to the BAY 59-3074 template. The resulting analogs exhibited higher affinities and receptor subtype binding profile. Here we report on the design, synthesis and biological evaluation of these analogs will be presented. Acknowledgment. This work has been supported by National Institutes of Health grants: DA07215 and DA023142.

MEDI 354

Novel CB2 selective bicyclic cannabinoids

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Cannabinoids elicit their biochemical and pharmacological effects primarily by interacting with two well-characterized G protein-coupled receptors (GPCRs), designated as CB1 and CB2. The CB1 receptors are found mainly in the central nervous system and to a lesser extent in the periphery whereas the CB2 receptors are expressed primarily in the immune cells and tissues. Research from our and other laboratories has shown that CB2-selective cannabinoids are very effective against neuropathic and inflammatory pain without any undesirable CNS side effects. We report here a new series of pinene-derived bicyclic cannabinoids bearing aryl side chains as structurally novel CB2 selective agonists. Several analogs from this class exhibited high affinity and selectivity for CB2 over CB1 receptor. Details of their design, synthesis and structure activity relationship studies will be presented.

MEDI 355

Synthesis and biological studies of androgen receptor ligands: Towards mutation-resistant nonsteroidal antagonism

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The human androgen receptor (AR) is a key target for the treatment of prostate cancer. Nonsteroidal antagonists are a promising alternative because they lack steroid-related side effects. The nonsteroidal AR antagonists bicalutamide, nilutamide, and hydroxyl flutamide have proven useful for the treatment of prostate cancer. However, bicalutamide, the most commonly used antiandrogen, can be rendered less effective by common mutations in the AR binding pocket. Other propionanilides have been published showing low binding affinity but resistance to several common AR mutations with the introduction of bulky substituents at the ortho position of the sulfone-linked phenyl ring of bicalutamide. (McGinley and Koh, *J. Am. Chem. Soc.*, 2007.) This study has compelled us to expand upon the set of mutation resistant antagonists with functional groups that enhance binding but maintain the pan-antagonism observed. In the present study, propionanilides with varied B-ring linkers (e.g. ether, sulphonyl, amine, substituted amine) and a variety of substituted B-rings (e.g. naphthyl, *p*-cyanophenyl) have been synthesized, some of which have been

shown to exhibit IC₅₀ values in the low nM range for AR binding. They represent the first nM-range pan antagonists yet reported.

MEDI 356

Discovery of 2,2-difluoro-2-phenylethyl-piperidines as NR2B-subtype selective NMDA receptor antagonists

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N-methyl-D-aspartate (NMDA) receptors are ligand-gated, ionotropic glutamate channels expressed throughout the CNS. 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-subtype selective antagonists are effective in animal models of pain and Parkinson's disease without the side effects of non-selective compounds. The identification of a structurally diverse oral agent with an improved profile relative to lead compound MK-0657 will be presented.

MEDI 357

Bifunctional dopamine D3 selective agonist as novel antiparkinsonian agents: Evaluation of selected compounds in Parkinson's disease animal model

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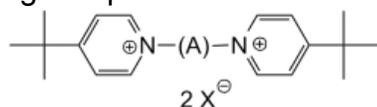
Parkinson's Disease (PD) is a progressive, chronic neurodegeneration disorder which is characterized by a gradual loss of dopaminergic neurons in the par compacta of the substantia nigra. It is primarily a sporadic disorder although a rare subset of population (<10%) acquires this disease due to several genetic defects. The etiology of PD is not fully understood although both oxidative stress and mitochondrial dysfunction have been strongly implicated in cell death. Due to complexity of the pathogenesis of PD, it is increasingly evident that drugs targeting only a single site may not be adequate to slow the disease progression and alleviate motor dysfunction at the same time. In our effort to develop bifunctional/multifunctional ligands to provide not only symptomatic relief but also to provide survival of more dopamine neurons as a part of neuroprotective therapy strategy, we have designed several bifunctional dopamine agonists. These bifunctional molecules are hypothesized to provide symptomatic relief via stimulation of post synaptic D2/D3 receptors and also to provide reduction of oxidative stress via different mechanistic pathways. We used our hybrid 7-[4-(4-Phenyl-piperazin-1-yl)-butyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol molecular scaffold to design such drugs. One of our lead molecules (S)-N⁶-(2-(4-(isoquinolin-1-yl)piperazin-1-yl)ethyl)-N⁶-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine exhibited potent selective functional activity (EC₅₀, 0.52 nM, D2/D3 > 223) for D3 receptor and also exhibited potent antioxidant activity. The lead molecule was evaluated in PD animal models, unilaterally lesioned 6-OHDA rat and reserpinized rat models, to evaluate its efficacy in motor stimulation. Detail structure activity relationship study along with in vitro and in vivo studies will be presented. Supported by NS047198 (AKD).

MEDI 358

Non-covalent interactions of quaternary heteroaromatic compounds with cholinesterases: Analogs of SAD-128

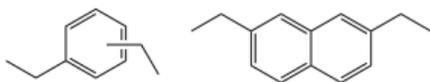
Kamil Musilek⁽¹⁾⁽²⁾, musilek@pmfhk.cz, Trebesska 1575, Hradec Kralove Czech Republic 50001, Czech Republic ; Jan Roder⁽³⁾; Ondrej Holas⁽³⁾; Anna Horova⁽¹⁾; Miroslav Pohanka⁽⁴⁾; Veronika Opletalova⁽³⁾; Kamil Kuca⁽⁴⁾⁽²⁾. (1) Department of Toxicology, University of Defence, Faculty of Military Health Sciences, Hradec Kralove Czech Republic 50001, Czech Republic (2) Department of Chemistry, University of Jan Evangelista Purkyně, Faculty of Science, Hradec Kralove Czech Republic 50001, Czech Republic (3) Department of Pharmaceutical Chemistry and Drug Control, Charles University, Faculty of Pharmacy, Hradec Kralove Czech Republic 50005, Czech Republic (4) Center of Advanced Studies, University of Defence, Faculty of Military Health Sciences, Hradec Kralove Czech Republic 50001, Czech Republic

Quaternary compounds are used and studied as cholinesterase inhibitors for several decades. Among them, the pseudo-reversible quaternary inhibitors (e.g. pyridostigmine bromide) are used as organophosphate pretreatment in various countries. Such carbamate compounds cause many side-effects (e.g. gastrointestinal) that originate from their covalent interactions with cholinesterases. Differently, compound SAD-128 [2-oxa-prop-1,3-diyl-1,1'-bis(4-*tert*-butylpyridinium) dichloride] was found to be non-covalent cholinesterase inhibitor able to protect experimental animals from organophosphate induced toxicity. Currently, some quaternary heteroaromatic compounds based on *tert*-butylpyridinium moiety and varying in the connecting linker were designed and synthesized. Several compounds displayed promising cholinesterase (AChE/BChE) inhibition *in vitro* (IC₅₀) and the kinetic data confirmed their non-covalent mechanism of inhibition. The ligand-enzyme interactions of the most promising compounds were studied *via* docking study.



X = Cl, Br

A = (CH₂)₁₋₁₂; (E/Z)-CH₂CH=CHCH₂; (CH₂)₁₋₂O(CH₂)₁₋₂



MEDI 359

Design, synthesis and biological activity of novel α,β -unsaturated carbonyl compounds as acetylcholinesterase inhibitors

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Alzheimer's disease (AD) is a progressive, degenerative disease, which impairs the brain functions and nervous system of an effected individual. Reduction in the activity of the cholinergic system is a well-known feature of AD. To combat the loss, efforts are invested in the design and synthesis of acteylcholinesterase (AChE) inhibitors. It is known that an efficient AChE inhibitor should be able to reach both the active site and the peripheral anion site. In our present work detailed docking studies were done to understand the binding orientation and interactions of donezepil in the active site of human acetylcholinesterase. Based on these observations molecules containing two binding moieties bridged by a suitable linker were designed and synthesized. A class of compounds with α,β -unsaturated carbonyl group as a linker has shown appreciable inhibition of the enzyme. The SAR study of these compounds led to the identification of lead

compounds for future studies.

[Figure1]

MEDI 360

WITHDRAWN

MEDI 361

Synthesis

and evaluation of a homologous series of 3,5-trisubstituted gamma-butyrolactones as potential muscarinic ligands

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Muscarinic acetylcholine receptors (mAChRs) are divided into five subtypes (M₁-M₅) that have a wide range of physiological effects making them important targets for drug discovery efforts. Muscarinic ligands have been investigated as potential therapeutic agents for Alzheimer's Disease, Parkinson's Disease, peptic ulcer disease, COPD, urinary incontinence, and as anti-spasmodic agents. Canney and coworkers have reported a series of lactone-based compounds as lead molecules for the development of muscarinic ligands. Molecular modifications of these leads have been made utilizing a recently reported, carefully controlled Prins reaction to provide a key hydroxyethyl-lactone precursor in high yield. The precursor was used to afford a novel series of structurally diverse substituted g-butyrolactones. The synthesis, characterization and preliminary evaluation of the ligands in a general muscarinic binding assay will be reported. The selectivity of several compounds for muscarinic receptor subtypes and the SAR data for the series will be discussed.

MEDI 362

Synthesis, nicotinic acetylcholine receptors binding and antinociceptive properties of 3'-(substituted pyridine)epibatidine analogs

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A series of 3'-(substituted pyridine)epibatidine analogs, with or without substitution at the 2'-position, were synthesized and evaluated in vitro for binding at nicotinic acetylcholine receptors (nAChRs) and for pharmacological activity in the mouse tail-flick, hot-plate, hypothermia and locomotor tests. All the compounds showed high affinity for $\alpha 4\beta 2$ binding with low affinity at $\alpha 7$ nAChRs relative to epibatidine. All the compounds showed low agonist activity in all four mouse tests. However, some of the compounds were potent antagonists of antinociception in the tail-flick and hot-plate tests.

MEDI 363

Synthesis, nicotinic acetylcholine receptors binding and antinociceptive properties of 2'-fluoro-3'-(substituted pyridine)deschloroepibatidine analogs

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A series of 2'-fluoro-3'-(substituted pyridine)deschloroepibatidine analogues showed high affinity for inhibition of [³H]epibatidine binding using rat brain tissues, with relatively low affinity at $\alpha 7$ nAChRs as determined by inhibition of [¹²⁵I]iodoMLA binding. 2'-Fluoro-3'-(2-fluoro-4-pyridinyl) and 2'-fluoro-3'-(2-chloro-4-pyridinyl)deschloroepibatidine with K_i values of 0.049 and 0.063 nM respectively had the highest binding affinity. Analogues with unsubstituted pyridines, 2'-fluoro-3'-(4-pyridinyl and 3-pyridinyl)deschloroepibatidine had K_i values of 0.35 and 0.12 nM respectively. All the compounds showed weak agonists effects in the antinociceptive, hypothermia and spontaneous activity test in mice. In general, the 2'-fluoro-3'-(substituted pyridine)deschloroepibatidine analogues were potent antagonists in the tail-flick test with less potency in the hot-plate test.

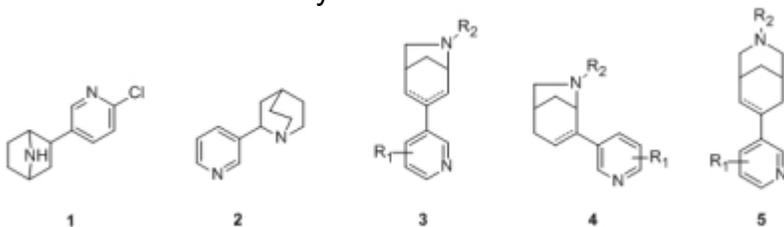
MEDI 364

Adventures in pyridyl azabicycloalkenes: In search of dual affinity nicotinic ligands

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The potential for nicotinic ligands with affinity for the $\alpha 4\beta 2$ subtype to treat such diverse disease states as nicotine addiction, pain, ADHD and cognitive disorders has been exhibited both preclinically and clinically with compounds such as

varenicline, tebanicline, sofinicline and ispronicline. Similarly, nicotinic ligands with affinity for the $\alpha 7$ subtype have shown promise for treatment of cognitive disorders and schizophrenia. For several of our programs, we sought nicotinic ligands with high affinity for both the $\alpha 4\beta 2$ and $\alpha 7$ subtypes to explore the possibility of a synergistic effect. We were particularly interested in exploring pyridylazabicyclic scaffolds as permutations of the known pan-nicotinic ligands epibatidine (**1**) and TC-2429 (**2**). We now wish to present the synthesis and SAR around three such genera (Compounds **3-5**), examples of which demonstrated the desired dual affinity.



MEDI 365

1-Acyl-4-sulfonylpiperazines as a new class of selective cannabinoid 1 receptor (CB1R) inverse agonists for the treatment of obesity: Correlation between peripherally vs. CNS-expressed CB1R and efficacy

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For a decade, the potential utilization of CB1R as a target for the treatment of obesity has been faced with a critical question: Are the food intake and body weight effects driven by engaging CNS- vs. peripherally-expressed CB1Rs? We present here data consistent with the necessity of drug-engagement of the CNS-expressed receptors to achieve *in vivo* efficacy. This thesis is consistent with plasma and brain pharmacokinetics in the rodents and brain receptor-occupancy data in the context of taranabant, a brain-penetrant CB1R inverse agonist. Our results were accomplished by utilizing novel CB1R inverse agonists, 1-acyl-4-

sulfonyl-piperazines, which were rationally optimized for efficacy and to produce compounds with both full and limited ability to penetrate the blood-brain barrier and thus interacting with centrally-, peripherally-, as well as predominantly peripherally-expressed CB1R. 1-acyl-4-sulfonyl-piperazines were considered for development as backup to taranabant. Unlike taranabant, 1-acyl-4-sulfonyl-piperazines exhibited a mixed metabolic clearance potentially advantageous for drug-drug interaction adverse effect mitigation.

MEDI 366

Development of *N*-aryl piperazines as selective mGluR₅ potentiators

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SAR and *in vitro* and *in vivo* pharmacological profile of a novel non-MPEP derived mGluR5 positive allosteric modulator (PAM) based upon an *N*-aryl piperazine chemotype will be presented. This mGluR5 chemotype displays the ability to act as either a non-competitive antagonist/negative allosteric modulator (NAM) or potentiator of the glutamate response depending on the identity of the amide substituent, i.e., a 'molecular switch'. A rapidly optimized PAM (VU0364289) with appropriate physicochemical properties for *in vivo* studies was shown to be both highly potent and specific for the rat mGluR5 receptor.

MEDI 367

Design and synthesis of tryptamine-based 5HT_{2C} agonists for the treatment of certain CNS disorders

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Serotonin is a major neurotransmitter that it thought to be involved in many CNS processes through at least 14 different receptor subtypes that have been classified into seven major families, 5-HT₁₋₇(1). The 5-HT₂ subfamily contains three distinct receptor subtypes, 2A, 2B and 2C. Human 5-HT_{2C} receptor is

predominantly expressed in the central nervous system (CNS), and has been proposed as a therapeutic target for the treatment of CNS disorders, including epilepsy, obsessive compulsive disorder, Parkinson's disease, schizophrenia, depression and anxiety, sleep disorders, and drug abuse. 5-HT_{2C} receptor agonists have been shown to regulate body weight in both rodent and humans. However, achieving a high degree of selectivity for 5-HT_{2C} versus 5-HT_{2A} and 5-HT_{2B} agonism is critical because of the potential liabilities of hallucinations associated with 5-HT_{2A} agonism and valvular heart disease associated with 5-HT_{2B} agonism. In humans, the search for potent and selective agonists has identified ADP-356 (Lorcaserin) which has been shown to decrease food intake and is currently in Phase III clinical trials and SCA-136 (Vabicaserin) as a potential therapy for schizophrenia.

We have discovered a novel series of compounds that are potent 5-HT_{2C} agonists, selective over 5-HT_{2A} and 5-HT_{2B} and display high degree of selectivity against off-target panels. After medicinal chemistry optimization and SAR studies, we identified a novel tryptamine chemotype that exhibits significant brain penetration, oral bioavailability and *in-vivo* efficacy in rat pre-clinical models of appetite suppression. We will describe the SAR and *in-vivo* efficacy of these novel agonists and profile them against current 5-HT_{2C} agonists in clinical development.

MEDI 368

Synthesis and SAR of piperazinyl and homopiperazinyl analogs as positive allosteric modulators of mGluR4

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Using a functional high-throughput screening and subsequent parallel synthesis approach, we have discovered two novel series of selective positive allosteric modulators for mGluR4, a G-protein coupled receptor. These two series comprised of a piperazine and homopiperazine central core respectively. The synthesis and SAR of analogs derived from these two series will be presented. Both series of selective positive allosteric modulators of mGluR4 provide critical research tools to further probe the mGluR4-mediated effects in Parkinson's disease.

MEDI 369

Corticotropin releasing factor receptor-1 (CRF1) antagonists: Synthesis and

structure-activity relationship studies of pyrazinones with carbamate and ether-based substituents

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Corticotropin-releasing factor (CRF), a 41-amino acid neuropeptide, plays a key role in hypothalamic–pituitary–adrenal (HPA) axis stress response. Clinical studies suggest that central CRF hypersecretion causes extreme or prolonged HPA axis activation leading to stress-related psychiatric disorders, such as anxiety and depression. Thus, antagonism of CRF₁ receptors may be a promising approach for the treatment of anxiety and depression. A series of potent pyrazinones with carbamate and ether-based substituents was synthesized and evaluated. Structure–activity relationship (SAR) studies led to the identification of potent analogs and suggest that the pocket into which this substituent binds can accommodate a wide variety of substituents. Compound **3**, a highly potent and selective CRF₁ receptor antagonist with an IC₅₀ value of 1.49 nM, was efficacious in the Defensive Withdrawal test (an animal model of anxiety) in rats. The synthesis and SAR of compounds with carbamate and ether-based substituents is described.

MEDI 370

Hybrid adamantyl cannabinoids

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D⁹-THC, the major psychoactive ingredient of marijuana, produces its physiological response through its interaction with two well-characterized cannabinoid receptors (CB1 and CB2) which belong to the superfamily of GPCRs. Extensive structure-activity relationship studies of tricyclic classical cannabinoids have established that the C-3 side chain plays a pivotal role in determining ligand's affinity, selectivity as well as potency towards these two receptors. Earlier we reported that AM411, a tricyclic cannabinoid bearing a

pendant 1-adamantyl group at the C-3 position exhibit improved affinity and selectivity for CB1 cannabinoid receptor. Later studies incorporating norhearn aliphatic hydroxyl (NAH) functionality in the tricyclic structure of AM411 identified AM4054 as a very potent and highly efficacious CB1-selective ligand. The present work describes our approach to enhance CB1 selectivity and potency of this molecule by incorporating aliphatic functionality at C-6b position. We have synthesized several chiral hybrid cannabinoids encompassing 1-adamantyl moiety at C-3 position, NAH at C-11 and various functionalities at the C-6b position. Design, synthesis and biological evaluations of these hybrid cannabinoids will be discussed.

MEDI 371

Fused oxacyclic-thiazolylidines as a novel series of potent CB₂ agonists

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CB₁ and CB₂ are the two known subtypes of cannabinoid (CB) receptors which belong to the class A rhodopsin-like GPCR family. The CB₁ receptor is predominantly expressed in the CNS and is thought to be responsible for most of the psychotropic effects produced by CB receptor agonists. The CB₂ receptor, in contrast, is largely expressed in the periphery on cells of immunological origin. Recent studies have shown that CB₂ selective agonists produce analgesia without the undesirable CNS side effects associated with CB₁ receptor activation. In our research efforts, we identified several fused oxacyclic thiazolylidine compounds as novel and potent (1-100 nM) CB₂ agonists with >1000 fold selectivity over CB₁. The synthesis and SAR characterization of this new series of CB₂ selective compounds will be presented.

[Fused Oxacyclic-Thiazolylidines]

MEDI 372

Parachute strategy for drug discovery: Design and synthesis of trypanosomal phosphodiesterase inhibitors towards African sleeping sickness therapeutics

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Human African trypanosomiasis (HAT sleeping sickness), is a significant neglected tropical disease that is prevalent in sub-Saharan Africa. Patients with HAT are faced with sub-optimal treatment due to an inadequate healthcare infrastructure, the inefficacy and toxicity of the currently available drugs, as well as the lack of funding for new drug development. The recent discovery of phosphodiesterases PDEB1 and PEDB2 in *Trypanosoma brucei*, enzymes that are approximately 30% homologous to the well-studied human PDEs, set the stage for pursuit of a 'parachute' strategy for drug discovery. This approach enables the rapid development of small molecule therapeutics that are based on human PDE inhibitors, but are modified to become selective for the parasitic enzymes. To begin the project, known human PDE inhibitors have been screened against TbrPDEB1. Based on this preliminary data, a series of compounds were designed and synthesized for assessment. Described herein are our efforts to optimize these compounds, which have led to analogs of improved potency at TbrPDEB1 and B2 .

