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J. Zablocki, Program Chair

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MEDI 1

Acyclic nucleoside ProTides: From antiherpetic to broad spectrum antiviral compounds

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Acyclic nucleoside derivatives such as acyclovir, ganciclovir and penciclovir are extensively used in the clinic to treat herpetic infections. To show their antiviral activity, these compounds need to be converted into their triphosphates, and in this form they can act as a DNA chain terminator and/or as an inhibitor of the viral DNA polymerase. As for the majority of the nucleoside analogues, the first phosphorylation to the monophosphate form is the rate-limiting step. However, several technologies have been developed to overcome this issue. In this context, the application of the ProTide approach to acyclovir showed an extension of its activity versus human immunodeficiency virus 1 and 2. The success of this approach for acyclovir, prompted us to apply this technology to other acyclic nucleosides. In this work, the design, synthesis and biological evaluation of a series of acyclic nucleosides and their ProTides will be reported.

MEDI 2

Design and synthesis of potent, orally bioavailable cathepsin K inhibitors displaying whole blood stability

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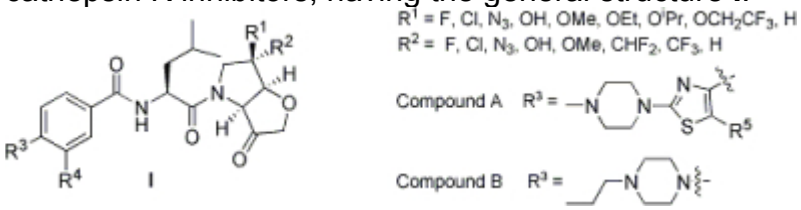
The potent cathepsin K inhibitor MIV-701, **I** (Compound A; R^2 = F; R^4 & R^5 = H) [figure 1], previously developed by Medivir, in phase I studies for osteoporosis demonstrated potent anti-resorptive activities and an excellent safety profile. Unexpectedly however, it was seen that MIV-701, although stable in human blood plasma, was rapidly metabolized to an inactive form in human whole blood. We now report on the development of a follow-on series of novel potent

cathepsin K inhibitors, having the general structure **I**.



On investigation, MIV-701 **I** was found to be stereoselectively reduced to the corresponding alcohol at C3 having exclusively the C-3OH *R* stereochemistry, resulting in an inactive cathepsin K inhibitor. Herein, we disclose our rationale for this stereoselective reduction and successful efforts to address this undesired metabolism by introducing a selection of *R* and *S* substituents at the C-6 position of the bicycle. Ultimately, in this series we identified compounds with no whole blood liability in humans or cynomolgus monkey, possessing excellent overall DMPK properties which ultimately led to the successful discovery of two new Candidate Drugs – MIV-710 and MIV-711 which are now being progressed towards phase I.

MEDI 3

Identification and optimization of a series of indolo[2,3-c]quinoline IRAK4 inhibitors

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Toll-Like receptor signaling is mediated by a serine/threonine kinase known as Interleukin-1 Receptor Associated Kinase-4 (IRAK4). Downstream signaling from IRAK4 results in increased production of TNFα and IFNα which are thought to be important mediators of the pathophysiology of rheumatoid arthritis and lupus, respectively. We will describe the unexpected identification of a series of indolo[3,2-c]quinolines that potently inhibit IRAK4 function. Molecular modeling reveals a binding mode wherein the quinoline nitrogen forms a H-bond with the hinge while a strategically placed nitrile forms a H-bond with the catalytic lysine. The functional activity, kinase selectivity, and physiochemical properties of this series of compounds were optimized resulting in sub-10 nM inhibitors with acceptable PK exposure. Two compounds were advanced into an LPS-induced cytokine mouse model. Biochemical evidence will be presented which strongly suggests that the functional activity is mediated by the inhibition of IRAK4.

MEDI 4

Brain-penetrant microtubule-stabilizing agents as potential treatment for Alzheimer's disease and related disorders

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Neurodegenerative tauopathies, which include Alzheimer's disease (AD), Pick's disease and approximately 50% of all frontotemporal dementias (FTDs), are characterized by the presence of insoluble aggregates comprised of hyperphosphorylated tau proteins. Tau is an endogenous MT-stabilizing agent that is highly expressed in the axons of neurons. The MT-stabilizing function of tau is essential for the axonal transport of proteins, neurotransmitters and other cellular constituents. Under pathological conditions, tau becomes sequestered into insoluble aggregates (*e.g.*, neurofibrillary tangles) and no longer can bind to and stabilize MTs; this phenomenon triggers axonal transport deficits that have deleterious consequences for the affected neurons. As a result, one potential therapeutic strategy for the treatment of AD and related “tauopathies” is to employ small-molecule MT-stabilizing agents that could restore/maintain an effective axonal transport machinery by compensating for the loss of normal tau function. Central to this strategy, however, is the identification of MT-stabilizing agents that could reach effective brain concentrations and doses that would not be systemically toxic. Towards this end, we conducted a comparative pharmacokinetic study involving MT-stabilizing agents from different classes of natural products and identified epothilone D (EpoD) as a potentially viable candidate with promising pharmacokinetics and pharmacodynamics profiles. Treatment of tau transgenic mice (PS19) with weekly doses of EpoD (1 or 3 mg/kg, i.p.) resulted in improved MT-density, axonal integrity and cognition in compound-treated animals, without overt signs of side-effects. These results suggest that brain-penetrant MT-stabilizing agents provide a promising therapeutic strategy for the treatment of AD and FTDs.

MEDI 5

Novel cyano and arylsulfonyl pyridopyrimidines as potent and selective kinase inhibitors

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Protein kinases (PKs) are an important class of intracellular enzymes involved in the regulation of a large variety of biochemical pathways. Rational design of kinase inhibitor cocktails to achieve the reduction of tumor burden has been shown in pre-clinical and clinical trials with a very modest success. In this presentation we will focus on selectivity and potency of kinase targeting by designing novel drug-like chemotypes. As a part of this study, we undertook the synthesis and development of a novel ATP mimetic chemotypes that resulted in identification of biologically activel pyridopyrimidine compounds. Extensive screening of compounds of this series resulted in the identification of ON123300 exhibiting potent cytotoxicity against the entire panel of breast tumor and leukemic cell lines with little or no apparent toxicity to normal, non-neoplastic cells. ON123300 is a potent inhibitor of both CDK4 and Ark5, two kinases intimately associated with growth, survival and metastasis of human tumor cells. This type of dual specificity has not previously been described and could be of value in anticancer therapy for melanoma and breast tumors.

MEDI 6

Discovery and a scalable synthesis of class I PI3K inhibitor CH5132799

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The PI3K pathway regulates various cellular processes, such as proliferation and apoptosis. Therefore PI3K should be a promising therapeutic target for the treatment of cancer. We identified novel PI3K inhibitors using SBDD. In the first lead compound, the importance of the phenolic hydroxyl group in the binding to the enzyme was revealed by structure analysis but the compound was metabolically unstable. We explored a bioisostere of the phenol, and then the 2-aminopyrimidin-5-yl group was identified. Our second lead was metabolically stable and showed antitumor activity *in vivo*. Further chemical modification led us to identify the clinical candidate, CH5132799. CH5132799 inhibited class I PI3Ks, with particular inhibition against PI3Kα. CH5132799 exhibited good oral bioavailability in mouse and monkey. In a human breast cancer (KPL-4) xenograft model in mice, oral treatment with CH5132799 showed tumor

regression. The discovery of the inhibitors, their biological profiles and a scalable synthesis of CH5132799 will be discussed.

MEDI 7

Design & optimization of 2-*N*-arylamino-heterocyclic inhibitors of b-Raf kinase

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The Raf kinases (A-Raf, B-Raf, and C-Raf) are key regulators of cell proliferation and survival that control signaling through the mitogen-activated protein kinase (MAPK) pathway. This pathway is frequently deregulated in cancer by protein mutations, leading to increased cancer cell proliferation and survival. In particular, Ras oncogenes are mutated in 15% of all cancers and the B-Raf oncogene is mutated in 7% of all cancers, including 66% of melanoma, 40% of thyroid cancer, and 12% of colon cancer, making B-Raf an attractive anti-cancer therapeutic target. This presentation will describe the discovery and optimization of two series of b-Raf kinase inhibitors based on 2-*N*-arylaminothiazole and 2-*N*-arylaminopyrazine scaffolds that resulted in the identification of two pre-clinical development candidates that exhibit excellent biochemical and cellular potency, good oral exposure, good selectivity profile vs panels of other kinases and enzyme & receptor targets, and *in vivo* efficacy in a mouse xenograft model of melanoma.

MEDI 8

Molecular probes for cancer imaging

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Molecular imaging has been widely used as a powerful tool in the diagnosis and treatment of cancer. Thus, we have developed a series of novel molecular probes for cancer imaging. In this presentation, we will discuss our recent

progress in imaging of two cancer targets. On one hand, current cancer treatments rely heavily on chemotherapeutic agents to induce cytotoxic DNA damages and programmed cell death in cancer cells. However, the efficacy of DNA-targeted agents such as temozolomide is often compromised by intrinsic cellular responses such as DNA base excision repair (BER). Previous studies have shown that BER pathway results in formation of abasic or apurinic/apyrimidinic (AP) sites and inhibition of AP sites leads to significant reduction of drug resistance and enhancement of drug sensitivity. Thus, AP-site formation has been identified as an important biomarker in DNA-targeted chemotherapies. To date, we have developed positron-emitting [11C]methoxyamine for positron emission tomography (PET) that allows for quantification of AP sites in vivo. On the other hand, the mesenchymal-epithelial transition (MET) receptor plays prominent role in human tumorigenesis, tumor progression and metastasis. Overexpression or mutation of MET results in activation of oncogenic signaling pathways and leads to up-regulation of diverse tumor cell functions. For efficacy evaluation of various MET-targeted anticancer therapies currently under development, it is critical to develop an imaging tool that permits detection and quantification of MET expression in vivo. Here, we report the radiosynthesis and evaluation of a molecular imaging probe, [11C]SU11274, for quantification of MET receptors in human cancers in vivo. These studies demonstrated that [11C]methoxy amine and [11C]SU11274-PET can facilitate efficacy evaluation in the clinical development of cancer therapeutics.

MEDI 9

Novel macropolycyclic compounds highly potent as HCV inhibitors

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Hepatitis C virus (HCV) is a single-stranded positive RNA virus in the Flaviviridae family. The HCV includes a nucleocapsid protein (C), envelope proteins (El and E2), and several non-structural proteins such as NS1, NS2, NS3, NS4a, NS5a, and NS5b. The NS3 protein possesses serine protease activity and is determined essential for viral replication and infectivity. This presentation discloses the discovery and development of novel macrocyclic compounds highly effective for inhibiting HCV replication. Currently, a series of new macrocyclic compounds has been prepared, and several novel macrocyclic compounds have been determined to be very potent in inhibiting the HCV NS3/NS4a proteases (IC_{50} and EC_{50} for NS3/NS4a: 0.1nM-5nM), which is further developed as valuable lead compounds. Moreover, preparation of new macrocyclic building blocks and 15-20 membered macrocyclic compounds have been obtained, and further SAR optimization and preclinical study are ongoing for Zannan to develop some novel potent and non-toxic HCV inhibitors.

MEDI 10

Drug discovery using metabolomics biased fragment screening

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We describe a novel fragment library termed Fragments of Life (FOL) for structure-based drug discovery. The FOL library includes natural small molecules of life, derivatives thereof, and biaryl protein architecture mimetics. The choice of fragments facilitates the interrogation of protein active sites, allosteric binding sites, and protein-protein interaction surfaces for fragment binding. We have screened the FOL library against leukotriene A4 hydrolase (LTA4H) by X-ray crystallography and identified a diverse set of fragments including derivatives of resveratrol, nicotinamide, and indole. These fragments were elaborated in a small number of synthetic cycles into potent inhibitors of LTA4H representing multiple novel chemotypes for modulating leukotriene biosynthesis. Similarly, FOL was used to screen the isoprenoid biosynthesis enzyme IspF from *Burkholderia pseudomallei* as part of the Seattle Structural Genomics Center for Infectious Disease (www.ssgcid.org). Fragments of cytidine and novel zinc-binding fragments were identified and have been linked to form lead-like inhibitors of IspF. Finally, we have used FOL to identify putative regulatory ligands for EAG1, an orphan ion channel receptor involved in cell cycle regulation and tumor progression. Together, these studies validate the FOL library against a diverse set of targets, and demonstrate how the library can be applied to multiple screening technologies including X-ray crystallography, NMR, SPR and *in vitro* enzyme assays.

MEDI 11

Discovery and characterization of novel, orally biovailable CGRP antagonists for the treatment of migraine

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The 37 amino acid neuropeptide Calcitonin gene-related peptide (CGRP) is involved in the pathogenesis of migraine. Proof of concept for the acute treatment of migraine with CGRP-antagonists has been shown in Phase II clinical trials with the intravenously administered, potent CGRP antagonist olcegepant (BIBN4096). Therefore, our research program was focused on the identification of potent, selective and orally active CGRP antagonists. SAR studies based on BIBN4096 led to BIBP5371, an orally active CGRP antagonist with an overall profile suited for clinical development. However, detailed toxicological evaluation of BIBP5371 revealed phospholipidosis findings, thus preventing any further development. Further optimization efforts resulted in the identification of BI44370, a second clinical candidate with an improved safety profile.

MEDI 12

P2X7 antagonists for the treatment of pain

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The P2X family of nucleotide receptors contains nonspecific, ligand-gated cation channels that participate in multiple physiological processes. Peripheral immune cells, including macrophages and epidermal Langerhans cells, express the homomeric receptor subtype $P2X_7$. Microglia and astrocytes express $P2X_{-7}$ in the CNS. Activation of $P2X_7$ by ATP initiates a sequence including ion influx, caspase-1 activation, release of the pro-inflammatory cytokine IL-1b, and p38 MAP kinase activation. Several disease states, including inflammation, neurodegeneration, and neuropathic pain, have been linked to $P2X_7$ receptor activation. Abbott pursued a program to discover small molecule $P2X_7$ antagonists for the treatment of pain. Several series of structurally distinct antagonists were identified, and optimization efforts led to potent compounds that produced analgesic effects in preclinical behavioral pain models. The structure-activity relationship studies, pharmacokinetic properties, and efficacy in the pain models for lead compounds will be presented. In addition, electrophysiology and mechanism-of-action investigations using selected compounds will be described.

MEDI 13

In pursuit of FAAH inhibitors with desirable properties

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A series of inhibitors of fatty acid amide hydrolase (FAAH) is described. SAR trends and *in vivo* data are presented.

MEDI 14

Optimization of selective CB2 receptor agonists

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The discovery and identification of two distinct cannabinoid receptors, CB1 and CB2, has stimulated the interest in the medicinal chemistry and pharmacology of cannabinoids. Specifically, since the CB1 receptor is abundant in the CNS and the central effects of the cannabinoids are related to the CB1 receptor, many research groups have endeavored in an effort to identify CB2 selective compounds which could be beneficial in the treatment of various diseases such as pain and inflammation while avoiding the undesired CB1 mediated central effects. We are particularly interested in the identification of novel CB2 selective compounds as novel immune modulators and analgesics. In this communication we will discuss the lead identification and optimization of the a-amidosulfone class resulting in compounds with attractive pharmacokinetic and pharmacological properties.

MEDI 15

Discovery of P2X3 receptor antagonists for the treatment of chronic pain

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The P2X3 receptor is an ATP-gated ion channel expressed on primary afferent neurons that sense painful stimuli (nociceptors), with limited receptor expression in other tissues. This selective expression pattern makes the P2X3 receptor an attractive analgesic target with the potential to provide a safe treatment of chronic pain states such as occurs in osteoarthritis (OA). Elements of the internal target validation and lead identification efforts that led to the construction of the target

preclinical candidate profile will be presented. The lead optimization strategy and progress versus this target profile will be disclosed.

MEDI 16

Property based analyses of OATP1B1 and OATP1B3 competitive inhibitors

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Organic anion transporter polypeptides (OATP) are critically involved in regulating the uptake of biomolecules throughout the body. Inhibition of these transporters can result in a number of safety concerns relating to the disposition of endogenous compounds and therapeutic agents via drug-drug interactions (DDI). Though of critical importance to drug development, there are fairly limited structure-activity relationships (SAR) for the OATP family reported to date. Due to their selective tissue distribution in the liver, OATP1B1 and OATP1B3 play pivotal roles in the hepatoselective uptake of several marketed agents. Developing a broad based SAR for interaction with these transporters will allow for a predictive approach to circumventing potential DDI with new chemical entities. This paper details our results from screening a diverse chemical library composed of 150,000 compounds against OATP1B1 and OATP1B3. Analyses of property space and pharmacophore requirements for interaction with OATP1B1/OATP1B3 will be discussed.

MEDI 17

Pyrazoloquinoline-5-Ureas as negative modulators of $GABA_A$ α5

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The inhibitory neurotransmitter γ-aminobutyric acid (GABA), is an agonist at the $GABA_A$, $GABA_B$, and $GABA_C$ receptors. The ligand-gated ion channel receptor $GABA_A$ mediates the majority of inhibitory synaptic activity of GABA in the central nervous system. A growing body of evidence indicates that selective negative modulation of the $GABA_A$ α5βγ2/3 receptor stimulates a marked improvement of performance in several animal models of memory function with minimal side effects such as increased anxiety, sedation and convulsion. In an attempt to develop cognitive enhancers with minimal side effects we explored the impact of negative modulation of the $GABA_A$ α5 subtype on memory in a target-based selectivity screening program. Helicon developed several potent pyrazoloquinoline-urea negative modulators in an effort to optimize their pharmacological and physicochemical properties. Select compounds from this series enhanced cognition in rodent models. The synthetic approach and structure activity relationship of this series of novel compounds will be presented.

MEDI 18

Molecular probes for the A_{2A} adenosine receptor based on a pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine scaffold

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Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine derivatives such as SCH 442416 display high affinity and selectivity as antagonists for the human A_{2A} adenosine receptor (AR). We extended ether-linked chain substituents such as fluoropropyl, alkyl esters, carboxylic acid, amines, alkynes, and fluorophore reporter groups at the *p*-position of the phenyl group using optimized *O*-alkylation, amide condensation and click chemistry protocols to generate molecular probes of the A_{2A}AR. In general, these compounds have shown excellent binding affinities and high selectivity at the A_{2A}AR in comparison to the A_1 and A_3ARs. Alexa Fluor-488 conjugated derivative proved to be a useful probe in fluorescence polarization (FP) assays. The fluorescent dye, AlexaFluor 488 is a suitable fluorophore for FP because of its prolonged lifetime of 4.1 ns, which proved to be appropriate in our experiments and in other studies. If the fluorescent lifetime is either too short or too long, a significant FP signal is unattainable. Tetramethylrhodamine and BODIPY 650/665-X conjugated derivatives are designed for fluorescence microscopy experiments to detect A_{2A}AR in transfected or control cells with the advantage of a long wavelength of

emission. An A_{2A}AR selective *O*-(3-fluoropropyl) analogue was designed for use as a PET tracer. Molecular modeling results highlighted the key interactions between the pyrazolotriazolopyrimidine core and the binding pocket of the receptor as well as the distal anchoring of the fluorophore on an AlexaFluor conjugate. *N*-aminoethylacetamide and *N*-[2-(2-aminoethyl)-aminoethyl]acetamide derivatives were conjugated to the polyamidoamine G3.5 dendrimer by amide coupling. In conclusion, we have synthesized high affinity functionalized congeners for studying the A_{2A}AR.

MEDI 19

Investigating the prevalence of queuine in *Escherichia coli* RNA via incorporation of tritium labeled precursor, preQ$_1$

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Queuine is a modified nucleotide known to occur in the anticodon of four tRNAs. Prior *in vitro* work demonstrated that the modification can be incorporated into RNA species other than presently known tRNAs. Queuine is unusual in that, unlike the majority of modified nucleotides that result from changes to genetically encoded bases, it is incorporated into RNA by transglycosylation. Due to this method of incorporation the modification can be studied with small molecule probes. PreQ$_1$, the precursor to queuine incorporated by eubacteria, was tritium-labeled to investigate the prevalence of base modification in *E. coli.* Three cell lines were utilized to conduct the *in vivo* experiments of this study: a *ΔqueC* knockout of *E. coli* that is unable to synthesize preQ$_1$ so that tritium labeled compound will be incorporated exclusively, a Δ*tgt* knockout strain of *E. coli* that is unable to incorporate preQ$_1$ and a wild-type *E. coli* strain. We will report on the prevalence of queuine ascertained from the degree of radiolabel incorporation as well as an estimation of the size ranges and types of RNA affected.

MEDI 20

Optimization and biophysical characterization of small molecules that inhibit influenza virus replication via binding to nucleoprotein (NP)

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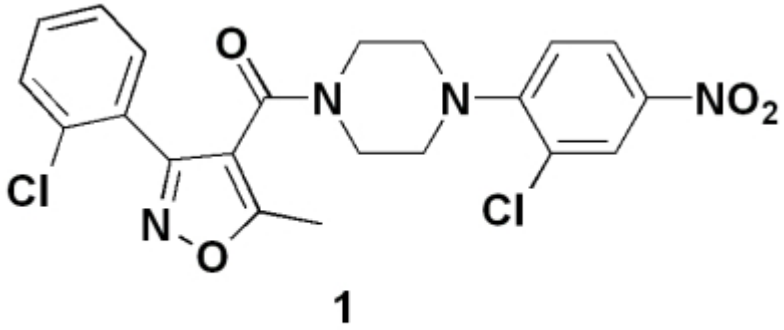
Worldwide seasonal influenza epidemics are responsible for 250,000-500,000 deaths per year, yet the therapeutic options (i.e. vaccines, neuraminidase inhibitors, M1 channel blockers) have remained static for over a decade, even in the face of mounting viral resistance. New antiviral targets are clearly needed. In a parallel effort to that described by Kao et al. (*Nature Biotechnology* **2010**, *28*, 600-605), we identified compound **1** as a promising lead with potent antiviral activity against the A/H1N1/WSN/33 strain of influenza. Resistance mapping implicated nucleoprotein (NP) as the viral target for this chemotype, and site-directed mutagenesis experiments provided additional information about the putative ligand binding site(s). In this presentation, we report the optimization of **1** to afford analogs with improved aqueous solubility and metabolic stability, which facilitated the detailed biophysical characterization of the NP:ligand complex and confirmation of antiviral activity in a mouse model of influenza.



1

A/H1N1/WSN/33 EC_{50} = 60 nM

MEDI 21

Molecular properties and drug attrition: Are we responding to the challenge?

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Acidic, basic and neutral compounds from large pharmaceutical company patents published during 2000-9 were compared with oral drugs launched worldwide. These compound groups occupy distinctly different molecular weight, lipophilicity, and aromatic/aliphatic chemical space. 'Molecular inflation,' and concomitant increased ADMET risk, is occurring in most target classes in patent compounds versus oral drugs and is largely caused by increases in lipophilicity and aromaticity. Independently of lipophilicity, molecular weight or ion class, oral drugs have lower aromatic - aliphatic atom differences than patent compounds. A

target-unbiased analysis of the patents in the major target classes from ten pharmaceutical companies was performed by pairwise comparisons of the molecular properties of compounds in all specific targets shared between the companies. The results show that corporate strategy plays a dominant role in determining relative patent molecular properties. Medicinal design practice and behaviour can therefore help alleviate the current disastrously high pipeline attrition rates.

MEDI 22

Discovery of a highly potent and selective imidazolone-based glucagon receptor antagonist

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Glucagon is a 29 amino acid peptide hormone liberated in alpha cells of pancreatic islets. The main physiological role of glucagon is to stimulate hepatic glucose production by activating glycogenolysis and gluconeogenesis. The effects of glucagon are mediated through the glucagon receptor, a seven-transmembrane G-protein-coupled receptor, with a large *N*-terminus that is required for endogenous agonist binding. Stimulation of the receptor leads to increased cyclic adenosine monophosphate (cAMP) production in tissues including liver and kidney. Antagonizing the glucagon receptor is expected to result in reduced hepatic glucose overproduction, leading to overall glycemic control. In this regard, development of structural and functional glucagon receptor antagonists represents a potential approach to decrease hepatic glucose production and lower blood glucose in patients with Type 2 diabetes. We will describe the discovery of a highly potent and selective glucagon receptor antagonist.

MEDI 23

Identification of a potent NHE1 inhibitor with a suitable profile for chronic dosing and demonstrated cardioprotective effects in a preclinical model of myocardial infarction in the rat

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The central role of NHE1 in myocardial pH regulation has prompted considerable interest in the development of NHE1 inhibitors for the treatment of ischemia-reperfusion injury. Recent emergence of data to support a role for NHE1 inhibition in heart failure led to our interest in pursuing an NHE1 inhibitor as a treatment for chronic heart failure. This report outlines our efforts to identify a NHE1 inhibitor suitable for once daily oral administration with minimal potential for drug-drug interactions. Our discovery efforts initiated from sabiporide, beginning with a change to the basic scaffold structure to move outside of the previously explored chemical space. Subsequent optimization focused on improvements in potency, reduction of DDI potential as measured by CYP inhibition, and improvements in pharmacokinetics. These efforts resulted in the successful identification of a compound that displays high potency, very low CYP inhibition, and improved pharmacokinetics. The pharmacological evaluation of this compound in an isolated heart model of ischemia reperfusion injury (Langendorff isolated heart preparation) revealed the ability to potently prevent ischemic damage.

MEDI 24

Application of parallel medicinal chemistry methods for the rapid and efficient optimization of Hits-to-Leads-to-Clinical Candidates

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The job of the medicinal chemist is to prepare novel compounds that have the appropriate properties to advance into clinical trials and test the desired mechanism of action in human subjects. This talk will describe the application of a number of contemporary design and chemical synthesis strategies utilizing concurrent parallel (library) chemistry and physicochemical optimization to efficiently identify compounds that have successfully completed toxicology studies and have entered clinical trials. Case studies leading to the discovery of a glycine-type 1 transport inhibitor, a phosphodiesterase 9 inhibitor, and a Janus kinase 1/3 inhibitor will be presented.

MEDI 25

Discovery of AMG 369, a potent and selective thiazolo[5,4-b]pyridine agonist of sphingosine-1-phosphate receptors 1 and 5 ($S1P_1$ and $S1P_5$)

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Sphingosine-1-phosphate type 1 ($S1P_1$) receptor agonists with limited activity at the related $S1P_3$ receptor represent potential treatments of inflammatory and autoimmune conditions with reduced side effects relative to first generation pan-S1P receptor agonists. Our initial research in this area in collaboration with Epix Pharmaceuticals focused on a benzofuranyl series of $S1P_1$ agonists with limited activity at $S1P_3$. This series was characterized by calculated physicochemical properties (CLogP~4.5, tPSA~50 $Å^2$) associated with attrition in preclinical toxicology studies, and an effort to identify candidates residing in more favorable physicochemical property space (CLogP<3, tPSA>75 $Å^2$) was undertaken. This effort led to the identification of 1-(3-fluoro-4-(5-(1-phenylcyclopropyl)thiazolo-[5,4-b]pyridin-2-yl)benzyl)azetidine-3-carboxylic acid (AMG 369; CLogP=3.2, tPSA=65 $Å^2$), a potent dual $S1P_1$/$S1P_5$ agonist with limited activity at $S1P_3$ and no measurable activity at $S1P_2$/$S1P_4$. The challenge of optimizing both ligand physicochemical properties and potency for a lipid GPCR target will be discussed.

MEDI 26

Explanation for structure-genotoxicity relationships of heteroaromatic amines revealed by theoretical studies of oxygenation pathways in CYP1A2

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Activation of most carcinogenic aromatic amines starts with N-hydroxylation by CYP1A2. Poor understanding of structure-genotoxicity relationships of heteroaromatic amines limit their use as building blocks in drug discovery programs. In this report, the structure-based understanding of structure-genotoxicity relationships of heteroaromatic amines is attained by exploring oxidative pathways of aromatic substrates in CYP1A2 using DFT calculations at the UM06-2X/TZP level. The active oxygen of Compound I, the postulated oxidant of P450s, is unsuitably positioned with respect to bound substrates in CYP1A2 to explain the observed metabolism. Assuming Compound II with the H-bonded OH radical as the oxidant in CYP1A2, we readily explained experimental facts, including the central role of residues L382 and T321 in substrate specificity and enzymatic activity in the Cyp1 family, the sites of aromatic and benzylic

hydroxylation, N-oxygenation and epoxidation, and structure-genotoxicity relationships of heteroaromatic amines. The substrate activation event is suggested to represent one-electron oxidation of aromatic ligands by the OH radical from two principal positions. One is preorganized for hydrogen abstraction from the ligand edge, i.e. for abstraction of aromatic, benzylic, aromatic amine hydrogens or hydrogens of protonated heteroatoms. Another targets the ligand face to form radical adducts. Concomitant hydrogen abstraction by the Compound II ferryl oxygen leads to metabolized final products. Particular spin localization in anion-radicals of nongenotoxic heteroaromatic amines facilitates OH radical addition to the alpha-carbon, which overtakes N-hydroxylation. Nongenotoxic heteroaromatic amines can be designed by properly positioning the formal p-orbital electron pair in the heteroaromatic system or by engineering geometric incompatibility with CYP1A2.

MEDI 27

Discovery, development and biological validation of boronic acid-based inhibitors of autotaxin

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Autotaxin (ATX) is an extracellular enzyme that hydrolyzes lysophosphatidylcholine (LPC) to produce the lipid mediator lysophosphatidic acid (LPA). The ATX-LPA signaling axis has been implicated in diverse physiological and pathological processes, including vascular development, inflammation, fibrotic disease and tumor progression. By screening a chemical library, we have identified thiazolidinediones that selectively inhibit ATX-mediated LPA production. Inhibitor potency was a 100-fold increased (IC_{50} ~30 nM) after the incorporation of a boronic acid moiety, designed to target the active-site threonine (T210) in ATX (Albers, *J.Med.Chem.*, 2010). Intravenous injection of this inhibitor into mice resulted in a surprisingly rapid decrease in plasma LPA levels demonstrating that ATX can be targeted by small molecule inhibitors *in vivo* (Albers, *PNAS*, 2010). Thus, boronic acid-based small molecules hold promise as candidate drugs to target ATX.

MEDI 28

Discovery and characterization of CEP-26401: A potent, selective histamine H_3 receptor inverse agonist

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H_3Rs are expressed predominantly on the presynaptic terminals of CNS neurons and function as autoreceptors to modulate histamine (HIS) release, and as inhibitory heteroreceptors, regulating the release of key neurotransmitters including acetylcholine (ACh), dopamine (DA), norepinephrine (NE) and serotonin (5-HT) that are involved in attention, vigilance and cognition. Thus, H_3 antagonists may have potential utility in addressing a variety of CNS disorders, including deficits in wakefulness, attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, and schizophrenia. Optimization of a novel series of pyridazin-3-one H_3R antagonists/ inverse agonists identified CEP-26401 as a lead candidate for potential use in the treatment of attentional and cognitive disorders. Presented will be the SAR, and preclinical pharmacological, pharmaceutical and safety profiles that aided in advancing CEP-26401 into clinical development.

MEDI 29

Discovery of BMS-663068, an HIV attachment inhibitor for the treatment of HIV-1

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Despite the effectiveness of combination antiretroviral therapy, there is an expanding population of HIV infected patients on existing therapies whose medical needs are not completely satisfied. Members of a previously disclosed class of oral, small molecule HIV-1 attachment inhibitors (AIs) have been shown to bind to the HIV-1 viral envelope gp120 protein and interfere with attachment to cellular CD4 receptors, the initial point of entry for the virus. Clinical studies with BMS-488043 previously validated the AIs as a novel class of small molecules with potent activity in HIV-1-infected subjects. This presentation will describe the further chemical optimization of BMS-488043 to realize compounds with an improved pre-clinical virology profile. One such compound, BMS-626529, and its water soluble phosponoxymethyl prodrug, BMS-663068, were advanced into early clinical studies. The promising clinical efficacy of the prodrug, which was enhanced by further refinements made in development, will also be discussed.

MEDI 30

Discovery and development of LX1031, a novel serotonin synthesis inhibitor for the treatment of irritable bowel syndrome

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The serotonergic axis is an important regulator of GI motility and nociception. The novel orally-active Serotonin Synthesis Inhibitor LX1031, acts locally in the GI tract to inhibit tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of serotonin. We will present the discovery and development of LX1031 for the treatment of irritable bowel syndrome and will show the utility of biomarkers observed in the KO mouse to guide the Phase 1 and Phase 2 clinical development program.

MEDI 31

Discovery of MK-0893: A glucagon receptor antagonist for the treatment of type II diabetes

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Blood glucose levels are maintained by the balance of glucose production in the liver and glucose uptake in peripheral tissues. An inappropriately high rate of hepatic glucose production (HGP) is the predominant cause of fasting hyperglycemia and a major contributor to the postprandial hyperglycemia characteristic of type 2 diabetes (T2DM). The glucagon receptor is predominantly located in the liver and upon activation stimulates hepatic glycogenolysis and gluconeogenesis. Studies in T2DM patients have demonstrated a causal role for

glucagon in promoting excessive HGP. Glucagon receptor antagonists (GRAs) therefore have the potential to reduce HGP and be effective antidiabetic agents. This presentation will describe the discovery of MK-0893, a novel GRA which has undergone extensive clinical evaluation for the treatment of T2DM.

MEDI 32

Discovery of ELND006: A selective γ-secretase inhibitor

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Alzheimer's Disease is a form of senile dementia, characterized by a progressive loss of memory and cognitive ability. The pathology of this neurodegenerative disease manifests itself with the presence of extraneuronal aggregation of plaques composed of β-amyloid peptides (Aβ). Aβ-peptides are derived from the sequential proteolytic cleavage of the β-amyloid precursor protein by two aspartic acid proteases, referred to as β- and γ-secretase, respectively. Inhibitors of either protease offer attractive candidates as disease-modifying treatments for people afflicted with this debilitating malady. Between these two proteases, γ-secretase has proven to be the more tractable target. But γ-secretase processes a myriad of substrates, such as Notch, giving rise to concerns of mechanism-based side-effects. Thus, a chronically administered γ-secretase inhibitor (GSI) must be selective. Our research produced ELND006, a potent (IC_{50}=340 pM) and selective GSI (16-fold and 74-fold in an enzymatic and a cellular assay, respectively), that reduces Aβ in preclinical animal models.

MEDI 33

Structure based design of cyclic sulfoxide hydroxyethylamine BACE1 inhibitors

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia. Although the ethiology of AD is heterogeneous,

strong evidence indicates that aggregation of the β-amyloid peptide (Aβ) in brain plays a central role in AD pathogenesis. It is believed that therapeutic agents lowering Aβ will be beneficial for the treatment of AD. Aβ is produced from membrane-bound β-amyloid precursor protein (APP) by sequential proteolytic cleavage by β-secretase (BACE1) and γ-secretase. Therefore, BACE1 is an attractive therapeutic target for AD . A structure-based design approach and the synthesis of novel cyclic sulfoxide hydroxyethylamine BACE inhibitors that penetrate the CNS and acutely lower brain Aβ levels in APP transgenic mice will be disclosed.

MEDI 34

Prevention of the amyloid cascade in Alzheimer's: Synthesis of homotaurine analogs

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In Alzheimer's disease, when the Amyloid Precursor Protein (APP) is digested, water insoluble amino acid fragments Aβ1-40 and Aβ1-42 are produced. The manufacturing and accumulation of these fragments leads to the formation of amyloid-β fibrils and ultimately to amyloid plaque. Inhibition of plaque formation via the suppression of β-secretase is one area of research. We however are exploring whether a compound will instead bind to Aβ1-40 and Aβ1-42, allowing it to remain water soluble, thus promoting further digestion. Simple homotaurine has been shown to bind to Aβ1-40 and Aβ1-42 and has a very good bioavailability (>40%). However, any derivatives that have been synthesized with increased binding affinity are incapable of crossing the blood brain barrier (BBB). Our research focuses on the synthesis of homotaurine derivatives that will hopefully exhibit a high binding affinity as well as a logP values efficient enough to facilitate the crossing of the BBB.

MEDI 35

Discovery and structure activity relationship of small molecule inhibitors of toxic Abeta1-42 oligomerization

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. It has been hypothesized that progressive deposition of beta-amyloid peptides (Abeta) in the brain is a key pathogenic mechanism of the disease. Therefore, inhibition of Abeta accumulation has emerged as an attractive means of therapeutic intervention. To investigate if small molecules can modulate the formation of neurotoxic amyloid oligomers, we have employed 3-aminopyrazole as key fragment. In this poster, we present SAR data on linker optimization and different substitution patterns of the pyrazole moiety. We will present data from *in vitro* tests including Thioflavin-T-screening assay (ThT), Fluroscence-Correlation-Spectroscopy (FCS) measurements, and *in vitro* Abeta cell toxicity studies.

MEDI 36

Novel iminopyrimidinone β-secretase (BACE) inhibitors: P1-thiophenes

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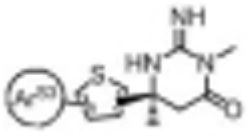
Inhibition of the membrane bound β-Secretase (BACE1) enzyme is a potential therapeutic target for the treatment of Alzheimer's disease. A structure based design approach has lead to the identification of potent inhibitors of BACE1 with an iminopyrimidione core possessing high potencies and good *in vivo* efficacies. The SAR and synthesis of a series of inhibitors based on P1-thiophenes will be disclosed.



MEDI 37

Synthesis and SAR study of tricyclic sulfone as gamma-secretase inhibitors

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Since it was first described more than 100 years ago by German psychiatrist and neuropathologist Alois Alzheimer, Alzheimer's disease (AD) has become the most common form of neurodegenerative disease. It is characterized by cognitive and memory deterioration, impairment of language, and a decline in the ability to perform daily activities of living. It is estimated that about 5 million Americans currently suffer from this disease, and an additional 360,000 people are newly diagnosed every year. Due to its enormous burden on patients and the healthcare system, research on the treatment of AD has drawn tremendous attention from both academia and industry. One of the major hypotheses for the progression of AD is a chronic imbalance between β-amyloid peptide (Aβ) production and clearance which results in the extracellular accumulation of Aβ in the brain. Subsequent Ab plaque formation leads to neurodegeneration, dementia, and ultimately death. The formation of Aβ is the result of sequential cleavage of β-amyloid precursor protein (APP) by two proteases, β-secretase (BACE) and γ-secretase. Thus both b- and γ-secretase are proposed as effective targets for treatment of AD because of their central role in the production of Aβ peptide. To date, many series of secretase inhibitors have been reported from different pharmaceutical companies. Recently, we have identified a series of tricyclic sulfones as orally active γ-secretase inhibitors. In this presentation a detailed SAR study focused on C-7 of a hexahydrobenzo[c]chromene core will be reported.

MEDI 38

Design and synthesis of small molecule antibacterials: Targeting the bacterial fatty acid biosynthesis pathway

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The fatty acid biosynthesis (FASII) pathway in *Mycobacterium tuberculosis* is responsible for the synthesis of mycolic acids that are implicated in bacterial survival and persistence. Consequently, enzymes within the pathway are

promising targets for intervention. Our drug discovery efforts are focused on developing inhibitors with long residence times on their targets, a property that is known to be crucial for *in vivo* efficacy. We have developed a wide range of diaryl ethers that target the FASII the enoyl-ACP reductase InhA and that have promising kinetic and thermodynamic parameters, and also that have activity in an animal model of infection. We are also developing slow onset inhibitors of the FASII β-ketoacyl-ACP synthase KasA using fragment based design driven by X-ray crystallography and inter-ligand NOE NMR spectroscopy. These inhibitors are based off Thiolactomycin, a natural product antibiotic, as a lead molecule and involve elaboration around its thialactone core.

MEDI 39

WITHDRAWN

MEDI 40

Synthesis of callophycin A analogs and evaluation as potential chemopreventive and anticancer agents

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Both natural and synthetic tetrahydro-β-carbolines have attracted considerable attention due to their broad spectrum of biological actions, such as insecticidal, antidepressant, antiviral, anticancer, and antimalaria activities. One such compound, callophycin A, was originally isolated from the red algae *Callophycus oppositifolius* and shown to mediate anticancer and cytotoxic effects. In our collaborative effort to identify potential chemopreventive and anticancer agents with enhanced potency and selectivity, we employed callophycin A as a tetrahydro-β-carboline-based template for production of a chemical library. Utilizing a parallel synthetic approach, a focused compound library of various functionalized tetrahydro-β-carboline derivatives was prepared and assessed for activities related to cancer chemoprevention or cancer treatment: inhibition of tumor necrosis factor (TNF)-α-induced NFκB activity, aromatase, nitric oxide (NO) production, and induction of quinone reductase 1 (QR1). Divergent activities were observed depending on different substitution patterns associated with the tetrahydro-β-carboline scaffold. Synthesis and structure-activity relationships of callophycin A analogues will be presented. (Supported by P01 CA48112 awarded by the NCI and INBRE program P20 RR016467 awarded by NCRR).

MEDI 41

Structure-activity relationships in NOD1-agonistic glutamyl-diaminopimelate derivatives

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Members of the NLR family of intracellular pathogen associated receptors play an important role in recognizing pathogens, and trigger NF-kappa-B-mediated proinflammatory cytokine release. Although it is recognized that *N*-acylglutamyldiaminopimelic acid (typified by the commercially available C12-iE-DAP) is a ligand for NOD1 (nucleotide-binding and oligomerization domain 1), detailed structure-activity relationships of this chemotype have remained unexplored. We report a detailed SAR of C_{12}-D-Glu-DAP. Analogues with glutaric or γ-aminobutyric acid replacing the glutamic acid show greatly attenuated NOD1-agonistic activity. Substitution of the diaminopimelic (DAP) acid part of the molecule with monoaminopimelic acid, L- or D-lysine, or cadaverine also results in reduced activity. The free amine on DAP is crucial, and *N*-acyl,*N*-alkyl, guanidino, or otherwise modified analogues show complete loss of activity. However, the *N*-acyl group on the D-glutamyl residue can be substituted with *N*-alkyl groups with full preservation of activity. The free carboxylates on the DAP and Glu components can also be esterified, resulting in more lipophilic, but active analogues. These results are likely to be of value in designing vaccine adjuvants.

MEDI 42

YK5 is a novel dual Hsc/Hsp70 inhibitor that is selective for tumor Hsp70 and is a valuable lead for the development of molecules with therapeutic potential in breast cancer

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Breast cancer is a complex disease encompassing a number of distinct biological entities. Therapies that target a single activating molecule cannot overpower the multitude of aberrant cellular processes and may be of limited therapeutic benefit in metastatic disease. To overcome these limitations, we have designed a class of small molecule Hsp70 inhibitors that act selectively on tumor-specific Hsp70 complexes. Pharmacologic Hsp70 modulation by a representative molecule, YK5, disrupts the formation of Hsp70/oncoprotein complexes, leading to proteasomal degradation of several breast cancer driving proteins, but not of nononcogenic proteins and potently inhibits the growth of a large panel of breast cancer cells. Due to powerful anti-apoptotic roles played by Hsp70, its pharmacologic inhibition by YK5 results in prominent, but yet selective cytotoxicity against cancer cells, mainly through an apoptotic mechanism. Because of its biological activity in breast cancer cells and its selective targeting of cancer-specific Hsp70, YK5 represents a novel lead targeted agent with therapeutic potential in breast cancer.

MEDI 43

Functional adenosine A_{2A} receptor antagonists as potential therapeutics for the treatment of hypoxic tumors

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Istradefylline (KW-6002) is one of many xanthines that act as antagonists of the A_{2A} adenosine receptor. While this molecule has recently been involved in phase III clinical trials as a target therapeutic for Parkinson's disease, its' target pathway also implicated in tumorigenesis. Our current interest is in developing prodrugs of KW-6002 that retain selectivity or the A_{2A} receptor, but achieve decreased blood-brain barrier permeability, as potential therapeutics for hypoxic tumors. Specific prodrugs of KW-6002 have the capability of not only targeting hypoxic tumors, but also combating existing issues of aqueous solubility and lipophilicity. Utilizing molecular modeling, functional derivatives have been designed and developed, including polyethylene gycol (PEG) and nanoparticle conjugates. Synthetic methodology and preliminary bioanalysis will be presented.

MEDI 44

New inhibitors of Rac1 in metastatic breast cancer

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The objective is to develop new compounds derivatives of NSC23766 as Rac1 inhibitors to reduce and prevent breast cancer metastasis. The compounds were synthesized via nucleophilic aromatic substitution connecting a hetero-bicyclic arylamino group to the 4-position of the pyrimidine core and a primary or secondary aliphatic amine, with a tail-ended amino group, to the 2-position of the pyrimidine group. The cell viability and cell migration were examined for Rac inhibitors using MTT-survival and proliferation kit and Transwell migration assays, respectively. Several of the NSC23766 derivatives were shown to inhibit Rac1 activity of cancer cells with higher efficiency than NSC23766. The new compounds are not toxic to normal mammary epithelial cells and are more efficient than NSC23766 in inhibiting cell migration and reducing cell spreading and extension of lamellipodia. Based on the results, the new compounds show promise of further development as small molecule inhibitors of invasive breast cancer progression.

MEDI 45

Design, synthesis and evaluation of 4,5-dioxo-1,4,5,6-tetrahydropyrimido[4,5-*c*]pyridazines as dihydropteroate synthase inhibitors

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Dihydropteroate synthase (DHPS) has been a validated drug target for antimicrobial therapy. DHPS is the target enzyme of the sulfonamide class of antimicrobial agents. The sulfonamides have been used as synthetic antibiotics for over 60 years to treat a wide variety of Gram-positive and Gram-negative infections. However, bacterial resistance and undesirable side effects have limited the clinical usefulness of these antibiotics. Thus, there is an urgent need for novel antibacterial agents for treating infections caused by resistant organisms. The pterin binding pocket in DHPS has a high degree of conservation and there is no mutation reported in this site, thus it is an attractive alternative target for the design of novel antibacterial agents. We designed and synthesized a series of 4,5-dioxo-1,4,5,6-tetrahydropyrimido[4,5-*c*]pyridazines as DHPS inhibitors. Some of these compounds showed more than 50% of enzyme inhibition at 250 μM and had IC_{50} in micromolar range. The design, synthesis,

enzyme inhibition activities and molecule modeling of these 4,5-dioxo-1,4,5,6-tetrahydropyrimido[4,5-*c*]pyridazines will be presented and discussed.

MEDI 46

Target identification and SAR of the Nampt inhibitor CB30865

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Drug discovery based on cellular phenotypes is impeded by the lack of knowledge concerning the molecular target responsible for that phenotype. To address this shortcoming, Myrexis has developed a chemical proteomics technology to identify cellular proteins that bind to biologically active small molecules. CB30865 was shown to be a compound with potent tumoricidal activity, but with unknown mechanism of action. Using our technology, we have demonstrated that the tumoricidal activity of CB30865 is due to inhibition of nicotinamide phosphoribosyltransferase (Nampt). With its cellular target known, we sought to optimize both the biochemical and cellular activities of CB30865. It was determined that the 3-pyridylmethyl amide was critical for tumoricidal potency. Small, unsaturated groups attached to the analinic nitrogen were optimal, with 3,3-dimethylallyl yielding the greatest potency. Also, the distal region required a quinazolin-4-one or 1,2,3-benzotriazin-4-one group for optimal activity.

MEDI 47

Zinc phthalocyanine nanowire sensitizer for dual photodynamic and photothermal cancer therapy

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Both photodynamic therapy (PDT) and photothermal therapy (PTT) are emerging therapeutic methods in management of cancer disease. These kinds of phototherapies are generally accomplished by employing combination of sensitizer and light. When appropriate light is exposed to sensitizer, significant amount of heat and reactive oxygen species (ROS) are generated to induced cancer cell death. These therapeutic techniques are currently accepted for

clinical usages for several types of cancer due to their minimal side effects, noninvasive manner and high selectivity depending on the wavelength of light. Zinc phthalocyanine (ZnPc) is one of the potential sensitizer candidates since it has a strong absorption cross-section in the spectral range (600-800 nm) that guarantees maximum tissue penetration. One of the critical issue of using ZnPc as a biocompatible sensitizer is that ZnPc easily aggregates in aqueous solution, unless specially functionalzed, due to its strong hydrophobic nature. To overcome this problem and improve cell-penetrating efficiency, we have synthesized ZnPc nanowires by vapor-condensation-recrystallization (VCR) process. The ZnPc nanowire is readily dispersed in aqueous media, and its solution is quite stable for a long time. For the application of PDT and PTT of ZnPc nanowire, the double phototherapeutic effect has been confirmed through both in vitro and in vivo experiments. The results show strong photodynamic and photothermal effect to enhance cytotoxic efficiency comparable to zinc phthalocyanine tetrasulfonate ($ZnPcS_4$) which is one of the promising sensitizers for phototherapy.

MEDI 48

Size extended pyrimidine nucleosides: Probing DNA polymerases

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Modified nucleosides have been mainstay of antiviral and anticancer drug design, as well as to investigate DNA. In an effort to understand DNA structure and function we have introduced structural modification to nucleosides by incorporating a heterocyclic spacer ring into the purine and pyrimidine scaffold. The size expansion and extension to the natural nucleosides results in an increased aromatic surface area enabling better hydrophobic interactions while keeping the hydrogen bonding elements intact. These structural modifications render them interesting candidates to probe polymerase fidelity. Their synthesis and preliminary biological results is reported.

MEDI 49

Design and synthesis of boron-containing alpha-aminonitriles as potential Hepatocyte Growth Factor (HGF) mimetics

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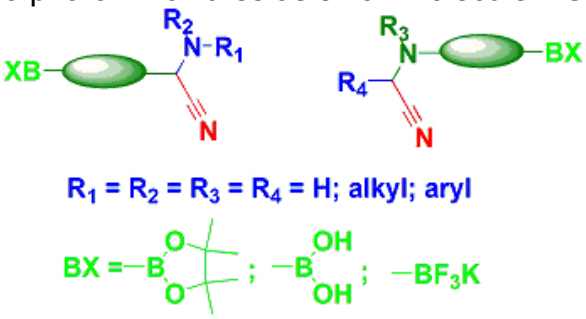
Hepatocyte growth factor (HGF) is a critical factor in the two most common liver pathologies, hepatitis and cirrhosis. Exogenous supplementation of HGF has been shown to attenuate disease progression not only in the liver but also in animal models of renal and pulmonary fibrosis. Thus, identifying the most effective strategies to administer its biological effects in injured tissues is of high priority. Previous approaches to HGF-therapies were focused on peptides and antibodies that are unstable and costly to produce. We utilized a Limited Rational Design Approach (LRD) and computational modeling to design boron-containing alpha-aminonitrles as small molecule HGF mimetics.



They were synthesized via a three-component condensation of the boron-containing aldehyde and/or amine and TMSCN (trimethylsilyl cyanide) in the presence of a catalytic amount of indium (III) chloride in water. The biological activity of compounds is being evaluated in established cell culture based assays for HGF-activity.

MEDI 50

Design and synthesis of novel retinoids containing oxadiazole

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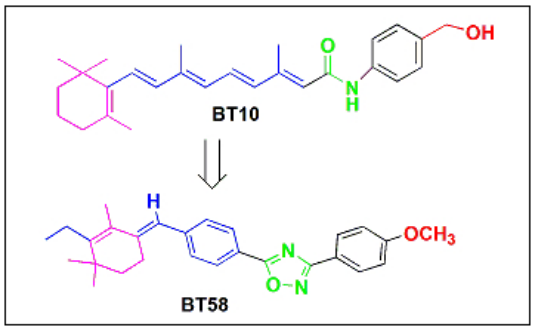
In the context of our ongoing chemical biology project, studying the role of retinoic acid signaling pathways during zebrafish embryogenesis, we synthesized novel retinoid libraries and screened for bioactivity. We found one compound

BT10 

that is a retinoid receptor agonist and produces specific cardiovascular defects when added to zebrafish embryos 1 day post fertilization. This lead compound was further derivatized by using SAR and LRD to incorporate oxadiazole. Compound BT58 was designed and synthesized as a new retinoic acid analogue by introducing a constrained phenyl ring system in the place of a conjugated alkene backbone (spacers in all-trans retinoic acid, ATRA) to suppress the metabolism of ATRA into its isomers, 9-cis-RA and 13-cis-RA. The methyl alcohol group was further derivatized to a methoxy group and the amide group replaced by an amide isostere group like oxadiazole to potentially increase efficacy and potency. New oxadiazole-containing retinoids were synthesized by reacting acid and amidoxime in DMF using EDCI as a coupling reagent

MEDI 51

Development and evaluation of a predictive quantitative structure-activity-relationship (QSAR) model for the TAB generation of isoprenylcysteine carboxylmethyl transferase (Icmt) inhibitors

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Icmt is the last downstream enzyme to perform post-translational modifications on Ras. Mutant Ras is implicated in 30% of all cancers and greater than 90% of all pancreatic cancers. Inactivating Icmt causes Ras to mislocalize and blocks it from signaling. Icmt is an enzyme that is embedded in the ER. There is no experimental or calculated structure for Icmt. In the absence of structural information, we have adopted a substrate-based approach and have synthesized a library of compounds that are nanomolar inhibitors of Icmt. To understand the inhibition requirements of this class of compounds, we have initiated a QSAR effort. Initial development of the QSAR model (using Raptor) has provided us with a predictive model with a R^2 of 0.83 and a predictive R^2 of 0.72. Efforts are

ongoing to evaluate the predictive power of the QSAR model by synthesizing analogs predicted by the model and evaluating them against Icmt.

MEDI 52

Novel vinylpiperidine derivatives as sodium channel blockers

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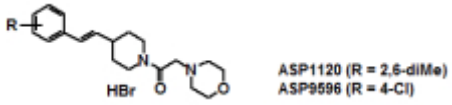
Voltage-gated sodium channels are attractive therapeutic targets for pain and a number of compounds including Ralfinamide are reported as sodium channel blockers. A new series of vinylpiperidine analog was designed, synthesized and evaluated for ability to block sodium channels. These efforts led to ASP1120 and ASP9596 possessing potent oral analgesic activity on spinal nerve ligation model (Chung model) in rats (ED_{50} = 2.1 and 0.18 mg/kg, respectively). We describe synthesis, structure-activity relationships and biological properties of vinylpiperidine derivatives.



ASP1120 (R = 2,6-diMe)
ASP9596 (R = 4-Cl)

MEDI 53

Metal-charge-shielded manganese porphyrins are potent orally active peroxynitrite decomposition catalysts

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One third of Americans suffer from some form of chronic pain. The overproduction of peroxynitrite has now been implicated as a key mediator of

inflammatory and chronic neuropathic pain states in addition to the development of morphine-induced antinociceptive tolerance. Herein we will present the synthesis, characterization and in vivo performance of a series of orally active manganese(III)-porphyrins which function as peroxynitrite decomposition catalysts. Our goal has been to identify catalysts with actual drug-like properties first and then screen them for significant peroxynitrite decomposition activity. This strategy has led us away from well known catalysts with polar meso-substitutions, such as $MnTMPyP^{5+}$, and toward a design which utilizes symmetric zones of lipophilicity at the beta-positions to shield the charged metal center. We will present the in vitro characterization of peroxynitrite decomposition activity of these new catalysts and data profiling their potent oral activity in animal models of inflammatory and neuropathic pain.

MEDI 54

Kv1.3 as therapeutic target – PoC animal models

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The voltage-gated potassium channel Kv1.3 represents a promising target for the treatment of autoimmune diseases like multiple sclerosis, rheumatoid arthritis, diabetes and psoriasis. Applying virtual high throughput screening (vHTS) in combination with conventional patch-clamp electrophysiology and MedChem efforts resulted in the identification of two lead classes with IC_{50} values on the Kv1.3 down to 40 nM and optimized physicochemical and PK properties. Selectivities over other members of the Kv1.x family could be enhanced by rational SAR analysis. Proof-of-concept (PoC) data from different animal models will be presented. Furthermore, the role of Kv1.3 in type 2 diabetes will be scrutinized.

MEDI 55

Functionally selective anti-inflammatory ligands for somatostatin receptor $sstr_2$

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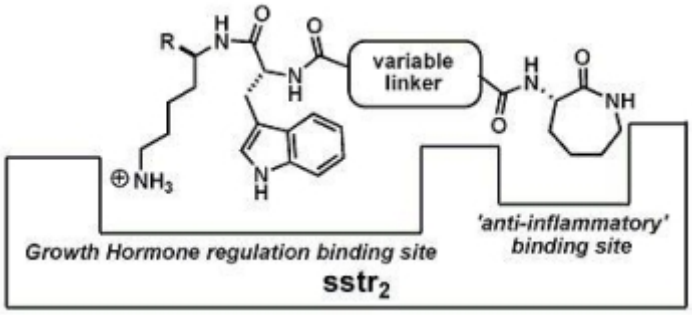
The new anti-inflammatory drug FX125L, a broad-spectrum chemokine inhibitor now in phase 2 clinical trials, acts via agonism at the somatostatin receptor $sstr_2$. Agonism of $sstr_2$ by other ligands (e.g. somatostain or cortistatin) regulates growth hormone production. In this study we synthesise hybrid bitopic $sstr_2$ ligands designed to bind in both an ortho- and allosteric fashion, and investigate

the structural requirements for antiinflammatory / growth-hormone-regulation functional selectivity at this receptor.



MEDI 56

Design and synthesis of a potent, selective, brain penetrate PDE9 inhibitor as a potential treatment for Alzheimer's disease

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Phosphodiesterase 9 (PDE9) inhibitors have been shown to impact cognitive deficits in pre-clinical models, thus suggesting utility in the treatment of Alzheimer's disease. The focus of the presentation will show how we have 1) identified potent, selective, and brain penetrate compounds using parallel chemistry and structure based drug design, 2) converted the initial racemic synthetic route to a high yielding and enantiospecific route that has been used to successfully scale compounds for toxicology studies.

MEDI 57

Design, synthesis and evaluation of a novel series of sulphonamide compounds to target chemokine receptor type 4

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The interaction of C-X-C chemokine receptor type 4 (CXCR4) with stromal cell derived factor-1 (SDF-1) play an important role in metastasis and inflammation. Previously, we reported a series of novel CXCR4 antagonists with a dipyrimidine amine motif. One of the most potent compounds - WZ811, showed a nanomolar EC_{50} in Matrigel invasion assay. Recently, we synthesized a structurally different, brand-new class of molecules that contain a sulphonamide moiety. A few of these compounds showed promising results in initial screenings. Encouraged by

the preliminary results, more sulphonamide based analogs have been synthesized and tested in three in vitro assays - competitive binding affinity, Matrigel invasion, and cyclic adenosine monophosphate (cAMP) modulation assays. The selected compounds were further tested in the Carrageenan-induced paw edema model for a proof-of-principle *in vivo* efficacy against inflammation. The synthesis of these sulphonamide analogs and the results of the above-mentioned assays will be presented.

MEDI 58

Synthesis and evaluation of pyrimidinone based fenobam analogs as metabotropic glutamate receptor subtype 5 antagonists

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Glutamate is the major excitatory neurotransmitter in the central nervous system and functions through both ionotropic and metabotropic receptors. Metabotropic glutamate receptor subtype 5 (mGluR5) has been shown to play a role in addiction, pain, depression and anxiety. In an effort to discover potent and selective mGluR5 antagonists, we synthesized twelve pyrimidinone analogs of 1-(3-Chloro-phenyl)-3-(1-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl)-urea (fenobam). Fenobam has been shown to be a potent and selective mGluR5 antagonist. Fluorometric Ca^{2+}/flux assay was used to evaluate the compounds for antagonism at mGluR5. The highest affinity was observed for 1-(3-chlorophenyl)-3-(1-methyl-4-oxo-1,4,5,6-tetrahydropyridin-2-yl)urea (RTI-4229-982), IC_{50} = 50 nM compared to fenobam, IC_{50} = 43 nM. The cLogP value for RTI-4229-982 is 0.63 log units lower than that for fenobam, suggesting that RTI-4229-982 may have better brain penetration

MEDI 59

SAR studies of C2 2H-pyrano[2,3-d]pyrimidine ethers as nicotinic acid receptor agonist

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Low density lipid cholesterol (LDL-C) is well documented as being an independent risk factor for increased cardiovascular risk. In contrast, high density lipid cholesterol (HDL-C) is believed to exhibit beneficiary effects. Niacin, a nicotinic acid receptor agonist, has proven to be safe and efficacious as a lipid lowering drug for over 30 years and has helped to decrease VLDL-C, LDL-C, triglyceride, and to increase HDL-C. However, patients need to take gram amounts of niacin multiple times per day with food, and a high percentage of patients experience intense flushing of the face and upper body with severe itching. In addition, some patients suffer GI side effects. Due to these undesired side effects, the discovery of a new NAR agonist with minimal side effect liabilities is highly desirable. The receptor for nicotinic acid (NAR) was identified in 2003, which provides the opportunity for rational drug discovery of a NAR agonist with an improved profile. Recently, we have identified a partial NAR agoinst 5-methyl-2-(methylsulfinyl)-3H-pyrano[2,3-d]pyrimidine-4,7-dione (**1**) from in-house screening. Further SAR studies that focus on the C2 ether of the pyrano [2,3-d]pyrimidine have generated novel NAR agonists with improved efficacy and ancillary profile. The result of our SAR studies will be discussed in this presentation.

MEDI 60

Synthesis and SAR study of imidazoquinolines as a novel structural class of mPGES-1 inhibitors

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Prostaglandin E2 (PGE2) is the crucial eicosanoid involved in the development of inflammation. The biosynthesis of PGE2 requires transformation of arachidonic acid by COX-1 or COX-2 to PGH2, which is subsequently converted by PGE2 synthases to PGE2. Among PGE2 synthases, microsomal PGE synthase-1 (mPGES-1), which is functionally linked to COX-2, is inducible by pro-inflammatory stimuli. Therefore, mPGES-1 has received much more attention as a novel drug target in the treatment of various inflammatory disorders. In the course of our mPGES-1 inhibitor program, we found a lead compound, imidazoquinoline derivative (**1**), which exhibits a moderate inhibitory activity for mPGES-1 (IC_{50} = 9.5 microM). To further improve inhibitory activity, we designed

and synthesized a series of imidazoquinolines on the basis of the lead **1**. In this report, we describe the results of our SAR studies on the imidazoquinolines as a novel structural class of mPGES-1 inhibitors.

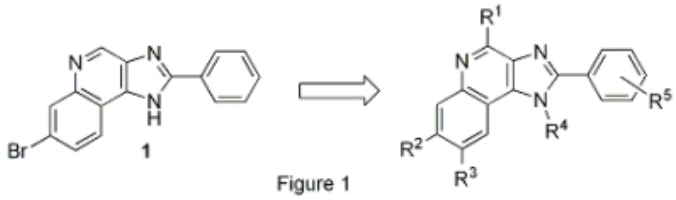

Figure 1

MEDI 61

Benzimidazole derivatives as potent mGluR5 antagonists

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The development of potent and selective metabotropic glutamate receptor (mGluR5) antagonists, as potential therapeutic agents for the treatment of various conditions such as pain, Parkinson's disease, migraine, and fragile X syndrome has been the focus of significant research in our laboratories. We have recently disclosed a new series of mGluR5 antagonists based on a nicotinamide [1]. We will present here subsequent scaffold morphing efforts that led to the identification of another series of mGluR5 antagonists based on an imidazole heterocycle. The initial derivatives synthesized exhibited modest micromolar potency. Further medicinal chemistry optimization led to target-selective benzimidazole derivatives with low nanomolar potency. We will also report the structure-activity relationship (SAR) around this novel chemotype. [1] C. Spanka *et al.*, Bioorg. Med. Chem. Lett. (2010), 20, 184-188

MEDI 62

Novel aryl sulfonamides as potent, selective and brain penetrant 5-HT$_6$ receptor antagonists

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Considerable attention has been focused on the usefulness of 5-HT_6 receptors as target of choice for various neurological disorders. Several compounds like SB-742457, SAM-531 and our internally discovered compound SUVN-502 are currently in clinical trials for cognition related disorders. We have earlier disclosed a potent series, N-(substituted aryl)-3-piperidinylaminophenylsulfonamides with good oral bioavailability and activity in animal models of cognition. However the series in general lacked adequate brain penetration (brain: Plasma ratio < 0.1), which makes them unsuitable for further development. To improve upon the brain penetration to the desired levels while retaining the efficacy, we have designed and developed novel sulfonamide compounds wherein we replaced the nitrogen-bearing aryl moiety with indolyl, azaindolyl, indazolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl and 1,4-benzoxazinyl moieties. The resultant compounds are potent (K_b = 0.01 to 10 nM), highly selective, orally active and adequately brain penetrant (brain: Plasma ratio > 1) with no hERG liability. The details will be discussed.