MEDI 373

Selective and potent benzoxazole inhibitors of *Cryptosporidium parvum* inosine 5'-monophosphate dehydrogenase

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Cryptosporidium parvum is an enteric protozoan parasite that has emerged as a major cause of diarrhoea, malnutrition, gastroenteritis and potential bioterrorism agent. *C. parvum* cannot salvage guanine directly from the host; instead, guanine nucleotides are synthesized from adenosine in a streamlined pathway that relies on inosine 5'-monophosphate dehydrogenase (CpIMPDH). We have previously identified several parasite-selective IMPDH inhibitors through high-throughput screening. In this poster, we report the structure-activity relationship for a series of benzoxazole derivatives. A 2-substituted pyridine or small aromatic ring on the benzoxazole is crucial for activity. The IC₅₀ values for these inhibitors are in the

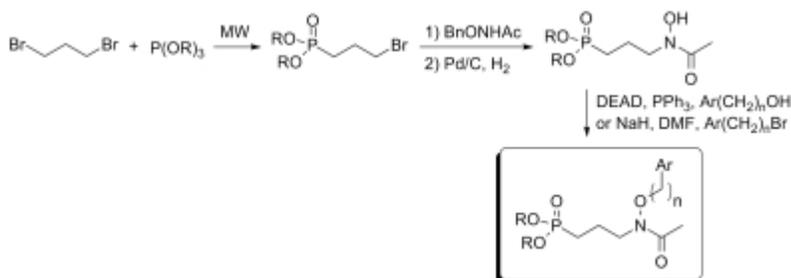
nanomolar range and show greater than 500-fold selectivity over human IMPDH (hIMPDH). The anti-parasitic activity of these compounds is currently under evaluation.

MEDI 374

Synthesis of small molecule inhibitors of Mtb Dxr from *Mycobacterium tuberculosis*

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Tuberculosis is responsible for 2 million deaths annually. This infectious disease is caused by *Mycobacterium tuberculosis*. Isoprenoid biosynthesis, essential for mycobacterial survival, uses the nonmevalonate pathway; the second step being mediated by the enzyme Dxr. Inhibitors of Dxr are potential antitubercular agents. The goal of this project is to synthesize analogs of fosmidomycin, a known inhibitor of Dxr, in order to study structure-activity relationships. We will describe the design, synthesis, and biological activity of a series of *N*-alkoxyacetamide inhibitors.



MEDI 375

Parachute strategy for drug discovery: Design and synthesis of trypanosomal histone deacetylase inhibitors towards trypanosomal disease therapeutics

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Trypanosomal diseases, including human African trypanosomiasis (HAT, sleeping sickness), Chagas disease, and leishmaniases represent a constellation of neglected tropical diseases that impact over 20 million patients per year, globally. In all three diseases, patients are faced with sub-optimal treatment due to inadequate healthcare infrastructure, the inefficacy and toxicity of the currently available drugs, and a lack of funding for new drug development. Histone deacetylases (HDACs) are enzymes involved in cellular transcription regulation, and are a target of therapeutic intervention in human cancers. Trypanosomatids *T. brucei*, *T. cruzi*, and *L. major* all possess these enzymes, providing an opportunity for repurposing the extensive knowledge in human HDAC medicinal chemistry for inhibitor discovery against trypanosomal deacetylases (TrypDACs). Using this knowledge, the goal of this research project is to prepare analogs of known HDAC inhibitors to begin to understand the driving factors for selectivity between TrypDACs and human HDACs. We will describe the development of library design and synthesis methodology, involving solid-supported parallel synthesis of hydroxamates from carboxylic acids and initial structure-activity relationship studies.

MEDI 376

Isolation of leishmania amastigote protein fractions which induced lymphocyte stimulation and remission of psoriasis

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A first generation polyvalent vaccine (AS1001) manufactured with protein from several cultured leishmania (L) species, was effective in the treatment of 2,770 patients with psoriasis. To determine the effective factor, a single blind trial with four monovalent second generation vaccines (AS1002) was done which resulted in remission of psoriasis. AS1002 vaccines were further purified, resulting in seven chromatography fractions (AS200) per species. Subsequently, a single-blind trial with AS200 fractions from *Leishmania brasiliensis* also induced remission of Psoriasis. In vitro testing of AS200 fractions on blood lymphocytes resulted in low or high responders subjects before treatment. AS200 fractions induced linear delayed type hypersensitivity reactions in guinea pigs and remission of forepaw inflammation in a DBA-1 mouse collagen induced arthritis model. AS1001 also induced clinical remission of psoriatic arthritis. Two HIV+

subjects with plaque psoriasis experienced remission after treatment with AS1001. There are factors in leishmania species which induce remission of psoriasis by stimulating lymphocytes.

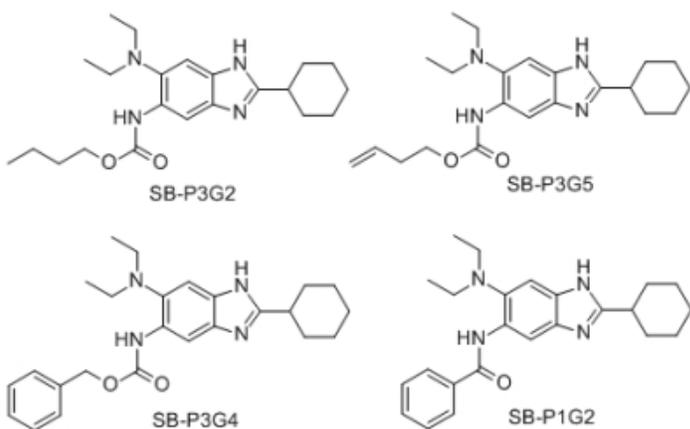
MEDI 377

Biological

evaluation of novel antitubercular trisubstituted benzimidazoles on *Mtb*-FtsZ: Discovery of novel mechanism of action

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FtsZ protein, which bears limited sequence homology to tubulin in eukaryotic cells, is involved in bacterial cell division. Interference of the assembly-disassembly of this essential protein has been shown to affect the cell division processes, leading to cell elongation due to inhibition of septation. Our laboratory has synthesized libraries of novel trisubstituted benzimidazoles based on rational drug design to target FtsZ protein. The hit/lead compounds arising from the *Mtb* bacterial growth inhibitory screening have been found to inhibit FtsZ polymerization in a dose dependent manner. Interestingly, it has been observed that the lead compounds enhance the GTPase activity of FtsZ. We will present and discuss the SEM images and TEM images of *Mtb*-FtsZ treated with the lead compounds, as well as the GTPase assay data. These clearly indicate the drug target and the impressive efficacy of the lead compounds, and also the likely mechanism of action.



MEDI 378

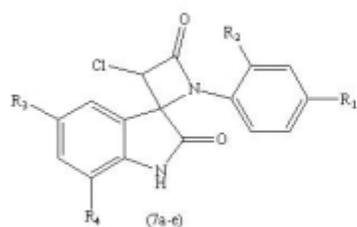
Design, synthesis and *in-vitro* antibacterial and antifungal activities of some novel spiro[azetidino-2, 3'-indole]-2, 4(1'H)-dione

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The present study deals with the synthesis of novel spiro[azetidino-2, 3'-indole]-2, 4(1'H)-dione derivative from the reactions of 3-(phenylimino)-1,3-dihydro 2H-indol-2-one derivatives with chloroacetyl chloride in presence of triethylamine (TEA). All the compounds were characterized using IR, ¹H NMR, MS and elemental analysis. They were screened for their antibacterial and antifungal activities. The bacterial strains used were Gram- positive *Staphylococcus aureus* (MTCC-96) and Gram- negative *Escherichia coli* (MTCC-521) and *Pseudomonas aeruginosa* (MTCC-647). The antifungal screening was done on *Candida albicans* (MTCC-183) and *Asperigillus niger* (MTCC-343) fungal strains. Results revealed that, compounds **(7a)**, **(7b)**, **(7c)**, **(7d)** and **(7e)** showed very good activity with MIC value of 6.25-12.5 µg/mL against three evaluated bacterial strains and the remaining compounds showed good to moderate activity comparable to standard drugs as antibacterial agents. Compounds **(7c)** and **(7h)** displayed equipotent antifungal activity in comparison to standard drugs. Amoxicillin, gentamycin and streptomycin were used as standard drugs for antibacterial activity while fluconazole and itraconazole were used as standard drugs for antifungal activity. Structure-activity relationship study of the compounds showed that the presence of electron withdrawing group substitution

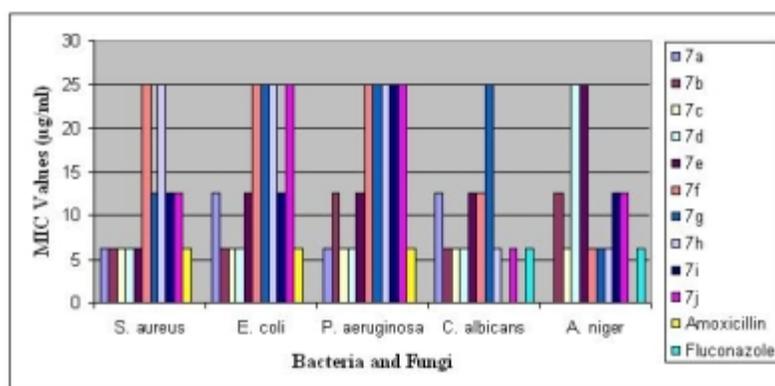
at 5' and 7' positions of indoline ring and on ortho or para position of phenyl ring increases both antibacterial and antifungal activity of the compound. Henceforth, our findings will have a good impact on chemists and biochemists for further investigations in search of spiro fused antimicrobial agents.

Scheme - 1
Schematic representation of novel compounds.



Where,

Com. No.	R ₁	R ₂	R ₃	R ₄
7a	CH ₃	H	Br	Br
7b	H	CH ₃	Br	Br
7c	NO ₂	H	Br	Br
7d	H	NO ₂	Br	Br
7e	H	H	Br	Br
7f	CH ₃	H	H	H
7g	H	CH ₃	H	H
7h	NO ₂	H	H	H
7i	H	NO ₂	H	H
7j	H	H	H	H



MEDI 379

Discovery of novel hit compounds for *Trypanosoma cruzi* sterol 14 α -demethylase through structure-based virtual screening

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One potential new target for Chagas' disease chemotherapy is sterol 14 α -demethylase (CYP51), a cytochrome P450 enzyme involved in biosynthesis of membrane sterols. In search of inhibitors of CYP51 from *Trypanosoma cruzi*, we

used a novel approach to develop energetically optimized, structure-based pharmacophores for use in rapid *in silico* screening. The method combines pharmacophore perception and database screening with protein-ligand energetic terms computed by the Glide XP scoring function to rank the importance of pharmacophore features. This hybrid ligand- and structure-based methodology uses an atomic breakdown of the energy terms from the Glide XP scoring function

to locate key features from the docked fragments. Docking poses were employed for generating a structure-based pharmacophore model, which was later used for virtual screening. Hits compounds were obtained and the binding free energy was

calculated and compared with the known inhibitors. Finally, proposals for novel inhibitors are suggested.

MEDI 380

Inhibitors of trypanosomal Aurora kinases as an approach for treatments of African sleeping sickness

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Human African trypanosomiasis (HAT) is a vector-borne disease caused by two subspecies of *Trypanosoma brucei*. HAT is lethal when untreated, and spreads rapidly when surveillance and treatment programs are interrupted. Current therapies are limited by the cost, route of administration, toxicity to the patient, and also by the fact that some drugs are rendered useless by the growing population of drug resistant trypanosomes. There is an acute need for new lead compounds for HAT. Repurposing of known drugs towards HAT represents a new strategy for speedy drug discovery. Aurora kinases are enzymes shown to be essential to cell division and Aurora kinase inhibitors are currently under development as human anti-cancer agents. Cell division is also essential for the virulence of *T. brucei*, which involves Aurora kinase-1, TbAUK1, that is both essential for infection and accessible to small molecule inhibitors. The current work efforts described here are focused on the synthesis of analogs of Aurora kinase inhibitors such as AT-9283 and PHA-680632, with systematic changes made to improve potency at TbAUK1 and kinase selectivity, with designs guided by homology models .

MEDI 381

Synthesis, characterization, and antimicrobial properties of silver carbene complexes encapsulated in polyethylene glycol-poly(lactic acid) micelles

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Silver has been used for many years as an antimicrobial agent on a wide array of bacteria. Our research group has synthesized silver carbene complexes (SCCs) that have shown effectiveness against many different strains of bacteria, including Anthrax, MRSA, and VRSA while having low toxicity. To prolong the life of these drugs in the body, SCCs have been encapsulated in PEG-PLA micelles. These particles have been characterized by their size and stability and have been tested *in vitro* and *in vivo* against bacteria strains. The results of these studies have shown a prolonged release of the SCCs from the micelles and retention or enhancement of the antimicrobial effects on the organisms when compared to the free drug. Due to the ability of the particles to resuspend and nebulize well, this system could have promise for the treatment of pulmonary and systemic infections.

MEDI 382

Synthesis and structural studies of the antimicrobial action of some amphiphatic cyclopeptides

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Emerging antibiotic resistant bacteria has increased the need for more effective antimicrobials that can overcome the development of new virulent bacterial strains. Recently antimicrobial peptides have been reported to kill bacteria by acting on bacterial membranes. Information about these peptides and their interactions with the bacterial membrane milieu are thus fundamental to developing effective antimicrobials that can be tailored for antibiotic targeting or as a synergist. We have synthesized some amphiphatic cationic cyclopeptides and a representative bis-cyclopeptide by microwave-assisted peptide synthesis to investigate their interactions with bacterial membranes and associated divalent metal ions. Their propensity to adopt beta-sheet structures in membrane-mimicking detergents and divalent metal ions were assessed by Circular Dichroism. The associated thermodynamic parameters were measured by Isothermal Titration Calorimetry. Their invitro intrinsic antimicrobial activities were tested against Gram-positive and -negative bacterial by the microdilution

antimicrobial susceptibility test. The correlation between antimicrobial activities of the peptides and their propensity to adopt beta-sheet like structures and/or interact with divalent metal ions will be discussed.

MEDI 383

Identification and structure-activity relationships 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.

MEDI 384

Highly potent and selective inhibitors for *Cryptosporidium parvum* inosine 5'-monophosphate dehydrogenase: SAR and anticryptosporidial activity

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Cryptosporidium parvum is an important mammalian pathogen and class B bioterrorism agent. This waterborne protozoan parasite relies exclusively on the salvage of adenosine to obtain guanine nucleotides in a pathway that includes inosine 5'-monophosphate dehydrogenase (IMPDH). Structural differences between human

IMPDH (hIMPDH) and *C. parvum* IMPDH (CpIMPDH) suggested a strategy for the design of CpIMPDH-selective inhibitors. Here, we report the SAR of a urea-based inhibitor series. All inhibitors show greater than 10³-fold selectivity for CpIMPDH with nanomolar to sub-nanomolar IC₅₀ values. Several compounds display excellent potency and selectivity in a *Toxoplasma gondii* model of *C. parvum* infection. The best compounds have anti-cryptosporidial activity in a tissue culture model of infection, are stable in mouse liver microsomes, mouse plasma and acidic conditions. These compounds are promising candidates for treating cryptosporidiosis.

MEDI 385

Antifungal agents from multivalent antimicrobial peptides design

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Antifungals work by taking advantage of differences between mammalian and fungal cells to kill the fungal organism without dangerous effects on the host. Unlike bacteria, both fungi and humans are eukaryotes. Therefore, fungal and human cells are similar at the molecular level. This makes it more difficult to find or design drugs that target fungi without affecting human cells. Antimicrobial peptides (APs) have been proposed as prospective antibiotics agents because their effect is rapid, broad spectrum and indifference to resistant towards standard antibiotics. Among the promising approaches, multivalent designs by polymerizing APs can enhance the potency and efficacy of existing antimicrobial monomeric peptides. In the present study, antifungal and hemolysis studies were carried out to assess to evaluate these new antifungal agents.

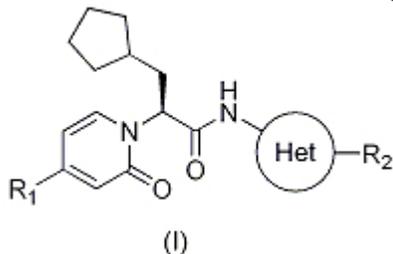
MEDI 386

Synthesis of pyridone-based glucokinase activators

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Small molecule gluokinase activators represent a promising opportunity for the treatment of type 2 diabetes. Herein, we report the asymmetric synthesis of a series of pyridone-based glucokinase activators (I). These efforts included

construction of the chiral template from methyl (2*R*)-glycidate and optimization of amidation conditions to mitigate epimerization of the α -stereocenter.



MEDI 387

Development of diaryl ether-based ligands for estrogen-related receptor α as potential anti-diabetic agents

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Estrogen-related receptor α (ERR α) is an orphan nuclear receptor that has been functionally implicated in the regulation of energy homeostasis, though the effects of selective modulation of this receptor *in vivo* have not yet been described. We have identified and optimized a series of diaryl ether-based thiazolidenediones, which function *in vitro* as selective ligands for this receptor. Several series analogues displayed favorable pharmacokinetic properties, including high oral bioavailabilities, thereby allowing for their evaluation *in vivo*. In animal models of obesity and diabetes, the lead compound normalized insulin and circulating triglyceride levels and improved insulin sensitivity. This provides the first demonstration of functional activities of an ERR α ligand in metabolic models *in vivo*. A summary of SAR, ADME properties, and efficacy data from this series will be presented. In addition, the mode of interaction between the protein and ligand will be discussed in light of co-crystallographic and competition binding data.

MEDI 388

Pyrimidine carboxamides as potent and selective CCK1R agonists

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Cholecystinin (CCK) receptors have physiological roles in stimulation of pancreatic and biliary secretions, regulation of gastrointestinal mobility, postprandial inhibition of gastric emptying, and regulation of food intake. At least two different CCK receptors have been identified that mediate the biological actions of CCK, the CCK1 receptor (CCK1R) and the CCK2 receptor (CCK2R). Biological actions mediated by the CCK1R suggest that CCK1R agonists may be used for the treatment of obesity.

Recently, a novel series of imidazole carboxamides were reported as potent and selective CCK1R agonists. We now describe the synthesis and evaluation of a series of 6-membered heteroaromatic carboxamides as CCK1R agonists. Pyrimidine was discovered to be the optimal heterocyclic core to replace the imidazole core present in previously reported CCK1R agonists. SAR studies of the pyrimidine carboxamides resulted in the discovery of structurally diverse potent and selective CCK1R agonists.

MEDI 389

Discovery of new phenylthiazolyl PPAR α /d selective agonists

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In an effort to obtain new PPAR α /delta selective agonists, we designed a new series of 2-methyl-2-phenoxy propanoic acids. Compounds have the characteristic feature of a phenylthiazolyl moiety linked to the phenoxy propanoic acid moiety by a three carbon alkyl linker. More than 30 compounds were designed, synthesized and their biological activities were examined. The most interesting compounds have been shown to have a strong in vitro potency on the PPAR α and delta subtypes and residual activity on PPAR γ . Compound 18 (EC₅₀=6 nM PPAR α , 740 nM PPAR γ , 47 nM PPARd) induced significant VLDL-cholesterol and triglyceride decrease and significant HDL-cholesterol increase in hApoE2/E2 transgenic mice (20 mpk, 8 days).

Such compounds represent an alternative to address dyslipidemia by a combined action on the two PPAR isoforms.

MEDI 390

Discovery of a potent, proteolytically stable, and cell permeable human SIRT1 and SIRT2 peptidomimetic inhibitor containing N^ε-thioacetyl-lysine

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Silent information regulator 2

(sirtuins) enzymes are a class of evolutionarily conserved intracellular protein deacetylases that catalyze the nicotinamide adenine dinucleotide-dependant

protein lysine N^ε-deacetylation

reaction. In humans, seven sirtuins, i.e. SIRT1-7, have been identified and been demonstrated to play a critical role in important biological processes such as gene transcription, apoptosis, DNA repair, metabolism, aging, and neurodegeneration. Therefore, inhibitors of this reaction could be potential therapeutics for metabolic and age-related diseases and cancer. Built upon our previously discovered potent N^ε-thioacetyllysine

(ThAcK)-containing lead peptide inhibitor for human SIRT1 and SIRT2, we performed a structure-activity-relationship (SAR) study. We found that (i) ThAcK-containing pentapeptides maintained the potent SIRT1 inhibition exhibited by the ThAcK-containing 18-amino acid lead peptide inhibitor, (ii) amino acid residues at the -1 and +1 positions relative to the ThAcK warhead could be modified to afford similarly potent pentapeptide SIRT1 inhibitors, and (iii) a potent, proteolytically stable, and cell permeable ThAcK-containing peptidomimetic SIRT1 and SIRT2 inhibitor of molecular weight less than 600 Da was identified from this SAR study.

MEDI 391

Antileishmanial activities of new histone deacetylase inhibitors

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Obesity is increasing worldwide, the main reason being the overeating of highly palatable food containing fat and sucrose. Basic appetite mechanisms are maladapted to this type of energy-rich diet, satiety signals being too weak postprandially to ensure energy balance. The gastrointestinal tract is the primary site for satiety signals. In principle satiety is promoted as long as intestinal digestion is going on with the release of the satiety hormones cholecystokinin

and enterostatin. Intestinal fat digestion is a highly efficient process performed by pancreatic lipase and its protein cofactor colipase. Hypothetically a reduced rate of fat digestion would promote satiety signalling.

We found that chloroplast membranes (thylakoids, composed of hydrophobic proteins, galactolipids and pigments) efficiently reduced the rate of triglyceride hydrolysis by pancreatic lipase and colipase in vitro. We also found that these membranes when added to food in either mice or rat pellets significantly reduced food intake and body weight compared to control animals. The reduced food intake occurred through significantly elevated levels of the satiety hormone cholecystokinin and of enterostatin. At the metabolic level serum triglycerides were reduced as well as body fat. Glucose and insulin levels were also reduced suggesting a general reduction of absorption of nutrients by the gastrointestinal tract. There was no sign of steatorrhea, the chloroplast membranes eventually being digested by the intestinal and pancreatic enzymes with no rest side-product in the intestine.