MEDI 63

HYDAMTIQ: A new, potent PARP-1 inhibitor with neuroprotective properties

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Poly(ADP-ribose) polymerase 1 (PARP-1) is a ubiquitous enzyme that plays an active role in several cellular responses, including DNA repair, telomere integrity, gene expression, cell survival or death. As a consequence, PARP-1 inhibitors are now considered excellent drug candidates to treat different pathological conditions such as cancer, cardiovascular and inflammatory diseases, as well as brain ischemia. As an extension of our work in the field, we report the design, synthesis and biological evaluation of 2-((dimethylamino)methyl)-9-hydroxythieno[2,3- c]isoquinolin-5(4*H*)-one (HYDAMTIQ), a novel PARP-1 inhibitor with excellent potency and efficacy in models of brain ischemia. *In vitro* physicochemical and pharmacokinetic characterization shows that HYDAMTIQ has a good water solubility (70 mg/mL), good permeability in BBB-PAMPA assays (Pe: 4.6 x 10^{-6} cm/s), and minimal CYP inhibition, while the human

microsomal and hepatocyte stability results to be moderate ($t_{1/2}$: 30 min, 22.2 mL/min/10^6 cells). Altogether our data qualifies HYDAMTIQ as a novel lead candidate to advance into clinical studies.

MEDI 64

Design, synthesis, and pharmacophore generation of SSRIs with dual action: A new approach toward efficient autism treatment

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Repetitive behaviors together with social skills deficit, and communication impairment are three domains characteristics of autism. Repetitive behaviors are currently treated with Selective Serotonin (5HT) Reuptake Inhibitors (SSRIs). However, the delayed onset of action of SSRIs (3-6 weeks) considers drawback and questions their efficiency. Co-administration of SSRIs with $5HT_{1B/1D}$ antagonists proved to increase efficiency over SSRIs alone, which motivates us to design novel and high affinity ligands combining SSRIs with $5HT_{1B/1D}$ antagonists. Pharmacophore models were generated derived from 22 structurally diverse SSRIs (Ki=0.013nM to 5000nM). Steric refinement was added using inactive compounds to increase pharmacophore' reliability. Our chosen pharmacophore model possess three features and was used as a 3D query to retrieve potential inhibitors from proposed compounds (virtual screening). Compounds with fit values (≥ 2) were chosen for synthesis and *in vitro* biological evaluation. Our resulted pharmacophore is a promising milestone to a new class of SSRIs with dual action

MEDI 65

Imidazo[1,5-a]quinoxalines as selective PDE10A inhibitors for the treatment of schizophrenia

Michael Malamas[(1)]*, malamas.michael@gmail.com, CN 8000, Princeton NJ, United States ; Yike Ni*[(1)]*; James Erdei*[(1)]*; Kristi Fan*[(1)]*; Norbert Hoefgen*[(2)]*; Hans Stange*[(2)]*; Rudolf Schindler*[(2)]*; Christian Grunwald*[(2)]*; Ute Egerland*[(2)]*; Barbara Langen*[(2)]*; Thorsten Hage*[(2)]*; Thomas Kronbach*[(2)]*; Steven Grauer*[(1)]*; Boyd Harrison*[(1)]*; Albert Robichaud*[(1)]*; Karen Marquis*[(1)]*; Thomas Comery*[(1)]*; Menelas Pangalos*[(1)]*; Nicholas Brandon*[(1)]*. (1) Wyeth, United States (2) Biotie Therapies GmbH, Germany*

Cyclic nucleotide phosphodiesterases (PDEs) catalyze the degradation of cAMP and cGMP and are thus key regulators of intracellular cyclic nucleotide levels. Phosphodiesterase PDE10A is a ~89 kD PDE family member expressed only in brain and testes and is abundant 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 and regulates their production from these brain regions, all of which have been implicated in schizophrenia. Mechanistically, PDE10A inhibition mimics the effects of D2 antagonism, the standard treatment for psychosis, along with D1 agonism, which may decrease the side-effect liabilities while contributing to a pro-cognitive profile. In this paper, we report new imidazo[1,5-a]quinoxalines as potent and selective PDE10A inhibitors. The scope of this work was to further improve the potency and selectivity of our previous imidazo[1,5-a]quinoxalines PDE10A inhibitors. We have identified that introduction of bulky groups at position-8 of the quinoxaline moiety has eliminated the adenosine receptor activity present in our previous quinoxaline inhibitors. In addition, SAR/SPR studies have improved the compound's potency and physicochemical properties. Crystallographic studies will be presented as part of the SAR evolution. Several compounds have demonstrated very robust activity in a range of preclinical models of antipsychotic efficacy. This includes a reversal of MK-801 hyperactivity, a reversal of apomorphine induced climbing and also an inhibition of the avoidance response in the Conditioned Avoidance Model. Furthermore, these PDE10A inhibitors have produced low levels of catalepsy, suggesting a minimal risk of EPS.

MEDI 66

Benzo[e]imidazo[5,1-c][1,2,4]triazines as selective PDE10A inhibitors for the treatment of schizophrenia

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Cyclic nucleotide phosphodiesterases (PDEs) catalyze the degradation of cAMP and cGMP and are thus key regulators of intracellular cyclic nucleotide levels. Phosphodiesterase PDE10A is a ~89 kD PDE family member expressed only in brain and testes and is abundant 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 and regulates their production from these brain regions, all of which have been implicated in schizophrenia. Mechanistically, PDE10A inhibition mimics the effects of D2 antagonism, the standard treatment for psychosis, along with D1 agonism, which may decrease the side-effect liabilities while contributing to a pro-cognitive profile. In this paper, we report new benzo[e]imidazo[5,1-c][1,2,4]triazines as potent and selective PDE10A inhibitors. This work represents an extension of our previously disclosed imidazo[1,5-a]quinoxaline PDE10A inhibitors studies. The optimization

process of these new PDE10 inhibitors has followed a based-structure drug design approach with multiple crystallographic studies. Several compounds have demonstrated low manomolar potency in vitro and very robust activity in a range of preclinical models of antipsychotic efficacy. This includes a reversal of MK-801 hyperactivity, a reversal of apomorphine induced climbing and also an inhibition of the avoidance response in the Conditioned Avoidance Model. Furthermore, these PDE10A inhibitors have produced low levels of catalepsy, suggesting a minimal risk of EPS.

MEDI 67

Discovery of potent and selective inhibitors of neuronal nitric oxide synthase

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Nitric oxide synthase (NOS) is a family of enzymes that produce nitric oxide for use in regulating blood pressure, in immune system functioning, and in brain development, memory, and learning. Under pathological conditions, excess nitric oxide is generated, which can result in damage to tissues, leading to neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, stroke, and cerebral palsy. The broad objective of selective inhibition of neuronal nitric oxide synthase is the development of treatments for these diseases. It is critical to selectively inhibit nNOS over endothelial NOS (eNOS) and macrophage NOS (iNOS) in order to prevent hypertension and interference with the immune defense system, respectively. We have developed the first class of dual-selective nNOS inhibitors, which are remarkably active in a rabbit model for cerebral palsy without showing any adverse cardiovascular effects. Unfortunately, the two positive charges on these inhibitors result in their failure of crossing the blood-brain barrier. This is essential for oral administration. Based on the current results, a new class of inhibitors has been designed that contains less positive charge, and the structures are ready for optimization.

MEDI 68

Design, synthesis, and biological evaluation of α3 GABAergic subtype selective ligands for anxiety disorders

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GABAergic/BzR agonists at α3β2γ2 subtype exhibit anxyolytic activity. If such agonists are nearly silent at α1 and α5β2γ2 subtypes, they will be devoid of tolerance, ataxia and amnesic side effects. Bivalent ligands often enhance the selectivity and potency relative to their monovalent progenitors. Based on the receptor binding selectivity of the monomeric ligands previously developed in our laboratory, a series of homodimeric ligands with varying linker lengths have been designed and synthesized. This was designed to rapidly enhance subtype selectivity by subtle changes in structure. Additionally, heterodimeric ligands have also been prepared to evaluate their effect on subtype selectivity. The target ligands were screened in an *in vitro* eceptor binding assay. The selected ligands were further tested for efficacy at $GABA_A$/BzR subtypes in *Xenopus laevis* oocytes. Many of these ligands exhibited subtype selective efficacy at α3β2γ2 GABAergic subtypes and might be important to treat GAD, SAD, OCD, PTSD and other anxiety disorders.

MEDI 69

Structure activity relationships in a series of potential allosteric muscarinic ligands

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Muscarinic acetylcholine receptors (mAchRs) belong to the class of G protein-coupled receptors, with five well characterized subtypes distributed throughout the body. These receptors represent potential therapeutic targets for conditions such as Alzheimer's disease, schizophrenia and irritable bowel disease. Functional and radioligand binding studies provide evidence for allosteric binding sites on each mAChR subtype thereby providing a new way of enhancing subtype selectivity without the potential for adverse effects. A novel series of compounds was synthesized using a 1,2,5-thiadiazole moiety along with varying

lengths of a polyethylene glycol linker. *In vitro* biological evaluation using the phosphatidylinositol turnover assay (for G_q coupled receptors) revealed the modulating properties of these compounds. Within the series, none of the compounds exhibited potential allosteric activity. However, compounds were found to possess antagonist activity at the M_5 muscarinic receptor subtype. A Schild analysis was conducted for the identified lead compound in order to confirm the allosteric properties.

MEDI 70

Toward benzoxazole heterocycles exhibiting atypical antipsychotic binding affinity

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The dopaminergic and serotonergic neurotransmitter systems are thought to play a critical role in the regulation of emotion and mood, and have been implicated in a spectrum of neuropsychiatric disorders. There has long been considerable interest in DA/SE receptors as potential targets for the design of new antipsychotic agents. The focus of this project was to use a structure-based drug design approach to design and to synthesize a library of structurally altered benzoxazole lead heterocycles, which possess an atypical-like dopamine/serotonin binding profile. Various benzoxazole moieties were docked into a 5-HT_{1A} receptor homolog to predict the binding affinity profiles of each structure. Select compounds were synthesized and underwent receptor binding affinity studies to validate the molecular model used. Using this structure-based drug design model produced a new diverse class of atypical antipsychotic agents.

MEDI 71

Synthesis and SAR of a novel class of tetrahydroisoquinoline-based potentiators of NR2C/D containing NMDA receptors

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Department of Pharmacology, Emory University School of Medicine, Atlanta GA 30322, United States

The N-methyl-D-aspartate (NMDA) receptor is a member of the ionotropic glutamate receptor family and plays a prominent role in learning and memory, synaptic plasticity, and neuronal development. Dysfunction of these receptors is implicated in a wide range of neurological disorders including schizophrenia, Parkinson's disease, Huntington's chorea and depression. The four NR2 subunits (A-D) each endow the receptor with a specific and distinguishable open probability, single channel conductance, deactivation time course, and expression pattern. These differences strengthen the therapeutic rationale for development of subunit-selective modulators. A novel NR2C/D subunit selective potentiator, with an EC_{50} of 11.4 and 12.3 μM and a max of 145% and 156% at NR2C- and NR2D- receptors, respectively, was identified in a high-throughput screening assay. A structure activity relationship (SAR) was developed around the screening hit. The key step of the synthesis of the tetrahydroisoquinoline core utilized Bischler-Napieralski conditions.

MEDI 72

Dipyrazolopyridines as modulators of α5 containing $GABA_A$ receptors

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The inhibitory neurotransmitter γ-aminobutyric acid (GABA), is an agonist at the $GABA_A$, $GABA_B$, and $GABA_C$ receptors. Of these three distinct classes of receptors, we have focused on the ligand-gated ion channel $GABA_A$ receptor, which mediates the majority of inhibitory synaptic activity of GABA in the central nervous system. A growing body of evidence indicates that selective negative modulation of the $GABA_A$ α5βγ2/3 receptor stimulates a marked improvement of performance in several animal models of memory function. In an attempt to develop cognitive enhancers with minimal side effects, we explored the effect of selective negative modulation of the $GABA_A$ α5 subtype in a target-based screening program. Helicon has developed several potent dipyrazolopyridine negative modulators in an effort to optimize their pharmacology and physicochemical properties. The synthetic approach and structure activity relationship of this series of novel compounds will be presented.

MEDI 73

Design and optimization of a series of potent and novel HCV NS3 protease inhibitors leading to the discovery of BMS-650032

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Abstract: In this presentation, we will describe studies leading to the discovery of BMS-650032, a potent HCV NS3 protease inhibitor that is currently being tested in Phase II clinical trials for the treatment of hepatitis C virus (HCV) infection. A key element in the identification of BMS-650032 was to mitigate the cardiovascular effects seen with an earlier clinical compound, BMS-605339, by using a Langendorff isolated rabbit heart model as a preclinical screening tool. Details of the campaign leading to the discovery of BMS-650032 and its early clinical results will be discussed. HCV infection is predominantly a chronic viral disease of the liver affecting more than 170 million people worldwide with 4 to 5 million cases in the United States alone. This represents a human epidemic nearly five times more prevalent than infections caused by HIV-1. There are 25,000-40,000 new infections annually 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 optimal therapy for chronically infected HCV patients is a combination of pegylated interferon and ribavirin, neither of which are specific HCV antiviral agents, that has limited efficacy and a significant incidence of side effects. Therefore, there is a clear unmet medical need to develop HCV-specific antiviral agents. The HCV NS3 protease is essential for viral replication and has been validated as an antiviral target in clinical trials.

MEDI 74

Phosphoramidate ProTide technology applied to purine 2'-deoxy-2'-fluororibosides: Design, synthesis and biological evaluation

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Nucleoside analogues are widely used in the anticancer and antiviral field. One of the major issues related to their efficient use is the poor biological response, especially due to the poor bioactivation of the compound to the active form (triphosphate). In particular, the first phosphorylation step is considered crucial in the bioactivation pathway and the delivery of a monophosphate prodrug derivative inside the cell may improve the therapeutic activity of many nucleoside analogues. Among several technologies, the phosphoramidate ProTide approach has shown to be effective for both antiviral and anticancer applications by delivering nucleoside analogue monophosphates directly inside the cells. In the present work, this technology was applied to purine 2'-fluoro-2'-deoxy nucleosides that were selected as candidates. The synthesis, biological results against a broad spectrum of viruses, enzymatic assays using carboxypeptidase and molecular modelling studies on the human-HINT enzyme will be reported.

MEDI 75

Design, synthesis and biological evaluation of uridine analogs as phosphate prodrugs

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Uridine-based nucleoside analogues have been often found to exert relatively poor antiviral activity. Their lack of activity could be related to the inefficient phosphorylation to the triphosphate species, particularly, as observed for the majority of the nucleoside analogues, the first step of phosphorylation to the monophosphate. This step may be successful bypass by applying the phosphoramidate ProTides approach to the nucleoside. An enzymatic assay, evaluating inhibition of influenza virus RNA polymerase activity using the viral ribonucleoprotein (vRNP), showed that some uridine derivative triphosphates have anti-influenza activity. From these results a series of uridine derivatives were selected for application of the phosphoramidate approach, with the purpose to deliver the monophosphate inside the intact cells thereby increasing the activity of the nucleoside analogues against influenza A virus. The synthesis, antiviral activity, enzyme and molecular modeling studies will be reported.

MEDI 76

Discovery of benzodiazepine derivatives as Apo A-1 upregulators

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Atherosclerosis is a leading cause of death in Western societies. Currently, statins are widely used for the treatment of atherosclerosis. However, despite their high usage, there remains a significant unmet need for treatments directed at preventing or limiting the effects of atherosclerosis. Apolipoprotein A-I (Apo A-I) is a major protein component of the high density lipoprotein (HDL). Increased levels of HDL have been correlated with a decreased risk for atherosclerosis and overexpression of Apo A-I is known to raise HDL cholesterol levels. Thus, upregulation of Apo A-I is considered to be one of the most promising approaches for the development of new therapies for atherosclerosis. Here, we will describe the discovery of benzodiazepine derivatives as Apo A-1 upregulators. We will illustrate the synthesis and structure-activity relationships of the series as well as some pharmacokinetic results.

MEDI 77

Synthesis, characterization and biological screening of apolipoprotein-E (apoE) modulators based upon a triaryl-substituted pharcacophore

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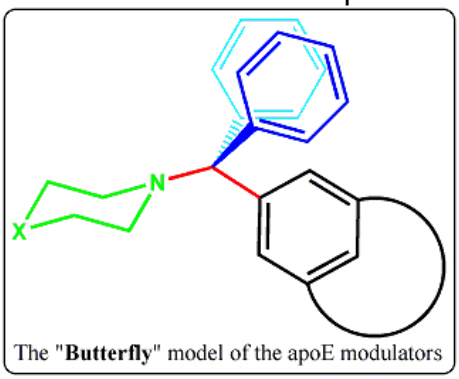
Apolipoprotein–E (apoE) is a cholesterol- and lipid-carrier protein that has been implicated in aging, atherosclerosis, Alzheimer Disease (AD), and few other neurological and lipid-related disorders. ApoE plays several roles in the body including reverse transport of cholesterol, anti-atherogenic activities independent of lipid homeostasis, blood-brain barrier maintenance, synaptic regeneration, and clearance as well as aggregation of AD-specific neurotoxin. High levels of plasma and brain apoE are risk-factors for AD independent of apoE genotype. We have found new classes of compounds that can modulate apoE gene expression. Two diverse pharmacophore models have emerged through the design, synthesis and screening of small focused libraries. Small molecules

based on a tri-aryl substituted scaffold generally described as the “butterfly” model have exhibited cell-line specific modulation of apoE gene expression. The synthesis, characterization and biological study of this class of apoE modulators will be discussed in this presentation.



The "**Butterfly**" model of the apoE modulators

MEDI 78

Docking and 3D-QSAR studies of HIV-1 integrase inhibitors

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HIV-1 integrase, along with reverse transcriptase and protease, is essential for viral replication and offers a promising target for the development of HIV-1 integrase inhibitors. In our continued efforts, we herein report the docking studies conducted on a series of 3-keto salicylic acid derivatives onto a homology model of HIV-1 integrase. To gain further insights into the structural requirements for integrase inhibition, a detailed 3D-QSAR study was conducted using our synthesized compounds and other compounds including the clinically used MK-0518 and advanced clinical candidate GS-9137 integrase inhibitors. Cross-validated coefficient, q^2 values of 0.79 and 0.71 with non-validated r^2 values of 0.93 and 0.94 were obtained for the CoMFA and the CoMSIA models, respectively. The CoMFA and CoMSIA contour maps complemented the integrase binding topology and can thus be interactively used to rationally design and predict the activity of novel and potent HIV-1 integrase inhibitors.

MEDI 79

Characterization of arginine derivatives as a virucidal agents

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Based on the previous findings that arginine can inactivate variety of enveloped viruses under mildly acidic conditions, we have systematically examined the virucidal activities and cytotoxicities of arginine derivatives. Among the compounds, butyroylarginine and cocoyl-L-arginine ethyl ester (CAE), a cationic surfactant, showed a marked virucidal activity against both HSV-1 and HSV-2 with a mild cytotoxicity, suggesting a potential use of CAE as a therapeutic agent against HSV infections on body surface. For CAE , the activity was more than 10-fold higher at pH 4 than pH 5 and HSV-1 was significantly more sensitive than HSV-2. Although other surfactants, such as SDS (anionic surfactant) and benzalkonium chloride (a quaternary cationic surfactant), also showed a similar virucidal activity, the cytotoxic effects of CAE were much weaker than those of the latter two surfactants. In addition, CAE significantly suppressed viral multiplication at the concentrations, at which its virucidal effect was negligible.

MEDI 80

Inhibition of virus multiplication by caffeic acid

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Caffeic acid inhibited the multiplication of both DNA and RNA viruses at the concentrations where the reagent showed marginal cytopathogenic effects. In the presence of the reagents, the progeny virus yield of herpes simplex virus type 1 (HSV-1), influenza A virus (IAV) and poliovirus decreased with increasing concentrations of the reagent, although HSV-1 was much more sensitive to the reagent than other viruses. None of these viruses were directly inactivated by caffeic acid at the concentrations tested. Quantitative characterization of the mode of action of caffeic acid against HSV-1 and influenza virus multiplication, such as time of addition experiments and one-step growth experiments, revealed that the reagent inhibits multiplication of both viruses mainly at an early stage of the infection (before and at the time of viral genome replication).

MEDI 81

SAR studies of quinoline derivatives as novel anti-influenza agents

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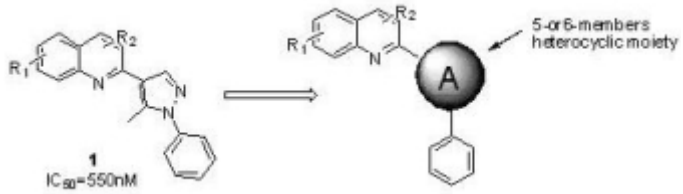
Influenza is an infectious disease of birds and mammals caused by RNA viruses of the family Orthomyxoviridae. Tamiflu and Relenza are recommended therapeutics drugs which were targeted against the neuraminidase (NA) and had been reported as an increasing clinical problem. Thus there is an urgent need to identify novel compounds with inhibitory activity against influenza virus. Recently we had identified a novel compound **1** inhibited influenza virus induced cytopathic effect in MDCK cell within nanomolar range. Then we had focused on the effect of pharmacophore A to improve the anti-influenza activity. In present work, we synthesized 17 analogs and compared the *in vitro* activity of those compounds with compound **1**.



MEDI 82

Synthesis of antiviral compounds against West Nile virus and Japanese encephalitis virus

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West Nile virus (WNV) and Japanese encephalitis virus (JEV) are significant human pathogens, and further work to develop antiviral drugs is needed. Recently, four sultam thiourea compounds were reported to inhibit WNV and JEV replication in cells and appear to be non-toxic. Few sultam thioureas have been reported in the literature, but here we describe the synthesis of ~20 sultam thioureas with various groups at four different positions. In addition, ~20 thiourea derivatives with five different heterocyclic ring systems have also been synthesized. X-ray crystal structures have been obtained for a number of sultam thioureas and thiourea derivatives, which has confirmed the structure of these compounds. These new compounds will be tested against WNV and JEV, to

obtain structure-activity-relationship (SAR) data and to identify more potent compounds.

MEDI 83

Novel broad-spectrum antiviral targeting entry of enveloped viruses

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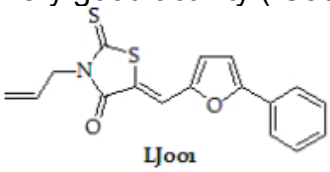
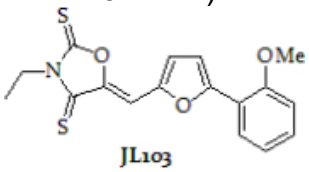
The number of emerging viral pathogens is rapidly increasing but we have only limited resources to develop therapeutics on a single-pathogen basis. A few licensed and efficacious broad-spectrum antivirals such as ribavirin and a-IFN exist, but those broad-spectrum antivirals have unwanted side effects and are also impractically expensive for widespread use. Therefore there is a need to develop broad-spectrum antivirals that target a common component of large classes of viruses. Viruses are divided into two classes: lipid-enveloped or non-enveloped (naked). Although the viral envelope derives from the host cell, it differs from cellular membranes in several biochemical and biophysical properties such as biogenic reparative capacity. We identified a hit compound LJ001, an arylmethylidene rhodanine derivative, by HTS (high-throughput screening) and carried out a structure-activity relationship study to identify new analogues and to propose a mechanism of action. LJ001 showed good activities against numerous enveloped viruses including Influenza A, poxviruses, paramixoviruses and HIV 1. We developed the new JL series which are arylmethylidene oxazolidin-2,4-dithione derivatives. For example, JL103 showed very good activity (IC50, 5.2 nM for NDV).



LJ001



JL103

MEDI 84

Exploring metal coordination in HIV integrase inhibitors

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Human Immunodeficiency Virus (HIV) is a retrovirus that causes the disease known as acquired immunodeficiency syndrome (AIDS). HIV replication requires

three enzymes: integrase (HIV-IN), reverse transcriptase, and protease. HIV-IN is unique among the three HIV targets in that it is a magnesium(II)-dependent protein with a dinuclear metal active site. HIV-IN is responsible for 3'-processing of the viral cDNA and strand transfer of that DNA into the host genome. This enzyme has been a challenging target, with only one compound approved by the FDA (Raltegravir, Merck, approved 2007). In order to specifically probe the effect of different metal binding groups (MGBs) on an HIV-IN inhibitor scaffold, several Raltegravir derivatives have been prepared with varying MGBs. These compounds will be screened against HIV-IN to determine which MGBs produce inhibitors with comparable or better activity than Raltegravir. These studies will also reveal what features of the MBG are critical for obtaining active compounds.

MEDI 85

Ten years of bicyclic nucleoside analogs: From the bench to clinical trials

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In 1999, a new class of potent and selective anti-varicella zoster virus (VZV) compounds (bicyclic nucleoside analogues, BCNAs), was discovered. The optimization of the lead compound resulted in a series of 6-*p*-alkylphenyl derivatives. The 6-pentylphenyl, designated Cf1743, is 1000 to 10000 times more active than acyclovir against VZV. The mechanism of action is not completely understood yet. BCNAs need to be converted at least to the monophosphate derivative by VZV-encoded thymidine kinase (TK) since the compounds proved inactive in VZV TK^--infected cell cultures. Although VZV DNA polymerase would be the most likely target, other steps in the VZV infection process cannot be excluded. The high selectivity and poor, if any toxicity of Cf1743 promoted its development as potential new anti-VZV drug and its valyl ester, designated FV100, is currently completing phase II clinical trials. We report an overview on the development of this unique class of potent anti-VZV compounds.

MEDI 86

Classification and similarity analysis of leads and drug-like molecules using artificial neural networks, decision trees and virtual screening methods

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Investigation of the logical relationship between the structure of compounds and their biological activities has received great attention in modern drug discovery. The main aim of the present contribution was to collect and classify a large number of compounds for deriving general structure-activity relationship (SAR) patterns and rules. The database was consisted of 1203 CCR5 modulators, 1577 HIV-reverse transcriptase, 1116 HIV-integrase, 1684 HIV-protease, 843 glutamate, 2343 dipeptidyl peptidase IV and 933 dipeptidyl peptidase VIII inhibitors. The results revealed that counter propagation artificial neural network models and decision trees are able to classify correctly more than ninety percent of the data. Moreover, similarity-potency trees (SPT) and network-like similarity graphs (NSG) were used for obtaining continues SAR patterns and calculating SAR indices. The parameters of average molecular weight, number of halogen atoms, relative negative charge, hydrophilic factors and number of –PhCOOR groups were found to be important in determining the mechanism of the activity of compounds.

MEDI 87

1-Glycosyl-1,2,3-triazoles as antiviral nucleoside analogs

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1,2,3-Triazoles were prepared through cycloadditions of enol ethers with azides bearing a protected ribose analogue. Subsequent functionalization of the triazole ring and deprotection of the sugar afforded nucleoside analogues with a triazole as the nucleobase. Synthetic details and preliminary antiviral activity data are presented.

MEDI 88

Methionine based aminoacyl-tRNA synthetase inhibitors as novel anti-infective agents

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The emergence of bacterial resistance to available antibiotics has caused great concern in the medical community and has created a need for the discovery of

novel antibiotic agents. Aminoacyl-tRNA synthetases (aaRSs) play a crucial role in protein biosynthesis by catalyzing the binding of a specific amino acid to its corresponding tRNA to form an aminoacyl–tRNA which is a substrate for translation in protein synthesis. When one aminoacyl transferase is inhibited, the corresponding tRNA is unavailable for translation leading to protein synthesis inhibition and cell growth arrest. Although aminoacyl transferases are essential proteins in all living organisms, significant differences in structure exist between bacterial transferases and their eukaryotic counterparts, providing an opportunity for developing species-selective inhibitors. Mupirocin, a natural product (isolated from *Pseudamonas fluorescens*) that inhibits isoleucyl-tRNA synthetase, is currently marketed as a topical antibiotic. Bioxiness has developed a series of close analogues of methionine incorporating a nucleophilic “Head” group that is appropriate for adenylation, a “Sidechain” that mimics methionine, and a “Tail” group that can be either an unsubstituted or substituted amine. Details of compound synthesis and preliminary SAR observations against various bacterial strains will be presented.

MEDI 89

Synthesis and screening of a chiral pyrrolidine-based library for activity against Chagas disease

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IRL's Carbohydrate Chemistry group has developed world-leading expertise in 'iminosugar' chemistry through its highly successful program of transition-state-based drug discovery with the Albert Einstein College of Medicine in New York. This led to the now-patented Immucillins. Two picomolar inhibitors, Fodosine™ and BXC4208, have progressed to Phase II clinical trials for treatment of T- and B-cell cancers and psoriasis. Another three analogs are currently being examined as treatments for certain solid tumors, bacterial infections, and as antimalarials. All of these compounds contain a chiral pyrrolidine scaffold. Capitalizing on this success, a library of *N*-substituted chiral pyrrolidine scaffolds has been prepared and screened for activity against *Trypanosoma cruzi*, a protozoal parasite causing Chagas Disease which is a neglected disease that affects about 10 million people in South and Central America and causes more deaths than any other parasitic disease. Current treatments are ineffective and come with severe side effects. Syntheses and screening results including cytotoxicity data are described.

MEDI 90

Pyridazinone derivatives as proinflammatory cytokine production inhibitors

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TNFα is one of proinflammatory cytokines implicated in the development of inflammatory response. TNFα production inhibitors have been postulated to have significant therapeutic potential for the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis and psoriasis. We identified a pyrazolo[1,5-*a*]pyridinyl-pyridazinone based compound as a potent TNFα production inhibitor from our compound library. The compound inhibited TNFα production in the THP-1 cell assay (IC_{50} = 14 nM) and displayed potent efficacy in rat LPS-induced TNFα production (rat-LPS) with 43% reduction of TNFα levels when orally dosed at 3.2 mg/kg 4 h prior to LPS challenge. Our efforts to improve its pharmacological properties led to the discovery of a series of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidinyl-pyridazinones as TNFα production inhibitors which showed remarkable efficacy in the rat-LPS assay at 1 mg/kg. Efficacy of several derivatives in this series in a rat adjuvant-induced arthritis model will also be presented.

MEDI 91

Discovery and SAR of novel pyrazole derivatives as potent TNF α production inhibitors

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Increased levels of proinflammatory cytokines like tumor necrosis factor (TNF α) are characteristic of chronic inflammatory and autoimmune disease, such as rheumatoid arthritis, asthma and psoriasis. In our effort to discover potent TNF α production inhibitors, we identified a small molecule lead from our compound

library, a pyrazolopyridinylpyridazinone derivative. Based on the hypothesis that the pyridazinone could be a pharmacophore, conversion of the pyrazolopyridine moiety to other heterocycles, and further optimization led to discover novel pyrazole TNF α inhibitors which showed potential inhibitions of TNF α production; human THP-1 cell assay (IC_{50} ≤ 20 nM) and LPS-induced TNF α production in rat, > 50 % inhibition at 1.0 mg/kg po (4 h prior to LPS challenge). And then, these compounds showed significant efficacy in a rat adjuvant-induced arthritis model.

MEDI 92

Pharmacokinetic optimization of six soluble epoxide hydrolase inhibitors for the therapeutic use in a murine model of anorexia

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The inhibitors of soluble epoxide hydrolase (sEHIs) are anti-inflammatory, analgesic, anti-hypertensive, cardio-protective and renal-protective in multiple animal models. However the earlier adamantyl urea-based inhibitors are metabolically susceptible which limited their pharmacological use. Therefore novel potent inhibitors with the replacement of adamantyl by a substituted phenyl are synthesized to presumptively offer better pharmacokinetic (PK) properties including metabolic stability. Here we present the PK profiles of six such inhibitors in a murine model and the *in vivo* efficacy of the most promising one in a murine model of anorexia. The PK profiles of inhibitors were determined following p.o. administration and serial bleeding in mice. Subsequently the PK of 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl)urea (TPPU), the most promising inhibitor, was further studied following *i.v.* injections. Finally, the anti-anorexia effect of TPPU was evaluated using a LPS-challenged murine model. Compared with the earlier adamantyl urea-based inhibitors, substituted phenyl urea-based inhibitors afford more favorable PK properties such as higher C_{max}s, huger AUCs and longer $t_{1/2}$s, which, as expected, shows more stable metabolic stability. The oral bioavailabilities of TPPU were 61±25%, 36±5%, 31±2%, and 18±3% for the doses of 0.1, 0.3, 1.0 and 3.0 mg/kg, respectively. Moreover, oral administration of TPPU dramatically reversed the shifts from LPS-challenge in epoxides and corresponding diols expected as a sEHI, and it significantly alleviated the anorexia from LPS-challenge. These data suggest that TPPU is a potent sEHI with improved PK properties, which will be a useful tool for pharmacological research and a promising start point for drug development.