In single-meal experiments the effect of thylakoids were investigated in man. Healthy individuals of normal weight were offered a high-fat meal with and without the addition of thylakoids. Blood samples were taken 0 (prior to meal), 30, 60, 120, 180, 240, 300 and 360 min after the start of the meal. Blood samples were analysed for satiety and hunger hormones (CCK, leptin and ghrelin), insulin and blood metabolites (glucose and free fatty acids). The CCK level increased, in particular between the 120 min time-point and onwards, whereas the insulin levels and free fatty acid levels were reduced. The addition of thylakoids hence promotes satiety signals and reduces insulin response in man. The mechanisms for the effects will be further discussed.

MEDI 392

Discovery of aminopyrimidine derivatives as novel GPR119 receptor agonists

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GPR119 is a G protein-coupled receptor highly expressed in pancreatic beta-cells and its activation enhances the effect of glucose-stimulated insulin secretion via the elevation of intracellular cAMP concentration. Therefore, activation of GPR119 could provide a new therapeutic approach to the treatment of type 2 diabetes. In our research for novel GPR119 receptor agonists, we chose the

aminopyrimidine derivative in our library as a lead and performed conventional structural modifications on the compound resulting in the identification of potent and orally active GPR119 receptor agonists. We will describe the synthesis and structure-activity relationships of aminopyrimidine derivatives.

MEDI 393

6-Amino-4-(pyrimidin-4-yl)pyridones: Novel glycogen synthase kinase-3b inhibitors

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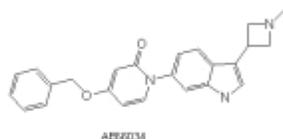
The synthesis and structure-activity relationships for a novel series of 6-amino-4-(pyrimidin-4-yl)pyridones derived from a high throughput screening hit are discussed. Optimization of lead matter afforded compounds with good potency, selectivity and central nervous system (CNS) exposure.

MEDI 394

Strategy to control hERG activity of brain penetrant Melanin-concentrating hormone 1 receptor (MCH1r) antagonists

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The inhibition of hERG channel has severely impeded the development of new Melanin concentrating hormone1 receptor (MCH1r) antagonists. A potassium channel structure and 3D-COMFA model was utilized to develop a medicinal chemistry strategy to overcome hERG channel activity and these results will be presented. Lead optimization of the novel template, represented by AE66034 gave compounds with improved properties and reduced hERG channel activity



MEDI 395

Diamine template as novel Melanin-concentrating hormone 1 receptor (MCH1r) antagonists with improved cardiovascular safety

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Melanin concentrating hormone (MCH) is involved in regulation of feeding, water balance, energy metabolism, general arousal/attention state, memory, cognitive functions and psychiatric disorders. The synthesis of a new chemical series exemplified by 2-methylamino-*N*-(4-methyl-3-{1-[4-(2,4,5-trifluoro-phenoxy)-benzyl]-piperidin-4-yl}-phenyl)-acetamide **AA41793** is reported. These compounds were designed to improve the affinity, physico-chemical properties and cardiovascular (CV) safety of the previous lead compound, **AA34729 (SNAP94847)**. Pharmacokinetic properties and efficacy in MCH-evoked drinking and MCH-evoked hypothermia are also reported.

MEDI 397

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

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The present study deals with the synthesis of novel 2-(2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-phenylacetamide derivatives (**6a-j**) from isatin (**3**) and 5, 7-dibromoisatin (**4**). All newly synthesized compounds were characterized using IR, ¹H NMR, MS and elemental analysis followed by evaluation of their cytotoxic activity by XTT assay on breast cancer cell line MCF-7 and non-cancer African green

monkey cell line VERO. Correlation study for QSAR and *in-vitro* assay was performed. The outcomes indicated that electron withdrawing substitutions at para position of phenyl ring and 5, 7 position of isatin ring and increasing lipophilicity of the compound increased the cytotoxic activity. The 2-(5, 7-dibromo-2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-(4-nitrophenyl)acetamide (**6b**) was found to be the most active compound in the series and demonstrated higher selectivity toward MCF-7 cell

line. The IC₅₀ values were 1.96 μM and 1.90 μM for test compound (**6b**) and vinblastin (reference drug), respectively. This indicates compound (**6b**) may possess equipotent cytotoxic activity to vinblastine. The compound (**6b**) is particularly promising, since it could kill cancer cells 19-20 times more effectively than the non-cancer cells. This property of (**6b**) may enable us to effectively control tumors with low side effects. Hence, we propose that 2-(5, 7-dibromo-2, 3-dioxo-2, 3-dihydro-1H-indol-1-yl)-N-(4-nitrophenyl)acetamide may be used as lead for further development.

Scheme - 1
Schematic representation of novel compounds.

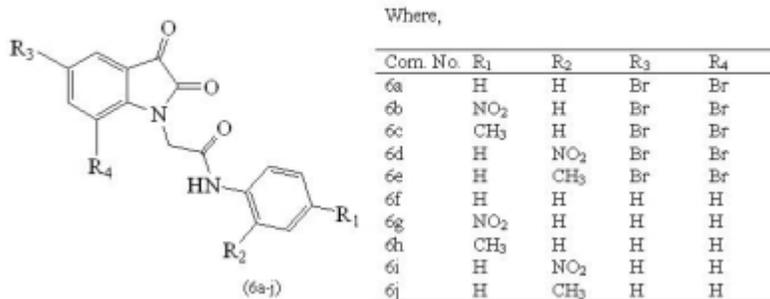
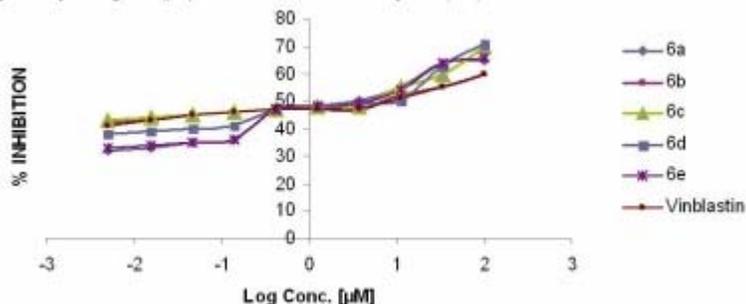


Figure: Graph of Log conc. (μM) vs % inhibition of different compounds (6a-e) and vinblastine



MEDI 398

Extraction of chemical information from documents

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Drug discovery projects have increased their reliance on external data in their evolution. Arguably, one of the most significant challenges for discovery research informatics lies in the integration of external sources of data into proprietary information to develop comprehensive knowledge. We discuss some of the challenges faced in automating the identification and extraction of chemicals named in patents and other chemistry rich documents, and their conversion into chemical databases that can be mined effectively.

We apply the tools developed to compare the chemical content of different patents for kinases and nuclear hormone receptors. A comparison of the libraries was carried out to identify overlaps and identify difference between patent disclosures and published information. The ChemDox technology provides an automated avenue to quickly extract and transform compound names and images from document sources into editable molecular structures. At the same time Boolean operations at the chemotype level can be carried out to effectively using different software tools.

MEDI 399

Application of the interligand Overhauser effect to fragment linking and screening

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Fragment based drug discovery involves the identification, study and elaboration of relatively small molecules (<250 Da), “fragments”, which bind weakly to target macromolecule. Information about the relative binding mode of two fragments bound simultaneously to the protein is crucial for their successful linking. One possible way of obtaining this is application of Interligand Overhauser Effect (ILOE). Such ILOE peaks on the NOESY spectra provide the information on relative binding mode of ligands which can be used in their further linking.

However, its application to screening using high concentrations of relatively hydrophobic fragments is problematic because of their aggregation and nonspecific binding effects. Here we report how these problems can be overcome and the ILOE used to screen for fragments in adjacent pocket and guide the iterative assembly of a potent inhibitor of our model enzyme – M.tuberculosis pantothenate synthetase – a potential drug target against TB.

MEDI 400

Covalent inhibitor design: Quantum mechanical calculation of electrophilicity for optimization of bond-forming functional groups

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Targeted covalent drugs require highly selective bond-forming functionality to ensure efficient modification of the protein target without modifying other targets. The design of such functionality can be accelerated by *in silico* assessment of their predicted reactivity toward biological nucleophiles (e.g., cysteine) and correlation of those predictions with the rates of relevant model reactions. We have used quantum mechanical methods to compute the potential surfaces for the reactions of methanethiol with α,β -unsaturated carbonyl compounds to obtain theoretical reaction rates for nonpolar and aqueous environments. The relative stabilities of the intermediate enolates provide a rapid qualitative ranking of reactivities. The structural determinants of the energetics of thiolate addition will be discussed in relation to experimental rates of reaction of representative electrophiles with biological nucleophiles.

MEDI 401

CoMFA analysis of pyrrolo[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines as multiple receptor tyrosine kinase inhibitors

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Inhibition of multiple kinases has opened a new paradigm in the treatment of several cancers. We have previously published the design, synthesis and biological evaluation of pyrrolo[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines as potent inhibitors

of multiple receptor tyrosine kinases. Our studies indicate that the nature of substitutions at the 4- and/or 5- and/or 6- positions of pyrrolo[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines dictate the potency and selectivity against EGFR, VEGFR2 and PDGFR- β . Thus, a dataset of 60 inhibitors reported from our laboratory was used to

develop 3D QSAR models that correlate chemical structure and inhibitory potency

for EGFR, VEGFR2 and PDGFR- β using CoMFA (Comparative Molecular Field Analysis). The details of these models and their potential predictive power will be reported.

MEDI 402

Trainable QSAR model of plasma protein binding and its application for predicting volume of distribution

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This study presents novel QSAR models for the prediction of two key pharmacokinetic properties of drugs – the extent of plasma protein binding (PPB) and apparent volume of distribution (Vd) in humans. Experimental PPB data were represented by almost 1500 percentage bound values and about 300 human serum albumin affinity constants. Predictive models were developed using recently introduced GALAS modeling methodology that allows estimating reliability of resulting predictions and provides the basis for model trainability. Vd was modeled using mechanistic approach accounting for drug binding in both plasma and tissues. 800 original Vd values collected from literature were corrected for free fraction in plasma yielding 'unbound Vd' (Vdu) values that represent drugs' affinity to tissues. pVdu was then described by a nonlinear model in terms of simple physicochemical properties (logP and pKa). Validation

results indicate good predictive power of the obtained model with RMSE of pVdu prediction being 0.4 log units.

MEDI 403

Approach to quick lead optimization including physicochemical and ADME profiling

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In recent years the pharma/biotech industries have made a concerted effort to focus on the quality of compounds produced in discovery versus quantity. Scientists are consequently required to consider all relevant properties of compounds to produce candidates with drug-like profiles. Balancing these inter-related molecular properties (such as solubility and permeability) can be a significant challenge. Tools that can help address these concerns are of considerable value. We will discuss case studies that illustrate how inter-related physical properties such as pKa, log*P*, and log*D* can be modified to improve physical properties, such as solubility, using a software tool that combines physicochemical property predictors with a database of substituents. Structural modifications are addressed through subtle alterations, such as heterocyclic group replacement, functional group interchange, or more drastic changes, such as the addition of substituents.

MEDI 404

How internal data marries public information in chemical and biological universes in drug discovery

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The amount of information in chemical and biological space grows exponentially thanks to the technological advances and the leap in research funding. However, due to the complexity of the data in pharmaceutical research, our understanding of how drug molecules affect biological processes has not yet been fundamentally changed by the explosion in the volume of experimental data, which is reflected in the small number of new molecular entities approved by the regulatory authorities in recent years. It is an urgent task to harness the full potential of the information by organically integrating data from internal and external resources in chemical and biological universes. Recently, we described

Advanced Biological and Chemical Discovery (ABCD), an integrated information platform based on a data warehouse strategy. It provides scientists with a unifying framework for accessing vast amounts of discovery knowledge collected at Johnson & Johnson Pharmaceutical Research & Development (J&JPRD). Here we present a further attempt of seamlessly integrating the internal and public data in chemical and biological universes. The resulting prototype system allows the simultaneous mining of the public and private data spanning the chemical, biological, genomic, and pharmacological aspects of genes, protein targets, diseases, and small molecules, which could greatly facilitate the target prioritization, lead identification and optimization, drug repurposing, and even the strategic portfolio design for long-term sustainable enterprise development.

MEDI 405

Using open source descriptors and algorithms for modeling ADME properties

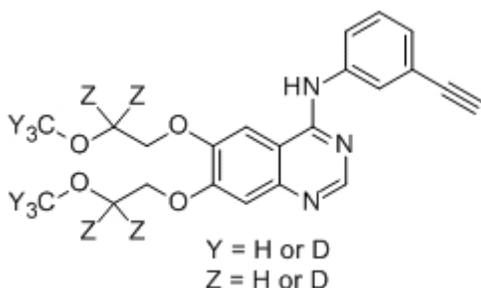
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Computational models could be more readily shared with collaborators if they were generated with open source descriptors (e.g. Chemistry development kit, CDK) and modeling algorithms. We evaluated open source descriptors and model building algorithms using a training set of ~50K molecules and a test set of ~25K molecules with human microsomal metabolic stability data. A C5.0 decision tree model demonstrated that open CDK+SMARTS keys (Kappa = 0.43, sensitivity = 0.57, specificity 0.91, positive predicted value (PPV) = 0.64) are equivalent to models built with commercial MOE2D+SMARTS keys (Kappa = 0.43, sensitivity = 0.58, specificity 0.91, PPV = 0.63). Extending the dataset to ~ 200K molecules confirmed this observation. The same combination of descriptor set and modeling method was applied to a variety of other ADME endpoints such as solubility etc. and the results were encouraging. The Huuskonen aqueous solubility dataset used for regression modeling with open descriptors (N >1000 training set and > 200 test set), was comparable to that published ($R^2 = 0.92$). Open source descriptors and algorithms demonstrated comparable results to commercial descriptors with cost savings.

MEDI 406

Design and synthesis of deuterated erlotinib analogs with enhanced pharmacokinetic properties

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Erlotinib (Tarceva®) is an important member of a class of targeted anticancer drugs that inhibit the activity of the epidermal growth factor receptor (EGFR). Our exploration of deuterium-modified tyrosine kinase inhibitors has led to the discovery of novel analogs with enhanced pharmacokinetic properties. Design and synthesis of our lead compound utilizing a route that allows for precision deuterium incorporation will be described. Additionally, *in vitro* and *in vivo* pharmacokinetic data along with *in vitro* anti-tumor efficacy data will be presented.

MEDI 407

Third-generation synthetic inhibitors of plasminogen activator inhibitor-1

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A series of polyphenolic inhibitors of plasminogen activator inhibitor-1 (PAI-1) have been synthesized and screened for biological activity. These compounds were designed to improve on previous generations of ester-

based

polyphenolic inhibitors of the mammalian serpin PAI-1, which has been implicated in a variety of conditions, such as myocardial infarction and stroke. The design rationale, synthesis, and structure-activity relationships of this series of compounds will be addressed.

MEDI 408

Design, synthesis, structure-activity relationships and biological evaluation of phenolic inhibitors of plasminogen activator inhibitor-1

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Pathologic levels of plasminogen activator inhibitor-1 (PAI-1) have been implicated in a variety of conditions, including myocardial infarction, cancer, atherosclerosis, and type 2 diabetes, prompting a search for potent, specific inhibitors. The design and synthesis of a series of polyphenolic PAI-1 inhibitors containing various aromatic substitution patterns and linking units will be described. The structure-activity relationships of these substitutions will be examined, as will the effect of modifying the length and rigidity of the linking units between the phenolic moieties.

MEDI 409

Discovery of new lead tetrapeptides reversible inhibitors of thrombin using 2D-transferred NOESY NMR

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A structure-activity relationship (SAR) for reversible tetrapeptides inhibitors D-Phe-Pro-DArg-P1'-CONH₂ of thrombin is reported. The P1' position was varied with D and L natural and unnatural amino acids. The significant differences between the inhibitory constants (K_i) of tetrapeptides from the series D-Phe-Pro-D-Arg-P1'-CONH₂ suggest that the interaction between the amino acid at P1' position and the S1' subpocket in thrombin is very specific. In order to confirm the kinetics of inhibition we performed additional in solution binding experiments

using the 2D-transferred NOESY method and thrombin in complex with two lead tetrapeptides (P1'=Gly and P1'=Ala). The NMR data suggests that the peptides inhibitors (K_i of 6.6 and 16.6 μM, respectively) were best described by a mixed inhibition behavior with respect to thrombin since the ternary complexes between each inhibitor and thrombin in the presence of a strong competitive inhibitor (thromstop, K_i 15 nM) were characterized by residual negative NOEs.

MEDI 410

Chemoenzymatic route to uncommon sugar nucleotides

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Complex carbohydrates containing GlcNAc/GalNAc residues play important roles in biological systems. A number of tumor-associated carbohydrate antigens which are useful tools for the development of therapeutic cancer vaccines, are GlcNAc/GalNAc containing oligosaccharides. Furthermore, GlcNAc/GalNAc forms the glycosaminoglycans which are of pharmaceutical significance. Chemical modification of GlcNAc/GalNAc residues by an unnatural analogue in such a polysaccharide would thus be a valuable tool to investigate the carbohydrate associated pathways and discover carbohydrate-based drugs. However, this study is often problematic due to the limited availability of sugar nucleotides which are universal sugar donors and utilized by glycosyltransferases for the enzymatic synthesis of modified carbohydrate molecules. We discovered a pathway in which GlcNAc/GalNAc and their analogues were phosphorylated by NahK and subsequently pyrophosphorylated by GlmU to give a library of UDP-GlcNAc/GalNAc analogues on a preparative scale. We then are primed to incorporate the structurally modified GlcNAc/GalNAc analogues into those carbohydrate-containing biomolecules using different glycosyltransferases to eventually realize the glycorandomized chemistry.

MEDI 411

Triarylcarboxylic acid derivatives as novel xanthine oxidase inhibitors

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Xanthine oxidase plays a critical role of controlling the biosynthesis of uric acid. Therefore, xanthine oxidase inhibitors are effective for the treatment of hyperuricemia and gout.

We previously found that a phenylpyridinecarboxylic acid derivative possessed xanthine oxidase inhibitory activity. Further SAR study of this series produced triarylcarboxylic acid derivatives as potent xanthine oxidase inhibitors with nanomolar IC₅₀s. Some of these triaryl derivatives decreased the serum uric acid in oxonate-treated hyperuricemic rats with ED₅₀ values of less than 1mg/kg after oral administration. We also discovered that several compounds showed long duration of action in this animal model at a dose of 10 mg/kg.

We will report the synthesis, the SAR and the pharmacological properties of the triarylcarboxylic acid derivatives.

MEDI 412

Synthesis of carbon-11-labeled cholesterol-based cationic lipids as new potential PET probes for imaging of gene delivery

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Gene therapy based on gene delivery is a promising strategy for the treatment of various human diseases such as cancer. Cationic lipids represent one of the synthetic gene delivery systems. The development of noninvasive imaging procedures such as the biomedical imaging technique positron emission tomography (PET) for gene delivery could provide valuable information regarding gene therapy. Recently a series of new biodegradable cholesterol-based cationic lipids has been developed by Medvedeva et al. for gene delivery. This study was designed to develop carbon-11-labeled cholesterol-based cationic lipids as new PET probes for imaging of gene delivery. Unlabeled quaternary amine reference standards, *N*-methyl-*N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]pyrrolidinium iodide, *N*-methyl-*N*'-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]imidazolium iodide, *N*-methyl-*N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]piperidinium iodide, *N*-methyl-*N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]-4-methylpiperidinium iodide, and *N*-methyl-*N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]morpholinium iodide, and their tertiary amine precursors, *N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]pyrrolidine, *N*-[4-(cholest-5-en-3 β -yloxycarbonyl)butyl]imidazole, *N*-[4-(cholest-5-en-3 β -

ylloxycarbonyl)butyl]piperidine, *N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]-4-methylpiperidine, and *N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]morpholine, were synthesized from the starting material cholesterol in multiple steps with moderate to excellent yields. The [^{11}C -methyl]quaternary amine target tracers, *N*-[^{11}C]methyl-*N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]pyrrolidinium iodide, *N*-[^{11}C]methyl-*N'*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]imidazolium iodide, *N*-[^{11}C]methyl-*N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]piperidinium iodide, *N*-[^{11}C]methyl-*N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]-4-methylpiperidinium iodide, and *N*-[^{11}C]methyl-*N*-[4-(cholest-5-en-3 β -ylloxycarbonyl)butyl]morpholinium iodide, were prepared from their corresponding precursors with [^{11}C]methyl iodide ([^{11}C]CH₃I) through *N*-[^{11}C]methylation and isolated by a simplified solid-phase extraction (SPE) method using a Silica Sep-Pak cartridge in 50-60% radiochemical yields decay corrected to end of bombardment (EOB), based on [^{11}C]CO₂, and 111-185 GBq/ μmol specific activity at the end of synthesis (EOS).

MEDI 413

Automating gradient method development in flash chromatography for greater productivity and minimizing solvent use

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Productivity demands in today's laboratories require the chemist to minimize time spent purifying compounds. Faster, 'greener' flash chromatography methods increase throughput, improve productivity, save solvent, and reduce operating costs. Meeting these goals requires gradient methods that deliver the required resolution in the fastest possible time. The RevealX™ Operating System of the Reveleris® flash chromatography system automatically generates gradient profiles using only two chromatographic separations (TLC or HPLC) as inputs provides methods for both normal phase and reversed phase systems. The chemist can choose a gradient profile based on either highest purity or fastest speed.