MEDI 93

Dual LFA-1/Mac-1 antagonist compounds as novel treatments for inflammatory diseases

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The β-2 integrins, in particular LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), play important roles in leukocyte adhesion and migration to inflamed tissues via binding to their ligand ICAM-1. We have identified a series of compounds which block the *in vitro* interaction of both LFA-1 and Mac-1 with ICAM-1. We report here their synthesis, the SAR, *in vitro*, PK properties and *in vivo* studies. Compounds **1** and **2** inhibited human LFA-1/ICAM-1 binding with IC_{50} values of 8 nM and 40 nM and human Mac-1/ICAM-1 binding with IC_{50} values of 89 nM and 102 nM, respectively. In addition, we demonstrate *in vivo* activity with these dual LFA-1/Mac-1 antagonists in preclinical models of neutrophil migration to the skin and lungs. Our results demonstrate that these antagonists represent potential treatments for inflammatory diseases such as severe asthma and COPD.

MEDI 94

Potential drug ligands of the macrophage migration inhibitory factor

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Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine/growth factor, which has been reported to play a critical role in initiation and/or preservation of various tumors. Several reports indicate that MIF expression closely associates with tumor aggressiveness and metastatic potential. This research will be a structure-based computational approach to discover a drug which will potentially inhibit MIF. The atomic resolution structure of MIF is available in the RCSB Protein Data Bank, which was identified using X-ray diffraction. Pharmacophores will be constructed based on the known inhibitors, such as 4-IPP and ISO-1. The binding energies of known inhibitors and all pharmacophores, with MIF, will be determined using AutoDock 4.0. We will report on a number of potential drug ligands that have been identified using this approach.

MEDI 95

Histamine H_3 antagonists: Improving the pharmacokinetic profile

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The histamine H_3 receptor is a G-protein coupled presynaptic auto- and hetero-receptor expressed in various regions of the brain. As such, H_3 receptors not only regulate the release of histamine in the brain, but can also affect the release of other neurotransmitters including dopamine, noradrenaline, serotonin and acetylcholine. The modulation of these neurotransmitters by H_3 receptor antagonists suggests therapeutic potential for the treatment of a variety of cognitive and sleep disorders including attention deficit hyperactivity disorder (ADHD), Alzheimer's, schizophrenia and narcolepsy. The pharmacophore of many early H_3 receptor antagonists, including the natural product aplysamine-1, consisted of two basic amine moieties flanking an aromatic, lipophilic core. While potent and efficacious, many of the compounds with this phamacophore had an unacceptably long half-life in both rat and dog. The development and progression of novel H_3 receptor antagonist chemotypes with improved pharmacokinetic profiles will be discussed.

MEDI 96

Potent and selective agonists of Sphingosine-1-Phosphate 1 (S1P1): The discovery and SAR of a novel isoxazole based series

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Sphingosine-1-phosphate (S1P) is the endogenous ligand for the sphingosine-1-phophate receptors (S1P1-5) and evokes a variety of cellular responses through their stimulation. S1P and its interaction with the S1P receptors plays a fundamental physiological role in a number of processes including vascular stabilization, heart development, lymphocyte homing, and cancer angiogenesis. Agonism of S1P1, in particular, has been shown to play a significant role in lymphocyte trafficking from the thymus and secondary lymphoid organs, resulting in immunosuppression. This presentation will detail the discovery and SAR of a potent and selective series of isoxazole based agonists of S1P1. Compounds in this series demonstrated impressive efficacy when administered orally in rodent models of arthritis and in a mouse experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis.

MEDI 97

Fragment development towards the advancement of selective metalloenzyme inhibitors

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Drug design from a fragment-based lead discovery (FBLD) approach is a unique alternative compared to more traditional methods of drug discovery, such as high-throughput screening. Drug development via FBLD begins with screening of small, low-affinity fragments to probe the active site of interest. Promising fragment hits can then be further developed into molecules that are both potent and specific to their target. Computational docking can be used to assess how hits interact with the active site to guide further development and optimization of the most promising fragments into full-length inhibitors. The focus of this work is to construct inhibitors that are tailored for metalloenzymes such as matrix metalloproteinases (MMPs). The development of fragment hits from a novel metal-chelator library via guidance from computational docking studies has been implemented to achieve full-length inhibitors with high metalloenzyme specificity. The design, synthesis, and inhibitory activity of these libraries will be discussed.

MEDI 98

Discovery of 2-(7-(5-phenyl-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acids: Potent and selective sphingosine-1-phosphate ($S1P_1$) receptor agonists

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Sequestration of lymphocytes into lymph nodes and other secondary lymphoid tissues by selective $S1P_1$ receptor agonists has been of therapeutic interest for the treatment of a variety of autoimmune diseases recently. Gilenya®, a potent non-selective S1P agonist, affords profound immunomodulation via this mechanism. Selective $S1P_1$ agonists with reduced side effect profiles have become highly sought after in this competitive area of research. Starting from a prototypical series of 4-oxo-4-(5-(5-phenyl-1,2,4-oxadiazol-3-yl)indolin-1-yl)butanoic acids, herein we will highlight the design and synthesis of a new 2^o generation class of potent and selective $S1P_1$ agonists the 2-(7-(5-phenyl-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acids which are both potent and selective and have desirable safety, and ADME profiles. We also disclose efficacious activity for inducing peripheral lymphocyte lowering in mouse after oral dosing and subsequent LO efforts.

MEDI 99

Discovery and characterization of 4-oxo-4-(5-(5-phenyl-1,2,4-oxadiazol-3-yl)indolin-1-yl)butanoic acids as potent and selective human $S1P_1$ receptor agonists

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FDA approval of Gilenya® for the treatment relapsing remitting multiple sclerosis (RRMS) has opened the door for development of next generation $S1P_1$ agonists both for RRMS and other autoimmune disorders. $S1P_1$ receptor mediated sequestration of lymphocytes in the lymph nodes and secondary lymphoid tissues represents a fundamental mechanism of immunosuppression that may have utility in the treatment of an array of autoimmune disease states. Herein we describe a series of 4-oxo-4-(5-(5-phenyl-1,2,4-oxadiazol-3-yl)indolin-1-

yl)butanoic acids which were identified as potent and selective agonists of the human $S1P_1$ receptor. Analogues from within this unique chemical series were demonstrated to possess desirable safety and ADME profiles, and to be efficacious at reducing circulating murine lymphocytes following administration of a peroral dose. Subsequent lead optimization studies resulted in analogs with dramatically improved *in vitro* and *in vivo* potencies.

MEDI 100

Discovery of a novel and highly selective spiroindoline-based series of Sky kinase inhibitors

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Coronary heart disease is the leading cause of mortality & morbidity in the US with 40 million people at risk for thrombotic events. As the current front-line treatment for arterial thrombosis clopidogrel exhibits significant efficacy, resistance, and bleeding side-effect limitations, we were interested in identifying new anti-platelet therapies with a reduced risk of bleeding. Gas6 plays a critical role as a platelet response amplifier, signaling through Sky (Tyro3/Rse), Axl, & Mer tyrosine kinases expressed in human platelets. Inhibition of Sky kinase potentially represents an antithrombotic therapy not associated with bleeding side effects. We wish to report the discovery of a novel and highly selective series of Sky kinase inhibitors based on a spiroindoline scaffold.

MEDI 101

Design & optimization of 2-*N*-arylaminothiazoles as b-Raf kinase inhibitors

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The Raf kinases (A-Raf, B-Raf, and C-Raf) are key regulators of cell proliferation and survival that control signaling through the mitogen-activated protein kinase (MAPK) pathway. This pathway is frequently deregulated in cancer by protein

mutations, leading to increased cancer cell proliferation and survival. In particular, Ras oncogenes are mutated in 15% of all cancers and the B-Raf oncogene is mutated in 7% of all cancers, including 66% of melanoma, 40% of thyroid cancer, and 12% of colon cancer, making B-Raf an attractive anti-cancer therapeutic target. We wish to report the discovery and optimization of a series of 2-*N*-arylaminothiazoles with potent b-Raf biochemical & cellular inhibition. Structure-based drug design was utilized to design the initial lead, which was further optimized for biochemical & cellular potency, in vitro ADME and in vivo PK properties, and in vivo efficacy in a mouse xenograft model of melanoma.

MEDI 102

Design & optimization of 2-*N*-arylaminopyrazines as b-Raf kinase inhibitors

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The Raf kinases (A-Raf, B-Raf, and C-Raf) are key regulators of cell proliferation and survival that control signaling through the mitogen-activated protein kinase (MAPK) pathway. This pathway is frequently deregulated in cancer by protein mutations, leading to increased cancer cell proliferation and survival. In particular, Ras oncogenes are mutated in 15% of all cancers and the B-Raf oncogene is mutated in 7% of all cancers, including 66% of melanoma, 40% of thyroid cancer, and 12% of colon cancer, making B-Raf an attractive anti-cancer therapeutic target. We wish to report the discovery and optimization of a series of 2-N-arylaminopyrazines with potent b-Raf biochemical & cellular inhibition. Structure-based drug design was utilized to design the initial lead, which was further optimized for biochemical & cellular potency, in vitro ADME and in vivo PK properties, and in vivo efficacy in a mouse xenograft model of melanoma.

MEDI 103

In vitro & in vivo profiles of advanced 2-*N*-arylaminoheterocyclic inhibitors of b-Raf kinase

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The Raf kinases (A-Raf, B-Raf, and C-Raf) are key regulators of cell proliferation and survival that control signaling through the mitogen-activated protein kinase (MAPK) pathway. This pathway is frequently deregulated in cancer by protein mutations, leading to increased cancer cell proliferation and survival. In particular, Ras oncogenes are mutated in 15% of all cancers and the B-Raf oncogene is mutated in 7% of all cancers, including 66% of melanoma, 40% of thyroid cancer, and 12% of colon cancer, making B-Raf kinase an attractive & compelling anti-cancer therapeutic target. In the preceeding presentations, we have discussed the design and optimization of two series of b-Raf kinase inhibitors based on 2-*N*-arylaminothiazole and 2-*N*-arylaminopyrazine scaffolds. This presentation will detail the in vitro and in vivo profiles, selectivity, PK/PD relationships, and in vivo efficacy of two preclinical developmental candidates from these series.

MEDI 104

Synthesis and SAR of bi-dentate compounds as potent JNK inhibitors

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The design and synthesis of potent and selective kinase inhibitors is at the center of considerable efforts from both the pharmaceutical sector and academic research. These efforts are nearly exclusively devoted to the design and potent inhibitors, targeting the highly conserved ATP binding pocket of kinases. Protein and small molecule kinases also possess binding pockets for substrates and scaffolding proteins that could be equally used to design specific inhibitors. However, these binding surfaces are usually large and shallow hence not particularly suitable for the design of small drug like inhibitors with sufficient potency. Hence, we propose that the design and synthesis of bi-dentate compounds linking the binding energies of weakly interacting ATP and substrate mimetics could result in potent and selective inhibitors. As an application, we describe a bi-dentate molecule, BI87G9, designed against the protein kinase JNK. In view of its favorable inhibition profile, selectivity, and ability to function in the cellular milieu and *in vivo*, this compound represents a first class of dual ATP- and substrate-competitive kinase inhibitor as well as a promising stepping stone towards the development of a novel class of bi-dentate therapeutics.

MEDI 105

Development for Taspase1 inhibitors

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Taspase1 is a threonine protease responsible for cleaving MLL (Mixed-Lineage Leukemia) to achieve proper HOX gene expression. Taspase1 is essential for cell proliferation and is overexpressed in many cancer cell lines. Currently no small molecule inhibitors of this enzyme have been described. Here, we report the synthesis and evaluation of vinyl sulfone, vinyl ketone, epoxy ketone, and boronic acid inhibitors designed based on the preferred Taspase1 cleavage site (Ac-Ile-Ser-Gln-Leu-Asp). Specifically, we evaluated compounds in which the reactive warhead is positioned in place of the P1 aspartic acid side chain as well as at the C-terminus of the peptide. Interestingly, both classes of inhibitors were effective and vinyl ketones and vinyl sulfones showed the greatest potency for the target protease. These results suggest that Taspase1 has unique substrate recognition properties that could potentially be exploited in the design of potent and selective inhibitors of this enzyme.

MEDI 106

ESTYBON™ (ON 01910.Na) - a clinical stage multi kinase inhibitor: Synthesis, structure activity relationship and biological activity

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Cyclin D proteins are elevated in many cancer cells and targeted deletion of Cyclin D1 gene in the mammary tissues protects mice from breast cancer. Accordingly, there is an increasing awareness of this novel non-enzymatic therapeutic target for cancer. We have developed novel, non-alkylating styryl benzyl sulfones that are finding success in clinical trials in advanced cancer patients and in Myelodysplastic Syndromes (MDS), which are associated with aberrant expression of Cyclin D proteins. Here we describe the structure

function analysis of sodium (*E*)-2-(2-methoxy-5-((2,4,6 trimethoxystyrylsulfonyl)methyl) phenylamino)acetate, (ON 01910.Na, ESTYBON™) which is in Phase 3 trials for MDS. Invitro studies with ESTYBON™ showed the inhibition of PI3K/AKT pathway, downregulation of cyclin D1, induction of NOXA and BIM and activation of JNK pathway. The fact that MDS patients bone marrow (particularly trisomy 8) over expresses cyclin D1 and in vitro studies have demonstrated the activity of ESTYBON™ against cytogenetically abnormal cells and blasts despite minimal inhibition ofnormal hematopoiesis provides a rationale for it use in MDS. The FDA has granted Orphan Drug Designation for the use of ESTYBON™ in MDS.

MEDI 107

Searching for the macromolecular target(s) of novel modulators of Rho signaling that inhibit prostate cancer metastasis

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RhoA and RhoC have been found to play important roles in metastasis of multiple cancers. While known for their role in cytoskeletal reorganization, they also have less well understood effects on gene transcription. We recently identified a novel small molecule inhibitor (CCG-1423) of RhoA/C-mediated gene transcription via HTS. Furthermore, CCG-1423 inhibited the invasion of PC-3 prostate cancer cells in a Matrigel model of metastasis. We examined structure-activity relationships focusing on bioisosteric replacement of amide bonds and conformational restriction and identified two compounds with improved selectivity for inhibition of RhoA/C-mediated gene transcription and reduced cytotoxicity in comparison to CCG-1423. Both compounds also inhibited PC-3 prostate cancer cell invasion, but without associated cytotoxicity. Our compounds are acting on an unknown target in the RhoA/RhoC pathway. Current efforts are aimed at identifying the macromolecular target(s) of our compounds using affinity reagents, which may provide a novel target for anti-metastatic therapies for prostate cancer.

MEDI 108

From hit to lead: Rapid development of novel CDK5 inhibitors

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Cyclin Dependant Kinase 5 (CDK5) was a high profile target for the Pfizer Neuroscience Hit to Lead efforts. The goal was to identify a potent and selective lead compound that was <100nm and >50x selective vs other CDK's. This poster will detail how our inhouse HTS provided a hit that was rapidly expanded on through judicious use of targeted synthesis, parallel chemistry and structural biology to afford novel, potent and selective CDK5 inhibitors.

MEDI 109

Design and synthesis of novel and selective IKK inhibitors

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As part of a multidisciplinary project targeting hormone refractory prostate cancer, a collection of small molecules were screened against IKK and NF-kB. Initial screening revealed a purine-like scaffold as a moderate inhibitor of IKK. Derivatization of this initial hit allowed us to develop a single-digit micromolar inhibitor of IKK, with a 30-fold selectivity of one isoform over the other and good P450 metabolism profile. In order to understand the structure activity relationship (SAR), we built a homology model using Accelrys Discovery Studio software. This hypothetical 3D model, guided us through the design of new chiral amine ligands for our scaffold in order to increase potency and control selectivity. Here we would like to present the asymmetric synthesis of enantiopure *cis*-3 and *trans*-3-arylcyclohexylamines, 3-aminocyclopentane-1,2-diols and 4-aminocyclopentane-1,2,3-triols as ligands for our IKK inhibitor scaffold.

MEDI 110

Design, synthesis, and SAR of a novel series of p38α MAP kinase inhibitors

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The p38 MAP kinase is a key enzyme in inflammatory diseases as it is involved in the biosynthesis of pro-inflammatory cytokines such as TNF-a and IL-1b. Small molecule inhibitors suppress the production of these cytokines and therefore p38 is a promising drug target for novel anti-inflammatory therapeutics. This paper will describe the discovery of a novel series of p38 MAP kinase inhibitors and present SAR that allowed rapid optimisation to give compounds with properties suitable for *in-vivo* investigation. We will also discuss how, by employing X-ray crystallography, we were able to demonstrate that this series bind to the DFG-out form of the enzyme and also describe the kinetics of binding to p38 MAP kinase.

MEDI 111

KSP inhibitors based on the thienyl-5, 6, 7, 8-tetrahydro [2, 3-*b*] quinoline scaffold: Discovery of a novel binding mode

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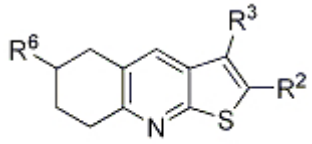
Kinesin Spindle Proein (KSP), which is a motor protein involved in microtubule dynamics, has emerged as an attractive new target to disrupt spindle assembly and induce apoptosis. KSP inhibitors are expected to function as anti-tumor agents without the debilitating peripheral neuropathy associated with tubulin binders. Herein, we describe the discovery of KSP inhibitors based on the core **[1]** which show a novel binding mode. Efforts to improve cell potency and efficacy studies would be reported.



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MEDI 112

Discovery of orally bioavailable Aurora kinase inhibitors

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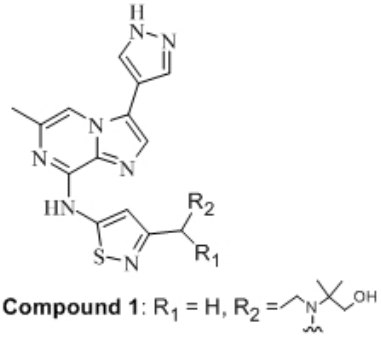
Aurora kinases play critical roles in regulation of mitosis. Aurora kinase inhibitors are promising anti-proliferative agents. We have previously reported compound **1** as a potent Aurora A and B dual inhibitor suitable for *iv* infusion. Herein, we disclose our lead optimization based on compound **1** to identify an orally bioavailable pan-Aurora kinase inhibitor. By introducing a heteroaromatic moiety at the benzylic position of the isothiazole ring, we discovered a series of orally bioavailable potent Aurora A and B inhibitors, which exhibit excellent *in-vivo* activities.



Compound 1: R_1 = H, R_2 =

MEDI 113

Novel series of cannabinoid modulators for the treatment of obesity associated disorders

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With more than 1 billion overweight adults worldwide, obesity continues to be an escalating threat to global human health. Circulating levels of the endocannabinoids acting on cannabinoid receptors CB1 and CB2 are elevated in obese individuals. A suitable strategy to reduce overactivation by endocannabinoids is to use compounds which antagonize corresponding binding and activation mechanisms. We aimed to further develop and optimize compounds antagonizing both CB1 and CB2 mediated activations by endocannabinoids as a novel and effective therapeutic approach for treatment of obesity associated disorders. Two series of novel canabinoid modulators based on two heterocyclic scaffolds, have been synthesized. Highly potent dual modulators for CB1 and CB_2 were identified in both series. Selected compounds have been tested on *in vivo* relevant models with CB1 and CB2 activities. Details

about the synthesis, CB_1 and CB_2 receptors *in vitro* data, resulting SAR, molecular modeling and *in vivo* activities will be presented.

MEDI 114

Optimization of human galactokinase (GALK) small molecule inhibitors

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In humans, inherited deficiency of galactose-1-phosphate uridylyltransferase (GALT) activity can lead to a potentially lethal disease called Classic Galactosemia. Although a galactose-restricted diet prevents the neonatal lethality of this disorder, many well-treated patients continue to develop debilitating complications like mental retardation, neurological deficits, and premature ovarian failure (POF). As elevated level of galactose-1-phosphate (gal-1P), the product of galactokinase (GALK), has long been regarded as the major pathogenic mechanism in Classic Galactosemia, we hypothesize that inhibition of GALK in the patient cells will relieve them from galactose toxicity. Previously, in a high-throughput screen, we identified over 150 small molecule compounds that inhibit human GALK activity *in vitro* at the level of 86.5% or more. Our SAR studies of selected compounds revealed a lead compound with thiazine structural motif, based on which we synthesized new derivatives for optimized pharmacokinetics. The design, synthesis and evaluation of these new analogs are reported here.

MEDI 115

Imidazolone-based glucagon receptor antagonists: Lead identification

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Glucagon is an incretin hormone which is responsible for glucose homeostasis *via* two mechanisms: glycogenolysis and gluconeogenesis. The glucagon receptor is a Class B GPCR which is primarily present in the liver. Our group desired to develop potent, orally bioavailable antagonists of the human glucagon

receptor (hGCGR) for the treatment of type II diabetes mellitus. To that end a series of imidazolone-based glucagon receptor antagonists were prepared. Optimization of the series led to compounds exhibiting acceptable hGCGR binding and functional potency as well as oral efficacy in an ICR-DIO mouse model of diabetes. This presentation will detail our lead identification efforts.

MEDI 116

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

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Pancreatic beta-cell dysfunction is a hallmark event in the pathogenesis of type 2 diabetes. Injectable peptide agonists of the GLP-1 receptor have shown significant promise as anti-diabetic agents by virtue of their ability to amplify glucose-dependent insulin release and preserve pancreatic beta-cell mass. These effects are mediated via stimulation of cyclic AMP through beta-cell GLP-1 receptors. The Ga_s-coupled receptor GPR119 is largely restricted to insulin-producing beta-cells of pancreatic islets and incretin producing K- and L-cells of the GI tract. Unlike receptors for GLP-1 and other peptides that mediate enhanced glucose-dependent insulin release, GPR119 appears to be a small-molecule receptor, responding to several fatty acid amides distinct from endocannabinoids selective for CB1 and CB2 receptors. JNJ-28630355 and related potent GPR119-specific agonists described herein significantly increased cyclic AMP accumulation in beta-cells *in vitro* and also enhanced glucose-dependent insulin release *in vitro* and *in vivo*, and improved oral glucose tolerance in wild-type mice, but not in GPR119-deficient mice. Dosing in diabetic rodents led to markedly improved glucose tolerance. Orally active GPR119 agonists may offer significant promise as novel anti-diabetics acting in a glucose-dependent fashion.

MEDI 117

Potent and efficacious piperazine substituted pyrimidine derived GPR119 agonists with improved physico-chemical properties

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GPR119 is a recently discovered rhodopsin-like GPCR highly expressed in pancreatic beta-cells and incretin releasing cells in the duodenum, ileum and colon of the gastrointestinal tract. Small molecule GPR119 agonists have been reported to promote incretin release and nutrient-stimulated insulin secretion and therefore, could provide a new therapeutic approach for the treatment of type 2 diabetes. Starting from an internally discovered prototypical agonist tool, AR231453, we herein describe the preparation of a unique a series of C6-piperazine substituted pyrimidine derivatives, that are robust full agonists in a cAMP HTRF assay using human GPR119 and that possess improved physicochemical properties. We will describe synthesis and structure-activity relationships; and present additional *in vitro* and *in vivo* profiling data for selected examples.

MEDI 118

Discovery of ASP1941 as a novel and selective SGLT2 inhibitor for the treatment of type 2 diabetes mellitus

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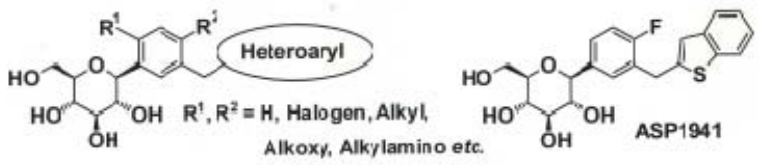
The sodium-glucose co-transporter 2 (SGLT2) is mainly expressed in the proximal tubules of the kidneys where it plays an important role in glucose re-absorption. SGLT2 inhibitors have recently been shown to enhance urinary glucose excretion, reducing hyperglycemia in patients with type 2 diabetes mellitus (T2DM). Through our research, some *C*-glycoside derivatives, including ASP1941, which is being developed for the treatment of T2DM, were found to be

novel SGLT2 inhibitors. The structure-activity relationship and characterization of the compounds will be described.



MEDI 119

Novel ADMET design tool for chemists

David Miller[(1)]*, david@simulations-plus.com, 42505 10th St West, Lancaster CA 93534, United States ; Robert Fraczkiewicz*[(1)]*; Robert Clark*[(1)]*. (1) Simulations Plus, Inc., Lancaster CA 93534, United States*

We present a new tool for molecule design called ADMET Sketcher™. The tool allows chemists to draw molecules inside of a canvas and immediately obtain predicted values of dozens of key ADMET properties. The sketcher itself includes several novel capabilities, including a feature to modify bond and torsional angles of molecule side chains, and an advanced structure-cleanup feature allowing one or more regions of the molecule to remain fixed in place. Yet the true power of the tool comes from the numerous ADMET predictions, which are updated dynamically as structures are edited, allowing near instantaneous feedback about which structural changes affect which properties. The ability to handle multiple structures means that a molecule found to have a desirable property profile can be kept as a reference, so properties of subsequently drawn molecules can easily be compared with the original. This is particularly useful when designing analogs of a known lead.

MEDI 120

QSAR approach in exploring diverse biological activities of *Aconitum* and *Delphinium* sp. alkaloids

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Diterpenoid alkaloids, naturally occurring in plants of the genera *Aconitum* and *Delphinium*, have been the targets of considerable interest of medicinal chemists for a broad range of demonstrated pharmacological activities including arrhythmogenic (neurocardiotoxic), local anaesthetic, antiarrhythmic, curariform,

analgesic, hypotensive, anti-inflammatory, spasmolytic, neurotropic and psychotropic. Here we report results of our molecular modelling studies and extensive QSAR analysis for toxicity, arrhythmogenic, antiarrhythmic, curare-like and local anaesthetic activities established earlier for diterpenoid alkaloids from our in-house collection (about 200 compounds). We showed that our results may serve as a good template for revealing some rules for enhancing potency and selectivity of studied alkaloids and more new promising medicinal candidates are yet to be developed on their basis.

MEDI 121

WITHDRAWN

MEDI 122

Identification of novel peptide inhibitors of the DR6-NAPP protein-protein interaction using a virtual screening approach

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Nikolaev and co-workers recently described a new apoptotic pathway that underlies neuronal development and axonal pruning. According to their model, the pathway, believed to be hijacked in Alzheimer's disease (AD), is engaged by binding between death receptor six (DR6) and an N-terminal fragment of amyloid precursor protein (NAPP) in response to nerve growth factor (NGF) withdrawal. In a previous study, a theoretical model of the DR6-NAPP interaction was constructed. The model implicates a lone NAPP alpha helix-loop motif as crucial to DR6 binding and recognition. We performed structure-based virtual screening experiments on NAPP using focused peptide libraries. Select peptide screening hits were docked to NAPP and the binding modes optimized. Final scoring and ranking was handled using a novel empirical method for estimating protein-peptide binding affinities. Our results suggest structure-based peptide virtual screening and optimization and scoring, are effective methods for identifying viable peptide inhibitors of the DR6-NAPP, protein-protein, interaction.

MEDI 123

Supramolecular chemistry in creation of discontinuous loop structures

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Creation of artificial receptors for protein surface recognition provides access to new biosensors and chemotherapeutics. Efficient recognition requires suitable non-covalent interactions as well as complementary shapes of the surfaces. Several strategies have been developed for mimicking peptide strands, turns, helices, and loops. While discontinuous loops are often found in antibody fragment antigen binding regions, only few scaffolds have been reported for mimicking them. We have taken an elegant approach for creating the discontinuous epitopes based on supramolecular chemistry. In this study, peptides were first conjugated with programmed DNA strands. Self-assembly of the DNA-peptide conjugates led to formation of multi-loops structures as evident from circular dichroism experiments.

MEDI 124

Molecular modeling as a tool for the structural stability evaluation of dendrimeric prodrugs

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Introduction and Purpose. Chagas´ disease and leishmaniasis are neglected tropical diseases and a severe public health concern. A second dendrimer generation (8 to 12 branches) as potentially antichagasic and antileishmanial prodrugs was investigated using molecular modeling methods. Quercetin, hydroxymethylnitrofurazone (NFOH), and 3-hydroxyflavone corresponds to the bioactive agents. Methodology. The dendrimer models were built up and their geometry was optimizated (MM+). A short molecular dynamics sampling at higher temperatures was performed for each model (MOLSIM 3.2 program). The total potential energy (E_{total}) and the number of intramolecular hydrogen bonds (nHb) were evaluated as structural stability parameters. Preliminary Results and Conclusions. The quercetin model with eight branches was the most energetically favorable (-905.49 kcal/mol) and presented a higher nHb value (12). The related NFOH model was energetically less negative probably because it has more freedom degrees. Conversely, the 3-hydroxyflavone model was the most thermodynamically unfavorable and also showed a lower nHb value.

MEDI 125

Density functional calculations of the structural, thermodynamic and spectroscopic properties of Spiroindolone

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Spiroindolone (1R,3S)-5'-Chloro-3-methyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3'-indol-2'(1'H)-one, has been shown to be effective against two species of malaria: Plasmodium falciparum in humans and P. berghei in rodents. Presented here are the detail structure, thermodynamic parameters and spectroscopic properties for the compound. The results were obtained from Density Functional Theory (DFT) calculation. The enthalpy $\Delta_f H°$ is 843.52 kJ/mole. The entropy S° is 638.53 J/mole K. The free energy $\Delta_f G°$ is 653.13 kJ/mole. A dipole moment of 5.37 Debye is also obtained. The IR spectra, the proton NMR spectra, the carbon 13 NMR spectra and the UV-VIS spectra were also investigated. These results have wide applications including the calculations of new lead compounds in drug development efforts. Where possible calculated and experimental results will be compared.

MEDI 126

Novel estrogen and cucurbitane analogs: Potential drug candidates targeting breast cancer

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Breast cancer is commonly diagnosed among women. Developing new drugs that are more effective in treating the breast cancer is needed. Cucurbitacins are known by their anti-cancer activity. Our goals are to study binding affinity using molecular modeling, physicochemical properties, and cytotoxicity for selection of potential drug candidates. A library of 900 estrogen and cucurbitane analogs were docked to estrogen receptors by using (Open Eye®). Docking study showed 76 analogs that had higher affinity to the molecular targets in comparison to some currently used drugs. Several novel estrogen and cucurbitane analogs synthesized in our group were among the higher affinity analogs and were selected to test our hypothesis. ADME studies of these analogs were conducted by using Filter (OpenEye®) application and indicated that analogs meet desirable physiochemical and toxicity characteristics of potential drug candidate. Cytotoxicity study using MCF7 and MDA- MB231 cell lines is in progress and will be presented.