In this work both of these gradient profiles were compared with traditional gradient development routes for normal and reversed phase chromatography examples. This work shows a productivity gain, when using this operating system for gradient method development, by increasing chromatographic resolution, reducing time spent optimizing the separation and reducing solvent used compared to traditional methods.

MEDI 414

Biosensor detection of early onset septicemia

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Sepsis is a major problem in clinical medicine and nearly 2 million lives per year are lost to complications arising from septicemia in the USA. The standard practice of care in the treatment for sepsis is antibiotics and fluid resuscitation. To date there is no exact measurement of when to initiate treatment. This arises from the fact that there has never been a way to detect particular bacterial toxins that cause and initiate the cascade of events that lead to septicemia and left unchecked to end organ dysfunction and ultimately to death. Using carbon nanotubes (CNT) with specific biological analogs for bacterial toxins, we have been able to create a very specific and sensitive biosensor for sepsis. Our initial results indicate that very low levels of bacterial toxins from bodily fluids can be analyzed to give an absolute number that correlates with patient toxicity levels.

MEDI 415

Synthesis and biological evaluation of nitroxide-functionalized silica nanoparticles

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Reactive oxygen species (ROS) are implicated in several cancers and neurodegenerative diseases. Our research focuses on covalent modification of silica nanoparticles with TEMPO, a stabilized nitroxyl radical, which functions as an ROS scavenger. Presented here are our current linker and payload release strategies. To validate possible therapeutic efficacy, macrophage uptake and superoxide scavenging abilities of the functionalized particles were assessed.

MEDI 416

Synthesis and evaluation of fluorine substituted CGRP receptor antagonists for the development of an ¹⁸F PET imaging agent

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The 37 amino acid neuropeptide Calcitonin Gene-Related Peptide (CGRP) has been implicated in the pathophysiology of migraine. CGRP receptor antagonists including olcegepant and telcagepant have demonstrated efficacy in the acute treatment of migraine comparable to the triptans in clinical trials. Although a potent vasodilator, CGRP is also thought to interact with centrally located CGRP receptors to mediate pain transmission during a migraine headache. To address the question of the effective site of action of CGRP receptor antagonists in migraine, development of a suitable PET tracer was desired. Positron Emission Tomography (PET) is a non-invasive clinical tool for addressing receptor occupancy in CNS, and commonly uses either ¹¹C or ¹⁸F radionuclides. ¹⁸F-labeled CGRP receptor antagonists were attractive targets for imaging, due to the longer half-life compared to ¹¹C-labeled compounds. A series of fluorinated analogs of CGRP receptor antagonists and the suitable precursors for ¹⁸F-labeling were synthesized in an effort to find a suitable PET tracer. The synthesis of these compounds along with preliminary imaging results will be discussed.

MEDI 417

RevealX™ technology improves isolation and purification of natural products by flash chromatography

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Natural products found to exist in nature play a dominant role in the development of new drugs for medicinal purposes. A crude extract typically contains lead compounds requiring multiple steps to isolate and purify. Conventional flash purification technique used for isolating such compounds either fail to detect those compounds that are non-chromophoric or lack the necessary sensitivity

often required for detection during separation.

This work investigates the purification of certain class of natural products using the RevealX™ detection technology of the Reveleris™ flash chromatography system. Equipped with integrated multiple detectors, one can separate, detect, and isolate complex matrix of compounds with higher sensitivity and speed. Natural product extracts that are both chromophoric and non-chromophoric are purified satisfactorily in a single step without the use of additional techniques such as preparative HPLC. Such a novel flash chromatography makes the exploration of nature's therapeutic agents less time consuming and tedious.

MEDI 418

RevealX™ technology improves purification of lead generation compounds by flash chromatography

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During pharmaceutical development of biologically active compounds, the identification and purification of unknown impurities is a key requirement for the successful registration of a new molecular entity. Traditional flash chromatography as preferred by synthetic chemists is equipped with ultraviolet (UV) detection that fails to detect targets and impurities that are either present at low levels or lack chromophores. This may result in producing impure targets and lead to false hits during biotesting.

This study investigates the detection and quantification of an impurity in the presence of the lead compound during purification using multiple signal-processing from UV and ELSD (Evaporative Light Scattering Detector). Using the RevealX™ detection technology in the Reveleris™ flash chromatography system, chemists can detect both chromophoric and non-chromophoric compounds present in the sample matrix. A system comparison to a preparative liquid chromatography with an ELSD shows that Reveleris™ can be more productive during purification for lead generation.

MEDI 419

Development of an analytical method for the production and measurement of singlet oxygen

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The following paper outlines and explains the generation of singlet oxygen of current interest in Photodynamic Therapy (PDT). PDT is a revolutionary treatment for cancer and other diseases without using surgery, chemotherapy or radiation. The chemical reaction is promoted by light and monitored spectrophotometrically. There is disappearance of 1,3-diphenylisobenzofuran as a chemical quencher in methanol, which is oxidized to o-dibenzoylbenzene in the presence of rose bengal, methylene blue or Fe₃O₄/ZnO core-shell nanoparticles for oxidation reactions. Photochemical properties of three photosensitizing molecules (rose bengal, methylene blue and Fe₃O₄/ZnO) were investigated in different solvents, light sources and quenchers including n,n-dimethyl-4-nitrosoaniline, furfuryl alcohol, sodium azide, citronellol, 2,5-diphenylfuran, 2,5-dimethylfuran and diphenylisobenzofuran.

Good first- order plots were obtained and the relative slopes used to determine β values and reaction constants. The β values obtained were 5.45×10^{-5} , 4.34×10^{-5} and 1.1×10^{-5} for rose bengal, methylene blue and Fe₃O₄/ZnO core-shell nanoparticles respectively. The photooxidation reaction constants 4.40×10^9 and 4.38×10^8 for rose bengal and methylene blue were values in accordance with the literature. Concentrations of the photosensitizers and chemical quenchers were optimized for photooxidation reactions. Photoluminescence measurements were made for each photosensitizer and quencher.

The quantum yields of the formation of singlet oxygen were 0.52 for methylene blue, 0.28 for Fe₃O₄/ZnO core-shell nanoparticles and 0.69 for rose bengal. This method is fast, efficient, precise and controllable in contributing to research in Photodynamic Therapy (PDT). This analytical method opens new windows to clinical studies in vivo.

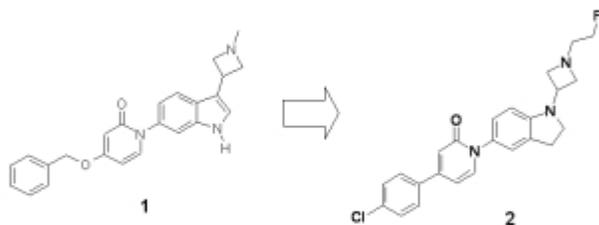
MEDI 420

Discovery of dihydroindolyl azetidone derivatives as potent MCH antagonists with low PgP efflux

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A series of potent indole azetidone MCH antagonists, exemplified by **1**, were found to have poor CNS penetration due to Pgp efflux. A strategy which focused on lowering pKa, changing the conformational flexibility motif and removing hydrogen bond donors was utilized to mitigate Pgp efflux. This led us to discover 1-dihydroindolyl pyridones, exemplified by **2**, with excellent binding affinity and CNS exposure.



MEDI 421

Novel ammonium prodrug: Synthesis, pharmacokinetics, mechanism of release and scope

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BMS-248, (1-(4-benzoylpiperazin-1-yl)-2-(4-fluoro-7-(1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)ethane-1,2-dione), a third generation HIV attachment inhibitor with excellent potency as well as *in vitro* and *in vivo* pharmacokinetic profiles, was nominated for preclinical evaluation in higher species and eventually as a candidate for clinical development. However, the poor oral

exposure displayed by BMS-248 at high doses due to low solubility (6 mg/mL) presented a challenge for its development. An ammonium prodrug was developed as a novel approach to increase the solubility of the parent compound and thus overcome the dissolution-limited absorption. Amination of the triazole moiety of BMS-248 afforded a prodrug with improved solubility (1.76 mg/mL) that showed markedly increased systemic exposure of the parent following oral administration to both rats and dogs. Several *in vitro* and *in vivo* experiments that provide an understanding of the mechanism of release of the parent as well as the potential to apply this novel technology to other chemotypes will be discussed.

MEDI 422

Hydrolytic properties of thymidine α -*P*-boranophosphate analogs

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Nucleoside

(N) inhibitors of HIV reverse transcriptase (RT) become effective antiviral drugs upon kinase activation from N to the triphosphate form (NTP). Resistant strains often have RT with impaired function. The isoelectronic substitution of borane ($-\text{BH}_3$) for one α -*P*-nonbridging oxygen in 2',3'-dideoxyCTP increases by ~30-fold the incorporation efficiency by viral RT relative to the parent N-analog, which might be useful to increase drug spectrum against resistant strains.

α -*P*-Borano-N-phosphates

should be stable before function or activation as drugs in target cells. Hydrolytic studies of thymidine (T) α -*P*-boranomono-, di- and triphosphates by LC-MS were carried out in buffers of different pH and temperature. Higher temperature and more acidic conditions increased the reaction rates. The RT pre-active nucleotide, α -*P*-borano-T-diphosphate *Rp* isomer, was completely stable over 40 hr in neutral and basic solutions at 37°C. The stabilities of α -*P*-boranonucleotides support the rationale for making similar borane modifications of clinically used dideoxynucleoside drugs.

MEDI 423

Synthesis of sulfonyl curcumin mimics exerting a vasodilatation effect on the basilar artery of rabbits

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In order to discover novel small vasodilatory molecules for potential use in the treatment of vascular disease, we tested the vasodilatation effect of two types of synthetic curcumin mimics, amide type (3) and sulfonyl amide type (4), upon the basilar artery of rabbits. In general, the sulfonyl amide type mimic (4) is more potent than the amide type (3). Curcumin (1) and compounds 12 and 20 effectively dilated the basilar artery of white rabbits

MEDI 424

Computed tomography (CT) contrast agents for determining cartilage health

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Today, there is a need for more precise, sensitive, and minimally invasive methods to quantitatively characterize the biochemical properties of articular cartilage. We have synthesized novel iodinated cationic contrast agents for use with computed tomography (CT) which allows for the quantification of glycosaminoglycans (GAGs) in cartilage. The heavily sulfated and carboxylated GAGs confer much of the tissue's resistance to compression, and GAG loss is a hallmark of early osteoarthritis (OA). In this study, we present the diffusion characteristics of our contrast agents and correlate contrast enhanced CT attenuation with tissue GAG content. Our cationic contrast agents achieve higher equilibrium attenuation in cartilage and correlate more strongly with GAG content than commercially available anionic contrast agents.

MEDI 425

Design and optimization of benzimidazole-containing cold menthol receptor (TRPM8) antagonists

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The design and synthesis of a class of selective TRPM8 antagonists based on a benzimidazole platform is described, the evolution of which began from a class of selective TRPV1 antagonists. Optimization of this design led to the identification of a key compound, which exhibited an IC₅₀ value of 4 nM in a cell-based TRPM8 functional assay. In a TRPM8-selective pharmacodynamic model, the compound produced greater than 90% inhibition of icilin induced 'wet dog' shakes at 3 mg/kg p.o. In a time course study for a chronic constriction injury (CCI)-induced allodynia model in rats dosed at 10 mg/kg (p.o.), the compound inhibited acetone (cold) induced responses by 91.4%, 82.9% and 74.3% at 2, 3, and 4 h, respectively.

MEDI 426

Dendrimer based CT contrast agents for GAG quantification

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Osteoarthritis (OA), a degenerative joint disease caused by the breakdown of articular cartilage, affects an estimated 27 million Americans and 140 million people worldwide. One of the earliest signs of OA is the loss of glycosaminoglycans (GAGs) from the cartilage tissue. A non-invasive imaging technique to quantify GAGs would aid in the early diagnosis of OA and in monitoring the effectiveness of treatment regimes. Dendrimer based cationic iodinated contrast agents have been synthesized for the imaging of GAG content within cartilage plugs by computed tomography (CT). The charge of the contrast agents can be increased by appending lysines to the highly iodinated aromatic core structure. It has been seen that size, composition, and charge play a role in the ability of the contrast agents to effectively measure GAG content.

MEDI 427

Synthesis, functionalization and photo-Bergman chemistry of enediynes bioconjugates

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One of the most promising means to address the problem of tumor targeting is through the use of monoclonal antibody (Mab) conjugates, where the antibody specifically and selectively targets a tumor cell surface antigen. The first FDA approved Mab conjugate was Wyeth's Mylotarg®, which is composed of an enediyne cytotoxin coupled through a linker group to an anti CD33 antibody [hP67.6]. Mylotarg® is clinically effective in the management of acute myeloid leukemia (AML) and its approval by the FDA was a watershed event in the development of targeted therapeutics. This program aims to apply nanoparticle targeting techniques in the synthesis and delivery of locally activated enediyne-conjugates of a variety of monoclonal antibodies. In pursuit of this goal we have coupled a number of enediyne prodrugs to select antibodies using heterobifunctional PEG linkers and applied to the technology to development of surface modified Au nanoparticles. The target of the enediyne toxin is nuclear DNA and it is expected that affinity for this target, hence effectiveness of the agents, can be enhanced using nanoparticle affinity ligands.

MEDI 428

Discovery, synthesis and biological evaluation of pyrrole derivatives as novel and highly selective potassium-competitive acid blockers (P-CABs)

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Proton pump inhibitors (PPIs) have been extensively prescribed in a wide range of acid-related disorders including gastroesophageal reflux disease (GERD), peptic ulcer, non-erosive esophagitis, non-steroidal anti-inflammatory drug (NSAID) induced gastrointestinal injury, and upper abdominal bleeding. Despite the undoubted efficacy of PPIs, there are still areas in which they could be improved: delayed onset of action, refractory GERD, nocturnal acid breakthrough, PPI non-responders and prevention/treatment of Barrett's esophagus.

Attempts have been made to develop a new class of acid suppressant, the

potassium-competitive acid blockers (P-CABs), which inhibit gastric H⁺,K⁺-ATPase activity in a K⁺ competitive manner, but they are not in worldwide clinical use due to insufficient efficacy and hepatic toxicity. Extensive screening efforts and compound evaluation led us to discover new pyrrole derivatives based on a novel scaffold as P-CABs. In this presentation, we report on the discovery, synthesis and structure-activity relationships (SARs) of these pyrrole derivatives.

MEDI 429

Drug-like properties of macrocyclic molecules derived from DNA-programmed combinatorial libraries

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Ensemble Discovery has developed an integrated platform for the synthesis and screening of macrocyclic molecules (EnsemblinsTM) using DNA_programmed chemistry. These compounds can interact with a variety of historically challenging drug discovery targets such as protein-protein interactions. While Ensemblins are outside of Lipinski 'Rule of Five' structural space, these macrocycles exhibit acceptable drug-like properties. They show good levels of membrane permeability and solubility, good pharmacokinetics including oral bioavailability, as well as pharmacological efficacy. We are systematically examining the correlation between the structural features of our Ensemblins and their drug-like properties.

MEDI 430

Optimization of affinity and relaxivity of peptide-based fibrin-targeted MRI contrast agents via N-terminal PNA modification

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Efficacy of targeted MRI contrast agents depends on affinity and selectivity for the target, but also on relaxivity, i.e. the magnetic efficiency of the agent for water relaxation. Relaxivity is strongly dependent on the rotational dynamics of the molecule, and for peptide-based contrast agents, relaxivity is often limited by rotational flexibility. We screened a series of fibrin-specific peptides modified with a PNA (peptide nucleic acid) monomer at the N-terminus and identified

modifications that improved overall affinity. When conjugated to four gadolinium chelates fibrin affinity was maintained and the relaxivity of the fibrin-bound agent was 50% higher. The increased relaxivity was traced to reduced internal motion due to the interaction of the PNA pharmacophore with the protein. This method of increasing affinity and relaxivity via minor N-terminal modification is likely general to other peptide-based MRI contrast agents.

MEDI 431

Electrochemical reactivity and interactions of quercetin with DNA in the presence of Cu(II) ions

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Quercetin is one of the most abundant molecules of the flavonoid group and affords many beneficial effects on human health, including cardiovascular protection, anticancer, anti-allergy, and antiviral activity. Although, it has been known to have anti-inflammatory and anti-oxidant properties, recent studies indicate that under certain conditions quercetin may act as a prooxidant and may induce oxidative DNA damage in the presence of transition metal ions. To evaluate the mutagenic activity of quercetin and its carcinogenic potential, we have investigated the interactions of quercetin with DNA and Cu(II) ions. The changes in DNA structure induced by the triple complex formation were investigated by monitoring the guanosine oxidation peak of DNA at glassy carbon electrode. The quercetin-DNA adduct formation was analyzed using the electrochemical quartz crystal nanobalance (EQCN). The interactions of quercetin with DNA and Cu(II) ions were also investigated in solution by resonance elastic light scattering (RELS) and UV-Vis absorbance spectroscopy.

MEDI 432

Crystal structures and hydrogen bonding patterns in some Schiff Bases of pharmacological importance

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The synthesis and structure of Schiff bases have attracted much attention in biology and chemistry. One of the aims of investigating the structural chemistry of Schiff bases is to develop protein and enzyme mimics. Structural information is useful in investigating the coordination properties of Schiff bases functioning as ligands. Some Schiff base derivatives were reported to possess antimicrobial, anti-inflammatory and central nervous system activities. Moreover, Schiff bases are also known to have biological activities such as antimicrobial, antifungal, antitumor and as herbicides.

The crystal structures and hydrogen bonding patterns in , (I) 4-[(2E)-2-(1-phenylethylidene)hydrazinyl]-8-(trifluoromethyl)-quinoline, (II) 4-[(2E)-2-[1-(3-bromophenyl)ethylidene]hydrazinyl]-8-(trifluoromethyl)-quinoline, (III) 4-[(1E)-1-{2-[8-(trifluoromethyl)quinolin-4-yl]-hydrazinylidene}ethyl]-phenol hydrate, (IV) 4-[(2E)-2-[1-(naphthalen-2-yl)ethylidene]-hydrazinyl]-8-(trifluoro-methyl)quinoline are described. Packing diagrams exposing hydrogen bonding interactions, Hirshfeld and fingerprint diagrams describing intermolecular hydrogen bonding interactions and HOMO-LUMO molecular orbital diagrams describing the charge distributions in these compounds are also provided.

A density functional (B3LYP) calculation for each of these structures supports the effects of intermolecular hydrogen bonding and p—p interactions having a significant influence on packing effects in the crystalline environments of each of these compounds.

MEDI 433

Synthesis of new hybrid materials designed for iron selective electrodes based on selective amino spacer organizations

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The main objective of this project is to build new analytical systems with biological applications. Herein, our goal is to synthesize new organic-inorganic hybrid materials with high affinity and selectivity for iron (III) metal. These materials could be used as iron selective electrodes to measure the iron concentration in patients suffering from iron overload.

The synthesis of new lower rim functionalized calix[4]arenes, in a partial cone or 1,3-alternated conformation, incorporating two tridentate selective iron ligands is reported. These multidendate ligands should possess high iron(III) affinity and stable complexation properties due to a preorganization of the calix[4]arene framework. The hydroxyl selective substitution by orthogonally protected amino

spacers will allow us to control the functionalization with iron ligands, the multidentate calix[4]arene are then grafted on an inorganic SBA-15 silica matrix by a nucleophilic reaction.

The synthesis and electrochemical properties of all these new hybrid materials are presented here.

MEDI 434

Crystal structures and hydrogen bonding patterns in picrate salts of pharmacologically active compounds-I

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Hydrogen bonding patterns in three picrate salts, (I) Propiverinium Picrate, (II) Chlorimipraminium Picrate and Imatinibium Dipicrate are examined from their crystal structure analysis. Significant structural features of each salt are described. Packing diagrams exposing cation-anion hydrogen bonding interactions, Hirshfeld and fingerprint diagrams describing intermolecular hydrogen bonding interactions and HOMO-LUMO molecular orbital diagrams describing potential charge transfer interactions in these compounds are also provided.

Propiverine is an anticholinergic drug used for the treatment of urinary urgency, frequency and urge incontinence, all symptoms of overactive bladder syndrome. *Chloroimipramine* is used in the treatment of obsessive-compulsive disorder, panic disorder and experimental anxiety disorder in humans. It is a non-toxic cancer-therapeutic having a strong selectivity between cancer cells and normal cells on the basis of their mitochondrial function. *Imatinib*, marked as a cancer drug by Novartis, is a synthetic tyrosine kinase inhibitor used in treating chronic myelogenous leukemia, gastrointestinal stromal tumors and a number of other malignancies.

A density functional (B3LYP) calculation for each of these structures supports the effects of intermolecular hydrogen bonding and p—p interactions having a significant influence on packing effects in the crystalline environments of each of these compounds.

MEDI 435

Crystal structures and hydrogen bonding patterns in picrates salts of pharmacologically active compounds-II

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Hydrogen bonding patterns in two picrate salts, (I) 2-Amino-4-methoxy-6-methyl pyrimidinium picrate and (II) 5,7-Dimethyl-2,3-dihydro-1*H*-1,4-diazepinium picrate are examined from their crystal structure analysis. Significant structural features of each salt are described. Packing diagrams exposing cation-anion hydrogen bonding interactions, Hirshfeld and fingerprint diagrams describing intermolecular hydrogen bonding interactions and HOMO-LUMO molecular orbital diagrams describing potential charge transfer interactions in these compounds are also provided.