MEDI 127

Dihydropyridone derived library of androgen receptor modulators

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Selective Androgen Receptor Modulators (SARM's) have the potential to be effective antineoplastic agents in the treatment of prostate cancer. Castrate-resistant prostate cancer is associated with deregulated androgen receptor (AR) signaling. A few examples of AR modulators have been shown to be clinically useful, albeit with significant side effects, indicating the need for further research in this area. In order to address some of these issues we have prepared orally-available small molecule modulators of AR based on a common dihydropyridone core. Modification of this core has led to the assembly of a library used to evaluate the structure-activity relationship relevant to AR modulation.
Acknowledgement: This Project has been funded with federal funds from the National Cancer Institute, NIH under contract No. HSN261200800001E

MEDI 128

Design, synthesis, and evaluation of benzamide derivatives as TRPV1 antagonists

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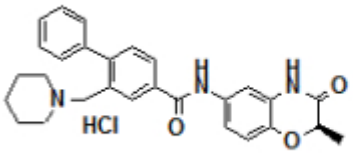
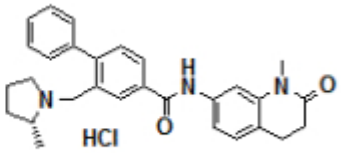
A series of TRPV1 antagonists derived from *N*-(3-hydroxyphenyl)biphenyl-4-carboxamide was designed, synthesized and tested for the functional potency of the TRPV1 ligand. These studies led to the identification of a potent and orally bioavailable TRPV1 antagonists (AS1725195, ASP8370). AS1725195 was orally bioavailable and showed significant effects on segmental spinal nerve ligation (Chung) model with an ED_{50} = 0.71 mg/kg and chronic constriction injury (Bennett) model with an ED_{50} = 1.2 mg/kg in rats. AS1725195 derivatives did not

increase the body temperature.



AS1725195



ASP8370

MEDI 129

Synthesis of nonsedating anxiolytics active against neuropathic pain as well as seizures

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Recently we have designed a series of subtype selective GABA (A) ergic ligands that are active as nonsedating anxiolytics in rodents and primates. These GABAergic/BzR agonists are nearly silent at a1 and a5b2g2 subtypes consequently tolerance does not develop to the anxiolytic or anticonvulsant or antihyperalgesic effects. Based on available literature these agents will exhibit little or no abuse potential in constrast to the well known tranquilizers (Valium, Xanax and Librium). Because they do not develop tolerance to the antinociceptive effects in rodents (in contrast to morphine) and do not cause amnesia, ataxia nor sedation they are targeted for treatment of neuropathic and inflammatory pain including ghost pain, diabetic neuropathy, neuropathy from treatment with anticancer agents and other pain disorders. The lead compound and analogs are not readily metabolized by human microsomes, or in plasma, kidney or brain tissue. However, they are still cleared in routine fashion. The goal is to get the lead compound or an analog in the clinic for neuropathic pain, and then try to get an indication for anxiety disorders and finally get approved as a non sedating, anticonvulsant for various seizure disorders including absence seizures. Again, these non toxic agents do not develop tolerance.

MEDI 130

Synthesis and biological evaluation of isoflavanone derivatives as aromatase inhibitors

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Aromatase is a new and attractive target in the treatment of hormone sensitive breast cancer. We present here the design, synthesis and bioactivity of isoflavanone derivatives. A small library of twenty isoflavanone compounds was developed utilizing the gold gold-catalyzed annulation reactions. The aromatase inhibitory effects of these compounds were determined by fluorescent binding assay. Computer modeling was used to investigate the crucial enzyme-inhibitor interactions.

MEDI 131

Evolving hERG model

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In 2005 the FDA recognized the correlation between hERG inhibition and a prolonged QT interval (a risk factor for ventricular tachyarrhythmias and sudden death) by issuing guidance for the evaluation of new non-antiarrythmic drugs against the hERG channel. Since then modeling hERG inhibition has significantly gained popularity. Here we present the evolution of our TOX_hERG model in consecutive releases of ADMET Predictor™. Examples detailing the impact of new and evolving descriptors on a TOX_hERG's applicability domain and performance on internal and external data are provided. Focus is given to a particularly interesting case where an earlier release of ADMET Predictor outperformed its successor on a client's proprietary data. Finally, we discuss how we are improving model selection criteria through the use of descriptor sensitivity analysis with artificial neural network ensembles in combination with a better understanding of the model's applicability domain, based on the World Drug Index.

MEDI 132

Vesicle encapsulated cisplatin analogs: An effort toward efficient drug delivery

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Cisplatin is the frequently utilized metal-based drug despite of the fact that it has significant amount of side effects. To address those issues there is an ongoing search for better analogs of cisplatin. Furthermore, there has been a quest for selective and efficient delivery method of metal-based drugs. Phospholipid vesicle encapsulated drug delivery is one of those approaches among others. In this work we have been utilizing 1,2-dioleyl-*sn*-glycero-3-phosphocholine (DOPC) to prepare vesicles of 100 nm diameters. Cisplatin analogs *cis*-[Pt^{II}(Hpgly)Cl_2] and [Pt^{II}(pala)Cl] were synthesized and extensively analyzed using elemental analysis, IR, UV-Vis, NMR and X-ray diffraction methods. These complexes are encapsulated in DOPC vesicles and monitored their reactions with Guanosine-5'-monophsphate (5'-GMP) by ^{1}H NMR spectroscopy. Corresponding reactions in aqueous solutions are also investigated. The cytotoxic effects of these two complexes in aqueous buffer and DOPC vesicle encapsulated form will be assayed with various human cancer cell lines. The size of the vesicles will be determined using dynamic light scattering (DLS) technique.

MEDI 133

Biological evaluation and chemical analysis of extracts from p*etiveria alliacea*

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Petiveria alliacea L. (Phytolaccaceae) is a perennial shrub indigenous from the Amazon Rainforest, although it can grow in other areas as Tropical and Central America, Caribbean and Southeastern United States. This plant belongs to the Phytolaccaceae family. In folk medicine, *Petiveria alliacea* is known for its anti-plasmodic, anti-rheumatic, anti-inflammatory and diuretic properties. In our continuous effort to identify and discover new compounds with potential anti-cancer therapeutic applications, we decided to study this plant order through a bio-guided fractionation using a brine shrimp lethality test. Leaves and bark were collected, dried and extracted with a mixture of dichloromethane-methanol (1:1). The resulting crude extract was suspended in water and extracted with a series of solvents of different polarity. The cytotoxicity against breast cancer cell lines and chemical analysis of pure products will be presented and discussed.

MEDI 134

Part 1: Application of parallel medicinal chemistry methods for the rapid and efficient optimization of hits-to-leads-to-clinical candidates

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The application of a number of contemporary medicinal chemistry design strategies utilizing parallel (library) chemistry and physicochmical optimization to efficiently identify novel compounds will be described. Case studies will demonstrate the use of these strategies in advancing compounds for a wide range of targets, such as transporters, phosphodiesterase inhibitors, and kinase inhibitors.

MEDI 135

Part 2: Application of parallel medicinal chemistry methods for the rapid and efficient optimization of hits-to-leads-to-clinical candidates

Christopher J Helal[(1)]*, chris.j.helal@pfizer.com, Eastern Point Road, Groton CT, United States . (1) Neuroscience Medicinal Chemistry, Pfizer Inc., Groton CT 06340, United States*

This poster will build on the application of a number of contemporary medicinal chemistry design strategies utilizing parallel (library) chemistry and physicochmical optimization to efficiently identify novel compounds. Case studies will demonstrate the use of these strategies in advancing compounds for a wide range of targets, such as transporters, phosphodiesterase inhibitors, and kinase inhibitors.

MEDI 136

Monamphilectine A, a potent antimalarial b-lactam from a marine sponge *Hymeniacidon* sp: Isolation, structure, semisynthesis, and bioactivity

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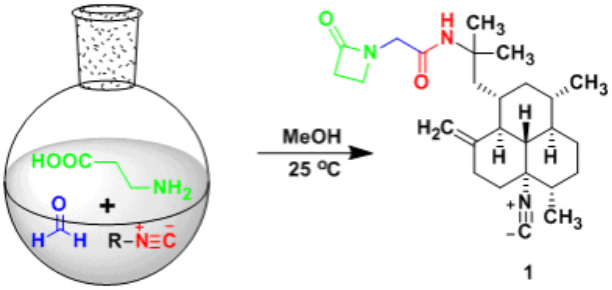

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Monamphilectine A (**1**), a new diterpenoid b-lactam alkaloid showing potent

antimalarial activity, was isolated in milligram quantities following bioassay-directed extraction of a Puerto Rican marine sponge *Hymeniacidon* sp. Its structure, established by interpretation of spectral data, was confirmed unequivocally by chemical interconversion and comparison of physical, chemical, and bioactivity data with the natural product. The one-step semisynthesis of monamphilectine A was based on a multicomponent Ugi reaction that also established its absolute stereostructure.

MEDI 137

Preparation and evaluation of steroid-porphryin conjugates as PDT agents

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Photodynamic therapy (PDT) offers the potential to target neoplastic cells by utilizing a photosensitizer that specifically accumulates in tumors. Light (620-750 nm) is used to activate the photosensitizer, which generates singlet oxygen that subsequently destroys the cells. Currently available photosensitizers however have shown limited specificity to cancer cells and we are developing a series of steroid hormone conjugates where the steroid acts as a delivery vector for the photosensitizer. Examples include C17-α-alkynylestradiol porphyrin derivatives that can be converted to pegylated nanoparticles to enhance uptake via their improved transport properties. Synthesis and initial biological evaluation of these agents will be presented along with scope and future potential.

MEDI 138

Insights into the binding mode of propafenone type P-glycoprotein inhibitors

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Overexpression of the xenotoxin transporter P-glycoprotein (P-gp) is one major reason for the development of multidrug resistance (MDR) leading to the failure of antibiotic and cancer therapies. Inhibitors of P-gp have thus been advocated

as promising candidates for overcoming the problem of MDR. In order to identify binding hypotheses for propafenone-type P-gp inhibitors, we docked a small set of compounds into homology models of the apo and the posthydrolytic conformation of the transporter. According to a pose selection protocol combining common scaffold clustering with SAR information a small number of possible binding hypotheses could be identified, suggesting high involvement of transmembrane helices 5, 6, 7 and 8, and in particular interactions with Y307 and Y310. Subsequent MD simulations of these binding modes revealed the importance of water-mediated H-bonds and showed surprisingly stable complexes with the posthydrolytic conformation of P-gp. We acknowledge financial support provided by the Austrian Science Fund, grant F03502.

MEDI 139

Bioengineering small arteries using carbon nanotube scaffolds

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The field of Bioengineering offers a unique and exciting platform for the development of small arteries. In particular is the interface of nano-material science and biomedical science, where by exciting, cutting edge materials (e.g. Carbon Nanotubes-CNTS) have been crafted that posses both sound integral structure and porous capacity for nutrients and oxygen to flow through freely. Properties of the new materials allows for tissue scaffolding. We describe a thin film (8 microns thick) made from single walled carbon nanotubes that can be used as a scaffold for small artery tissue engineering. In crafting a small artery we cultured $2.5x10^5$ smooth muscle cells (SMC) mixed with type I bovine collagen on a 5mm x 5mm CNT film. SMCs grown on CNT films show no signs of inhibition of growth. SMCs show linear growth patterns on CNT film. This formation of linear patterns is critical for proper smooth muscle architectural formation of an artery. The carbon nanotube film scaffolds offer robust structures that hold shape and contour of design with pliability; along with inherent antibacterial properties that allow for long term culture.

MEDI 140

Synthesis and evaluation of PPADS analogs as P2X receptor antagonists

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Kwan-Young Jung[(1)]; Jung Sun Lee[(1)]; Min Hye Kim[(1)]; Bo Kyung Kim[(1)]; Hyun You[(2)]; Soo Jin Yi[(1)]; Hyo Jun Kim[(1)]; Yong-Chul Kim[(1)(2)]. (1) Department of Life Science, Gwangju Institute of Science & Technology, Gwangju 500-712, Republic of Korea (2) School of Medical System Engineering, Gwangju Institute of Science and Technology, Gwangju 500-712, Republic of Korea

Synthetic polyanionic azo derivatives of PPADS (pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid), and iso-PPADS (the 2,5-disulfonate isomer) were shown to be P2X receptor antagonists. In purpose of structure-activity relationship study, we synthesized derivatives of PPADS containing carboxylic acid side chains instead of strong anion phosphate. First, carboxylic acid analogues of pyridoxal or pyridoxic acid were synthesized to replace the phosphate group at the 5-position of PPADS by carboxylate group and investigate the antagonistic activity at P2X receptor subtypes. Among them, propionic acid analogs, **13** and **14** showed similar antagonistic effects in comparison to pyridoxal-5´-phosphate on mouse $P2X_1$ and human $P2X_3$ receptors. Second, corresponding PPADS analogs synthesized by azo coupling reactions of **13** and **14** with aniline-2,3-disulfonic acid, sulfanilic acid, and 4-aminobenzoic acid were tested for their antagonistic effects at mouse $P2X_1$ and human $P2X_3$ receptors. Most of the compounds showed the similar antagonisms with isoPPADS with nanomolar range of IC_{50} values (80 ~ 200 nM) at $P2X_1$ and $P2X_3$ receptors

MEDI 141

Characterization of protoberberine analogs employed as novel human $P2X_7$ receptor antagonists

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The $P2X_7$ receptor ($P2X_7R$), a member of the ATP-gated ion channel family, is regarded as a promising target for therapy of immune-related diseases including rheumatoid arthritis and chronic pain. A group of novel protoberberine analogs (compounds **3**-**5**), discovered by screening of chemical libraries, was here investigated with respect to their function as $P2X_7R$ antagonists. Compounds **3**-**5** non-competitively inhibited BzATP-induced ethidiumion influx into *$hP2X_7$*-expressing HEK293 cells, with IC_{50} values of 100-300 nM. This antagonistic action on the channel was further confirmed that both BzATP-induced inward currents and Ca^{2+} influx were strongly inhibited by compounds **3-5** in patch-

clamp and Ca^{2+} influx assays. The antagonists also effectively suppressed downstream signaling of $P2X_7$ receptors including IL-1? release and phosphorylation of ERK1/2 and p38 proteins in *$hP2X_7$*-expressing HEK293 cells or in differentiated human monocytes (THP-1 cells). These results imply that novel protoberberine analogs may modulate $P2X_7$ receptor-mediated immune responses by allosteric inhibition of the receptor.

MEDI 142

Synthesis of novel trifluoromethylated hexahydroquinoline derivatives as potential calcium channel modulators

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Organic compounds bearing a trifluoromethyl group have attracted considerable attention due to their role in organic, medicinal, and heterocyclic synthesis. The above is due in part to their ability to enhance metabolic stability, lipophilicity, and ligand –protein interaction. Our group is engaged in the design, synthesis and biological evaluation of bi-and tricyclic ring systems containing the trifluoromethyl group. In recent years, attention has been paid to the synthesis of hexahydroquinolines owing to their significant biological activities. They are well known as calcium channel modulators and have emerged as the most important classes of drugs for the treatment of cardiovascular diseases. In continuation of our effort towards the synthesis of fluorinated heterocyclics of biological potentials, we hereby present the synthesis of novel trifluoromethylated hexahydroquinolines [figure 1] as potential calcium channel modulators. This is the first report of such synthesis using our 5-trifluoromethyl-1, 3-cyclohexanedione, rather than dimedone.

MEDI 143

Drugging the undruggable

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Plasticity and conformational adaptability of proteins has begun to reveal new opportunities for drug discovery on targets previously assumed to be undruggable. First, protein-protein interfaces are generally flat and large, but infact are quite flexible and ligand inefficient. Small molecules can be found,

especially using fragment-based drug discovery approaches, that bind with much greater ligand efficiency to “hot-spots” and in crevices that protein partners do not exploit. Second, most drug discovery efforts focus on generating inhibitors leading to loss-of-function phenotypes. Many enzymes such as proteases and kinases are stored in dormant “off” forms that are subsequently activated through post-translational modification. My lab has been focusing on discovering ways to activate enzymes leading to gain-of-function phenotypes. Work will be presented for discovery of small molecule activators for the apoptotic proteases known as caspases, as well a Ser-Thr kinase PDK-1. The adaptability and flexibility of proteins dramatically expands the opportunities for drug discovery at protein-protein interfaces and allosteric sites.

MEDI 144

Adapting proteostasis for disease intervention

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The chemical information within the polypeptide chain, co- and post-translational modifications of the amino acids comprising the protein, including N-linked glycosylation, and the interactions of the polypeptide with protein homeostasis or proteostasis network components determine whether a lysosomal enzyme will fold and function, be degraded, remain natively unfolded or aggregate and create additional proteostatic challenges for the organism. The outset of the seminar will focus on the intrinsic forces that predispose polypeptides to fold, including conformational propensities, hydrogen bonding, the hydrophobic effect as well as the influence of post-translational modifications. The majority of the talk will focus on the mechanism by which the proteostasis network functions to facilitate protein structure acquisition, trafficking and function to facilitate life and avoid loss- and gain-of-function diseases. The influence of the proteostasis network, comprising transcriptional and post-translational control of protein synthesis, chaperone- and enzyme-assisted folding, disaggregation activities and degradation activities will be covered.

MEDI 145

How cotransin cyclopeptides block transmembrane protein integration by the Sec61 translocon

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Cotransins comprise a family of cyclopeptide natural products which bind the Sec61 translocon and inhibit cotranslational insertion of certain secretory proteins into the endoplasmic reticulum. By an obscure mechanism, sensitivity of a given secretory protein is determined by its N-terminal signal sequence, responsible for targeting nascent proteins to the translocon. In this talk, I will discuss our recent progress toward understanding the molecular mechanism by which cotransins block a decisive step in transmembrane protein biogenesis.

MEDI 146

Structure, function, and inhibition of the M2 proton channel from influenza A virus

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The M2 proton channel from influenza A virus is an essential component of the viral envelope, which is required for acidification of the inside of the virus once engulfed by the endosome. This channel is a prototype for "viroporins", which are found in a variety of envelope viruses. M2 is the target of the anti-influenza drugs amantadine and rimantadine. These drugs were used prophylactically for over three decades, but in the last few years drug-resistance has become a widespread problem and has precluded their use. We have solved the crystal structure of the transmembrane region of the protein to 1.5 Å resolution. Our structure illustrates the mechanism of proton transport, drug-binding and the mechanism of inhibition. Molecular dynamics and other computational methods have been used to design new compounds that inhibit drug-resistant forms of the channel. The design, synthesis, and pharmacological properties of these compounds will be discussed.

MEDI 147

Therapeutic targeting of USP7, a novel chemotherapeutic approach

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Post translational modification of proteins by ubiquitin regulates modify protein stability, localization and function. As a consequence the conjugation and deconjugation of ubiquitin from its protein substrates is tightly controlled by a family of enzymes, one of which is the deubiquitylating enzyme USP7 (HAUSP), which has been shown to deubiquitylate a number of therapeutically relevant substrates including the oncogene HDM2 and the DNA repair protein claspin,

and genetic ablation of USP7 expression results in tumor cell death. Using its proprietary Ub-CHOP screening platform Progenra conducted a screening campaign and identified P5091 a novel small molecule inhibitor of USP7. P5091 and related analogs were profiled in a series of focused *in vitro* and cell based assays. Data will be presented describing the hit to lead optimization program for the P5091 series.

MEDI 148

Biological probes for ubiquitin hydrolases

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Ubiquitin hydrolases mediate cellular homeostasis and are implicated in numerous diseases. Despite their importance, few if any molecules are available for use as scientific or clinical probes. We have taken a phage display approach to develop the common substrate of these enzymes, ubiquitin, into high-affinity and highly specific inhibitors. We generated a 10^10 library of ubiquitin mutants (our antibody set), and screened it for binding to particular ubiquitin hydrolases (our antigen set). So far, we processed two hydrolases, USP8 and USP21, finding ubiquitin variants that have affinities greater than 1000 fold over wildtype ubiquitin; our screens show over two fold magnitude selectivity across our antigen set. Complex structures were determined, revealing two modes of interaction: the USP21-Ubv complex showed a cannonical interaction where the substitution of a buried histidine with phenylanaline increases van der Waals interactions and excludes a buried water molecule that is found conserved in a number of complex structures. The USP8-Ubv complex structure reveals a new mode of binding associated with numerous Ub mutations. These studies provide new reagents for use as biological probes for the human ubiquitin hydrolase family.

MEDI 149

Allosteric small molecule inhibitor of CDC4-substrate interactions

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The ubiquitin-proteasome system is implicated in many disease states including cancer, neurodegenerative disorders, immune dysfunction, developmental syndromes and pathogenesis. The discovery of small molecules that modulate UPS function has the potential for widespread clinical applications. As a test case, we developed a high throughput fluorescence-based assay to screen for modulators of yeast SCF^{Cdc4}-substrate interactions. SCF^{Cdc4} recognizes and ubiquitinates the CDK inhibitor Sic1 and other proteins in a multi-site phosphorylation-dependent manner. A 50,000 compound library was screened for molecules that inhibited the high affinity binding of a fluorescein-labeled substrate phosphopeptide to Cdc4 in vitro. 44 compounds decreased binding affinity by greater than 50%; of these 9 were re-tested in secondary binding and ubiquitination assays against full length phosphorylated Sic1. Our analysis of one potent antagonist of Cdc4 uncovered an unanticipated allosteric mechanism of action. Structure determination of the Cdc4-drug complex revealed that the compound inserts between the b-strands of blades 5 and 6 of the WD40 propeller domain of Cdc4 at a site remote from the substrate binding pocket. Drug-side chain interactions cause a reordering of critical residues in the substrate binding region that effectively occlude part of the phospho-epitope binding pocket. The drug interaction was prevented by mutation of surface resides that engaged the drug and exhibited exquisite specificity for yeast versus human Cdc4/Fbw7. These results demonstrate that high affinity interactions in E3 enzyme-substrate complexes can be targeted via non-interfacial regions on protein surfaces. Our results further suggest that the many signal transduction pathways that depend on WD40 domain proteins, notably the b-subunits of G-protein coupled receptors (GPCRs), may be amenable to allosteric modulation by small molecules.

MEDI 150

Deubiquitinating enzymes as pharmacological targets: BRCA1 associated protein 1 (BAP1)

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BRCA1-associated protein-1 (BAP1) is a nuclear chromatin-associated deubiquitinating enzyme and tumor suppressor. The NCI-H226 lung carcinoma cell line carries a naturally-occurring homozygous deletion of the BAP1 gene ($BAP1^{-/-}$) and lentiviral-based restoration of BAP1 in these cells suppresses both tumor formation in mice and cell growth in monolayer cultures. BAP1 associates with and deubiquitinates host cell factor 1 (HCF-1). HCF-1 acts at the G_1/S boundary by recruiting the H3K4 histone methyltransferases Set1 and MLL to the E2F1 transcription factor. Thus, BAP1 influences G_1/S progression via HCF-1/E2F-regulated promoters and restoring BAP1 in NCI-H226 cells results in a

relaxation of the G_1/S checkpoint and induced cell death. To develop probes of BAP1 function we screened a chemical library for inhibitors of the catalytic activity of BAP1 but did not find useful inhibitors. However, other opportunities to target BAP1 function exist. For instance, we have found endogenous E2F1 and E2F4 proteins co-IP with BAP1 suggesting that BAP1 is a constituent of a large transcription complex. Second, DNA damage induces BAP1 phosphorylation by ATM and shuttling to the cytoplasm. Finally, binding of BAP1 to the cytoplasmic ubiquitin conjugating enzyme E2O induces BAP1 accumulation by altering stability or nuclear import. Thus, there are numerous opportunities to develop drugs targeting BAP1 via its catalytic activity, intracellular transport, phosphorylation, or other protein-protein interactions. A cell-based inhibitor assay for BAP1 function would facilitate identification of inhibitors with non-catalytic mechanisms. BAP1, HCF-1 and the YY1 transcription factor were recently shown to be required for activation of the *cox7c* promoter. This reporter system offers a cell-based assay approach to the identification of specific and active in vivo inhibitors of BAP1 for use as mechanistic probes and/or useful drugs.

MEDI 151

Identification of non-covalent, antiviral DUB inhibitors that block human SARS and NL63 coronaviruses

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Human coronaviruses (HCoV) can cause a variety of respiratory diseases ranging from common colds (HCoVs 229e and OC43), to croup and pneumonia (HCoVs NL63 and HKU1), to severe acute respiratory syndrome (SARS-CoV). Currently, there are no FDA approved vaccines or antivirals for the treatment of any human coronavirus infection. An attractive target for antiviral drug development is the coronavirus papain-like protease (PLpro) which is an essential enzyme for viral replication. PLpro not only catalyzes replicase polyprotein processing, but it also has deUbiqintinating (DUB) and deISGylating activities which are important for viral antagonism of the innate immune response. High-throughput compound screening of structurally diverse libraries has led to the identification of inhibitors of PLpro enzymatic activity. Synthetic optimization of these inhibitors has led to inhibitors with 200 nM potency against the enzyme and micromolar potencies against the SARS and NL63 viruses in cell culture. X-ray structural analysis of SARS PLpro in complex with these inhibitors along with the available X-ray structures of other ubiquitin hydrolases provides a rationale for the selective inhibition of the viral enzymes versus human DUB enzymes. Our results are very encouraging for the development of selective, non-covalent inhibitors of numerous deUbiquitinating enzymes involved in other diseases such as cancer and Parkinson's disease.

MEDI 152

Enhancing proteasome activity by inhibiting the proteasome-associated deubiquitinating enzyme USP14

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Proteasomes, the primary mediators of ubiquitin–protein conjugate degradation, are regulated through complex and poorly understood mechanisms. We have characterized the proteasome-associated deubiquitinating enzyme USP14, and found that it can inhibit the degradation of ubiquitin–protein conjugates both in vitro and in cells. A catalytically inactive variant of USP14 has reduced inhibitory activity, indicating that inhibition is mediated by trimming of the ubiquitin chain on the substrate. A high-throughput screen identified a selective small-molecule inhibitor of the deubiquitinating activity of human USP14. Treatment of cultured cells with this compound enhanced degradation of several proteasome substrates that have been implicated in neurodegenerative disease. USP14 inhibition accelerated the degradation of oxidized proteins and enhanced resistance to oxidative stress. Enhancement of proteasome activity through inhibition of USP14 may offer a strategy to reduce the levels of aberrant proteins in cells under proteotoxic stress.

MEDI 153

Drug-target residence time: An introduction to the concept

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Much of drug discovery today is predicated on the concept of selective targeting of bioactive macromolecules by small molecular weight drugs or by biopharmaceutical therapeutics. Hence, binding of drugs to their targets is seen as paramount for pharmacological activity. Assessment of drug-target interactions is classically quantified in terms of binding parameters such as the IC_{50} or K_d. An alternative perspective on the *in vitro* assessment of drug optimization is presented here, in terms of drug-target residence time, as quantified by the dissociative half-life of the drug-target binary complex. In most cases a long residence time of the drug-target complex results in an extended duration of pharmacodynamic activity, even when systemic concentrations of drug have been significantly reduced through metabolism and other elimination routes. Hence, long residence time for a drug at its biomolecular target can enhance the duration of drug efficacy *in vivo* and can also significantly diminish

the potential for off-target- mediated toxicities. Examples of how these concepts can be incorporated into compound optimization efforts will be presented.

MEDI 154

Irreversible inhibitors of serine proteases: Tools or drugs?

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Proteases are protein-degrading enzymes that are important signalling molecules involved in numerous vital processes. Protease signalling pathways are strictly regulated, and their dysregulation can lead to pathologies such as cardiovascular and inflammatory diseases, cancer, osteoporosis and neurological disorders. Several small-molecule protease inhibitors are on the market and are highly successful to treat the above mentioned diseases and viral infections. The recent introduction of a dipeptidyl peptidase 4 (DPP4) inhibitor to treat type 2 diabetes shows the increasing potential of serine proteases as drug targets. Different types of serine protease inhibitors will be shortly introduced, with special emphasis on irreversible inhibitors. The advantages and disadvantages of irreversible enzyme inhibition will be highlighted. Diaryl phosphonates are known as irreversible inhibitors of serine proteases by phosphorylation of the active site serine alcohol. The synthesis of these molecules and their mechanism of enzyme inhibition will be described. Their potential as research tools and/or drugs will be illustrated with examples from both our own research and literature. Our research in this area focussed on two enzyme families: prolyl peptidases related to DPP4 and trypsin-like serine proteases.

MEDI 155

Drug target residence time in design: A medicinal chemistry perspective

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Optimisation of primary biochemical activity is a common goal in hit-to-lead programmes, however biophysical techniques can provide unique insight that goes well 'beyond the IC_{50}' and has potential to significantly influence series selection and medicinal chemistry design direction. One such property that is emerging as an important parameter to understand, and optimise, is the residence time of the drug compound on the biological target. Methods such as surface plasmon resonance and x-ray crystallography, coupled with *in vitro* biochemical techniques can help deconvolute the IC_{50} and better understand the target residence time. In this presentation, the application of the aforementioned

techniques, as well as others, to Pfizer project examples will be disclosed to illustrate how these data can have a major influence on project medicinal chemistry strategy.

MEDI 156

Potent and selective irreversible inhibition of a viral protease by targeting a non-catalytic cysteine

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Designing selective irreversible inhibitors of viral proteases has proven problematic, in part because pharmacophores that confer potency exploit the conserved catalytic apparatus. We developed a fundamentally different approach by designing irreversible inhibitors that target non-catalytic cysteines. We have successfully applied this approach to the important therapeutic target HCV protease which has broad implications for the design of other selective protease inhibitors.

MEDI 157

Targeting protein kinases with irreversible inhibitors

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Reversible inhibitors of the epidermal growth factor receptor kinase (EGFR) are the first class of small molecules to improve progression-free survival of patients with EGFR-mutated lung cancers. Irreversible EGFR inhibitors introduced as second generation drugs to overcome acquired resistance by the T790M resistance mutation of EGFR have so far demonstrated limited clinical activity in patients with T790M-mutant tumors. In our studies, we systematically analyze the determinants of the activity and selectivity of second generation EGFR inhibitors. Focused libraries of irreversible as well as structurally corresponding reversible EGFR-inhibitors of the quinazolines and quinoline scaffold were synthesized for chemogenomic profiling involving over 98 genetically defined non-small cell lung cancer cell lines. Overall, our results show that the growth inhibitory potency of all irreversible inhibitors against the EGFR-T790M resistance mutation was limited by reduced target inhibition, linked to decreased binding velocity to the mutant kinase. Combined treatment of T790M-mutant tumor cells with BIBW-2992 and the phosphoinositide 3-kinase /mTOR inhibitor PI-103 led to synergistic induction of apoptosis. Furthermore, we generated a detection technique that allows direct measurements of covalent bond formation without relying on kinase activity, thereby allowing the straightforward investigation of the influence of

steric clashes on covalent inhibitors in different resistant kinase mutants. Our findings offer a mechanistic explanation for the limited efficacy of irreversible EGFR inhibitors in EGFR-T790M gatekeeper-mutant tumors.

MEDI 158

Slow onset inhibitors of bacterial fatty acid biosynthesis: Residence time, *in vivo* activity and *in vivo* imaging

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We have developed slow-onset inhibitors of the enoyl-ACP reductases from *Mycobacterium tuberculosis* and *Francisella tularensis* that have antibacterial activity in animal models of infection. The *in vivo* activity of these compounds correlates with their residence time on the drug target, rather than with their thermodynamic affinity for the drug target, supporting the importance of drug-target residence time measurements in lead optimization. We are using X-ray crystallography, MD simulations and NMR spectroscopy to determine the mechanistic basis for slow-onset inhibition and are using this information to develop inhibitors with longer residence times. We have also developed methods to introduce short-lived isotopes into these compounds and are using the labeled molecules to image drug distribution *in vivo*, with the long term goal of developing agents to non-invasively image bacterial pathogens in humans.

MEDI 159

Interplay between transporters and metabolizing enzymes on pharmacokinetic properties

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In 2005, Wu and Benet (Pharmaceutical Research 22:11-23) noted that a Biopharmaceutics Drug Disposition Classification System (BDDCS) could serve as the basis for predicting the importance of transporters in determining drug bioavailability and disposition. Highly permeable, poorly soluble, extensively

metabolized Class 2 compounds constitute the majority of new molecular entities (@ 70%) and present the most complicated relationship in defining the impact of transporters due to the marked effects of transporter-enzyme interplay. Uptake transporters appear to be unimportant for gut bioavailability, but can play a major role in hepatic elimination. Efflux transporters have major effects on bioavailability, metabolism and elimination of Class 2 drugs. Drug efflux by intestinal P-glycoprotein (P-gp) is known to decrease the bioavailability of many CYP3A4 substrates. In contrast for highly soluble, highly permeable Class 1 compounds, metabolism is the major route of elimination, but transporter effects on availability and disposition appear to be negligible.

MEDI 160

SAR of MRP2 interaction for drug discovery programs

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MRP2/ABCC2 is mainly expressed in the apical membrane of liver canaliculi, renal proximal tubules, gut enterocytes, placenta and blood-brain barriers and associates with ADME/Tox issues. Disturbance of MRP2 mediated hepatobiliary transport function can result in disorder of lipid homeostasis and toxic accumulation of compounds in the liver, hence is one of the causes of drug withdrawals from the market. On the other hand, hepatobiliary secretion mediated by Mrp2 lead to nonlinear saturable pharmacokinetics of drugs. Due to its important role in defining ADME/Tox properties, efforts have emerged to build the structure-activity relationship (SAR) for MRP2 at early stages of drug discovery process. The presentation will share the efforts in understanding structural requirements for the interaction of MRP2 protein by using various computational models.

MEDI 161

Role of P-gp in CNS drug discovery

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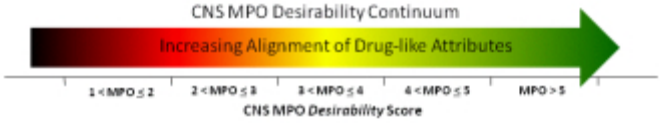
Several *in vitro* cell-based assays to assess blood brain barrier (BBB) permeability exist. Useful high-throughput assays have been developed employing cell lines such as MDCK stably transfected with the human multidrug resistance 1 (MDR1) p-glycoprotein (P-gp). Based on the prominent of P-gp in efflux mechanisms at the BBB, these assays have been instrumental in lead

development for optimizing brain permeability. One strategy to avoid P-gp and optimize brain availability of drug candidates is to understand how physicochemical properties impact P-gp liability and passive permeability. Advances in prospective design include the development of a novel approach to assess drug-likeness. A new multi-parameter design tool (CNS MPO Desirability) focuses on a holistic approach to drug discovery and aims to align drug-like attributes such as low P-gp liability and high passive permeability in one molecule. Examination of the *desirability* approach to drug discovery will be presented, including: case studies of past drug candidates, current clinical candidates and the application to prospective drug design.



MEDI 162

Development of the liver-targeted stearoyl coenzyme-A desaturase (SCD) inhibitor MK-8245 for the treatment of diabetes: Targeting the liver-specific organic anion transport proteins (OATPs)

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Stearoyl-CoA desaturase (SCD) is a key enzyme in fatty acid metabolism responsible for converting saturated fatty acids to mono-unsaturated fatty acids with the formation of a cis-double bond at the C-9 position. The mono-unsaturated products of SCD (palmitoleoyl- and oleoyl-CoA) are the main building blocks for the synthesis of triglycerides, cholesterol esters, phospholipids and wax esters. Rodent and human data indicates that inhibitors of SCD may represent a novel treatment for dyslipidemia and type-2 diabetes. Both SCD1 knockout mice and rodents treated with SCD inhibitors have unacceptable skin and eye toxicity due to reduced SCD-derived lubricating lipids in skin and harderian glands. In order to develop an SCD inhibitor with a therapeutic margin, a liver-targeting strategy was deployed. The approach utilized was to convert systemically-distributed SCD inhibitors into inhibitors of SCD which are

recognized by liver-specific organic anion transport proteins (OATPs) to facilitate active transport of SCD inhibitors into hepatocycte cells. The cellular assays used to gauge cell penetration and active OATP uptake will be described as well as the efforts to characterize tissue distribution and SCD inhibition in liver (efficacy organ) vs. harderian gland and skin (off-target organs). The SAR for SCD potency and liver-targeting will be described, culminating in the discovery of MK-8245, a potent and liver-targeted SCD inhibitor which maintains the beneficial effects on metabolic parameters with a significant improvement in chronic tolerability compared to systemically-distributed SCD inhibitors.

MEDI 163

Utility of influx transporters to enhance oral bioavailability

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Targeting drugs to intestinal uptake transporters has proven to be an effective means of overcoming poor permeability and thereby increasing oral bioavailability. The most frequently targeted influx transporter is the intestinal peptide transporter PepT1, which has the advantage of high capacity and relatively broad substrate specificity. However, additional transporters, such as MCT-1 and hASBT, have also been shown to have utility in drug absorption. Transporter targeting can be accomplished through the synthesis of prodrugs or by structural aspects of the drug itself. While actively transported prodrugs, such as valacyclovir and LY544344, have been successful, the interactions between apical and basolateral transport and prodrug activation can be complex and difficult to model in vitro. This presentation will describe the promise and challenges of transporter-driven uptake, and will review recent advances in transporter-targeted oral drugs.

MEDI 164

Discovery of a liver selective glucokinase activator clinical development candidate for the treatment of Type 2 diabetes

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Duignan[(1)]; Ayman El-Kattan[(1)]; Martin A. Berliner[(1)]; Joshua R. Dunetz[(1)]; Sharad Murdande[(1)]; Shenping Liu[(1)]; Mark Ammirati[(1)]; John Knafels[(1)]. (1) Pfizer Global Research & Development, Groton CT 06340, United States

Glucokinase is a regulator of glucose homeostasis and small molecule allosteric activators of this enzyme represent a promising opportunity for the treatment of diabetes. Systemically acting glucokinase activators have been reported to be efficacious, but in many cases present hypoglycemia risk due to activation of the enzyme at low glucose levels in the pancreas, leading to inappropriately excessive insulin secretion. It was postulated that a liver selective activator may offer glycemic control with reduced hypoglycemia risk. We report a series of carboxylic acid-based glucokinase activators designed as substrates for active liver uptake via OATP transporters. Analogs were characterized using in vivo tissue distribution studies leading to the identification of PFE GKA-2 as a potent activator with >50-fold liver-to-pancreas ratio of tissue distribution. In diabetic animal models, PFE-GKA-2 lowered glucose with no hypoglycemia, and it was subsequently selected as a clinical development candidate for treating Type 2 diabetes.

MEDI 165

Dual action therapy in AD: Tackling amyloid beta deposition and neuroinflammation with inhibitors of Glutaminyl Cyclase (QC)

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The progression of the Alzheimer 's disease (AD) pathology is hallmarked by the deposition of Amyloid-plaques containing the amyloid-beta peptide (Aβ). This process is paralleled by a loss of neuronal functionality of the brain due to inflammatory events. Up to date, no causal treatment is known, that influences both of these pathological processes. N-terminally modified forms of the Aβ-–peptide, especially the N-terminally pyro-glutamate-Abeta (pGlu-Aβ) containing derivatives, have now been identified to act as an early seeding nucleus for the formation of early Aβ aggregates in newly developed tg-animal models, thereby leading to an elevated total Aβ load in the brain. Moreover, these Aβ forms are found to be extremely toxic driving neuron loss and initiating neuro-inflammatory processes. We could show that the formation of pGlu-Aβ is linked to the brain abundant enzyme human Glutaminyl Cyclase (hQC). More intriguingly, the hQC-

activity is involved in gliosis by a mechanism linked to the activation of chemotactic cytokines, such as MCP-1 and fractalkine. The treatment of tg-animal models with hQC-inhibitors successfully led to Aβ-load reduction, attenuation of neuroinflammation as well as an improvement of behavioral phenotypes. Probiodug AG is accordingly developing hQC-inhibitors as a new and causal treatment for AD, tackling Aβ-deposition as well as neuro-inflammation, now entering the regulatory drug development phase. Data of this development will be presented.

MEDI 166

Optimization of potent, selective, and orally bioavailable heat shock protein 90 (Hsp90) pyrrolodinopyrimidine inhibitors and identification of development candidate PF-4942847

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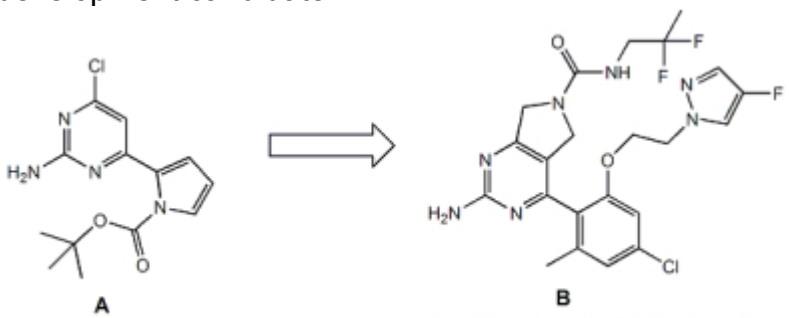
Heat shock protein (Hsp90) is an important target in the development of cancer therapy due to its role at the crossroads of multiple signaling pathways associated with cell proliferation and cell viability. An initial HTS hit, compound **A** (enzyme competitive binding IC_{50}=200 nM; cell IC_{50}=45 mM), was optimized using parallel synthesis, structure-based design, and metabolite identification analysis to provide compound **B**. The latter molecule displayed significantly improved Hsp90 binding affinity and cellular potency relative to compound **A** and also exhibited degradation effects on downstream client proteins (Akt, Her2). In addition, compound **B** displayed acceptable predicted human metabolic clearance, Cyp inhibition profiles, oral absorption, and hERG Ki. Based on these favorable properties, compound **B** (PF-4942847) was nominated as a development candidate.



A

IC_{50}= 0.2 μM, cell IC_{50}= 45 μM.

B

IC_{50}= 12 nM, cell (H1299) IC_{50}= 36 nM

MEDI 167

Discovery of S-nitrosoglutathione reductase (GSNOR) inhibitors as potential agents to treat asthma, COPD and IBD

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S-nitrosoglutathione reductase (GSNOR), a member of the alcohol dehydrogenase family (ADH5), has recently been discovered to regulate intracellular S□nitrosothiols (SNOs), a biologically important class of stable NO adducts, by reducing S-nitrosoglutathione (GSNO). GSNO is a major NO metabolite derived from the reaction of glutathione with reactive nitrogen species. GSNO has been shown to elicit many if not all of the biological functions of NO and also serves as a durable depot for NO which has a short biological half life. Knockout studies of GSNOR in mice have shown that GSNOR has an important influence on NO containing species and regulates the smooth muscle tone in airways and the function of adrenergic receptors in lungs and heart. Given such findings, GSNOR has emerged as a potentially important target for the development of therapeutic approaches for treating respiratory, cardiovascular and gastro□intestinal diseases, many of which have reduced NO as a basis to their patho□physiology. To this end, N30 Pharma initiated a structure□based drug discovery effort to identify useful small molecule inhibitors for GSNOR. In a murine asthma model, GSNOR inhibitors substantially reduce airway hyper□responsiveness to methacholine challenge, show potent anti□inflammatory effects, and increase circulating bioavailable NO consistent with the proposed mechanism of action. The data generated to date suggest these compounds have the potential to be an important novel class of therapeutics in inflammatory and reactive airway diseases such as asthma and COPD as well as cardiovascular disease characterized by reduced bioavailable NO. **N6022**, a potent GSNOR inhibitor with IC_{50} = 20 nM is currently under development as a potential agent for the treatment of acute asthma. In this paper, we will describe the structure-activity relationship of GSNOR inhibitors and findings of N6022 biological and pharmacological activities.

MEDI 168

WITHDRAWN

MEDI 169

Are there lessons to be learned from drugs which have recently entered the market?

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Which projects are most likely to lead to a launched drug? Many medicinal chemists will have posed this question as they survey a company's project portfolio. It is an important question to ask, since no amount of clever design will rectify pursuing the wrong project. This talk aims to delineate some guiding principles, by examining those drugs which have entered the market in recent years.

MEDI 170

Natural products as sources of and leads to drugs

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A recent analysis of approved drugs for all diseases World-wide for the 30 years from 1981 to the end of 2010, demonstrates that of the almost 1370 NCEs that include biologics and vaccines, less than 30% are totally synthetic rising to ~40% if synthetic spatial mimics of natural products are included. In the case of small molecules (almost 1100), synthetics are still less than 50% even including spatial mimics. The presentation will describe data showing that even in the second decade of the 21st Century, antibiotics and antitumor compounds are still significantly influenced by natural product skeletons.

MEDI 171

Natural products drug discovery: Challenges and strategies in the era of the convention on biological diversity

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Natural products continue to provide a diverse and unique source of bioactive lead compounds for drug discovery, but maintaining their continued eminence as source compounds is challenging in the face of the changing nature of the pharmaceutical industry and of biodiversity prospecting. This lecture will provide

an overview of some of these challenges, and will suggest ways in which they can be addressed so that natural products research can remain a viable and productive route to drug discovery. Results from International Cooperative Biodiversity Groups (ICBGs) working in Madagascar, Panama, and Suriname will be used as examples of what can be achieved when biodiversity conservation is linked to drug discovery.

MEDI 172

Plinabulin and marizomib: Seaside-to-bedside chronicles of marine microbe-derived anticancer agents

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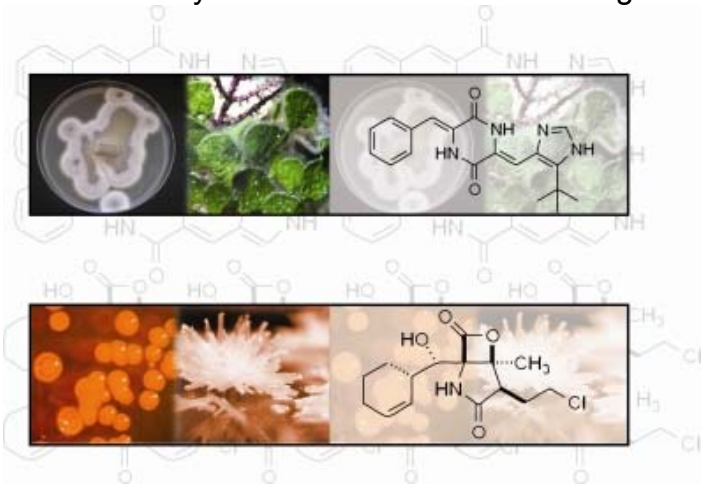
While the potential of marine natural products to fulfill unmet medical needs has been recognized, validation of marine bioprospecting for drug discovery and development will require a series of concrete successes. Seaside-to-bedside chronicles of two marine microbe-derived anticancer agents that mark important milestones along this validation pathway will be presented. Plinabulin, a synthetic analog of the natural product halimide (aka phenylahistin) derived from *Aspergillus* sp., is a vascular disrupting agent in late Phase 2 clinical trials for non-small cell lung cancer and other solid tumors. Marizomib, a secondary metabolite of the marine actinomycete *Salinispora tropica*, is a second generation proteasome inhibitor in late Phase 1 for multiple myeloma and lymphomas. These case studies, capturing events leading from discovery to clinical trials, demonstrate that marine microbiology is not only fertile ground for new chemistry but a viable resource for drug development.



MEDI 173

Ethnobotany and the discovery of plant-derived drugs used in western medicine

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Even as we reach the end of the first decade of the 21st century, medicinal plants continue to afford new drugs for the treatment of various types of human disease. Drug discovery from plants involves a multifaceted experimental approach, inclusive of botanical, phytochemical, biological, and molecular techniques. In a series of seminal publications, Dr. Norman R. Farnsworth and colleagues from the University of Illinois at Chicago showed a strong correlation between about 120 marketed plant drugs found in allopathic medicine and the earlier use of their species of origin in traditional medicine. Examples of how selected major plant-derived drugs in use today were obtained as a result of previous ethnomedical observations will be provided. It is contended that by including a consideration of the traditional uses of a given medicinal plant under study, in order to select the most relevant bioassays for screening, investigators may increase their prospects of success in drug discovery programs.

MEDI 174

Ayurveda for science: Drug discovery, development, and beyond

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Ayurveda has provided important leads to facilitate natural product drug discovery. While taking leads, it is important to respect, protect and promote from traditional knowledge. Scientifically validated and technologically standardized botanical products may be derived using traditional medicine-inspired reverse pharmacology approach. Appropriate models and protocols are needed to evaluate quality, safety, efficacy and clinical advantages of traditional medicine. Most of these medicines are poly herbal, multi targeted, slow acting and may have disease modulating activities rather than direct agonist or antagonist activities. Ayurveda offers better understanding of cause effect relationship and the individual constitution or Prakriti relevance in therapeutics indicate personalized approach. Pragmatic clinical trials with systems approach may be better suited for creating evidence base to traditional medicine. Better understanding of epistemology of Ayurveda may give many new ideas and innovative solutions in the process of progression of biomedicine. This lecture will

give an overview of important strategies for development of innovative botanical medicinal products to global standards by taking real examples from ongoing national networked research programs from India.

MEDI 175

Studies on Indian ginseng, an ancient traditional medicine, and its bioactive constituents

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In the ancient Ayurvedic medical tradition of India, preparations of dried roots of the plant *Withania somnifera* are called Indian Ginseng or Ashwagandha and have been used for over 3,000 years as a tonic to improve general health and reduce stress. The primary bioactive constituent of Indian Ginseng is the steroidal lactone, withaferin A. Recent studies have suggested *in vivo* anticancer activity for withaferin A and *in vitro* induction of cytoskeletal disruption, inhibition of cell mobility, inhibition of NFkB activation, induction of apoptosis, and inhibition of angiogenesis. Given its potential in cancer chemotherapy and in the treatment of other diseases, we have recently developed a soil-less method for large-scale production of withaferin A (WA) which also led to the discovery of the natural occurrence of its prodrug, 2,3-dihydrowithaferin A-3beta-*O*-sulfate (DWAS). In our studies directed towards identification of bioactive constituents in ancient traditional medicines, we have screened extracts derived from these in several functional assays including the heat shock induction assay (HSIA) that targets heat-shock response (HSR). Recent evidence in a wide range of model systems supports the pivotal role for the cellular HSR in helping cells cope with protein mis-folding and oxidative stress. Thus, modulation of HSR should have implications in cancer and neurodegeneration. Interestingly, an extract derived from *Withania somnifera* strongly modulated HSR as determined by its activity in HSIA. Bioactivity-guided fractionation suggested that this activity is associated with WA and DWAS. Given the therapeutic potential of WA, we have examined the activity of a number of its natural and semi-synthetic analogs for the purpose of discovering more potent small molecule natural products which could be used to treat cancer and/or neurological disorders. This work was supported by the U.S. National Cancer Institute/National Institutes of Health, U.S. Department of Agriculture, and Arizona Biomedical Research Commission.

MEDI 176

Eribulin: Discovery and challenges

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Eribulin mesylate (HALAVEN^{TM}) was recently approved by the US FDA to treat patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. Inspired by the marine natural product halichondrin B, this structurally complex drug is prepared by total synthesis, thereby allowing access to analogues unavailable through other means. The challenges associated with the discovery of this new anticancer drug and structure-activity relationships for new analogues will be discussed.

MEDI 177

Diversity oriented synthesis (DOS) leads to an effective new class of bifunctional linchpins uniting anion relay chemistry (ARC) with benzyne reactivity

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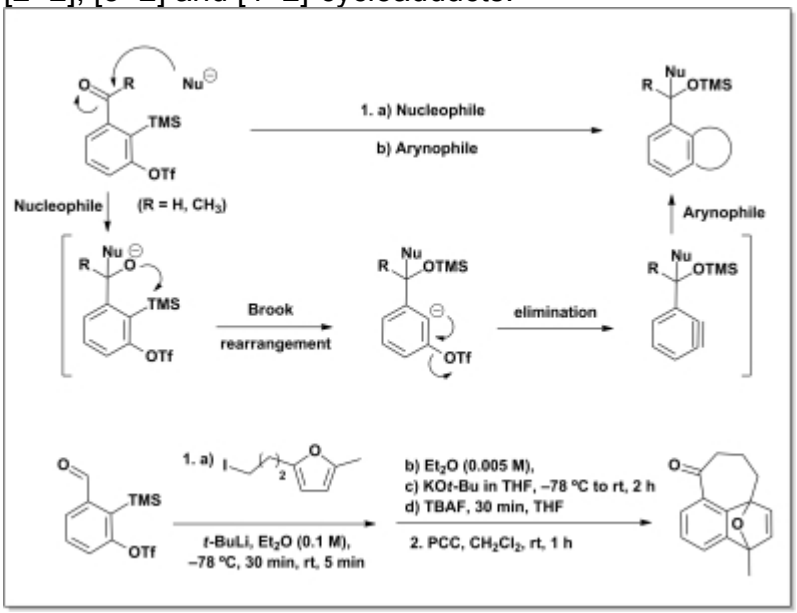
In conjunction with the construction of a DOS library of 10-memebered ring “natural product-like” macrolides, the design, synthesis and validation of a new class of bi-functional linchpins, uniting benzyne reactivity initiated by Type II Anion Relay Chemistry (ARC) has been achieved, permitting access to diverse [2+2], [3+2] and [4+2]-cycloadducts.



MEDI 178

Synthesis and evaluation of rocaglate derivatives as inhibitors of eukaryotic translation

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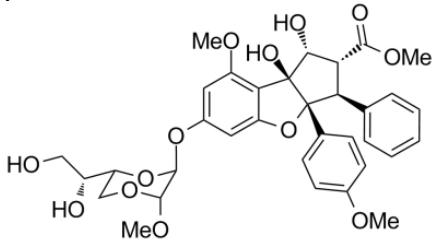
The plant genus *Aglaia* produces a number of secondary metabolites including the cyclopenta[*b*]benzofuran silvestrol **1**. Cyclopenta[*b*]benzofuran natural products possess potent anticancer properties due to modulation of the activity of the RNA helicase eukaryotic initiation factor 4A (eIF4A), which is involved in loading ribosomes onto mRNA templates during translation initiation, a step frequently deregulated in cancer. In this presentation, we will describe our efforts to synthesize silvestrol and rocaglate analogues using photocycloaddition of 3-hydroxyflavones with various dipolarophiles, and evaluation of the rocaglates produced as inhibitors of eukaryotic protein translation.



silvestrol **1**

MEDI 179

Synthetic studies of natural products targeting bacterial cell division

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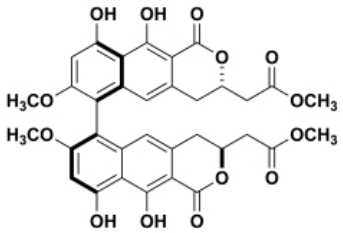
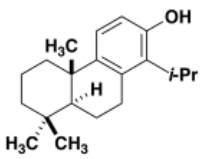
General routes to the syntheses of totarol and viriditoxin will be discussed. Totarol is a diterpenoid natural product targeting the central bacterial cell division protein FtsZ that is isolated from *Podocarpus totara.* We have developed an asymmetric route to this molecule that enables new structural modifications for SAR studies. We have also completed the first synthesis of viriditoxin, which is isolated from an Aspergillus extract and also targets FtsZ. This is the first synthesis of a 6-6'-binaphthopyranone natural product and our route has also enabled the synthesis of related compounds in this class for future studies of FtsZ inhibition.



(-)-viriditoxin



(+)-totarol

MEDI 180

Platensimycin and its effect in mouse models of diabetes

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Platensimycin (PTM) is a recently discovered broad spectrum antibiotic produced by *Streptomyces platensis*. It acts by selectively inhibiting the elongation-condensing enzyme FabF of the fatty acid biosynthesis machinery in bacteria. We now report that PTM is also a potent and highly selective inhibitor of mammalian fatty acid synthase. In contrast to two agents, C75 and cerulenin, widely used as inhibitors of mammalian fatty acid synthase, platensimycin specifically inhibits fatty acid synthesis but not sterol synthesis in rat primary hepatocytes. Platensimycin preferentially concentrates in liver when administered orally to mice and potently inhibits *de novo* lipogenesis, reduces fatty acid oxidation while increasing glucose oxidation. Upon chronic administration, platensimycin caused a net reduction of liver triglyceride levels and improved insulin sensitivity in *db*/+ mice fed a high fructose diet. PTM also reduced liver triglycerides and ambient glucose levels in *db/db* mice. These results provide pharmacological proof-of-concept of inhibiting fatty acid synthase for the treatment of diabetes and related metabolic disorders in animal models.

MEDI 181

Big drugs for very bad bugs

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In 1991 Selva et al reported the structure and antibiotic activity of GE2270 A. This thiopeptide-based natural product inhibits the prokaryotic elongation factor Tu (EF-Tu). The MIC profile against methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), and *Streptococcus pyogenes* (GAS) was exquisite (< 1 µg/mL). A high-throughput screen of the Novartis library identified GE2270 A and several related fermentation metabolites as potent Gram+ antibacterials. We then initiated medicinal chemistry efforts to identify development candidates for parenteral use against G+ infections. Semi-synthetic analogs of GE2270 A were designed, synthesized, and evaluated for MIC. A cocrystal structure-guided medicinal chemistry campaign identified novel, soluble, and potent analogs against staphylococci, enterococci, and streptococci (MIC <1 mg/mL). Potent and soluble compounds were evaluated in mouse sepsis and thigh models of infection and compared with vancomycin, linezolid, and daptomycin. More than 200 novel analogs were synthesized in 5-7 synthesis steps, structure activity relationships were defined, and potent in vitro antibacterial activities were achieved (MIC < 1 mg/mL). Cocrystal studies confirmed the location of ligand binding within EF-Tu and revealed important functional group interactions. Aq solubility was improved (from <0.001 mg/mL to >0.1 mg/mL) and in vivo efficacy was enhanced (*S. aureus* sepsis model: ED_{50} < 5 mg/kg; *S. aureus* thigh model: 3 log reduction of CFU at 40 mg/kg). A phenotypic HTS identified GE2270 A as an antibiotic drug discovery starting point. Medicinal chemistry optimization resulted in the identification of novel, soluble, and very potent antibacterials (in vitro and in vivo). Based on attractive in vitro and in vivo profiles, these studies culminated in the selection of several development candidates.

MEDI 182

Turbocharging academic drug discovery and development: A pharmaceutical commercialization initiative

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As their pipelines of new projects are beginning to dry up, biotechnology and pharmaceutical companies are increasingly looking toward academic institutions for new biological targets and proof-of-concept compounds. While this historically has been a rich area for drug discovery and development cooperation, colleges and universities are now viewing the potential for collaboration and licensing agreements as an attractive new source of funding as research dollars and endowments suffer through the recent global financial crisis. This being the case, many academic institutions have established drug discovery and development centers and institutes in the past few years. These research groups have been

largely charged with enhancing the commercialization potential of biological targets and compounds in the pipeline by developing new probes molecules and novel NCEs. To highlight one such initiative, a case study describing a Pharmaceutical Commercialization Initiative at the University of Minnesota will be presented. Additionally, the opportunities and challenges more generally posed by such initiatives will be addressed. For example, whether the pursuit of licensing opportunities are compatible with the educational role of academic institutions and whether the current models of drug discovery, as practiced in the pharmaceutical industry, are effective in an academic setting. As the drug discovery and development institute that sits at the center of this initiative, the broad capabilities of the Institute for Therapeutics Discovery and Development (ITDD) will also be showcased.

MEDI 183

Viridin-based PI-3 kinase inhibitors

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Over two decades, synthetic and biological studies of the viridin class of steroidal furans have revealed multiple opportunities for fundamental discoveries as well as advanced drug design. Wortmannin is a potent enzyme inhibitor that binds to the ATP site of regulatory kinases such as phosphatidylinositol-3-kinase (PI-3K) and Polo-like kinase. The natural product shares a unique mechanism-based biological activation pathway with other viridins. Todate, there is still ample room for improvements in synthetic strategies and tactics leading toward viridins, and the development of structurally simplified analogs that exert more specific biological effects and are devoid of toxicity issues that have thwarted the clinical development of the parent compounds. PX-866 is a novel small molecule drug derived from wortmannin that is the only irreversible, pan-isoform inhibitor of PI-3K in development. In a Phase 1 study conducted in 60 patients with advanced solid tumors, treatment with PX-866 was well tolerated and associated with inhibition of the PI-3K pathway as well as prolonged disease stabilization. Based on these results, PX-866 is slated to enter Phase 2 clinical development.

MEDI 184

Nonprofit organizations and pharmaceutical research and development

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Nonprofit or not-for-profit organizations (NPOs) play an increasingly important role in providing solutions to the significant challenges faced by both large pharmaceutical and smaller biotechnology companies in today's world. NPOs chartered for the public benefit are common in the US and certain other parts of the world. Examples of large NPOs in the US with bioscience programs are Battelle, RTI, Southern Research, and SRI International. To provide a perspective on NPO business models, case studies spanning a range of technical and business initiatives will be outlined, including basic and contract research, discovery of new drugs and biologics, pharmaceutical and biotech services, technology pivots, company spin-ins and spin-outs, and the creation of new NPOs. The presentation will conclude with lessons learned and food for thought for R&D, commercialization, outsourcing, and innovation.

MEDI 185

Accessible technologies for the discovery of small molecules as research tools and clinical agents

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Several new programs offer financial and technical support to allow researchers from academia and not-for-profit institutions to pursue drug discovery via the entry of new targets or agents into the development pipeline. The NIH Chemical Genomics Center employs a combination of state of the art high-throughput screening, informatics and chemical technologies to survey the landscape of small molecule discovery and forms the framework for an active drug discovery program. An introduction to the novel technologies, profiles and case studies that form the basis of our small molecule discovery platform through potential drug discovery programs will be presented. Several case studies will be highlighted including our efforts surrounding the discovery and development of small molecule activators of the critical metabolic enzyme pyruvate kinase M2 (PKM2).

MEDI 186

Probe and drug discovery at the University of Kansas

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Chemistry contributes to biomedical research in many ways that range from constructing libraries for speculative, early-stage screening campaigns to carrying out optimization of advanced drug candidates. Although all of these

activities have traditionally benefited from advances registered in an academic environment, recent trends suggest that directed drug discovery research is becoming more interesting to academic scientists. In this talk, the historic role of drug discovery within the University of Kansas School of Pharmacy will be reviewed and future prospects for continuing these activities considered.

MEDI 187

p21-Activated kinase-4: An emerging therapeutic target for oncogenic signaling and tumor growth

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The p21-activated kinase (PAK) family of serine/threonine kinases are key effectors for Rho family GTPase signaling required for the regulation of cell morphology, motility, proliferation, and survival in response to growth factor and oncogenic signaling. Despite their critical role in oncogenic signaling, there are no known potent PAK inhibitors. Through high-throughput screening and structure-based design methods, we identify PF-3758309, a potent, selective, ATP-competitive, pyrrolopyrazole inhibitor of PAK4. Studies with the inhibitor build upon our biological studies to provide a more complete understanding of the role of PAK4 in oncogenic signaling and tumor growth. Global cellular analysis confirms that PF-3758309 potently modulates known PAK4 signaling nodes and identifies unexpected links to additional pathways (e.g., p53 regulation). We define PAK-related pathways, provides additional support for PAK4 as a therapeutic target, and identify a potent, orally available small molecule inhibitor with significant promise for the treatment of cancer.

MEDI 188

Identification of clinical candidate, AZD8055: A potent, selective small molecule inhibitor of mTOR kinase

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The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and proliferation and can exist as two multiprotein complexes (mTORC1 and mTORC2). Rapamycin and its analogues (such as Everolimus and Temsirolimus) are known to act as allosteric inhibitors of mTORC1 but do not act

upon mTORC2. It is proposed that a compound directly targeting the kinase domain of mTOR will inhibit signalling through both complexes resulting in a different spectrum of activity compared with rapamycin. Two alternative approaches to identify selective inhibitors of the mTOR kinase domain resulted in the identification of two distinct lead series. The identification and optimisation of these series will be described culminating in the discovery of AZD8055, a potent and selective inhibitor of both mTORC1 and mTORC2. AZD8055 demonstrates dose-dependant tumour growth inhibition in xenograft studies and is currently undergoing clinical evaluation as a potential cancer therapy.

MEDI 189

PLK4 Inhibitors of novel structure as potent anti-proliferative agents

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The co-ordinated action of the Cyclin-dependent kinase (CDK), Polo-like kinase (PLK) and Aurora kinase families is required for mitosis and their deregulation is implicated in tumorigenesis. The PLK family has been identified as important kinases for the control of mitotic entry; PLK1 has been the focus of several industrial labs. PLK4 was identified by an in-house siRNA screen as a candidate anti-cancer target. PLK4 over-expression leads to centrosome amplification and the development of chromosomal instability (CIN), which confers a survival advantage. PLK4 is deregulated in multiple types of cancer (breast, colon, glioma) and prognosis in breast cancer is inversely correlated with expression. These findings prompted a search for potent inhibitors of PLK4 to understand its function and, ultimately, to identify a therapeutic agent. This presentation will introduce the target and describe lead generation efforts that resulted in the identification of novel PLK4 inhibitors. The body keys on the structure guided lead optimization efforts which yielded nanomolar PLK4 inhibitors with potent anti-proliferative activity (GI_{50} < 0.1 uM). Co-complex structures and results of mouse xenograft studies with optimized inhibitors will be described.