Pyrimidines are important compounds in pharmaceutical chemistry as antiviral agents, inotropic and β -blocking agents antifungal agents, benzodiazepine receptor agonists, and calcium channel blockers. 1,4-Diazepine derivatives display tranquilizing, muscle-relaxant, anti-convulsant and sedative effects. Today many diazepine derivatives are widely used as daytime sedatives, tranquilizers, sleep inducers, anesthetics, anticonvulsants and muscle relaxants.

A density functional (B3LYP) calculation for each of these structures supports the effects of intermolecular hydrogen bonding and p—p interactions having a significant influence on packing effects in the crystalline environments of each of these compounds.

MEDI 436

Effect of molecular charge in computed tomography imaging agents

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Osteoarthritis is the most common type of arthritis; affecting over 25 million people in the US, and totaling over \$125 billion in healthcare costs, each year. Current methods of diagnosis focus on patient-reported symptoms, magnetic resonance (MRI), and computed tomography (CT) imaging. Presently, all commercially available CT imaging agents possess an overall negative molecular charge. Since joint cartilage tissue possesses an overall negative charge, we have focused our research on determining the role the molecular charge plays in the efficacy of a CT imaging agent. We have found that positively charged imaging agents allow for better attenuation, deeper cartilage penetration, and show better correlation to the cartilage glycosaminoglycan (GAG) content. Specifically, we have synthesized several positively charged CT imaging agents, and their negatively charged, and neutral structural analogs. We have also obtained CT imaging data on cartilage tissue, using these differently charged imaging agents.

MEDI 437

Structural characterization and biological activities of various soluble beta-1,3/1,6-glucans

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Beta-1,3/1,6-glucan, a yeast cell wall polysaccharide, is a pathogen-associated molecular pattern recognized by a variety of innate immune cells. Beta-1,3/1,6-glucans possess numerous immune potentiating activities. In particular, antitumor activity has been demonstrated with the soluble beta glucan Imprime PGG® used in combination with complement activating antitumor monoclonal antibodies (MAb) in several tumor models. Different sources of beta glucans vary on the basis of main and side chain length, types of linkages, branching, and tertiary structure. The objective of this study is to compare the structural characteristics and the biological activities of several well characterized soluble beta-1,3/1,6-glucans.

MEDI 438

Annonacin isolated from *Asimina triloba* fruit pulp is toxic to rat primary cortical neurons

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Annonacin isolated from the fruit *Annona muricata* has been shown to be a potent mitochondrial complex-I inhibitor that causes tau accumulation and cell death in rat mesencephalic cultures. Annonacin, among other acetogenins is also present in various parts of the *Asimina triloba* tree and we have recently identified its presence in the fruit pulp. Currently the natural supplement Paw-Paw Cell-Reg™, which is made from twig extracts of *Asimina triloba* is marketed to the general public as being beneficial for overall health and promoted as a potential complement to chemotherapy in the treatment of cancer. To determine whether the *A. triloba* annonacin shares the *A. muricata* toxicity, rat primary cortical neurons were treated with annonacin isolated from *Asimina triloba* fruit pulp. Cell viability was determined by measuring absorption of the solubilized formazan product that is produced by mitochondria in living cells in the presence of the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). After 48 hours incubation with annonacin, the determined LD₅₀ was 44.8 μM (p = 0.003). Based on these findings, regular consumption of pawpaw fruit and the Cell-Reg™ capsule should be further scrutinized for potential risks of neurodegeneration.

MEDI 439

Identification of piperazine-bisamide GHSR antagonists for the treatment of obesity: Transformation from agonist to antagonist

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Piperazine-bisamide analogs derived from high throughput screen hit are discovered as partial agonists of human growth hormone secretagogue receptor (GHSR). Modification of the terminal phenyl A ring and the piperazine core significantly improved the potency. Transformation of agonist to antagonist through structure-activity relationship (SAR) exploration around the biaryl tail was performed and is herein disclosed. These efforts have led to the identification of a potent antagonist with favorable pharmacokinetic profile suitable as a tool compound for *in vivo* proof-of-concept studies.

MEDI 440

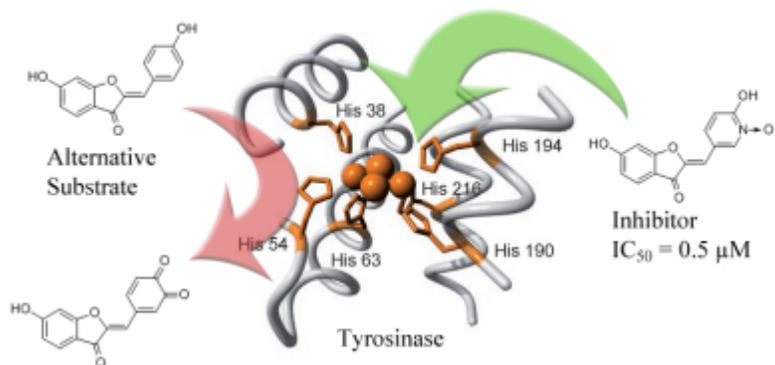
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MEDI 441

***N*-oxyde aurones as new, potent and non-toxic tyrosinase inhibitors**

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Inhibition of tyrosinase, a copper-containing metalloenzyme is an important issue because of its key role in melanogenesis. We have identified aurones as strong inhibitors of tyrosinase derived from human melanocytes. Later, these compounds were found to be alternative substrates (oxidized into quinones) and not inhibitors. Therefore, we have undertaken the synthesis of molecules with *N*-oxypyridine moiety. Such molecules are competitive inhibitors of tyrosinase by interacting with binuclear copper centers without oxidation of the *N*-oxypyridine moiety, as evidenced by model complexes.



MEDI 442

Synthesis and photophysical characterization of novel lanthanide-ion based luminescent probes for ultrasensitive detection of biopolymers

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Chelate complexes of four lanthanide ions (Eu^{3+} , Tb^{3+} , Dy^{3+} , and Sm^{3+}) were studied to determine luminescence lifetimes and spectra characterization when excited by excimer laser radiation at 351 nm. Luminescence collected by a photomultiplier tube mounted on a spectrograph averaged was to determine the luminescence lifetimes in deionized regular (H_2O) and heavy water (D_2O). Lifetimes ranged from microseconds for probes with Sm^{3+} and Dy^{3+} ions and milliseconds for Eu^{3+} and Tb^{3+} derivatives. Luminescence spectra acquired used a gated ICCD camera coupled to the spectrograph. Synthesized compounds were used in molecular beacon hybridization probes to assess their validity for biological applications. Time-gated mode of detection avoided short-lived background fluorescence of the media providing high sensitivity, which was better than 1 pM. This concentration is about 50-100 times lower than conventional fluorescence-based molecular beacons and 10-60 times better than previously reported lanthanide-based hybridization probes.

MEDI 443

Oral delivery of insulin through the vitamin B₁₂ uptake pathway

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The non-invasive delivery of insulin continues to be a major goal in the treatment of diabetes mellitus (DM). The improved ease of administration associated with the oral-enteric pathway provides an attractive means for the delivery of insulin since higher patient compliance and an improvement in glycemic control are likely.

Considering the susceptibility of insulin to proteolytic degradation and inefficient enteric uptake, the oral-enteric pathway is an unlikely route, however. Here we show that a

non-invasive oral delivery route *can* be achieved for insulin by utilizing the preexisting dietary uptake pathway of vitamin B₁₂ (B₁₂). We show here, in STZ-diabetic rat models, that insulin, conjugated to B₁₂, has the capacity to lower blood glucose levels when orally administered.

We also present the importance of insulin's conjugation site and the impact space between insulin and B₁₂ plays. We anticipate our findings to be a significant step toward developing an orally active, non-invasive basal insulin therapy in individuals with DM.

MEDI 444

Novel prodrug strategy for intracellular delivery of bisphosphonates

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Bisphosphonates (BPs) are currently used to treat disorders of calcium metabolism, hypercalcemia, osteoporosis and malignant bone disease. Clodronate, a non-nitrogen containing bisphosphonate, has been shown to undergo metabolism to form a non-hydrolyzable ATP analog, AppCCl₂p. The AppCCl₂p metabolite is believed to induce apoptosis through inhibition of ADP/ATP translocase. Clodronate has also been evaluated for anti-tumor activity; however, this BP exhibits minimal activity (IC₅₀ > 1mM) against cancer cell lines due to low membrane permeability. New prodrug strategies are required to overcome this critical barrier in the development of BPs as anti-tumor agents. We have designed a bisphosphonamidate prodrug of clodronate bearing two masking groups and two biodegradable delivery groups, requiring minimal bioactivation events to unmask multiple negative charges. The clodronate prodrug shows remarkably enhanced activity against lung, breast and prostate cancer cells compared to clodronate.

MEDI 445

Synthesis and characterization of a new generation of β -galactosidase-activated MRI contrast agents

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The ability to track gene expression in real time and in vivo would provide valuable insight into complex biological processes in development and disease. β -galactosidase is a reporter enzyme widely used to monitor gene expression in developmental processes. The presence of this enzyme is determined using stains such as X-gal; however, the organism of interest must be sacrificed in order for this method to be employed. We have previously developed a class of bioactivated magnetic resonance imaging (MRI) contrast agents designed to detect β -galactosidase in living organisms. We have recently developed a new

generation of agents that includes a self-immolative linker that allows rapid activation by β -galactosidase. We have performed enzyme kinetics studies which show that these agents demonstrate facile enzyme kinetics and are activated on a biologically-relevant time scale. Current work is focusing on studying this class of contrast agents in β -galactosidase-expressing cells.

MEDI 446

Novel synthesis of prostamide analogs for use in the physiological characterization of a specific target receptor

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Prostamides (prostaglandin-ethanolamides) are a group of pharmacologically unique endogenous lipids resulting from the COX-2 metabolism of anandamide. Prostamides have not been well characterized physiologically and the specific target receptor for these compounds has yet to be identified. To aid in the characterization of such possible prostamide receptors, a series of analogs has been proposed. A robust pathway that is applicable to the synthesis of a wide range of prostamide analogs containing head (α) and tail (ω) modifications has been designed using well-known chemical methods. These analogs will be used in probing studies for the purpose of identifying active receptors and building a structure-activity relationship. This synthesis incorporates the strategic use of silyl protecting groups for selective deprotection and functionalization of the ω terminus. Azide and isothiocyanate functionalities are introduced at this tail position to serve as probes that will covalently bind to receptors thus aiding in their identification.

MEDI 447

Design and synthesis of sortase binding peptide analogs and an SAR study of small molecule sortase A inhibitors

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Drug resistant bacteria, such as methicillin resistant *Staphylococcus aureus* (MRSA), have been major health problem for many years and the search for new antibacterial agents has been the goal of many scientific researchers in the biomedical field. Sortase A and its homologues, found in most of Gram positive bacteria, play key roles in displaying surface proteins that interact with host cells and tissues. Therefore, understanding the mechanism of how a Sortase enzyme interacts with cellular proteins and how it functions as a transpeptidase could provide a clue that might enable one to disrupt the virulence of Gram-positive pathogenic bacteria. For a structural study of Sortase A and B from *Staphylococcus aureus* and *Bacillus anthracis*, we designed and synthesized peptide analogues that mimic the sorting signals of the corresponding proteins and bind covalently to the enzymes. With the goal of discovering small molecule inhibitors of Sortase A, a Structure-Activity Relationship (SAR) study was performed based on the lead compounds identified via High Throughput Screening (HTS). Experimental results and discussion of our studies will be presented.

MEDI 448

Quantitation of prechafuroside A, Isovitexin 2''-sulfate and Isovitexin in teas and fresh tea leaves from spring to autumn

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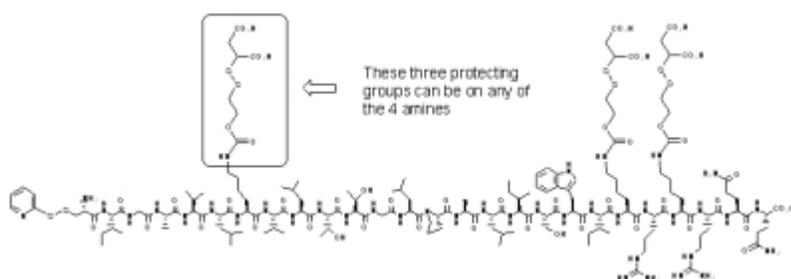
A procedure was developed for quantitative determination of prechafuroside A, a precursor of chafuroside A, a flavone C-glycoside with potent anti-inflammatory activity, as well as isovitexin, by SRM LC-MS/MS analysis. This method was successfully applied to commercial leaves of green tea, oolong tea and black tea and their fresh leaves collected at spring, summer and autumn in Japan. High levels of prechafuroside A and isovitexin were found in fresh tealeaves and tealeaves of all the oolong tea and black tea leaves. In case of green tea, most of tea species contained high levels of prechafuroside A and isovitexin. In contrast, prechafuroside A was not detected in fresh tealeaves of a few species, although high levels of isovitexin were found. The levels of isovitexin in all the fresh tealeaves decreased from summer to autumn, while of prechafuroside A increased. These results strongly suggested that isovitexin is a precursor of isovitexin-2''-sulfate.

MEDI 449

Synthesis of folate and siRNA conjugates derived from a water soluble melittin

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Melittin is a peptide consisting of 26 amino acids, the principal active component of bee venom (apitoxin), a stimulator of phospholipase A2, and a powerful lytic agent. In order to investigate the membrane disrupting potential of this agent for the delivery of active payloads from internalized endosomes, folate and siRNA conjugates of a derivative of cysteine modified L-melittin were synthesized. After activating the primary thiol of the cysteine modified L-melittin with aldrithiol-2, three of the four primary amines are reacted with 2-[2-(4-nitro-phenoxy-carbonyloxy)-ethyl-disulfanyl]-succinic acid. Capping of the amines with this reductively labile, bis-carboxylic acid greatly increases the water solubility of the resulting melittin adduct. The enhanced water solubility allows for facile conjugation with folate spacers and, more importantly, siRNA strands. Red blood cell lysis assay on the DTT reduced folate-melittin conjugate compares favorably to that of natural D-melittin



MEDI 450

Trainable *in-silico* screening filter for various human cytochrome P450 isoforms inhibition liability

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This study presents a series of in-silico models for the prediction of probable inhibitors of CYP450 isoforms 3A4, 2D6, 2C9, 2C19, and 1A2 developed using a novel GALAS modeling methodology allowing estimation of prediction Reliability Indices. Inhibition constant thresholds of 10 and 50 uM were used to classify compounds in the initial data sets ranging from ca. 5000 to 8000 compounds for five considered enzyme isoforms. Obtained *RI* values correlate with prediction accuracy. Predictions with low *RI* are outside model applicability domain and cannot be considered. For the predictions with acceptable *RI* values, the accuracy approaches 90% in all five internal test sets. All models have been externally validated using the latest data from PubChem screening program. GALAS modeling methodology utilized in this work enables fast and efficient training of the obtained models, i.e. extending their applicability domain, adjusting them to screen proprietary databases for potential CYP inhibitors.

MEDI 451

Screening for inhibitors of superoxide dismutase and characterization of inhibition using NMR

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Attempts to screen molecular libraries for compounds that inhibit superoxide dismutase (SOD) enzymes have been confounded by the high reactivity of the superoxide (SO) anion. SO reacts with functional groups found in many compounds from libraries giving rise to false positive results. We have developed a rapid NMR based assay that uses fluoride as a superoxide mimic. Using this method, we have discovered compounds that inhibit CuZnSOD and have characterized the interactions of these inhibitors with the enzyme.

MEDI 452

Pyrrrolo[1,2-a]quinoxalin-4(5H)-ones as novel adenosine A₃ antagonists

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Selective antagonists of the A₃ adenosine receptor are of interest for numerous clinical indications such as cancer, inflammation and glaucoma. Several A₃ antagonists were already described in the literature. Most of them are based on tricycle heterocycles or on nucleoside framework and suffer of poor water solubility.

We have generated at domain therapeutics nanomolar A3 antagonists based on pyrrolo[1,2-a]quinoxalin-4(5H)-one heterocycle. This heterocycle core was obtained in 2 steps via microwave irradiation. Various synthetic pathways were developed to generate focus libraries in order to get SAR information. 3 points of diversity were investigated on our scaffold. Nanomolar antagonist potency on A3 receptor, with selectivity versus other adenosine receptors and high water solubility were obtained.

MEDI 453

Effect of novel pp60^{c-src} inhibitors on mammalian glutathione S-transferase activity

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Glutathione S-transferases (GST, EC 2.5.1.18) are multifunctional enzymes and highly expressed in the various mammalian tissues. They have capacity to recognize diverse chemical structures, catalyze their conjugation to glutathione, and hence reduce cytotoxic reactivity of those chemicals. The increased activity levels of GSTs have been correlated with human cancers and the anticancer drug resistance. Similarly, pp60^{c-src}, the member of Src family kinases, has been reported in many cancers including breast, colon, lung, and skin with relatively high catalytic activity. Therefore, the inhibition of both GSTs and pp60^{c-src} may enhance the therapeutic efficacy of chemotherapeutics by increasing the sensitivity of cancer cells to those agents. The recent efforts of our laboratory to design and synthesize novel pp60^{c-src} inhibitors were accomplished with four *N*-benzyl 5-phenyl indole-3-amine, *N*-benzyl 5-(*p*-fluorophenyl) indole-3-amine derivatives I, II, III, and IV, with IC₅₀ values of 4.69, 74.79, 75.06, and 84.23 mM, respectively (Figure 1). In this present work, their inhibitory efficacy on GSTs is shown by virtue of kinetic studies with sheep liver cytosol. Among the analyzed compounds, the compounds I and III are found the best GST inhibitors with IC₅₀ values of 120.1, and 67.33 mM, respectively, and are reported as the pp60^{c-src} inhibitors with dual action. The compounds II and IV are also showed reasonable inhibitory levels of GSTs with IC₅₀ values of 161.1, and 272.2 mM, however their inhibition profile do not seem suitable for further developments. The inhibitory activities against pp60^{c-src} and GSTs were performed with the concentrations of compounds in the range of 250 to 7.15 mM. The kinase reactions were performed with 3.5x10⁻⁵ unit/ml pp60^{c-src} at 40 nM ATP, whereas the glutathione transferase reactions were performed with 925.6 unit/ml at 2.4 mM CDNB, and 3.2 mM GSH concentrations.

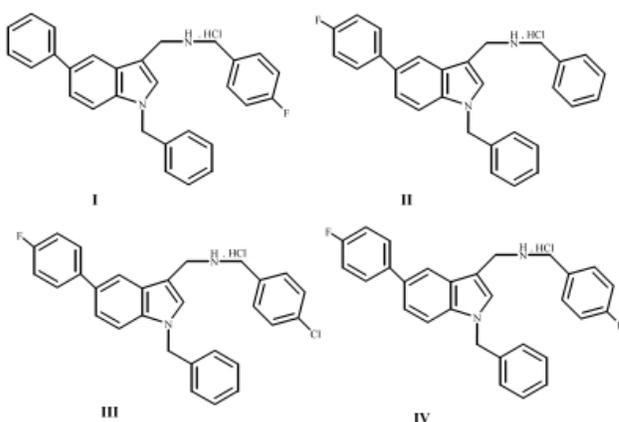


Figure 1. N, C5 substituted indole-3-amine derivatives.

MEDI 454

Inhibitors of adenosine deaminase containing 5:8-fused imidazo[4,5-f][1,4]diazocine ring system

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Adenosine deaminase (ADA) is an enzyme involved in purine metabolism. ADA catalyzes the irreversible deamination of adenosine and 2'-deoxyadenosine to form the corresponding inosine analogues. High levels of ADA have been observed in malignant human lymphocytes, thus making inhibitors of ADA as important therapeutic targets for certain leukemia's.

The specific aim of the project involves the synthesis of nucleoside analogs containing a 5:8 fused imidazo[4,5-f][1,4]diazocine heterocyclic ring system. The synthesis also includes the introduction of hydrophobic groups at the 4-position of the 8-membered ring which are anticipated to interact with many hydrophobic amino acid residues present in the vicinity of the active site of the enzyme. Our molecular modeling studies reveal that there are a number of hydrophobic amino acid residues such as Phe 300, Phe 61, and Leu 62, in the vicinity where active site zinc is coordinated with the 8-hydroxy group of coformycin. Ring expansion from the 7-membered to 8-membered ring in coformycin brings these hydrophobic amino acid residues even closer. Once the nucleosides are synthesized, ADA inhibitory studies will be performed using standard biochemical procedures. The K_i values will be computed from Line-weaver-Burk plots and the mode of inhibition, competitive, non-competitive, reversible or irreversible will be assessed.

MEDI 455

Solid phase synthesis of dendritic prodrugs of salicylic acid

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Salicylic acid has various medicinal uses ranging from aspirin to acne medications. In this project we are incorporating salicylic acid entities into a dendritic structure using solid-phase synthesis. Such a dendritic form of salicylic acid is considered a prodrug since the active medical ingredient, salicylic acid, will be released slowly and gradually by breaking the cascade linkage under certain physiological conditions. Use of the solid phase synthesis technique will allow us to build the dendrimers on solid support which makes the purification process much easier. Instead of doing tedious column chromatographies, all that will need to be done is a simple filtration. This is possible because the desired product is anchored onto the beads and the undesired impurities will stay in solution. High purity of the product will be easily achieved using this method. This research will provide a new methodology in dendrimer synthesis as well as produce a novel platform for drug delivery.