MEDI 190

Discovery and development of allosteric AKT inhibitors for the treatment of cancer

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AKT regulates a wide range of cellular processes including cell growth and survival. Activation of AKT signaling has been demonstrated in a significant proportion of human cancers. Consequently AKT inhibitors could have broad

utility in the treatment of cancer. Publications from these laboratories have described a class of allosteric AKT inhibitors. These compounds inhibit both the activity and activation of AKT and are inherently highly selective against other kinases. Development of an orally active compound suitable for clinical development required a re-assessment of the medicinal chemistry approach to these compounds. A new emphasis was placed on optimizing the core of the molecule, enabling the simultaneous improvement in physical properties, *in vivo* activity, oral bioavailability, and non-kinase off-target profile. This work resulted in the identification of orally active AKT inhibitors including MK-2206. Clinical development of MK-2206 in cancer patients is ongoing with a focus on tumors with PI3K pathway activation.

MEDI 191

Understanding the structural basis for highly selective inhibition of Aurora A

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Aurora kinase inhibitors have attracted a great deal of attention as potential anti-cancer agents. Because the two major Aurora kinases (Aurora A and Aurora B) have quite different mitotic functions, it has been debated extensively what the preferred inhibition profile of an Aurora drug might be. Although there is yet no definitive answer to this question, examples of Aurora A-selective, Aurora B-selective, and pan-selective inhibitors have entered human clinical trials. We have found a new and very selective class of Aurora A inhibitors. These inhibit Aurora A potently in enzymatic assays, and they produce Aurora A-related phenotypic changes in treated cells (lack of centrosome separation, loss of Aurora A phospho Thr288 immunostaining). These compounds do not inhibit Aurora B in cell-based assays. Based on crystal structures of these inhibitors bound to Aurora A, we propose that a single amino-acid difference in Aurora B is sufficient to render it insensitive to inhibition. This model has been tested using mutants of Aurora A and B. Because these inhibitors show very high selectivity for Aurora A, they are especially useful for drug combination studies. In particular, they can be used in combination with taxanes and other agents that require a functioning spindle assembly checkpoint for activity.

MEDI 192

Selective RAF inhibitor PLX4032: Discovery to clinic

Prabha Ibrahim[(1)]*, pibrahim@plexxikon.com, 91 Bolivar Drive, Berkeley CA 94710, United States . (1) Department of Non-Clinical Development, Plexxikon Inc., Berkeley CA 94710, United States*

BRAF is the most frequently mutated protein kinase with activating mutations in human cancers. The discovery of oncogenic BRAF mutations in 8% of all solid tumors (e.g. Thyroid, Colorectral Cancer, etc.) and particularly in 50% of patients with metastatic melanoma presents the opportunity to develop oncogene-selective inhibitors that could be beneficial to cancer patients. PLX4032 (RG7204) (N-[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]propane-1-sulfonamide), a potent inhibitor of oncogenic BRAF kinase activity, was discovered by the structure-guided approach. PLX4032 displays similar potency for $BRAF^{V600E}$ (31nM) and C-RAF (48nM), modest B-RAF (100 nM), and significant selectivity against many other kinases. Preclinical experiments demonstrated that PLX4032 selectively blocked the RAF/MEK/ERK pathway in *BRAF* mutant cells and caused regression of *BRAF* mutant xenografts Data from a multicenter Phase 1 clinical trial revealed a remarkably high 81% response rate in metastatic melanoma patients treated at an oral dose of 960 mg twice daily. The most common PLX4032-related Grade 2 or 3 toxicities observed were arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous squamous cell carcinoma, pruritus, and palmar-plantar dysethesia. These data demonstrate that *BRAF*-mutant melanomas are highly addicted to mutant kinase activity.

MEDI 193

Beating the “rule of 5”: It can be done but not too often

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Non RO5's occur with high aqueous solubility, permeability or potency, eg. macrolides. RO5 is based on monomeric compounds; self aggregation can lead to favorable absorption. RO5 is based on paracellular or transcellular permeable compounds. High log P bases are lymphatically absorbed. Base cellular internalization can occur via RES or lipid raft flips or through polybasic tags. Beating RO5 with acids is difficult. Very high MWT oral activity is sometimes possible, eg. LNA miRNAs. Locked 15 KDA helical peptides are cell permeable, eg. stapled peptides. Speculatively, compound rigidity might enhance penetrability. Neutral non RO5 accumulating in c-Elegans show a linear biphenyl motif. Apart from biophysics there are transporters. Unfortunately, the beneficial unknown lies in the many unstudied low capacity transporters. Using these requires high potency compounds, eg. 10 mg dose; finding these is more good luck than a logical process.

MEDI 194

Strategies for starting from a structurally intimidating molecule with very low oral bioavailability: Identification of an orally bioavailable taxane for human clinical evaluation

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We sought to identify a compound that could be used to determine whether the convenience and dosing flexibility offered by the oral administration of a novel taxane anticancer agent could provide efficacy advantages over current therapy. The oral bioavailability (F) of TAXOL and TAXOTERE, the taxane anticancer products approved for clinical use is low and neither, as a single agent, is suitable for oral administration. Paclitaxel, the active constituent of TAXOL has an F which is less than 2% in rats and its high molecular weight and structural features are outside of the parameters considered conducive for a good oral drug. This talk will describe the strategies that were used to generate orally bioavailable leads for medicinal chemistry and the subsequent optimization that ultimately led to the identification of BMS-275183, an efficacious oral taxane that was evaluated in Phase II clinical trials.

MEDI 195

Orally active drug candidates from complex natural product leads

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Complex natural products often present poor pharmacokinetic profiles due to poor solubility characteristics and stability liabilities. However, since a number of attractive biological targets have only natural products as leads, these challenges must be confronted. The cyclic-undecapeptide, cyclosporin A (CsA) and the triterpene enfumafungin represent two such examples, being inhibitors of cyclophilins and fungal b-1,3-D-glucan synthase (GS) respectively. While CsA has seen extensive clinical use as an immunosuppressive agent, its complex

pharmacokinetic profile limits its utility. This presentation will describe the optimization of non-immunosuppressive cyclosporin analogs as anti-HCV agents. The use of in-vitro metabolic stability, hepatic transporter, blood distribution and pharmacokinetic data to select a clinical candidate will be described. Enfumafungin has potent in-vitro activity in fungal susceptibility assays however it lacks in-vivo activity due to chemical and metabolic stability issues. The optimization of potency and pharmacokinetic properties of the lead to afford clinical candidates will be presented.

MEDI 196

Rule-breaking by necessity: Structure-based design of a protein-protein interaction inhibitor, ABT-263, for cancer

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The discovery of ABT-263, a rationally designed, orally bioavailable Bcl-2/Bcl-xL inhibitor currently in Phase II clinical trials for cancer, is described. The biology and structure of the targets are discussed, along with the likelihood of fashioning a large hydrophobic molecule for inhibition of Bcl-2 family proteins. The specific hurdles overcome due to the presence of this issue – hit and lead generation, extremely high protein binding, water insolubility – are presented. Also, several elements of structure-based drug design (SBDD), in particular as they relate to the nature of the targeted protein-protein interaction (PPI) are highlighted. We draw on observations from the experience of discovering ABT-263 and discuss them within the framework of the larger issue of discovering drugs targeting PPIs. Finally, the specific challenge of achieving sufficient oral bioavailability is discussed via SAR of physicochemical properties as well as potency.

MEDI 197

Towards orally bioavailable peptides and peptidomimetics

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Proteins and peptides have many potential uses in medicine, but to date their applications have been limited by high manufacturing costs, chemical instability, and low bioavailability. Traditionally considered to be insufficiently drug-like, recombinant proteins (especially monoclonal antibodies) and peptides have nevertheless become blockbuster therapeutics over the past decade. However,

their high costs, the incidence of non-responders, and the need for administration by injection with consequent low patient compliance are significant hurdles to surmount in order to realise their full potential as medicines. On the other hand, there is also growing interest in smaller peptides that could conceivably combine some advantages of small organic molecules (low cost, stability, bioavailability) with advantages of polypeptides (target specificity, solubility). Are there opportunities to develop target-specific peptides with MW>500 that are orally active and bioavailable? This presentation will address this question, reviewing progress towards making small peptides, cyclic peptides and peptidomimetics orally active.

MEDI 198

HTS identification and optimization of Rho Kinase inhibitors

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The criteria used to identify and prioritize the chemical matter from a HTS campaign will be outlined. Synthetic efforts to optimize the highest priority hits using parallel synthesis, structure-based drug design and multi-parameter optimization will be presented. Techniques used during this process include library design, protein crystallography, HT-ADME and medicinal chemistry principles.

MEDI 199

Small molecule c-jun-N-terminal kinase (JNK) inhibitors protect dopaminergic neurons in models of Parkinson's disease

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c-jun-N-terminal-kinase 3 is (JNK 3) a mitogen-activated protein (MAP) kinase family member expressed primary in the brain that phosphorylates many substrates associated with Parkinson's disease including c-jun and Tau. 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 JNK inhibitors which have good brain penetration, good drug metabolism and

pharmacokinetic (DMPK) properties, and show *in vivo* efficacy in animal models of Parkinson's disease. Nanomolar JNK3 inhibitors which had > 1000-fold selectivity over p38 were developed. Moreover, compounds were developed which had plasma:brain ratios of 2:1 or even 1:1 with good DMPK properties in rat. Furthermore, these compounds were shown to be efficacious in the 6-OHDA and MPTP animal models of Parkinson's disease.

MEDI 200

Discovery and optimization of a novel series of highly selective Btk inhibitors with application in autoimmune and inflammatory disease

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Bruton's tyrosine kinase (Btk) is expressed in a variety of hematopoietic cell types implicated in the pathogenesis of autoimmune and inflammatory disease, and is emerging as promising drug target. Here we describe a novel series of Btk inhibitors that stabilize an inactive enzyme conformation in which the key activating tyrosine is displaced ~18A relative to the apo structure, creating a novel selectivity pocket that is exploited by the ligand. The implications of this binding mode for structure based drug design will be discussed. This binding mode confers exceptional selectivity, allowing pharmacological interrogation of Btk function in various immune cell types. SAR and crystallography reveal the selectivity pharmacophore, allowing optimization to highly selective lead molecules with application in diseases such as rheumatoid arthritis and lupus.

MEDI 201

Targeting RIP1 and EphB3 kinases in cerebral ischemia

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Cerebral ischemia is a prevalent medical condition, currently the third leading cause of death in the United States and the primary cause of disability. However, effective treatments have been elusive. A better understanding of the cell death mechanisms initiated following a cerebral ischemic event and identification of key molecular targets in the cell death pathways would potentially allow effective pharmacological treatments to be devised. A number of kinases have been implicated in cerebral ischemic induced cell death. Understanding the role of these kinases in disease patho-physiology may lead to treatment strategies via kinase modulation. This presentation will describe two kinases,

RIP1 and EphB3, as they relate to cerebral ischemia and the identification and optimization of inhibitors as molecular and pharmacological probes.

MEDI 202

Plasmodium falciparum calcium dependent protein kinase 1 (PfCDPK1): A novel target for the treatment of malaria

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There are approximately 500 million clinical cases of malaria each year worldwide with over a million deaths. The increasing failure of antimalaria drugs due to parasite resistance has highlighted the need for novel antimalarial compounds. *Plasmodium falciparum* calcium dependent protein kinase 1 (PfCDPK1), a plant-like kinase not found in mammals, is essential for the asexual, blood-borne stage of malaria (the stage of the life cycle responsible for the manifestation of the disease), phosphorylating two key components of the actomyosin motor which powers cell invasion. Thus, PfCDPK1 presents an excellent target for an anti-malaria drug discovery program: if merozoites are prevented from invading fresh red blood cells, they rapidly die, multiplication is stopped and the infection is cleared. This talk will describe the discovery and development of a class of compounds that inhibit PfCDPK1 and which show promising levels of anti-parasitaemic effect in murine *in vivo* models.

MEDI 203

Optimization of microtubule affinity regulating kinase (MARK) inhibitors for the treatment of Alzheimer's disease

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Neurofibrillary pathology is a defining feature of Alzheimer's disease (AD) and tracks with cognitive decline. The protein component of these neurofibrillary tangles is hyperphosphorylated tau. It is known that mutations in the microtubule associated region in tau are causative for the neurodegenerative disease Frontotemperal Dementia (FTD). This is thought to be a consequence of tau/microtubule destabilization leading to phosphorylation of tau and subsequent

aggregation and tangle formation. It is postulated that in AD, increased phosphorylation of tau in the microtubule binding domain, particularly serine 262 (S262) similarly drives tau/microtubule destabilization and subsequent pathology. Microtubule Affinity Regulating Kinase (MARK) has been proposed to be the key S262 kinase in human brain. Lead MARK inhibitors were simultaneously optimized for potency, selectivity and appropriate physical properties to enable *in vivo* proof of concept (POC) studies.

MEDI 204

Dissecting down solubility: A diagnosis toolkit

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The most common strategy to increase water solubility at physiological pH without compromising potency is the addition of a solubilizing tag containing a basic ionizable group (usually a primary or secondary amine). The drawback of this approach is its inherent risk of promoting h-ERG binding. Aqueous solubility is the result of the interplay between three factors: ionization, solute-solvent interactions and crystal lattice energy. While these three parameters are not completely independent, one is usually dominant and represents the major solubility barrier. A toolkit to help medicinal chemists to dissect down which of these three parameters is the most important for a given molecule has been developed. The procedure also allows getting a semi-quantitative idea of the impact chemical modifications might have prior to synthesis. This approach offers a more appropriate and more diverse approach to solubility optimization

MEDI 205

Recent strategies for solving hERG channel inhibition

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Avoiding functional blockade of the hERG-encoded cardiac potassium channel during pre-clinical optimization is essential in drug discovery since it can delay ventricular cell repolarization *in vivo*, potentially leading to lethal cardiac arrhythmias. Serious cardiotoxicity associated with hERG inhibition has resulted in both the withdrawal of approved drugs and the discontinuation of clinical trials. This presentation focuses on recent examples of the strategies used to solve hERG liability, relating the tactics to the computational predictions discussed in the preceding talks and anticipating the case studies to follow. In addition to controlling pKa and lipophilicity, other approaches to attenuate hERG binding will

be presented with interesting and unexpected observations highlighted. Molecular properties that influence compound binding to the hERG channel may also impact solubility and this will be discussed. Novel hERG binding modes, the ambiguous role of a basic amine, and the significant function of H-bonding interactions will be compared to the more common pi-pi and cation-pi interactions of drugs with Phe656 and Tyr652 in mediating hERG binding.

MEDI 206

Strategies for addressing hERG activity and other issues in drug discovery

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One common way to improve the aqueous solubility of lead compounds is incorporation of a protonatable amine. Unfortunately, addition of such basic functionality can produce an undesirable activity: blockade of the hERG potassium channel. The application of "molecular transformations" methodology (Sheridan *et al*. *Journal of Chemical Information and Modeling* **2006**, *46*, 180) to large datasets can permit the identification of discrete modifications that have a significant impact on the property of interest across a range of structural classes. For example, this technique may be applied to in-house data to identify transformations that reduce affinity for the hERG channel and also increase aqueous solubility. The results of these and other molecular transformations analyses will be discussed and illustrated with examples from Merck drug discovery programs.

MEDI 207

Identifying non-basic amine building blocks with good solubilizing power that do not introduce hERG using computational informatics techniques

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This talk will describe our efforts to identify and provide medicinal chemists with solubilizing groups that lower the chance of introducing hERG. The common use of introducing a basic amine into a compound to improve solubility has, in many cases, lead to the introduction of undesireable hERG effects. The combination of the basic amine and other features or properties of the molecule (aromaticity, logP) typically leads to hERG. The practical problem, however, is that the awareness of other choices to the basic amine for solubility is lacking or limited to annecdotal experiences. We have therefore developed computational informatics procedures that try to identify solubilizing building blocks that can improve

solubility while lowering the chance of introducing hERG. Our talk will descibe the methodolgies and validatation studies.

MEDI 208

Multiparameter optimization strategies in the design of anticancer drug candidates

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The relationship between lipophilicity, basicity and hERG ion channel effects is well understood and incorporating a basic amine into a hydrophobic molecule (e.g. to increase solubility) generally leads to unwanted cardiovascular effects. Therefore there is a need for other, more creative strategies in medicinal chemistry to achieve a balance of potency, solubility and other desirable properties. This talk will give examples of the use of multiparameter design strategies and tools from recent Pfizer anti-cancer research projects, including dual PI3kinase/mTor inhibitors and PDK1 inhibitors. These examples will also illustrate how recent findings linking physicochemical properties to the outcome of pre-clinical toxicology studies have been incorporated into design strategies.

MEDI 209

Antiprotozoal activity landscape of benzimidazole derivatives: Dual activity-similarity maps

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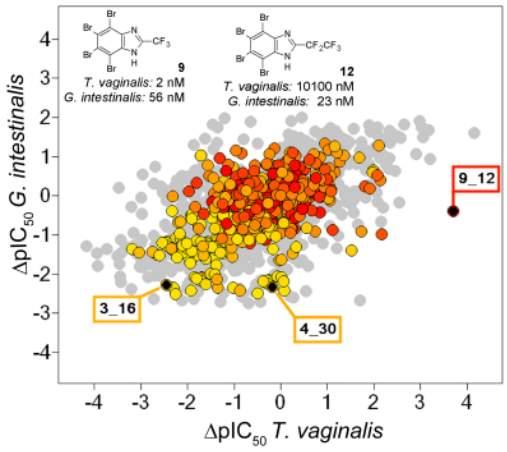
We report a systematic characterization of the SAR of benzimidazoles with activity against *T. vaginalis* and *G. intestinalis*. The analysis was based on pairwise comparisons of the activity similarity and molecular similarity using different molecular representations. The landscapes contained continuous regions and activity cliffs. Deep consensus activity cliffs and several pairs of compounds in smooth regions of the SAR were identified in the landscape of *T. vaginalis*. In contrast, a number of apparent and shallow cliffs were found for *G. intestinalis*. Several compounds active for both parasites showed similar SAR suggesting a common mechanism of action. In order to compare visually the SAR of the benzimidazoles against the two parasites, we developed the dual

activity-similarity (DAS) maps. DAS maps provided a quick means to identify compounds selective for each parasite and compounds with opposite effect against the two parasites. DAS maps are easy to implement and can be used for the analysis of large databases.



MEDI 210

Inhibition of the menaquinone biosynthesis pathway: A novel chemotherapeutic approach to treat *Mycobacterium tuberculosis* and *Staphylococcus aureus*

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The redox cofactor menaquinone is an essential component of the electron transport chain and enzymes in the menaquinone biosynthesis pathway are promising targets for antibacterial drug discovery. Currently, we have identified several classes of inhibitors using HTS that target the 1,4-dihydroxynaphthoyl-CoA synthases (MenB) in *Mycobacterium tuberculosis* and *Staphylococcus aureus*. The most potent series of compounds operate as prodrugs, and react with coenzyme A *in situ* to form the active drug molecule. SAR studies together with data from X-ray crystallography are being utilized to optimize the potency and antibacterial activity of these compounds and to make them more drug-like. Currently, the most potent compounds have MIC values of 0.65 and 0.5 mg/ml against *M. tuberculosis* and *S. aureus*, respectively. Target validation experiments demonstrate that these compounds decrease the menaquinone content in *S. aureus*.

MEDI 211

SAR studies on the substituted central phenyl ring of the biphenyl scaffold as potent CETP inhibitors

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Atherosclerosis and its clinical consequences, coronary heart disease (CHD), stroke and peripheral vascular disease, represent a truly enormous burden to the health care systems of the industrialized world. Metabolic control of lipoprotein levels is a complex and dynamic process involving many factors. One important metabolic control in man is the cholesteryl ester transfer protein (CETP), a plasma glycoprotein that catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL. It has been demonstrated that pharmacological inhibition of CETP in humans will result in increased levels of HDL-C and decreased concentration of LDL-C. The clinical benefit, if any, of such inhibition is still unknown. A number of CETP inhibitor scaffolds have been reported, most notably the tetrahydroquinoline core of Pfizer's torcetrapib and the acylaminobenzenethiol core of the Roche / JTT inhibitor R1628 (JTT-705). This presentation will highlight the SAR investigations into modification of the central phenyl ring of the biphenyl CETP inhibitor scaffold that has led to potent CETP inhibitors possessing both in vitro and in vivo activities.

MEDI 212

Novel small molecule inhibitors of STAT3 in cancer

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Signal transducers and activators of transcription 3 (STAT3) is recognized as one of the significant oncogenic signaling pathways. It has been shown that inhibiting

the STAT3 activation in human cancer cells suppresses proliferation; induce apoptosis in vitro and tumorigenicity in vivo. STA 21, a lead inhibitor of STAT3 dimerization has been discovered through virtual screening. STAT3 dimerization relies on the reciprocal phosphotyrosine-SH2 interactions of two STAT3 monomers. Molecular modeling showed that STA 21 binds at the same site where the pY-705 containing peptide binds. A series of compounds were designed through structural based approach, which bind in a similar mode as STA 21. All the inhibitors have been synthesized through conventional synthetic strategy. The compounds were tested for their abilities to inhibit STAT3-dependent STAT3 luciferase activity, STAT3-DNA binding activity, STAT3 dependent transcription activity, induction of apoptosis and STAT3 dimerization. Two compounds exhibited more potent activity than STA 21.

MEDI 213

Identification and isolation of cytotoxic constituent/s from *Artemisia douglasiana* toward breast cancer

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Previous experiments in this lab showed that extracts of mugwort (*Artemisia douglasiana*) leaves are cytotoxic towards breast cancer cells. The goal of this study is to isolate the cytotoxic constituent/s . It was determined that ethanol was the best solvent for the initial extraction, yielding the highest cytotoxicity. The ethanol extract was separated on a silica gel column using diethyl ether as eluate, and fractions were tested for cytotoxicity. Up to this point, GC-MS had been used to analyze the chemical composition of bioactive fractions. However, the bioactive compound/s may be nonvolatile, and so cannot be seen using GC. To determine if the bioactive compounds are volatile, vacuum distillation was performed, and the resultant distillate and leftover solution were tested for cytotoxicity. The inactivity of the distillate and the activity of the leftover clearly demonstrates that the cytotoxic constituent/s is/are not volatile. Therefore, from now on, HPLC will be used for purity analysis. .

MEDI 214

Novel chemical inhibitors specific for p53-inducible protein phosphatase PPM1D

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PPM1D (also known as Wip1 and PP2Cδ) is a p53-induced protein phosphatase. The PPM1D gene amplification and overexpression has been reported in many human tumors, including breast cancers. Because the phosphoatase activity of PPM1D is essential for its oncogenic effect, PPM1D inhibitor should be a viable anti-cancer agent. In this study, we identified highly potent and specific PPM1D inhibitors, SPI-001 and SPI-002, by screening of compounds in our own chemical library. Both of the compounds inhibited the PPM1D activity in PPM1D-overexpressed cells as well as *in vitro*. Structure activity relationship analysis suggested that the special configurations of two hydrophobic moieties in the compounds should play an important role in inhibitory activity. Furthermore, we showed a potential binding site of SPI-001 on PPM1D by using recombinant mutants. These findings should be very helpful to develop more potent and specific PPM1D inhibitors.

MEDI 215

Design, synthesis and X-ray crystallographic study of NAmPRTase inhibitors as anticancer agents

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NAmPRTase (PBEF/Visfatin) plays a pivotal role for the salvage pathway of NAD^+ biosynthesis. NAmPRTase has been an attractive target for anticancer agents that induce apoptosis of tumor cells via a declining plasma NAD^+ level. In this report, a series of structural analogues of FK866 (1), a known NAmPRTase inhibitor, was synthesized and tested for their inhibitory activities against the proliferation of cancer cells and human NAmPRTase. Among them, compound 7 showed similar anticancer and enzyme inhibitory activity with 1. Further investigation of 7 with the analysis of X-ray co-crystal structure in complex with human NAmPRTase suggested that Asp219 in the active site of enzyme could contribute to an additional interaction with the pyrrole nitrogen of 7.

MEDI 216

Anticancer properties of an important drug lead Podophyllotoxin can be efficiently mimicked by diverse heterocyclic scaffolds accessible by one-step synthesis

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Podophyllotoxin is a potent anticancer cyclolignan, whose structure was used for the development of such useful cancer fighting drugs as etoposide, teniposide and etoposide phosphate. Unfortunately the complex chemical structure of podophyllotoxin virtually prevents the generation of its analogues from simple commercially available materials and, therefore, derivatization of podophyllotoxin has been the main strategy to obtain structure-activity relationship (SAR) information. Our structural simplification of an antimitotic agent podophyllotoxin by designing mimetic heterocyclic scaffolds constructed using multicomponent reactions led to the identification of compounds exhibiting low nanomolar antiproliferative and apoptosis inducing properties. Similarly to podophyllotoxin, these heterocycles inhibit in vitro tubulin polymerization and disrupt the formation of mitotic spindle in dividing cells at low nanomolar concentrations. The active compounds can be prepared from commercially available starting materials by using a one-step three-component synthesis with good yields.

MEDI 217

Potential new agent for refractory lymphomas, ON 013100 esters as a novel class of potent mitotic inhibitors: Synthesis, SAR and target identification

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Targeting components of the mitotic machinery in order to block tumor progression has been an area of intense research. This effort has resulted in several marketed anticancer agents, which provide a proof of concept for the

approach. Examples include the taxanes and vinca alkaloids for which the principal target is the microtubule component of the mitotic spindle. More recently, alternate components of the mitotic machinery have been targeted in an attempt to develop novel anticancer agents. From a screen of a small molecule compound library looking for inhibitors of mitotic cell phase, we identified a novel group of molecules with biochemical IC_{50} in low nanomolar range. SAR analyses of this series of compounds led to ON 013100, a highly active agent arresting the tumor cells in mitotic phase. Modification of functional group in ON 013100 produced a variety of analogs with improved water solubility, bioavailability and anti-tumor activity. One of these analogs ON 013105 has entered clinical trials for refractory lymphoma (NCT01049113).In this presentation, we describe the synthesis, structure activity relationship, biotinylation of ON 013100 and its' target identification by protein pull down assay using streptavidin beads.

MEDI 218

Cucurbitane and estrone analogs: Targeting AR, HSP90, COX II, NF-kB, and iNOS receptors for prostate cancer treatment

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Prostate cancer (PCa) is the top male diagnosed cancer in the US. The Androgen receptor (AR) controls the functions of androgens within the prostate and is a major factor in PCa development. A strong correlation between cancer and inflammation (COXII, NF-kB, and iNOS) is also shown. Cucurbitacins have been recognized for their anti-inflammatory and anticancer activities. OpenEye molecular modeling software was used to dock over 900 cucurbitacin, hexanor, and estrone analogs in the AR, Hsp90, NF-kB, iNOS, COX receptors. An additional ADME filter was used. A number of analogs were tested on the MDA-PCa-2b cell line, IC_{50} values ranged from 0.62 to 0.92μM, while nilutamide and bicalutamide were 1.1μM and 1.3μM respectively. IC_{50} of these compounds towards the PC3 cell line ranged from 0.32 to 4.6μM, while nilutamide and bicalutamide were 1.2μM and 4.23μM respectively. Binding and *in vivo* studies are currently in progress and data will be presented.

MEDI 219

Fused uracil-containing heterocycles as novel topoisomerase-targeting agents

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After the initial discovery of antiproliferative and apoptosis-inducing properties of a camptothecin-inspired pentacycle based on 1*H*-indeno[2',1':5,6]dihydropyrido[2,3-*d*]pyrimidine scaffold, a library of its analogues as well as their oxidized planar counterparts were prepared utilizing a practical multicomponent synthetic protocol. The synthesized compounds exhibited submicromolar to low micromolar antiproliferative potencies toward a panel of human cancer cell lines. Biochemical experiments are consistent with the dihydropyridine library members undergoing intracellular oxidation to the corresponding planar pyridines, which then inhibit topoisomerase II activity leading to inhibition of proliferation and cell death. Because of facile synthetic preparation and promising antitopoisomerase activity, both the dihydropyridine and planar pyridine-based compounds represent a convenient starting point for anticancer drug discovery. Details of this work will be clarified at the meeting.

MEDI 220

3-hydroxy-pyridin-2-ones as a novel zinc binding group (ZBG) for selective HDAC8 inhibition

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Histone deacetylase (HDAC) inhibition is a promising strategy for cancer treatment and management. To date, several structurally distinct small molecule HDAC inhibitors (HDAC*i*) have been reported which generally conform to a pharmacophoric model consisting of zinc-binding group (ZBG), a hydrophobic linker chain, and a cap group. However, majority of HDAC*i* does not differentiate between 11 known zinc-dependent isoforms. Isoform or class selective inhibitors would be ideal chemical tool to elucidate the individual functions of each HDAC isoform. Such selective inhibitors will be critical for connecting HDAC activity to cancer formation, therefore will provide more effective chemotherapy compared to nonselective inhibitors. Modification of the cap group presents an opportunity for achieving HDAC isoform selectivity. Recently, we have shown that a nonpeptide analog such as macrolide shows excellent modulation for isoform

selectivity. In addition to cap group modification, changing metal binding moiety could also impart selectivity. For example, benzamide-based HDAC*i* have improved class I selectivity. Using tools of structure-based drug design, we investigated 3-hydroxy-pyridine-2-ones and its thione derivatives as a novel ZBG in HDAC*i* design against various isoforms. Inhibitor structure is optimized for selective HDAC8 inhibition and preliminary biological results are in accord with *in-silico* results. These HDAC8 selective inhibitors may assist medicinal chemistry efforts for the treatment of the T-cell derived malignancies such as lymphomas and leukemias. It is expected that macrolide-based non-hydroxamate HDAC*i* will further assist in isoform selectivity and will be part of the structure-activity relationship (SAR) efforts to impart potency in addition to selectivity. Design, synthesis and SAR of these selective inhibitors will be presented.

MEDI 221

Synthesis and biological evaluation of 1,2,4-triazole derivatives as selective glycine transporter 1 (GlyT1) inhibitors

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GlyT1 has widespread distribution in forebrain areas such as the cortex and hippocampus and is thought to be co-localized with the NMDA receptor, controlling NMDA receptor function. Medications which inhibit GlyT1 activity and thereby induce NMDA receptor function may be useful as therapeutic agents for treating schizophrenia, dementia, and other related disorders. To identify selective GlyT1 inhibitors, we synthesized a series of 4*H*-1,2,4-triazole derivatives derived from high-throughput screening. Structure-activity relationship (SAR) exploration afforded a benzonitrile analogue with potent and selective GlyT1 inhibitory activity. The restricted rotation at the C-N bond between triazole and benzonitrile provided thermally stable atropisomers at ambient temperatures. We successfully separated the atropisomers and found that (-)-3-[3-ethyl-5-(6-phenylpyridin-3-yl)-4*H*-1,2,4-triazol-4-yl]-2-methylbenzonitrile has 460-fold selectivity between GlyT1 and GlyT2. Here, we describe the SAR and synthesis of the (-)-atropisomer, including optical resolution, as well as detail its *in vivo* pharmacological profile.