MEDI 456

Synthesis of water-soluble salicylic acid analogs by sugar-conjugation

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Salicylic acid has been used as an anti-inflammatory drug for easing aches and pains and reducing fevers. Recent research has shown salicylic acid can also reduce toxic side effects of anticancer drugs. However, its low solubility in water (~ 2 mg/mL) results in a large dosage for medication. This research uses glycosylation to conjugate galactose and glucose molecules with salicylic acid, forming water-soluble glycans in order to enhance the solubility of salicylic acid in water. In addition, NMR, ESI-MS and IR techniques have been used to characterize the structures of synthesized galactosyl salicylic acid and glucosyl salicylic acid. These glycan forms of salicylic acid can dissolve in water up to 100 times in comparison with the original drug. Further tests are being conducted to test the effect of sugarlated salicylic acids on the reduction of the side-effects of

anticancer drug such as cisplatin while maintaining the drug's anticancer properties.

MEDI 457

Improved synthesis of the epoxy isoprostane phospholipid PEIPC and its analogs

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1-Palmitoyl-2-(5,6)-epoxyisoprostane E2-*sn*-glycero-3-phosphocholine (PEIPC), formed from the oxidation of 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (PAPC), was shown to activate several important inflammatory responses that contribute to atherosclerosis.

Herein, we describe an improved total synthesis of PEIPC and its analogues via a triply convergent preparation of a PMB ether protected EI derivative. This modified route allowed for the production in high purity of larger quantities of PEIPC and its structural analogues that may block the activity of oxidized phospholipids and inhibit atherogenesis.

[figure 1]

MEDI 458

Design and synthesis of new derivatives of YK-4-279 as inhibitors of EWS-FLI1

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Ewing's Sarcoma

Family of Tumors (ESFT) is characterized by the specific translocation of EWS and FLI1 transcription factors, which leads to EWS-FLI1 oncoprotein. Its interaction with RNA Helicase A (RHA) is believed to be important for its oncogenic potential. We validated the interaction between the tumor specific EWS-FLI1 of Ewing's Sarcoma and RNA as a therapeutic target. We showed that small molecule YK-4-279 prevented the binding of EWS-FLI1 to RHA. We also

demonstrated that YK-4-279 reduced tumor growth in Ewing's Sarcoma xenograft models while not affecting the growth of non-EWS-FLI1 containing tumors at similar dosages. A new class of derivatives of YK-4-279 has been designed and synthesized. Several derivatives showed potent inhibition towards Ewing's sarcoma cell lines with IC₅₀ around 1µM. These data suggest that our small molecules have the potential therapeutic effects in the treatment of ESTF.

MEDI 459

Design and synthesis of homo-dinuclear cyclen-based SH2 domain proteomimetics

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Src Homology 2 (SH2) domains are small intra-cellular protein binding domains that show high specificity towards phosphotyrosylated targets. Phosphorylation of a key Tyrosine (Y) residue in signal transducer and activator of transcription 3 (Stat3) protein has been shown to initiate Stat3–Stat3 protein dimerization. Transcriptionally active Stat3–Stat3 protein complexes are mediated through reciprocal pY:SH2 domain interactions and play an aberrant role in tumor cell growth and survival.

We have previously reported the application of substituted bis-dipicolylamine (BDPA) copper (II) coordination complexes as functional mimetics of the Stat3-SH2 domain. Our goal is to develop SH2 domain mimetics that display phosphopeptide specificity and thus protein specificity. Hence, we will present the synthesis, biophysical and biochemical evaluation of a novel family of homo-dimetallic di-cyclen coordinated complexes decorated with peptidic recognition sequences to confer phosphopeptide selectivity. Applications in disrupting protein-protein interactions will be discussed.

MEDI 460

Discovery of potent and selective inhibitors for ADAMTS-4 through encoded library technology (ELT)

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The aggrecan degrading metalloprotease ADAMTS-4 has been identified as a novel therapeutic target for osteoarthritis. Encoded Library Technology (ELT)¹ was employed to discover novel ADAMTS-4 inhibitors. We will describe the identification and ELT-derived SAR of novel hits from 3 ELT libraries. Potent, highly selective inhibitors for ADAMTS-4 with no conventional zinc binding group will be identified.

Reference

[1] Clark, Matthew A.; et al. *Nature Chemical Biology* **2009**, 5, 647-654.

MEDI 461

Novel chemical probes for p300 HAT inhibition

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Histone acetyltransferases (HATs) catalyze lysine acetylation in histones and other proteins and are potential therapeutic targets for cancer and other diseases. A crystal structure of the bisubstrate analog inhibitor Lys-CoA complexed to p300/HAT helped to identify a commercially available pyrazolone inhibitor of p300, C646. Here we report structure-activity relationship studies on pyrazolone and p300 HAT. Using a modular synthetic approach, we systematically explored each component of the polycyclic C646 compound and its effects on p300 inhibition.

MEDI 462

Studies of ciprofloxacin encapsulation on biogels in organic solvent mixtures

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Current oral administration of ciprofloxacin antibiotic is commonly associated to gastric and intestinal problems. Besides, ciprofloxacin has tendency to stacking with reduced biodisponibility. Encapsulation of the antibiotic on biogels, like alginates, is an alternative for oral delivery. However, the percentage of encapsulation on alginate (2.0 %) microspheres (600 μm diameter) is about 46 % under physiological aqueous conditions.

Alternatively, miscible organic aqueous (O-A) solvent mixtures can increase the encapsulation considering the low solubility of the drug. Screening procedures of O-A solvent mixtures showed an encapsulation increase up to 67.7% (ethanol 50%), 57.5% (1-propanol, 25%), 72.6% (ethylenglycol, 100%), 99.9% (1,2 propylenglycol, 50%).

58 and

93% of ciprofloxacin was release from alginate microspheres in 1,2 propylenglycol (50%) and water respectively at pH=1.2 (simulated gastric fluid) at 37 °C in 90 minutes. Alginate microspheres coated with pectin showed 48% ciprofloxacin release under the same experimental conditions.

MEDI 463

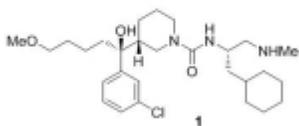
New and efficient synthesis of regiospecifically deuterated covalent probes for cannabinoid receptors

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D⁹-Tetrahydrocannabinol (D⁹-THC), the active ingredient of marijuana, produces its physiological response through the interaction with two cannabinoid receptors, CB1 and CB2. The extensive physiological transmission through these two cannabinoid receptors make them a promising target for treating several diseases including neurodegenerative diseases, cancer, obesity, inflammatory bowel disease, neuropathic pain, inflammation and immune disorders. Recent studies from our laboratory have identified the binding motifs of both CB1 and CB2 receptors using ligand-assisted protein structure approach (LAPS). To further advance these studies and for the elucidation of the biophysical interaction of cannabinergic ligands with the CB receptors, we required high affinity covalent probes in regiospecifically deuterated form. We have developed a new and efficient synthetic strategy for obtaining regiospecifically deuterated

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Renin is an attractive target for the control of hypertension and its associated end-organ damage. The previously described alkyl amine **1** has excellent potency against purified renin *in vitro* (IC₅₀ = 0.47 nM). However, it suffers a 28x loss in potency in the presence of human plasma and inhibits CYP3A4 with an IC₅₀ value of 1 μM. Structure-guided optimization of **1** led to compounds with greatly improved potency in the presence of plasma and significantly reduced CYP3A4 inhibition.



MEDI 466

Effects of lead and mercury on the blood proteome of children

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Lead and mercury exposure in children has been associated with a variety of physiological and neurological problems. Plasma and serum of 34 children from

the general population with low-level exposure to environmental Pb and Hg was analyzed by 2-D electrophoresis and LC-MS/MS. Apolipoprotein E, which was identified by both techniques and confirmed by Western blot analysis, demonstrated a significant association with lead concentrations that were significantly below CDC guidelines. This coincides with the finding that Apolipoprotein E genotype moderates neurobehavioral effects in adults occupationally exposed to lead. In addition, fifteen other proteins were identified by LC-MS/MS as proteins of interest.

MEDI 467

Helping build better pre-clinical drug candidates: Pharmaceutical development programs at the discovery-development interface

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Scientific and business needs have pushed the pharmaceutical industry to more closely align drug discovery and drug development efforts in order to progress optimal preclinical drug candidates (PDCs). Towards this end, an effective strategy is to embed a pharmaceutical sciences group inside Discovery. Pharmaceutical scientists can provide enabled formulations for key *in vivo* studies and work with medicinal chemists to optimize leads' physicochemical properties and identify a PDC's solid state phase that has appropriate physicochemical characteristics that allow for optimal performance in pre-clinical toxicology studies and clinical formulations.

This presentation describes the unique tools a Pharm Development group can bring to bear in Discovery and shows examples where partner groups from Discovery and Development worked together to increase the speed of drug lead identification/optimization and the preclinical candidate approval process. Finally, some work flows at the Development-Discovery interface are described along with an approach for pre-clinical candidate Pharmaceutical Risk Assessment.

MEDI 468

Correlative microscopy: Concurrent SEM and optical imaging of cells in an open system

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Optical microscopy is an indispensable tool in the study of cell biology. With fluorescent labels the understanding of protein localization and fine structure within cells and even dynamic processes can be observed. However, resolution is limited due to the diffraction limit of visible light. Higher resolution imaging can be achieved through electron microscopy but the sample typically requires time consuming pretreatment since the sample will be exposed to some level of vacuum. There is also a risk that this pretreatment will change the morphology of the structures that are to be studied.

To address these limitations, a new correlative microscopy tool has been developed which integrates a wide field optical microscope with a scanning electron microscope and allows the sample to remain in an open system at atmospheric pressure and temperature. This new correlative instrument will be described in more detail along with several applications in cell biology to chemistry.

MEDI 469

Active targeting with controlled delivery of therapeutic agents to bone using versatile, bifunctional bisphosphonates

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Active targeting with controlled delivery is an ideal approach for treatment of diseases.

In bone diseases like osteoporosis, active targeting is crucial because of drug uptake by non-targeted sites of the body and their undesired side effects. Bone is mainly made up with calcium phosphate and has a similar composition to hydroxyapatite. In this presentation, we will discuss the versatile nature of bifunctional bisphosphonates synthesized in our laboratory and their conjugation to therapeutic agents. A model drug was attached to the bisphosphonates with acid labile linkage and targeted to hydroxyapatite particles.

Moreover, controlled release of the attached drug from the immobilized conjugate was determined using a spectrometric method. The data demonstrate that bisphosphonates can be used in targeted drug delivery to bone tissue.

MEDI 470

Design and synthesis of Mycobacterial proteasome inhibitors

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Protein degradation is an essential cellular process. Disruption of protein degradation interferes with numerous cellular activities. Analogous multistep pathways to degrade proteins are common amongst all living cells. The proteasome, a catalytic enzyme complex, is a major component of proteolysis. Crystal structures of eukaryotic and an increasing number of prokaryotic proteasomes provide information on their composition and enzymatic activities. Proteasome inhibitors, already approved for use against cancers, might be significant additions to antibacterial therapies. Our work uses the crystal structure of the *Mycobacterium tuberculosis* (Mtb) proteasome as the basis for inhibitor design. Initial rounds of modeling and synthesis are based on analogues of bortezomib, a boronic acid dipeptide. Current synthetic efforts replace the leucine moiety of bortezomib with substituents that should provide a better fit into the protein active site, increasing inhibition of the Mtb enzyme. Modeling results, synthesis and biological activity of these new compounds will be presented.

MEDI 471

New and facile way to Flustramine analogs through radical cyclization

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Flustramides are precursors to flustramines, which are a class of compounds isolated from the marine invertebrate Bryozoa *Flusta foliacea*. Flustramines have been shown to exhibit antibacterial, skeletal and smooth muscle relaxant activities, as well as having blocking activity in potassium channels. Previous syntheses focus on building the tricyclic system from indole, indolinone, and carbodiimide substrates. We describe a synthesis that builds the three-ring system via radical cyclization from an aromatic precursor.



MEDI 472

Fundamental oxidation and reduction chemistry of isoniazid and its reactive intermediates

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Isoniazid is the front-line treatment for infections by *Mycobacterium tuberculosis*. Unfortunately, despite its simple structure and over half-a-century of therapeutic use its mechanism of action remains complex and unclear. Although complex there are several common features to the proposed mechanisms one of which is that isoniazid is a prodrug that once activated by the mycobacterial catalase-peroxidase KatG generates reactive intermediates that are responsible for its action. Electron spin resonance studies have indicated that these reactive intermediates are free radicals derived from isoniazid. However, the mechanism by which the free radicals are produced and their precise structure are still uncertain. While the mechanism of activation of isoniazid has been investigated using a variety of *in vitro* techniques very little is known about the basic free radical chemistry of this therapeutic. To begin to address this situation, we report here the reaction of the oxidizing hydroxyl radical and reducing hydrated electron with isoniazid using pulse radiolysis techniques. The studies have determined absolute reaction rate constants, transient radical spectra, and initial reaction sites and free-radicals produced for isoniazid under both oxidative and reductive conditions. In addition steady-state irradiations and EPR spin trapping experiments have examined the production of nitric oxide under various solution conditions by isoniazid.

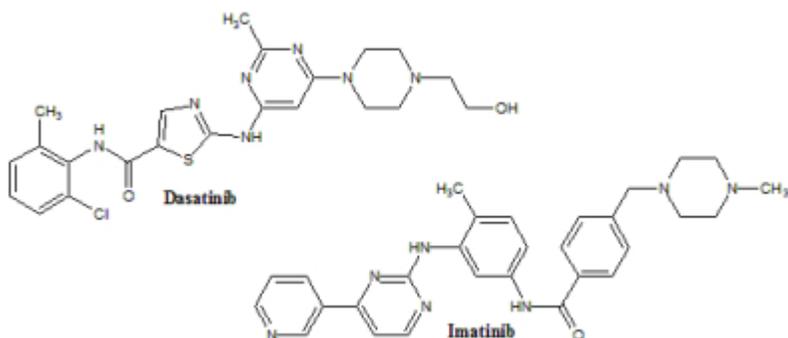
MEDI 473

Capture compound mass spectrometry: A novel chemical proteomics approach to profile small molecule-protein interactions for drug target discovery and off-target binding-induced toxicity

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The identification of the molecular target of a pharmaceutical compound is a key step in drug development. We have developed a novel technology, the Capture Compound Mass Spectrometry (CCMS), to unravel primary targets for drug

molecules as well as off-targets with potential toxicity effects. To comprehensively profile the drug-protein interactions, the selectivity function of the Capture Compound (the drug of interest) is attached in various orientations to the Capture Compound scaffold, that contains a photo-activatable reactivity function and a sorting function. We recently reported the validity of this approach in a study using the hepatotoxic catechol-O-methyltransferase inhibitor tolcapone as selectivity function and identified the primary target as well as mitochondrial membrane proteins as off-targets that may give rise to hepatotoxicity. We now addressed two kinase inhibitor drugs, dasatinib (Sprycel) and imatinib (Gleevec), and profiled their protein interactions. We here report preliminary data on previously unknown proteins that interact with these drugs.



MEDI 474

Pyrrolopyrimidine-based P2X₃ antagonists for the treatment of pain

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P2X₃ receptors, members of the P2 purinergic receptor family, are ligand-gated ion channels activated by extracellular ATP as an endogenous ligand. The expression of P2X₃ receptors is highly localized in the peripheral and central processes of sensory afferent neurons. Activation of P2X₃ receptors by ATP has been shown to initiate the pain signaling involved in chronic inflammatory nociception and neuropathic pain due to nerve injury. The poster will cover the progress made from HTS through the LO phase, including the use of *in silico* predictive models to support compound design, including a detailed discussion of the medicinal chemistry optimization of physicochemical and ADME properties, as well as CYP inhibition profile. The primary SAR of the series will be discussed,

along with data from *in vivo* characterization studies using preclinical pain models.



MEDI 475

Drug discovery: Natural herbal formulation

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Nutraceuticon, Inc. is a drug development company based on natural herbal products. Over long history of time, traditional herbal formulations are used successfully to treat different diseases over the world. These include diseases related to cancers, coronary, hypertension, diabetes, high cholesterol, obesity, Alzheimer, stroke, asthma, arthritis and others. Well established multi-ingredient herbal formulations are selected, prepared and processed. The source of the herbal ingredients and formulations are from global medical resources including e.g. from Asia and South America. Extracts from these processed formulations are screened with disease marker models for drug activities. Examples and results will be presented and discussed. Information is available in www.Nutraceuticon.net.

MEDI 476

Synthesis and preliminary biological evaluation of 20-epi-eldecalcitol [20-Epi-1alfa,25-dihydroxy-2beta-(3-hydroxypropoxy)vitamin D3: 20-Epi-ED-71]

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Eldecalcitol [1 α ,25-dihydroxy-2 β -(3-hydroxypropoxy)vitamin D₃, developing code; ED-71] is an analog of active vitamin D₃, 1 α ,25-dihydroxyvitamin D₃, that possesses a hydroxypropoxy substituent at the 2 β -position. Eldecalcitol has potent biological effects on bone and is now in preparation for approval as a promising medicine for the treatment of osteoporosis in Japan. To explore structure-biological activity relationships between eldecalcitol and related analogs, we have already synthesized 1-epi-eldecalcitol, 3-epi-eldecalcitol, and 1,3-diepi-eldecalcitol and evaluated their biological responses. As a continuation of our modification studies on eldecalcitol, we synthesized 20-epi-eldecalcitol by the Trost coupling reaction. In the induction of human myeloid leukemia cell differentiation, inhibition of the human histiocytic lymphoma cell proliferation, and increase in osteocalcin concentration in the human osteosarcoma cell, 20-epi-eldecalcitol showed greatly enhanced activity compared to eldecalcitol. Detailed synthetic method and preliminary biological evaluation of 20-epi-eldecalcitol will be presented.

MEDI 477

Investigation of preparative HPLC applications performed at both acidic and basic pH

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A general need for chromatographers is to find a versatile high performing and chemically stable reversed phase HPLC column. The column should also be available in several particle sizes in order to be scaled up or down. For preparative purposes, loadability should be high for a broad range of compounds, throughout a wide pH range, in order to facilitate small scale purification in pre-packed semi- preparative columns. Our most recent launched chemically stable product fulfills all of the above mentioned requirements, which categorize it as an excellent column for combinatorial chemistry and development labs.

In this poster, we are presenting several applications showing the stationary phase's broad applicability and suitability for semi preparative work throughout its full pH interval, pH 1 to 12. Band broadening during overloading conditions at different pH values has been investigated and will be shown. We are also presenting reproducible scale-up experiments between analytical and semi preparative column dimensions.

MEDI 478

Novel *lacZ* responsive enhanced Gd-based ^1H MRI agents

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The *lacZ* gene encoding β -galactosidase (β -gal) has been well characterized and extensively used with applications ranging from molecular biology to small animal investigations and to clinical trials including assays of clonal insertion, transcriptional activation, protein expression, and protein interaction. A variety of *lacZ* gene reporters has been developed, such as colorimetric, fluorescent, chemiluminescent, radiotracers for PET or SPECT, ^{19}F MRS/MRI, and MRI probes. We now report the exploration of a novel approach to *lacZ* responsive enhanced Gd-based ^1H MRI agents



, through the cleavage by β -gal, the released and activated aglycones will spontaneously trap endogenous Fe^{3+} at the site of enzyme activity forming a highly stable complex, exhibiting restricted motion of the Gd^{3+} chelates enhancing relaxivity and providing contrast based on gene stimulated local accumulation, then generating high relaxivity by forming higher molecular weight and rigidity of the complexes.

MEDI 479

Synthesis of tetralene- and chromene-based 4EGI-1 mimetics as inhibitors of eIF4E/eIF4G interaction

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Inhibition of translation initiation is emerging as a novel paradigm in anti-cancer therapy. 4EGI-1 (2-(2-(4-(3,4-dichlorophenyl)thiazol-2-yl)hydrazono)-3-(2-nitrophenyl)propanoic acid) has been explored as a prototypic inhibitor of translation initiation. It inhibits cap dependent translation by blocking the protein-protein interaction between eIF4E and eIF4G that together with eIF4A form eIF4F, one of the rate-limiting complexes in the translation initiation cascade. One of the directions undertaken in the hit-to-lead optimization of 4EGI-1 was to rigidify the substituted thiazol-2-yl system by replacing it with either 4,5-dihydronaphthol[1,2-*d*]thiazol-3-yl or 4*H*-chromeno[4,3-*d*]thiazol-3-yl moieties. The binding affinity of these novel 4EGI-1 mimetics to eIF4E was characterized by a fluorescent polarization assay and NMR titration studies. The observed enhancement in binding affinity as compared to the parent 4EGI-1 provides insight on the mode of interaction between eIF4E and these rigidified mimetics and will help in the structure-based optimization process.

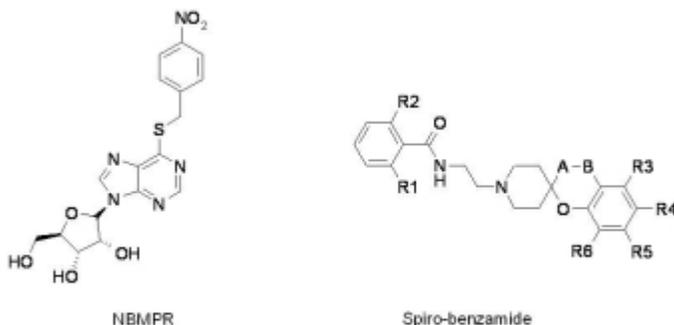
MEDI 480

Spiro-benzamides as ENT-1 inhibitors

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Adenosine is an endogenous purine nucleoside that is actively transported *via* specialized proteins to cross the cell membrane and is released in the event of ischemia, inflammation and pain. Upon administration of adenosine an analgesic effect is observed in various nociceptive models. Adenosine exhibits a short half-life thus there is considerable interest in reinforcing its endogenous effect. One way to block the uptake of adenosine into cells is by inhibiting the adenosine transporters. The principle is that blockage of the transport protein leads to an increased in extracellular concentration of adenosine thereby counteracting pain. These transporters that play a key role in the regulation of extracellular

adenosine concentration are selective for purine and pyrimidine nucleosides. The most studied transporter is hENT-1 that can be further characterized by its nano-molar range affinity with NBMPR (S6-(4-nitrobenzyl)mercaptapurine riboside). Here, we report for the first time the SAR optimization and synthesis of a non-nucleoside series of spiro-benzamide that act as ENT-1 inhibitors together with biological evaluation *in vivo* inflammation and pain models.



MEDI 481

Depth dependent swelling and mechanical behavior of cartilage

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Articular cartilage is a typical heterogeneous tissue composed of chondrocytes, extracellular matrix (ECM) and interstitial fluid. Its primary function is to provide lubrication and redistribution of forces within the joint without damage to the underlying bone. The structure, the mechanical properties and the chemical composition of cartilage vary in different regions throughout tissue depth. Its load bearing properties are primarily governed by the ECM. Structurally cartilage ECM consists of a dense network of collagen (mainly collagen II) fibrils the pores of which are filled with extended proteoglycan assemblies. To investigate the structure and interactions in this complex system, we apply a multiscale experimental approach that combines complementary osmotic and scattering

techniques to probe different characteristic length scales. We developed a method to create high-resolution osmotic modulus maps using the atomic force microscopy. Biochemical composition of cartilage layers was found to be correlated with tissue's osmotic and mechanical properties.

MEDI 482

Evaluation of select fractions of mineral oil in vaccine preparation

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Scientists at National Wildlife Research Center (NWRC) are presently formulating vaccines for use as an immunocontraceptive in animals containing mineral oil as an adjuvant. Adjuvants are included in a vaccine to increase the immune response to the vaccine. Alkane chain fractions smaller than 14-Carbons in length, in mineral oil, have been associated with injection site inflammation as a result of tissue necrosis. We developed a procedure using urea precipitation to separate the linear fraction of the mineral oil followed by GC/MS analysis to screen mineral oils for the relative abundance of these fractions. Details of the method and results for select mineral oil samples will be presented.

MEDI 483

Loading the dice by integrating lead optimization

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Drug development is a multi-objective endeavor - you want to increase lead potency while simultaneously improving selectivity and cultivating the kind of good solubility and pharmacokinetic properties that early screening hits generally lack. The process begins by identifying structural similarities among screening hits, then finding trends in activity within and between classes. Pairwise SARs can subsequently be used to identify abrupt property shifts that present unusual opportunities, challenges or misleading assay results. For cell-based assays, such activity cliffs can also convey valuable information about metabolism or cytotoxicity. Results within classes can be used to guide the mixing and matching of scaffolds and substituents for a follow-up library, with an eye towards enhancing activity and expected ADMET properties. Real-world screening data

will be used to show how the entire process can be carried out within a single program tied directly into the most reliable ADMET prediction tools currently available.

MEDI 484

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MEDI 484

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MEDI 485

Multicomponent reactions for the discovery of p53-Mdm2 antagonists: Synthesis, chemoinformatics and biological evaluations

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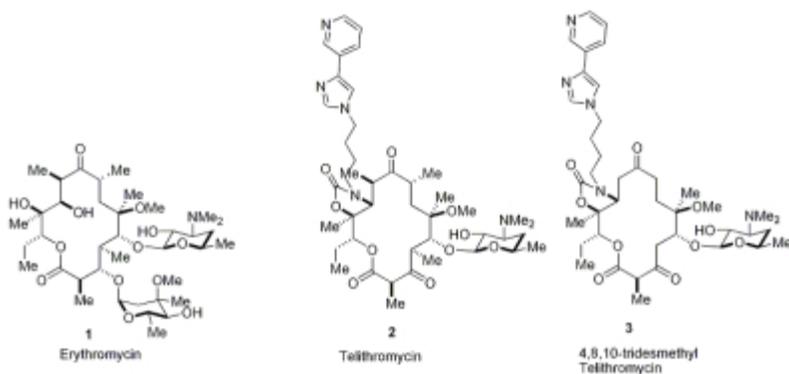
With the emergence of combinatorial chemistry and diversity-oriented synthesis for drug discovery applications, multicomponent reaction (MCR) has seen a resurgence of interest. MCR derived small molecule-based ligands have demonstrated the successful impact at different stages of drug discovery process, including the lead discovery, lead optimization, and pre-clinical development arenas. We integrated MCR approaches with computational method, library design and screening process, in order to generate new lead compounds as drug candidates. One approach to develop novel anti-cancer agents is the inhibition of the interaction between the tumor suppressor p53 and the oncogene products (Mdm2, Mdm4). Three new scaffolds of small molecular weight p53-Mdm2 antagonists were investigated by MCR integrated drug discovery approach. These scaffolds were designed by computational modeling and synthesized by Gewald and Ugi multicomponent reactions. The virtual compound libraries were generated and evaluated for chemical space distribution and drug-like properties. Biological evaluations demonstrated that some compounds exhibited promising antagonistic activity with p53-Mdm2. The binding mode of p53-Mdm2 antagonists were investigated by NMR, X-ray cocrystal structure analysis and computational modeling. Potential lead compounds are generated through this structure-based drug discovery approach.

MEDI 486

Discovery of novel macrolide antibiotics: Synthesis and biological evaluation of 4,8,10-tridesmethyl telithromycin

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The rapid emergence of antibiotic-resistant bacteria represents a serious health threat that shows no signs of abatement. A sharp decline in the number of pharmaceutical companies with active antimicrobial research programs underscores the need for new sources of antibiotics. As a part of a rational structure-based drug design program, we apply the paradigm of natural product structural simplification (i.e., desmethylation) to the 3rd-generation macrolide antibiotic telithromycin (**2**), which is an FDA-approved semisynthetic analogue of erythromycin (**1**) in clinical use since 2004. The rationale behind desmethylation comes from crystallographic studies of **1** and **2** bound to ribosomal subunits, which corroborate biochemical mechanisms of antibiotic resistance (e.g., ribosomal modification and mutation). We have recently accomplished the *de novo* synthesis of 4,8,10-tridesmethyl telithromycin (**3**), which was found to be biologically active against both wild type and mutant bacterial strains and comparable to **2** in potency.



MEDI 487

Engineered immunity: Development of multivalent artificial opsonins for the treatment of nosocomial infections

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Hospital-acquired infections remain a leading cause of death in the United States. Unfortunately, the emergence of antibiotic-resistant bacterial strains has

rendered traditional antibiotic therapy ineffective. Furthermore, many of the causative bacteria, such as staphylococci, are surrounded by a protective polysaccharide capsule which allows them to evade the host's immune system. For this reason, novel antibody therapies, including passive and active immunization, also have little efficacy. In an effort to enhance the body's natural immune response to infection, we have developed multivalent artificial opsonins to promote the recognition, phagocytosis, and destruction of pathogenic bacteria by human phagocytes. The structure of our artificial opsonins consists of multiple copies of both bacterial and phagocyte recognition molecules attached to a poly(L-lysine)-*g*-poly(ethylene glycol) polymeric support. Human immunoglobulin G (IgG) Fc antibody fragment serves as the phagocyte recognition molecule as it is recognized by the Fc γ cell surface receptors universally expressed on human phagocytic cells. For bacterial recognition, we employed a novel application for the glycopeptide antibiotic vancomycin as a high affinity targeting molecule. Our approach utilizes vancomycin's inherent ability to bind to multivalent structures naturally present in the cell wall of Gram-positive bacteria. Conjugation of vancomycin to PLL-*g*-PEG prevents its action as an antibiotic and allows it to function solely as a recognition molecule. Notably, our approach has efficacy against virulent multi-drug-resistant and polysaccharide-encapsulated strains which are notoriously difficult to treat. Additionally, the opsonins themselves are designed to be non-bactericidal, thereby minimizing or even eliminating the chance that bacteria would develop resistance mechanisms.

MEDI 488

Identification and SAR of novel furan-free imidazopyridine ligands as selective adenosine A2A-antagonists for Parkinson disease

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A2A-receptor antagonism is a novel therapeutic strategy for the treatment of Parkinson's Disease, a neurodegenerative disorder resulting from a gradual loss of dopaminergic neurons. A2A-receptor antagonists have shown efficacy in animal models and promising results in clinical evaluations. Whilst a number of different ligands were described as A2A-receptor antagonists, they can be broadly divided into two families: the xanthine and the non-xanthine, the majority of the latter containing a furan moiety that can be subject to an oxidative metabolism leading to reactive species.

At Domain Therapeutics, we have identified a novel series of imidazopyridine compounds as A2A-receptor ligands. These compounds are completely distinct from the known non-xanthine A2A-receptor antagonists. Their optimization led to

compounds with low-nanomolar affinity and efficacy for the A2A-receptor, good selectivity profile and no flag in early ADME-Tox. The best representatives were further evaluated in two rodent models of Parkinson's Disease and showed efficacies after oral administration.

MEDI 489

Discovery of BKM120, a pan class I PI3 kinase inhibitor in phase I/II clinical trials

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A substantial number of epidemiological and experimental studies support an important role for PI3K in the biology of human cancer. The activation of PI3K, and its downstream effectors, has been clearly validated as an essential step for the initiation and maintenance of the tumorigenic phenotype. Parallel to the clinical development of our dual pan-PI3K/mTOR modulators (e.g., NVP-BE2235), we continued our drug discovery activities to identify PI3K inhibitors with distinct biological and pharmacological profiles. Starting from potent 2-morpholino, 4-substituted, 6-(3-hydroxyphenyl) pyrimidines as lead series, a structure based design approach was adopted, with focus on replacing the phenol moiety while maintaining potent target inhibition and improving *in vivo* properties. These efforts led to the identification of a new clinical candidate, NVP-BKM120. This 2,6-dimorpholino pyrimidine derivative is a potent pan-PI3K (e.g., IC₅₀= 35 nM, p110a) that does not significantly inhibit other protein or lipid kinases (e.g., IC₅₀= 4.6 mM, mTOR). The compound exhibits antiproliferative activity against a broad panel of tumor cell lines by specifically blocking the biological function of PI3K signaling components (e.g. IC₅₀ = 93 nM S473P-Akt in Rat1-p110a cells). NVP-BKM120 shows good oral bioavailability in preclinical species and demonstrates significant antitumor activity at tolerated doses in mouse xenograft models of diverse cancer lineage. Analyses of tumor tissues after acute dosing or at the end of efficacy studies, shows a good correlation between compound exposure, PI3K pathway blockade (reduction in P-Akt levels) and antitumor activity. NVP-BKM120 is currently undergoing Phase I/II human clinical trials for the treatment of solid tumors and hematological malignancies

MEDI 490

Design and synthesis of dual adenosine A_{2A}/A₁ antagonists for the treatment of Parkinson's disease

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A novel series of arylindenopyrimidines have been identified as dual adenosine A_{2A}/A₁ antagonists having efficacy in several animal models of Parkinson's disease when dosed orally. This series of molecules are structurally and characteristically distinct from other adenosine antagonists in clinical trials. A number of program hurdles (i.e. Ames, hERG, solubility, and metabolism) were identified and overcome by several medicinal chemistry approaches. This program spans the entire discovery life-cycle from lead generation up to phase I.

MEDI 491

Synthesis and biological activity of 2H-quinolizin-2-one based p38-a MAP kinase inhibitors

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Over the last decade the pharmaceutical industry invested significant resources in developing a therapy to regulate tumor necrosis factor (TNF- α) for the treatment of such indications as rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease. Current TNF- α treatments include monoclonal antibodies infliximab (Remicade[®]), adalimumab (Humira[®]), and the fusion protein etanercept (Enbrel[®]).² Although current therapies successfully reduce TNF- α levels, long term patient compliance is compromised by safety, cost, and/or efficacy. Currently no small molecule therapy has been approved for attenuating TNF- α levels.

It has been demonstrated that inhibiting p38a mitogen-activated protein (MAP) kinase delays the onset of joint disease in animal models of arthritis by arresting the over production of pro-inflammatory cytokines such as TNF- α . This presentation will highlight the design and optimization of the 2H-quinolizin-2-one

series and will describe the progression of these compounds from early lead structures to mature p38a inhibitors.

MEDI 492

Evaluation of 4-cyano-4-arylpiperidine quinolizidinone carboxylic acid selective M₁ positive allosteric receptor modulators

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Elucidation of new mechanisms to treat the neurodegenerative effects of Alzheimer's disease (AD) represents a major unmet medical need. One approach to ameliorate the cognitive decline in AD has been to target the neurons of the basal forebrain cholinergic system via activation of the M₁ muscarinic receptor. A number of non-selective M₁ muscarinic agonists have previously shown positive effects on cognitive behaviors in AD patients, but were limited due to cholinergic adverse events thought to be mediated by activation of the M₂ to M₅ sub-types. One approach to confer selectivity for M₁ is the identification of a positive allosteric modulators, which would target an allosteric site on the M₁ receptor rather than the highly conserved orthosteric acetylcholine binding site. We have previously reported the quinolone carboxylic acid BQCA as a highly selective M₁ positive allosteric modulator with good pharmacokinetic and in vivo properties. This presentation will focus on the optimization of a novel quinolizidinone carboxylic acid scaffold leading to an M₁ allosteric modulator with higher plasma free fraction, enhanced CNS exposure, and improved efficacy in a rodent in vivo model of cognition for further safety evaluation.

MEDI 493

Discovery of the potent PI3K/mTOR dual inhibitor PF-04979064

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The key kinases in the PI3K signaling pathway, e.g. PI3K, AKT, mTOR, are attractive oncology targets. Previously, we reported the discovery of a dual PI3K/mTOR inhibitor PF-04691502 that is currently in phase 1 clinical trials. In order to search for a structurally differentiated back-up candidate to PF-04691502, lead optimization effort was carried out with the tricyclic imidazo[1,5]naphthyridine series. SBDD was carried out to address poor solubility and poor metabolic stability issues associated with the initial leads. In addition, the initial leads were also substrates for aldehyde oxidase. After addressing the aldehyde oxidase mediated clearance for this tricyclic series, 1-{1-[(2S)-2-hydroxypropanoyl]piperidin-4-yl}-3-methyl-8-(6-methylpyridin-3-yl)-1,3-dihydro-2H-imidazo[4,5-c][1,5]naphthyridin-2-one, PF-04979064, was identified as a back-up candidate that demonstrated potent *in vitro* activity against both PI3K and mTOR, good ADMET and excellent kinase selectivity. PF-04979064 is being considered to progress to clinical trial.

MEDI 494

Identification of PKI-179 as a potent and orally efficacious PI3 kinase inhibitor for the treatment of cancer

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Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase that is a central component in the PI3K/Akt/mTOR signaling pathway. An effective inhibitor of the PI3K/Akt/mTOR pathway could both prevent cancer cell proliferation and induce programmed cell death (apoptosis). A series of 3-oxa-8-azabicyclo[3.2.1]octane appendage bearing mono-morpholino triazine derivatives were prepared and evaluated for PI3 Kinase/mTOR activity. Replacement of one of the bis-morpholine in PKI-587 (**1**) with 3-oxa-8-azabicyclo[3.2.1]octane and reducing the molecular weight led to the identification of PKI-179 (**2**), an orally efficacious dual PI3K/mTOR inhibitor. The *in vitro*, *in vivo* and PK properties of **2** are discussed. In addition, the synthesis and stereochemical determination of an active metabolite of **2** is also described.

MEDI 495

Design and synthesis of tricyclic sulfones as g-secretase inhibitors with greatly reduced Notch toxicity

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A novel series of tricyclic g-secretase inhibitors was designed and synthesized via a conformational analysis of literature compounds. The preliminary results have shown that compounds in this new series have much improved in vitro potency and in vivo profiles. More importantly, they have greatly reduced Notch related toxicity that was associated with previous c-secretase inhibitors.

MEDI 496

Discovery of PPIs using chemical feature-based pharmacophore models

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Pharmacophore-based virtual screening methods have proven to be successful for the rapid identification of hit compounds for a wide variety of targets. In this paper we present the development and application of pharmacophore-based methods for identifying PPIs. Using both an heuristic approach (LigandScout, Fig. 1)¹ and an interaction energy-based method (GBPM)² bio-active compounds could be retrieved selectively from large 3D molecular databases.

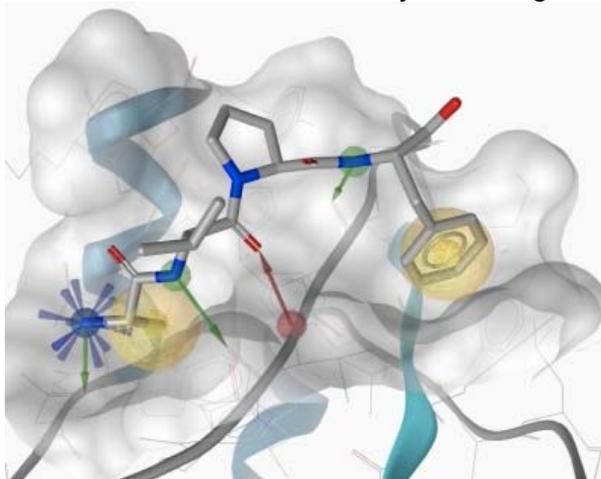


Figure 1: LigandScout representation of one of the pharmacophore models used for virtual screening

Activity was confirmed by the results of biological testing. The compounds were found to inhibit XIAP and therefore are interesting as promising starting points for further optimization as anti-cancer agents.

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² Ortuso, F., Langer, T., Alcaro, S.: *Bioinformatics* 2006 22 1456-1463

MEDI 497

Targeting endogenous cannabinoid catabolic enzymes in preclinical models of pain

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The endogenous cannabinoid system has been the focus of an intense amount of research for the development of new analgesics. This system consists of two cannabinoid receptors, endocannabinoid ligands, including anandamide (AEA) and 2-arachidonylglycerol (2-AG), and enzymes regulating the biosynthesis and catabolism of these ligands. The respective enzymes primarily responsible for AEA and 2-AG degradation, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), represent particularly promising therapeutic targets. Acute inhibition of each enzyme elicits comparable antinociceptive effects; however, prolonged blockade elicits dramatically different consequences. Whereas the antinociceptive effects of FAAH inhibitors are sustained following chronic blockade of FAAH, antinociception produced by the MAGL inhibitor JZL184 undergoes tolerance following repeated administration. Moreover, mice treated subchronically with JZL184 or MAGL(-/-) mice display cross-tolerance to exogenous cannabinoids that is accompanied with CB₁ receptor down-regulation. Collectively, these results suggest that FAAH has distinct advantages over MAGL as a therapeutic target to treat pain.

MEDI 498

Discovery of a novel series of potent, non-covalent fatty acid amide hydrolase (FAAH) inhibitors through rational design

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Fatty acid amide hydrolase is a serine hydrolase that plays a central role in regulating signaling of the endogenous cannabinoid receptor agonist, *N*-arachidonylethanolamine (AEA), also known as anandamide. The anti-nociceptive effects of agonizing the cannabinoid receptors have long been recognized and for some time it has been postulated that inhibiting FAAH will show similar therapeutic benefits through increasing lifetime of AEA in the both central nervous system and peripheral tissues. In this presentation, we describe our successful efforts to design a series of FAAH inhibitors that do not rely on covalent modification of the catalytic serine residue (S241) to achieve potency. Starting from mechanism-based inhibitors identified through high throughput screening, we designed a series of novel non-covalent FAAH inhibitors. The series shows potent inhibition of both human and rat FAAH, blocks AEA processing in T84 and RBL cells and has good pharmacokinetic properties. The design strategy, synthesis and SAR of these compounds will be described. Additionally, co-crystallization studies with rat FAAH that elucidated the binding mode of this series of compounds will be disclosed.

MEDI 499

Inhibitors of fatty acid amide hydrolase (FAAH): SAR and results in pre-clinical pain models

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Pharmacologically active preparations of *Cannabis sativa* have been recognized since ancient times as having potentially useful therapeutic effects, including analgesia. With the discovery and cloning of the cannabinoid receptors CB1 and CB2, and the subsequent discovery of anandamide, the first endogenous substance with agonist activity at both receptors, a rationale for the analgesic effects of cannabis was developed. Anandamide has a short half-life, due to rapid hydrolysis by the enzyme fatty acid amide hydrolase (FAAH) resulting in low resting concentrations in the CNS. FAAH knockout mice have been described and have elevated resting brain concentrations of anandamide, and manifest a phenotypic analgesia in several commonly used models of pain. Furthermore, known inhibitors of FAAH show amelioration of pain behaviours in rats. The present account describes the discovery of a novel classes of FAAH

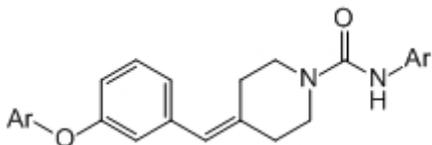
inhibitors and describes our work to characterize the SAR and pharmacological actions of these FAAH inhibitors.

MEDI 500

Discovery of PF-04457845, an irreversible FAAH inhibitor with exquisite selectivity

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Fatty acid amide hydrolase (FAAH) is an integral membrane serine hydrolase that degrades the fatty acid amide family of signaling lipids, including the endocannabinoid anandamide. Genetic or pharmacological inactivation of FAAH leads to analgesic and anti-inflammatory phenotypes in rodents without showing the undesirable side effects observed with direct cannabinoid receptor agonists, indicating that FAAH may represent an attractive therapeutic target for the treatment of inflammatory pain. This talk will describe the discovery and characterization of a series of irreversible FAAH piperidine urea inhibitors including our clinical candidate PF-04457845. These compounds covalently modify the active-site serine nucleophile of FAAH with exquisite selectivity relative to other members of the serine hydrolase superfamily as demonstrated by competitive activity-based protein profiling (ABPP) using a fluorophosphonate-rhodamine activity-based probe. Furthermore, the in vivo selectivity of a clickable covalent FAAH inhibitor was profiled using click chemistry (CC)-ABPP and shown to selectively react with FAAH.



MEDI 501

Discovery and development of inhibitors of fatty acid amide hydrolase (FAAH)

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A summary of studies leading to the discovery of Fatty Acid Amid Hydrolase (FAAH), the development of potent and selective inhibitors of the enzyme, and their use in the validation of the target as one useful for the treatment of pain and inflammation, will be presented.

MEDI 502

Nicotinamide derivatives as novel, potent and orally active mGlu5 receptor antagonists

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We here report on our efforts to identify and characterize novel mGlu5 receptor antagonists. High-throughput screening led to the identification of nicotinamide derivatives as structurally novel mGluR5 antagonists. Medicinal chemistry optimization efforts around a poorly soluble, micromolar hit finally led to target-selective compounds with low nanomolar potency, high selectivity and optimized drug-like properties. A selected candidate showed robust anxiolytic-like activity in different animal models as well as a good PK/PD correlation [1]. The central receptor occupancy was investigated at two time points in anesthetized rats *in vivo* using the mGluR5 PET tracer [¹¹C]-ABP688 [2] and a scintillating tip (beta probe) acutely implanted in the striatum of rats [3]. This experiment allowed an estimation of the mGlu5 receptor occupancy that is required to give rise to a significant behavioral effect *in vivo*.

[1] Spanka C *et al.*, *Bioorg Med Chem. Lett.* 2010; 20(1):184-188

[2] Hintermann S *et al.*, *Bioorg Med Chem.* 2007; 15(2):903-14

[3] Wyss MT *et al.*, *Neuroimage.* 2007; 35(3):1086-92

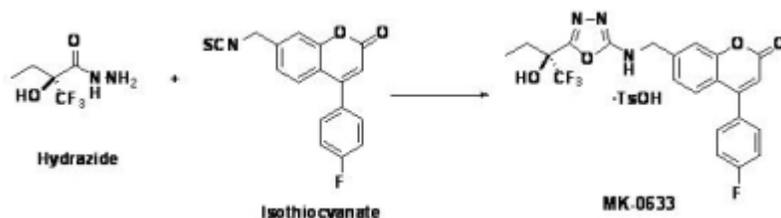
MEDI 503

Development of long term manufacturing process for MK-0633 (Setileuton)

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MK-0633 (Setileuton) is an inhibitor of the leukotriene pathway enzyme 5-lipoxygenase and is currently in development for the treatment of asthma. Due to

its anti-inflammatory properties, other potential indications include COPD and atherosclerosis. MK-0633 is synthesized in a convergent manner by combining hydrazide piece and isothiocyanate piece. This presentation will focus on the development of a shorter and more efficient synthesis for isothiocyanate unit and the definition of long term synthesis of MK-0633 for manufacturing process.



MEDI 504

Apolipoprotein B-100: A 3-iodothyronamine (T1AM) binding protein

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Thyronamines (TxAM) are a novel class of endogenous signaling compounds and so far, only two thyronamines, namely 3-iodothyronamine (T1AM) and thyronamine (T0AM), have been detected *in vivo* in various species. Although their physiological roles still remain elusive, T1AM and T0AM have exhibited short-term hypothermic, negative chronotropic, and negative inotropic effects that are opposite in direction to the actions of the classical active thyroid hormone T₃. More than 99.9% of the T₄ in blood is bound to carrier proteins, especially to thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin but the occurrence and extent of T1AM binding to proteins is currently unknown.

Recently we have identified a T1AM binding protein from human serum by covalently attaching T1AM to sepharose beads through a disulfide linker. Our results show that T1AM tightly binds (noncovalently) with apolipoproteinB-100 with K_d value 3 nM. ApolipoproteinB-100 mainly present in VLDL and LDL is responsible for the transport of lipids and cholesterol in the human circulation and is thus a key player in cholesterol transfer and metabolism. ApolipoproteinB-100 also serves as a ligand for receptor mediated uptake of LDL by a variety of cell types. The rise in the LDL cholesterol/HDL cholesterol ratio during hypothyroidism increases the risk for coronary heart diseases such as atherosclerosis. The effect of T1AM on lipoprotein metabolism and LDL cellular uptake will also be discussed.

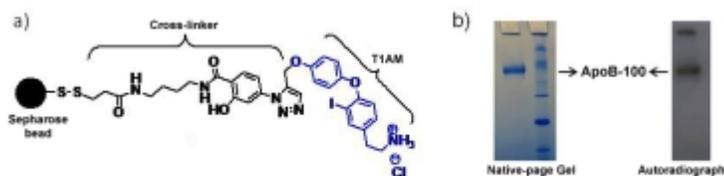


Figure 1. T1AM-attached sepharose bead containing disulfide linker was used for identification of T1AM binding protein in human serum (a). Native-page gel and autoradiography showing [125I]T1AM binding to ApoB-100 (b).

MEDI 505

Resorcinol-class HSP90 inhibitors for oral treatment in oncology

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Hans-Peter Buchstaller⁽¹⁾; **Christiane Amendt**⁽¹⁾; **Michael Wolf**⁽¹⁾; **Ulrich Grädler**⁽¹⁾;
Djordje Musil⁽¹⁾; **Edmund Hoppe**⁽¹⁾; **Astrid Zimmermann**⁽¹⁾; **Harry Schwartz**⁽¹⁾;
Joachim März⁽¹⁾; **Joerg Bomke**⁽¹⁾; **Ansgar Wegener**⁽¹⁾; **Thomas Mohr**⁽¹⁾; **Holger Bauer**⁽¹⁾;
Marian Braendle⁽¹⁾; **Marian Brändle**⁽¹⁾; **Johannes Gleitz**⁽¹⁾; **Nicole Huebler**⁽¹⁾;
Torsten Selzer⁽¹⁾. (1) Merck Serono Research & Development, Merck KGaA, Darmstadt 64293, Germany

Hsp90 is a molecular chaperone that plays an important role in the folding and function of oncogenes in tumor cells. Here we will present HTS and structure based design efforts to identify novel molecules that show potent binding to HSP90. The HSP90 co-crystal structure of HTS hits from the resorcinol-class revealed their binding mode to the N-terminal ATPase pocket and thus guided subsequent optimization towards potency and oral bioavailability. Especially the fact that a previously unobserved binding pocket is occupied by some hit structures opened the route for the introduction of a broad variety of substituents which modulate the metabolism of this compound-class to a degree that good oral bioavailability could be obtained. We will present here how the SAR evolved from the initial hits with respect to potency, physical-chemical properties and the pharmacokinetic properties towards a clinical candidate with improved oral bioavailability and *in vivo* potency.

MEDI 506

Design and synthesis of potent, dual action p53/MDM2/MDMX antagonists for the treatment of cancer

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Siglinde Wolf⁽²⁾; **Dömling Alexander**⁽¹⁾; **Tad A. Holak**⁽²⁾. (1) Department of Pharmaceutical Science, University of Pittsburgh, Pittsburgh PA 15260, United States (2) Max Planck Institute for Biochemistry, Martinsried, Germany

Tumor protein p53, which is negatively regulated by both MDM2 and MDMX, is a transcription factor that regulates the cell cycle in response to cellular stress leading to DNA damage. Dual action p53/MDM2/MDMX antagonists would provide promising new anticancer treatments. Anchor-based drug design and multicomponent reaction have been used to discovery novel small molecule antagonists of PPI p53/MDM2/MDMX. The SAR of imidazo-indole scaffold (**1** to **3**) was described. Indole-2-carboxylic acid group and amide side chain improve antagonist-MDM2 binding very much. The first reported antagonist (**3**)-MDMX cocrystal and several antagonist-MDM2 cocrystal complexes will be described.

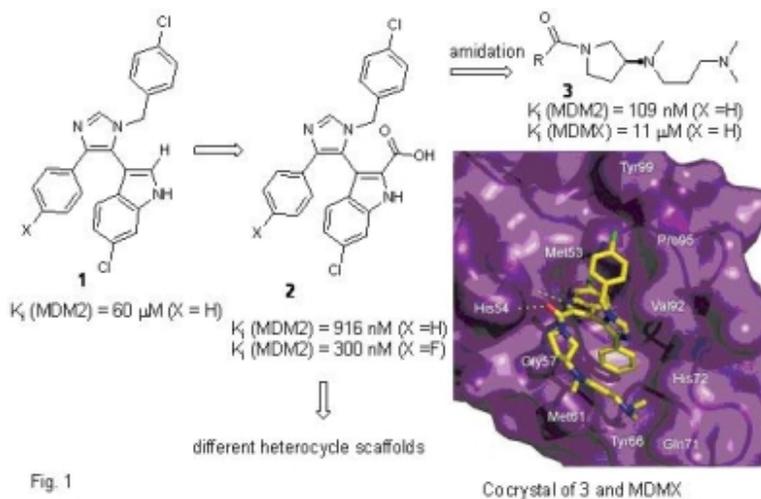


Fig. 1

MEDI 507

Synthesis and evaluation of hadacidin analogs

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Adenylosuccinate synthetase (AdSS) is a key enzyme involved in the de novo biosynthesis of adenosine monophosphate (AMP). Another source of AMP generation is through the salvage pathway which utilizes methylthioadenosine phosphorylase (MTAP). Cells in approximately 25–40% of many common human cancers are deficient of the enzyme MTAP and must follow the de novo route for AMP production. Therefore, developing small molecule inhibitors that tightly bind the active site of AdSS should provide an opportunity for selective cell death in MTAP deficient cancers. Hadacidin (*N*-formyl-*N*-hydroxyglycine) is a known aspartic acid mimic that competitively inhibits adenylosuccinate synthetase. The synthesis of hadacidin analogues and their effects on activity of adenylosuccinate synthetase will be discussed.

MEDI 508

Trypanosomal target of rapamycin: Repurposing of mammalian TOR inhibitors for neglected disease drug discovery

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Human African

trypanosomiasis and leishmaniasis are neglected diseases primarily affecting impoverished nations and are caused by trypanosomatid protozoans. Both diseases are in need of new treatments, but such improvements have been hindered by the high cost of drug discovery and development and the lack of economic incentive to develop new drugs. The repurposing of known pharmaceuticals for treatment of trypanosomal infections can speed up the process of new drug discovery. The trypanosomatids *Trypanosoma brucei* and *Leishmania major* possess multiple target of rapamycin (TOR) enzymes that are essential for cell growth and virulence. The mammalian homolog, mTOR, has been the focus of many industrial drug discovery programs for the treatment of cancer. Thus, there is a rich medicinal chemistry history associated with mTOR with many details regarding optimal chemical matter. These known mTOR inhibitor chemotypes can be repurposed to develop lead compounds for trypanosomiasis and leishmaniasis. Presented herein are the selection and initial screening results of a handful of commercially available mTOR inhibitors against *T. brucei* and *L. major* as well as the design and synthesis of a variety of analogs of two of these mTOR inhibitors, PI-103 and WYE-354.

MEDI 509

Discovery of a fluorescent cyclin-dependant kinase inhibitor with potent antiproliferative activity in human breast cancer cells

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Cancer is the second leading cause of death in the United States. Poor therapeutic outcomes and serious side effects, together with acquired resistance to multiple drugs, are common problems of current cancer therapies. Since the cancer cells have uncontrolled cell growth and cell Cycle Kinase enzymes (CDKs) are important in the control of the cell growth. Several classes of CDK inhibitors including natural and chemically synthesized agents have been reported and several are in clinical trials. Since the majority of CDK inhibitors target ATP binding sites, one of the major problems in developing CDK-based drugs is non-specificity due to strong homologies of CDKs with other kinases. Development of potent, selective and fluorescent CDK inhibitors could provide “trackable” compounds which might be useful for detailed *in vivo* and *in vitro* study of molecular pathways responsible for CDK activation. By taking the advantage of the inherent fluorescent property of a dansyl group, we for the first time synthesized a dansyl ethylenediamine conjugated to a purvalanol B, a known potent purine-based CDK inhibitor. The compounds were studied on human breast cancer cells for effects on CDK isotype activity, cell cycle and proliferation. Finally, the fluorescent capabilities of the analogs were used to detect intracellular distribution in human breast cancer cells.

MEDI 510

Discovery of phenoxy thiophene sulfonamides as new potentiators of Nerve Growth Factor (NGF)-induced neurite outgrowth

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Nerve growth factor (NGF) is a member of a family of proteins called neurotrophins. It is involved in the survival, development and function of neurons in the central and peripheral nervous system and stimulates neurite outgrowth in neuronal cells. NGF has been found to play a neuroprotective role and observations in animal models of neurodegeneration suggests that NGF may potentially be used in the treatment of neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD). Unfortunately, administration of exogenous NGF in human clinical trials failed to demonstrate any therapeutic benefit. This lack of efficacy may have been due to NGF's inability to penetrate the blood-brain barrier or metabolic instability. To overcome these hurdles, we have focused research efforts on developing small organic

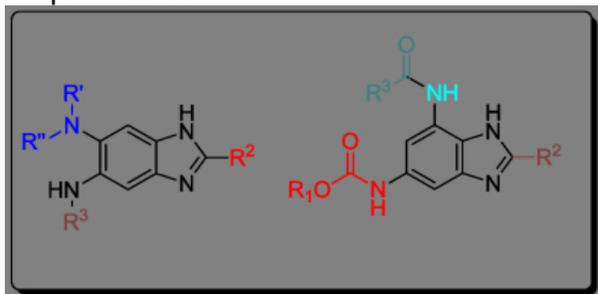
molecules that enhance neurite outgrowth by potentiating NGF dependent activity in neuronal cells. Through chemical library screening, we have discovered phenoxy thiophene sulfonamides which possess the ability to stimulate neurite outgrowths. The synthesis and SAR of these compounds will be discussed.

MEDI 511

Synthesis, SAR and biological evaluation of novel benzimidazoles targeting FtsZ for drug discovery of efficacious antitubercular agents

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FtsZ is a highly conserved and ubiquitous protein that plays an essential role in bacterial cytokinesis. It has been observed that inhibition of FtsZ assembly leads to absence of septum formation, eventually causing cell lethality. Therefore, we hypothesized that FtsZ-inhibitors can be developed into broad-spectrum antibacterial agents possessing novel mechanism of action. A library of novel trisubstituted-benzimidazoles was synthesized through a rational and systematic design. In preliminary screening, a number of these compounds exhibited MIC₉₉ values of ≤ 0.5 $\mu\text{g/mL}$ against *Mtb*. H37RV strain. Selected hits from the *Mtb* screening inhibited *Mtb*-FtsZ assembly in a dose dependent manner while enhancing the GTPase activity by 3-4 folds. SEM images of *Mtb* cells treated with lead compounds showed an absence of septum formation and slight cell elongation. TEM study of *Mtb*-FtsZ treated with lead compounds clearly indicated the remarkable inhibition of *Mtb*-FtsZ nucleation/polymerization. A lead compound was found to be active *in vivo* in the rapid animal model. Synthesis, SAR study, *in vitro* and *in vivo* biological evaluation of novel benzimidazoles will be presented



MEDI 512

De novo purine biosynthesis as a novel antibiotic target

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Arguably, one of the most significant advances in medicine was the discovery of antibiotics. Unfortunately, the rise of antibiotic resistant bacteria has begun to compromise our ability to treat infections and highlight the tremendous need for the development of new antibiotics. One promising, but unexplored area in antimicrobial drug design is *de novo* purine biosynthesis. Recent research has shown that *de novo* purine biosynthesis is different between humans and microbes. The differences are centered on the synthesis of 4-carboxyaminoimidazole ribonucleotide (CAIR). For the synthesis of CAIR, microbes require the enzyme N⁵-carboxyaminoimidazole ribonucleotide (N⁵-CAIR) synthetase whereas humans do not require and have no homologs of this enzyme. To exploit this difference, we have conducted high-throughput screening on 48,000 commercially available compounds. This screen identified 14 compounds with promising activity. Kinetic analysis revealed that isatin derivatives were allosteric inhibitors of the enzyme and these compounds possessed antibacterial activity against Gram negative bacteria. Analysis of the binding site for these isatin derivatives revealed that these agents possess unique and unexpected photochemistry that may be useful in the study of other enzyme systems.

MEDI 513

Imaging of amyloid beta species by using spectral unmixing with a “smart” fluorescence probe

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Differentiation of bound and unbound fluorescence probes in vivo is still an immense challenge. To face this challenge, using spectral unmixing technique with a “smart” fluorescence probe is a very promising approach. Previously, we have demonstrated that a family of curcumin-based fluorescence probes are “smart” probes for amyloid beta (A β) species. These probes' fluorescence properties, which include fluorescence intensity, emission wavelength peak, lifetime and quantum yield, have remarkable changes once they bind to A β species in in vitro solution tests. Here we demonstrated that by using commercial spectral unmixing technique together with our “smart” A β specific fluorescence probe CRANAD-3, we could differentiate bound and unbound probes for in vitro phantom imaging, tissue staining imaging, in vivo transgenic mice imaging and ex vivo imaging. Phantom unmixing imaging indicated that the fluorescence intensity of the unmixed bound signal is tightly correlated with the concentration of A β , but is not correlated with the amount of probe added. Tissue staining with a transgenic APP/PS1 mouse brain slice revealed that bound CRANAD-3 specifically distribute across the cortex region, and unbound CRANAD-3 randomly deposit in the whole tissue. Remarkably, the unmixing results of in vivo imaging with a 24-month old APP/PS1 mouse displayed that the signals of bound CRANAD-3 were consistent for different injection dosages at certain time-points, echoing with the phantom results. In addition, ex vivo unmixing imaging clearly showed that bound probe primarily located in the cortex, while unbound probe presented in blood vessels and across the whole brain. In summary, we believe this method will definitely be a useful tool for more reliable detection and progression monitoring of Ab species in vivo.

MEDI 514

New potential drug against obesity: Design and synthesis of ghrelin receptor antagonists

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A new promising strategy for the treatment of obesity consists in blocking ghrelin signaling. Ghrelin is reported as the only circulating hormone with high orexigenic activity. It is widely involved in the short-term regulation of food intake and the long-term regulation of body weight. The ghrelin receptor, Growth Hormone Secretagogue Receptor 1a (GHS-R1a), represents a hopeful target for the development of new and efficient drugs against obesity.

Our expertise enabled us to develop compound JMV1843 (Solorel™) which is currently in phase 3 clinical trials for the diagnostic of the GH deficiency. We now focus our work on the development of GHS-R1a antagonists based on the 3,4,5-trisubstituted 1,2,4-triazole since the ghrelin orexigenic properties have been brought to light.

This work led to several antagonists with subnanomolar affinities for the GHS-R1a. The promising *in vivo* results concerning compound JMV2959 demonstrate the great potential of this series.

MEDI 515

Inhibitors of protein-amyloid interactions protect cells from β -amyloid-induced oxidative stress and toxicity

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Aggregated forms of Alzheimer's-related β -amyloid (A β) peptides are proposed to interact strongly with intracellular proteins, leading to oxidative stress and toxicity in cells. This talk will describe a new molecular strategy for inhibiting harmful protein-amyloid interactions by generation of protein-resistive molecular surface coatings on aggregated A β peptides. We demonstrate that cytotoxic preparations of aggregated A β peptides results in significant intracellular co-localization of A β with catalase, resulting in increased cellular levels of H₂O₂. Molecular coatings on A β peptides protect the H₂O₂-degrading activity of catalase in A β -rich environments, leading to reduction of the co-localization of catalase and A β in cells, inhibition of A β -induced increases in cellular levels of H₂O₂, and neutralization of the toxicity of A β peptides. These studies provide evidence for the important role of intracellular catalase-amyloid interactions in A β -induced oxidative stress and propose a novel molecular strategy to inhibit such harmful interactions in Alzheimer's disease.

MEDI 516

The estrogen receptor: A locus for the interplay of medicinal chemistry, structural biology, and biomedicine

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We have used X-ray crystallography and molecular modeling to guide the development of novel ligands for the estrogen receptors (ERs): Using modular methods, adaptable to combinatorial approaches, we have prepared estrogens that are highly selective for the ER subtypes, ER α or ER β ; these ligands are useful as pharmacological probes of ER α and ER β biological functions. We have diversified the structure and elemental composition of ER ligands, introducing three-dimensional core elements and replacing a C=C bond with a B-N bond. We have designed estrogen conjugates that selectively activate extranuclear-initiated

ER action and show selective cardiovascular protection. Other ligands have unexpected neuroprotective and antitumor activities. The ER is a key target for breast cancer endocrine therapies that can be very effective, but only in some cases. We have labeled ER ligands with the radionuclide fluorine-18 for positron emission tomographic (PET) imaging ER in tumors, and we have developed a hormone challenge test to image hormone-induced changes in tumor metabolism. These non-invasive PET imaging methods appear effective in selecting breast cancer patients most likely to benefit from endocrine therapy. Thus, the estrogen receptor is a true locus for the interplay of medicinal chemistry, structural biology, and biomedicine.