MEDI 222

Synthesis of carbon-11-labeled bivalent β-carbolines as new PET agents for imaging of cholinesterase in Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder that attacks the brain by destroying brain cells, causing memory loss and affecting cognition, behavior, and function. Cholinesterase is a family of enzymes including acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). AChE and BChE are associated with cholinergic dysfunction. Central cholinergic systems play a vital role in a wide variety of brain functions, including memory and learning, and thus the development of AChE and BChE inhibitors to improve cholinergic signaling and overall cognition in patients is essential to the treatment of AD. Recently, a new series of bivalent β-carbolines has been found to be potent inhibitors of the AChE and BChE enzymes, these compounds have been developed as potential multi-target anti-Alzheimer agents. New carbon-11-labeled bivalent β-carbolines were first designed and synthesized as radioligands for biomedical imaging technique positron emission tomography (PET) to image cholinesterase in AD. Unlabeled bivalent β-carbolines (precursors and standards) were synthesized from norharmane and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole in multiple steps with moderate to excellent yields. The target tracers, 9,9'-(pentane-1,5-diyl)bis(2-[^{11}C]methyl-9*H*-pyrido[3,4-*b*]indol-2-ium)iodide, 9,9'-(nonane-1,9-diyl)bis(2-[^{11}C]methyl-9*H*-pyrido[3,4-*b*]indol-2-ium)iodide, 9,9'-(dodecane-1,12-diyl)bis(2-[^{11}C]methyl-9*H*-pyrido[3,4-*b*]indol-2-ium)iodide, and 1,9-bis(2-[^{11}C]methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-9(2*H*)-yl)nonane, were prepared from their corresponding precursors, 1,5-di(9*H*-pyrido[3,4-*b*]indol-9-yl)pentane, 1,9-di(9*H*-pyrido[3,4-*b*]indol-9-yl)nonane, 1,12-di(9*H*-pyrido[3,4-*b*]indol-9-yl)dodecane, and 9-(9-(3,4-dihydro-1*H*-pyrido[3,4-b]indol-9(2*H*)-yl)nonyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole, with [^{11}C]CH_3I through *N*-[^{11}C]methylation and isolated either by a simplified solid-phase extraction (SPE) method using a CM Sep-Pak cartridge or by HPLC in 40-60% radiochemical yields decay corrected to end of bombardment (EOB) with 185-370 GBq/mmol specific activity at end of synthesis (EOS).

MEDI 223

Facile synthesis of new carbon-11-labeled celecoxib derivatives as PET radioligands for imaging of COX-2 in inflammation

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The enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX) catalyses the biosynthesis of prostaglandin, prostacyclin and thromboxane from arachidonic acid. Three COX isozymes including COX-1, COX-2 and COX-3 are actually described. COX-1 is present in healthy tissues and responsible for the thrombogensis and the homeostasis. COX-2 is almost undetectable under physiologic conditions and mainly induced by inflammatory stimuli. COX-3 is located in the central nervous system and could be the pharmacological target of acetaminophen. COX-2 over expression is associated with inflammation processes and cancer progression and contributes to the pathogenesis of several types of cancers such as breast cancer and prostate cancer and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Celecoxib is a selective COX-2 inhibitor. A novel series of celecoxib derivatives have been recently developed as more potent anti-inflammatory agents. New carbon-11-labeled celecoxib derivatives were designed and synthesized as radioligands for biomedical imaging technique positron emission tomography (PET) to image COX-2 in inflammation. Unlabeled celecoxib derivatives (precursors and standards) were synthesized from substituted acetophenones in multiple steps with moderate to excellent yields. The target tracers, 4-(5-(2-[^{11}C]methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, 4-(5-(3-[^{11}C]methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, 4-(5-(4-[^{11}C]methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, [^{11}C]methyl 4-(5-(2-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoate, [^{11}C]methyl 4-(5-(3-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoate, [^{11}C]methyl 4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoate, and [^{11}C]methyl 4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoate, were prepared from their corresponding precursors, 4-(5-(2-hydroxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, 4-(5-(3-hydroxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, 4-(5-(4-hydroxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, 4-(5-(2-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoic acid, 4-(5-(3-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoic acid, 4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoic acid, and 4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoic acid, with [^{11}C]CH_3OTf under basic conditions through *O*-[^{11}C]methylation and isolated by a simplified solid-phase extraction (SPE) method in 50-60% radiochemical yields decay corrected to end of bombardment (EOB) with 185-370 GBq/mmol specific activity at end of synthesis (EOS).

MEDI 224

Discovery of novel, potent and orally bioavailable CRTH2 antagonists

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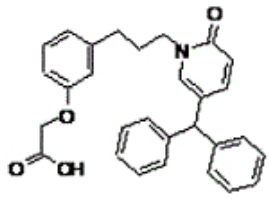
Prostaglandin D2 (PGD2) elicits its biological actions through the G-protein coupled receptors (GPCRs) DP1 and DP2. DP2, which is also known as CRTH2, is expressed on Th2 cells, eosinophils and basophils, and is involved in migration and activation of these cells. Therefore, a CRTH2 antagonist is expected to be an anti-inflammatory medicine for the treatment of asthma and other allergic diseases.



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High throughput screening of our chemical library for CRTH2 antagonists provided a lead compound **1** as a hit, which had moderate human CRTH2 antagonist activity with IC50 values of 42 nM. Optimization of compound **1** led to the discovery of more potent and orally bioavailable compounds, which demonstrated potent in vivo efficacy in a guinea pig model of airway hyperresponsiveness.

MEDI 225

Modification of pyrimidine nucleotides with 4-alkoxyamino and δ-esters of terminal phosphate as selective agonist of the P_2Y_4 receptor

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The $P2Y_4$ receptor is a G protein-coupled receptor (GPCR), activated by UTP and dinucleoside tetraphosphates, which is widely distributed in epithelial cells, smooth muscle, and other tissues. We modified the phosphate and uracil moieties in analogues of pyrimidine nucleoside 5′-triphosphates and 5′-phosphoesters, which were evaluated in stimulation of phospholipase C in stably transfected 1321N1 astrocytoma cells. The 4 position of cytidine was appended with alkyloxy groups, which enhanced $P2Y_4$ receptor potency. Hydroxyl groups

on a terminal d-glucose phosphoester of uridine 5′-tetraphosphate were either inverted or substituted with hydrogen or fluorine to probe the effect of H-bonding in molecular recognition. N^4-(Benzyloxy)-CTP (MRS2976) and Up_4-[1]3′-deoxy-3′-fluoroglucose (MRS2927) were selective for the $P2Y_4$ receptor with EC_{50} values of 97 and 62 nM, respectively. Thus, the potency, selectivity, and stability of extended uridine tetraphosphate derivatives may be modulated by distal structural changes, and we have identified the first reported $P2Y_4$ receptor agonists.

MEDI 226

New class of heterocycles for the study of nicotinic receptors: Secondary and tertiary 1-(3-pyridyl) cyclic amidines

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Alzheimer's disease (AD) is the most common form of dementia. Nicotinic acetylcholine receptors (nAChRs) are down regulated in the brains of AD patients. The α7 nAChR is important in cognitive functions including memory and learning. β-Amyloid peptides in AD act as antagonists of the α7 nAChR inhibiting the influx of calcium ions thus potentiating the symptoms of AD. β-Amyloid peptides are the major component of senile plaques, which accumulate throughout the progression of AD. The goal of this project is to improve the quality of life for AD patients by generating compounds that stimulate the α7 nAChR. The analogs being pursued have a pyridine ring substituted at the 3 position with cyclic amidines. These compounds will be tested for binding to the acetylcholine binding protein, (AChBP) a surrogate of the α7 nAChR. The data obtained will be used to develop a pharmacophore model for this new ligand class.

MEDI 227

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

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Neuropathic pain is among the most challenging types of chronic pain to treat, resulting in 8% of people worldwide with a "burning" or "electrical" pain. With the exact disease mechanisms still poorly elucidated, the most common causes of neuropathic pain include diabetes, nerve injury, exposure to toxins, and inadequate blood supply. Conventional painkillers have been poorly effective in treating neuropathic pain, which is refractory to traditional analgesia. The cannabinoid receptor CB2, has emerged as a new target for the treatment of inflammatory disorders, without the CB1 mediated psychotropic side effects. We sought to develop selective CB2 agonists and assess their potency. Novel cannabinoid modulators based on a tricyclic scaffold, have been prepared. Selected compounds were tested on *in vivo* relevant models of neuropathic pain with the goal of reversing allodynia and hyperalgesia. We will report details of the synthesis, *in vitro* characterization, molecular modeling and *in vivo* testing of the new analogues.

MEDI 228

CCR2b-specific antagonist, Part 4: New design, synthesis and SAR of (4-heteroarylthiophen-2-yl)methyl-(R)-3-aminopyrrolidine derivatives

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The Chemokine Receptor CCR2b is a member of G protein coupled receptor family and has been known to play an important role in chronic inflammatory diseases including multiple sclerosis, rheumatoid arthritis and atherosclerosis. In our exploring studies for the CCR2b receptor antagonists we constructed a QSAR model of the ligand binding site with several compounds by using Sybyl/CoMFA and the other method, and we have made use of the model in the optimization of 1-substituted-(R)-3-aminopyrrolidines. After the synthetic work of various derivatives, we have identified (4-heteroarylthiophen-2-yl)-methyl-(R)-3-aminopyrrolidine derivatives with potent inhibitory activity. We will present the structure-activity-relationship of the (R)-3-aminopyrrolidine series with early ADME properties and so on.

MEDI 229

Novel pyrazolylidene derivatives as selective CB_2 agonists

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Non-selective cannabinoid agonists have been validated both clinically and preclinically for the treatment of chronic pain. However, their broad therapeutic utility is limited by adverse CNS-mediated effects that arise through CB_1 receptor activation. Recent studies have demonstrated that CB_2 selective agonists are active in a variety of neuropathic and inflammatory pain models at doses that do not elicit the centrally mediated effects that plague non-selective CB agonists such as Δ^9-THC. Unlike CB_1 receptors, which are highly expressed within the CNS with a neuronal localization, CB_2 receptors are either absent from or expressed at very low levels within the brain, and appear to be localized primarily on glial cell types. CB_2 agonists are able to normalize glial function over time, and as a consequence of this action, CB_2 agonists may possess a novel mechanism as pain therapeutics. We have identified a series of pyrazolylidene analogs that demonstrate selectivity for the CB_2 receptor, high affinity towards the CB_2 binding site, excellent agonist potency in *in vitro* functional assays, and robust efficacy in multiple preclinical pain models. Relative to a related thiazolylidene structural class, these pyrazolylidene derivatives possess a more basic pyrazole core that provides increased microsomal stability, improved physicochemical properties, and significantly decreased CYP induction activity. We report herein the structure activity relationship studies and pharmacological evaluation of pyrazolylidene analogs as novel and potent CB_2 cannabinoid receptor agonists.

MEDI 230

Potential drug candidates toward smoking cessation

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Cytisine, a natural alkaloid, is a partial agonist of nicotinic acetylcholine receptors (nAChrs) with a high affinity for the α4β2 subtype of nAChr. Therefore, it can be used to prevent nicotine binding to the receptor, minimizing the dopaminergic response. Our approach involves the use of molecular docking software, OpenEye®, to develop new cytisine analogs that express a higher affinity for nAChr α4β2 than commercially available drugs, specifically varenicline. Higher affinity analogs would reduce the dose needed to suppress the dopaminergic response and the toxic side effects of cytisine. Seven cytisine analogs, with a higher predicted affinity for nAChr α4β2, in comparison with varenicline and nicotine, were synthesized by adding *n*-benzyl and *n*-cinnamyl derivatives at the

secondary amine of cytisine. The structures were verified by ^{1}H and ^{13}C NMR and MS analysis. Current work focuses on the development of more cytisine analogs, and binding studies of the synthesized compounds toward the nAChr α4β2. Results of this investigation will be presented.

MEDI 231

Pyrazolonaphthyridines as modulators of α5 containing $GABA_A$ receptors

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The inhibitory neurotransmitter γ-aminobutyric acid (GABA), is an agonist at $GABA_A$, $GABA_B$, and $GABA_C$ receptors. We have focused on $GABA_A$ receptors, which mediate the vast majority of inhibitory synaptic transmission in the central nervous system. Evidence indicates that negative modulation of the $GABA_A$ α5βγ2/3 receptor stimulates a marked improvement of performance in several animal models of memory function, and that this can be achieved with minimal side effects such as sedation or hypnosis. In an attempt to develop a new class of such cognitive enhancers we explored negative modulation of the $GABA_A$ α5 subtype in a target-based binding and electrophysiology screening program to identify compounds that improve cognitive function. We have developed several potent pyrazolonaphthyridine negative modulators in an effort to optimize their pharmacology and physicochemical properties. The synthetic approach and structure activity relationship of this series of novel compounds will be presented.

MEDI 232

Design and synthesis of novel chalcone derivatives as potent Nrf2 activators in mice and human lung epithelial cells

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Nrf2-mediated activation of antioxidant response element (ARE) target genes is a central part of molecular mechanisms governing the protective function of phase II detoxification and antioxidant enzymes against chemical carcinogenesis and oxidative stress. Nrf2 is sequestered in the cytoplasm by interacting with its inhibitor Keap-1. Interaction with cysteine thiol groups located in Keap1 leads to the formation of disulfide bonds which results in a conformational change that renders Keap-1 unable to bind to Nrf2, thereby translocating Nrf2 to the nucleus. A wide variety of dietary and synthetic compounds that function as potent inducers of ARE-regulated gene expression have been shown to exert chemopreventive activities, e.g. sulforaphane, dithiolethione, curcumin, caffeic acid phenethyl ester (CAPE), etc. It is notable that both curcumin and CAPE bear an a,b-unsaturated ketone moiety, and can therefore act as Michael acceptors that are able to modify cycteine thios present in Keap-1. Chalcones or 1,2-diphenyl-2-propen-1-ones are also Michael acceptors and have been reported to possess wide variety of biological properties including anti-inflammatory, analgesic, antipyretic, antioxidant, antibacterial, antifungal and antiprotozoal activities. Our ongoing studies of chalocones have lead to design of novel compounds which show Nrf2 activation on human bronchial epithelial cells. Further, the Structure-Activity Relationship studies have resulted in potent compound that is more active and less toxic than clinical candidates. Detailed results and possible mechanism of action will be discussed.
Acknowledgement: This Project has been funded with federal funds from the National Cancer Institute, NIH under contract No. HSN261200800001E

MEDI 233

Synthesis and antifungal activity of functionalized isomers of 2,3-spirostanes

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Invasive fungal infections are a major complication for individuals with compromised immune systems. One of the most significant challenges in the treatment of invasive fungal infections is the increased resistance of many organisms to widely used antifungals, making the development of novel antifungal agents essential. Many naturally occurring products have been found to be effective antimicrobial agents. In particular, the natural saponin- or steroidal glycosides isolated from plant and marine species- have been shown to possess a range of functional antimicrobial properties. Nonetheless, the significance of

substitutions to either the 2 or the 3 the position of the spirostane steroid moiety present in numerous saponins has been poorly defined with respect to antifungal activities. In this report, we outline a novel approach to the synthesis of a number of functionalized spirostane molecules that can be further used as building blocks for novel saponins and present results from the *in vitro* screenings of the antifungal activities of each derivative against four fungal species, including *Candida albicans, Cryptococcus neoformans, Candida glabrata,* and the filamentous fungus *Aspergillus fumigatus.*

MEDI 234

Synthesis and pharmacological evaluation of sulfur analogs of Ebselen and their role in inhibiting a plasma membrane H^+-ATPase pump (pma1p) in pathogenic and drug resistant strains of fungi

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Fluconazole(FLU) is an antifungal agent for immunocompromised patients, with opportunistic fungal infections. Resistant strains of fungi have evolved due to excess usage of FLU. Ebselen is an antifungal agent, whose activity is attributed to inhibition of a H^+-ATPase (Pma1p) pump in the fungal plasma membrane. Design and syntheses of thirteen N-substituted sulfur analogs of ebselen and evaluation of their antifungal activity against FLU sensitive & resistant strains of *Candida albicans* is reported. The order of activity versus the sensitive strain was N-substituted 3-I-4-$CH_3C_6H_3$ > NH > 4-$OCH_3C_6H_4$ > 4-Cl-2,5-$(OCH_3)_2C_6H_2$ > C_6H_5 > 6-OCH_3-3-C_6H_3N > 4-$OC_2H_5C_6H_4$ > 4-$CH_3C_6H_4$ and versus the resistant strain C_6H_5 > 4-Cl-2,5-$(OCH_3)_2C_6H_2$ > NH > 6-OCH_3-3-C_6H_3N > 4-$CH_3C_6H_4$. Decreasing order of Pma1p inhibition was: 6-OCH_3-3-C_6H_3N(7j) > C_6H_5 > 4-$CH_3C_6H_4$ > 4-Cl-2, 5-$(OCH_3)_2C_6H_2$. Compound 7j (IC_{50} = 2.15µM) was more potent than Ebselen. Thus sulfur analogs of ebselen that inhibit Pma1p may serve as potential antifungal drugs. [Figure 1]

MEDI 235

New inhibitors for an old target: Pyrrolidines and piperidines - promising new scaffolds to block HIV protease

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HIV infections are still among the most serious global health problems causing about two million fatalities per year. The low fidelity of the viral reverse transcriptase and the fast replication rate are the main driving factors for the high mutation rate of the HI virus. This leads to extensive resistance development diminishing the efficacy of several marketed drugs thus necessitating a steadfast and continuous search for new inhibitors favorably possessing a new mechanism of action. Previous work in our group has revealed 3,4-disubstituted pyrrolidines to be a promising starting point for the development of non-peptidic nanomolar HIV protease inhibitors. Based on the initial X-ray structure, the 3,4-di-substituted pyrrolidines were further optimised. Several docking solutions also suggested 3,5-di-substituted piperidines to be equally suitable core fragments. The design, synthesis, first structure activity relationships as well as X-ray structures of the enzyme-inhibitor complexes of these non-peptidic HIV protease inhibitors will be presented.

MEDI 236

Investigating the prevalence of queuine in *Escherichia coli* RNA via incorporation of tritium labeled precursor, preQ$_1$

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Queuine is a modified nucleotide known to occur in the anticodon of four tRNAs. Prior *in vitro* work demonstrated that the modification can be incorporated into RNA species other than presently known tRNAs. Queuine is unusual in that, unlike the majority of modified nucleotides that result from changes to genetically encoded bases, it is incorporated into RNA by transglycosylation. Due to this method of incorporation the modification can be studied with small molecule probes. PreQ$_1$, the precursor to queuine incorporated by eubacteria, was tritium-labeled to investigate the prevalence of base modification in *E. coli.* Three cell lines were utilized to conduct the *in vivo* experiments of this study: a *ΔqueC* knockout of *E. coli* that is unable to synthesize preQ$_1$ so that tritium labeled compound will be incorporated exclusively, a Δ*tgt* knockout strain of *E. coli* that is unable to incorporate preQ$_1$ and a wild-type *E. coli* strain. We will report on the prevalence of queuine ascertained from the degree of radiolabel incorporation as well as an estimation of the size ranges and types of RNA affected.

MEDI 237

Evaluation of azide congeners of preQ$_1$ as substrates for tRNA guanine transglycosylase

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$PreQ_1$ is a precursor of queuine that in eubacteria is incorporated into RNA by tRNA guanine transglycosylase before being further elaborated into queuine. The queuine modification occurs across all eukaryotes and eubacteria with few exceptions, but its function remains unclear. Base modification by transglycosylation is unusual and represents an interesting point of entry for study. As the modified nucleotide occurs through incorporation of a specially synthesized nucleotide instead of via modification of a genetically encoded base, a study of the sites of modification by prepared probes is possible. The syntheses of two novel azide congeners were undertaken for this purpose and will be presented. The evaluation of their interaction with tRNA guanine transglycosylase to determine if they are substrates is under study. The azide probes, if substrates, will present an opportunity to discover novel sites of queuine incorporation into RNA.

MEDI 238

Novel nitrotriazole/imidazole-based amides and sulfonamides as potential anti-trypanosomal drugs, III

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Chagas' disease or American trypanosomiasis, is caused by infection with the parasite *Trypanosoma cruzi* and is the cause of an estimated 14,000 deaths per year and 8 million new cases, with 100 million at risk of infection in 21 Latin American countries. Drugs currently used in the treatment of Chagas are old, active mainly in the acute rather chronic stage of the disease and require a long treatment period with significant dose-dependent toxicity. In our previous *in vitro* work we have found that 3-nitro-1,2,4-triazole- and 2-nitroimidazole-based aromatic and aliphatic amines demonstrate significant and selective activity against *T. cruzi* amastigotes in infected L6 cells. In addition, some of them showed activity against *T. b. rhodesiense* bloodstream form (BSF) trypomastigotes. The present work expands our efforts to the synthesis and *in vitro* evaluation of 3-nitro-1,2,4-triazole- and 2-nitroimidazole-based amides and sulfonamides. Our data demonstrate that 14/16 nitrotriazole-based amides/sulfonamides were 2 to 60 fold more active than the reference drug

benznidazole (Bnz) towards *T. cruzi* amastigotes and 13 of them have selectivity indexes (toxicity to L6 cells/toxicity against *T. cruzi* amastigotes) > 200. In addition, 3 of them were active and selective towards *T. b. rhodesiense* BSF trypomastigotes. The most active derivatives against *T. cruzi* amastigotes were sulfonamide NS-44, and amides NS-43 and NS-24 with IC_{50}s of 28 nM, 42 and 113 nM, respectively. The corresponding selectivities were 1764, 2782 and >2381, respectively. Seven compounds were tested against *T. b. brucei* BSF trypomastigotes, engineered to overexpress the oxygen insensitive, type I nitroreductase, known to be involved in the activation of nitrocompounds; two amides and one sulfonamide were activated by this enzyme.

MEDI 239

AApeptides as antimicrobial peptidomimetics

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AApeptides as Antimicrobial Peptidomimetics SHRUTI PADHEE Dr. Jianfeng Cai Department of Chemistry, University of South Florida The emergent resistance of bacteria against the conventional antibiotics has motivated the search for novel antimicrobial agents. Nature abounds with a number of antimicrobial peptides that are a part of our innate immune system and protect us against a variety of pathogenic bacteria. While they are broadspectrum in their activity and show less drug-resistance induction, their intrinsic metabolic stability limits their potential therapeutic applications. Herein we describe the development of novel broad-spectrum bioactive antimicrobial peptidomimetics-AApeptides. AApeptides were designed based on chiral PNA backbone. Substitution of the nucleobases yields AApeptides that are resistant to proteolysis and are capable of mimicking peptides. AApeptides showing antibacterial activity were prepared by synthesizing cationic amphipathic antibacterial peptide mimics of varying lengths. The therapeutic potential of these AApeptides were accessed by conducting antibacterial assays against a series of both gram-positive and gram-negative bacteria. The toxicity of the AA-peptides was evaluated against human erythrocytes and these AApeptides were found to be almost non-hemolytic up to 100 ug/ml.

MEDI 240

Thiazole, oxadiazole, and carboxamide derivatives of artemisinin are highly selective and potent inhibitors of *Toxoplasma gondii*

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We have prepared 23 new dehydroartemisinin (DART) trioxane derivatives (11 thiazoles, 2 oxadiazoles, and 10 carboxamides) and have screened them for in vitro activity in the *Toxoplasma* lytic cycle. Fifteen (65%) of the derivatives were noncytotoxic to host cells (TD_{50} ≥ 320 μM). Eight thiazole derivatives and two carboxamide derivatives displayed effective inhibition of *Toxoplasma* growth (IC_{50} = 0.25−0.42 μM), comparable in potency to artemether (IC_{50} = 0.31 μM) and >100 times more inhibitory than the currently employed front-line drug trimethoprim (IC_{50} = 46 μM). The thiazoles as a group were more effective than the other derivatives at inhibiting growth of extracellular as well as intracellular parasites. Unexpectedly, two thiazole trioxanes were parasiticidal; both inhibited parasite replication irreversibly after parasite exposure to 10 μM of drug for 24 h, whereas the standard trioxane drugs artemisinin and artemether were not parasiticidal. Some of the new derivatives of artemisinin described here represent effective anti-*Toxoplasma* trioxanes as well as molecular probes for elucidating the mechanism of action of the DART class of artemisinin derivatives.

MEDI 241

Amastigote but not promastigote of *Leishmania* are inhibited by a molybdenum containing polyoxometalate

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Leishmaniasis is a disease caused by *Leishmania* parasites that are transmitted by sand flies, and about 12 million people worldwide are affected. The current treatments are costly and have adverse side effects. The development of new anti-leishmaniasis drugs is a long term goal for this research project. Molybdenum containing polyoxometalates (POM) have been investigated as anticancer agents. JD86 is a POM that exhibited an IC_{50} of ~ 10 μM against three tumor cell lines (Compain et al.). To test the effect of this POM, experiments were conducted in which two different stages of *Leishmania tarentolae* were grown in culture and given a single 10 μM dose of JD86. The cell viability was evaluated each day by the MTT viability assay and light microscopy. JD86

appears to inhibit the amastigote stage but not affect the promastigote stage. These preliminary data indicate that JD86 has some potential to be developed as a new class of pharmaceuticals to treat leishmaniasis.

MEDI 242

Discovery of 5-thiazolyl ketoxime fragment as a pharmacophore for TNF-a release inhibition

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Tumor Necrosis factor-a (TNF- α) is one of the most important mediators of inflammation. Drug discovery literature has several evidences wherein inhibitors of TNF- α were found to be efficacious for treating various inflammatory conditions. Therefore by taking romazarit which was a clinical candidate as a model and by using the template based approach we have designed and synthesized a series of 5-thiazolyl ketoxime derivatives and tested them for their anti-inflammatory and TNF- α release inhibitory potential. These compounds were found to be anti-inflammatory (in vivo), promising inhibitors of TNF-a release by WBC and also inhibitors of LPS induced TNF-a release by human peripheral blood mononuclear cells (hPBMC). In this presentation the utility of novel 5-thiazolyl ketoxime as a useful epitope for designing potential inhibitors of TNF- α release and its utility as anti-inflammatory agents will be discussed.

MEDI 243

Identification of coumarin-3-carboxamide derivatives as potential anti-tuberculosis agents

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As a result of our phenotypic screening-based project, several coumarin-3-carboxamide analogs were identified as having anti-tuberculosis (TB) activity in our whole cell assay. To understand the chemical requirement of this scaffold for the desired activity and to generate a meaningful SAR, a set of compounds was designed and synthesized. Based on the screening results, and the synthesized analogs, structure-activity relationships were determined. Several compounds exhibited promising activity in term of minimum inhibitory concentration (MIC)

against replicating and non-replicating tuberculosis with attractive cytotoxicity profile against mammalian (Vero) cell lines. These compounds were also found to be active against mutants which were resistant to known TB drugs. This compound was also subjected to pharmacokinetic and pharmacodynamic profiling and further taken to various *in vivo* experiments. The outcome of these studies will be discussed in this presentation.

MEDI 244

Pharmacokinetic screening of soluble epoxide hydrolase inhibitors for use in a rat inflammatory pain model

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Soluble epoxide hydrolase (sEH) is the major enzyme involved in the metabolism of epoxyeicosatrienoic acids (EETs) which have anti-inflammatory property. sEH inhibitors have emerged as therapeutic drug agents for treating inflammatory diseases. The pharmacokinetic profiles of 8 sEH inhibitors were determined by p.o. (oral) administration in rats. Better pharmacokinetic parameters (higher C_{max}, longer $t_{1/2}$ and greater AUC) were obtained from 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU), compared to the rest of the inhibitors. The pharmacokinetic profiles of TPPU were further investigated by subcutaneous and intravenous administrations, and the bioavailability at 0.1 mg/kg was 71±18%. The anti-inflammatory and analgesic effect of TPPU was then evaluated by using a lipopolysaccharide (LPS) treated rat model. Inhibition of sEH by TPPU blocked inflammatory and neuropathic pain in a dose-dependent manner. We conclude that TPPU is a potent sEH inhibitor and a promising tool for pharmacological investigation of the effect of sEH inhibition *in vivo*.

MEDI 245

Synthesis and evaluation of new cathepsin D inhibitors

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Cathepsin D is an aspartyl lysosomal protease that catalyzes protein cleavage. It is involved in the process of tumor invasion and metastasis. The cathepsin D

enzyme has been considered as a potential target for cancer therapy. Cathepsin D from human liver purchased from Sigma was used to develop an activity assay. The synthetic compounds have been evaluated for their inhibition of human cathepsin D and have also been tested on MCF-7 breast cancer cells. Data analysis of the effectiveness of these synthetic inhibitors will be used to foster development of newer effective inhibitors that may be used for cancer therapy. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 246

Development and evaluation of new cathepsin K inhibitors

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Cathepsin K has recently been identified at the major cysteine protease expressed in osteoclasts. The abundance and selective location of cathepsin K in cells responsible for bone resorption has lead to a new interest in design of cathepsin K inhibitors for the treatment of osteoporsis. Increased bone resorption may release factors from the extracellular matrix that contribute to tumor growth. In fact, recent reports indicate that interactions between prostate cancer cells, osteoblasts, osteoclasts, and bone matrix are essential in the formation of bone metastases. The synthesis and evaluation of new synthetic compounds using cathepsin K is reported, including testing on MCF-7 breast cancer cells. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 247

Development and evaluation of new cathepsin B inhibitors containing thiosemicarbazones

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Cathepsin B, a lysosomal protease, has been proposed to be involved in the progression and metastatic spread of breast cancer. Associations have been

made between high concentrations of cathepsin B and poor patient prognosis in primary breast cancer. Active cathepsin B localized to the plasma membrane has been shown in invasive bladder tumor cells whereas non-invasive tumor cells have cathepsin B confined to the lysosomes. This suggests that membrane associated cathepsins may participate in tumor invasion. Specific proteinase inhibitors could lead to the development of theraputic agents for treatment of many types of carcinomas. Described is the design and synthesis of inhibitors containing C-terminal thiosemicarbazones. Inhibition data for these cathepsin B inhibitors is reported using N-Carbobenzoxy-L-Phenylalanyl-Arginine-4-nitroanilide hydrochloride as the substrate. Additionally the testing of the synthetic compounds on MCF-7 breast cancer cells is reported. Supported by National Cancer Institute at NIH (Grant No. 3R15CA086933-04 and 3R15CA086933-04A2S1) and Western Illinois University.

MEDI 248

Benzimidazole derivatives as a novel prostaglandin D synthase inhibitor

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Prostaglandin (PG) D_2 is an allergic and inflammatory mediator produced by mast cells and Th2 cells. Hematopoietic PGD synthase (H-PGDS) is localized in mast cells, Th2 cells etc. and participates in allergic and inflammatory reactions. Therefore, selective H-PGDS inhibitors are expected for a candidate of anti-allergic and anti-inflammatory drugs. We have already reported 4-benzoylbenzene-1-carboxamide derivatives (**1**) showed H-PGDS inhibitory activity. Recently, we found 5-benzoylbenzimidazole derivatives as a new lead compound, and after optimization, we have developed orally available H-PGDS selective inhibitors (**2**). The details of this work will be presented.

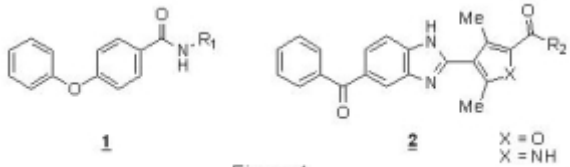

Figure 1

MEDI 249

Fused thiazolo tetrahydropyridinyl amides as potent and selective histamine H_3 receptor antagonists

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There is considerable interest both in industry and academia for the usefulness of histamine H_3 receptor antagonist as a potential target for the treatments of several CNS disorders including Alzheimer's disease, schizophrenia, ADHD, obesity and narcolepsy. Herein we report our initial findings towards identification and pharmacological profiling of fused thiazolo tetrahydropyridinyl amides as novel, potent (hH_3 Ki = 1 to 10 nM), and selective (>100 fold) H_3 receptor antagonists. The lead compound blocked R-α-methylhistamine-induced water intake, suggesting that it behaves as a functional antagonist. The series in general have favorable pharmacokinetic properties, good oral bioavailability, no CYP liability and excellent brain penetration. The lead compound is orally active in preclinical model of cognition (NORT and Morris water maze), showed excellent receptor occupancy and activity in microdialysis assay at lower doses. The design, synthesis, SAR and pharmacological profile of these new analogs as potential treatments for cognitive dysfunction will be presented.

MEDI 250

Hydrogen peroxide activated matrix metalloproteinase proinhibitors

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The misregulation of matrix metalloproteinases (MMPs) is implicated in a variety of diseases including cancer and cardiovascular disease, prompting research into the development of MMP inhibitors (MMPi). Currently, MMPi are administered systemically and are constitutively active, thereby inhibiting MMPs important for normal function. To mask the cytotoxic effects of MMPi, this research investigates the use of boronic ester protecting groups for the development of prodrug MMPi for activation by H_2O_2. This approach is expected to improve both spatial and temporal delivery of MMPi for the treatment of brain injury as a result of ischemic damage during stroke. Specifically, the boronic ester is incorporated through a self-immolative linker at the zinc-binding group of the MMPi to render them inactive. Upon activation by H_2O_2, the prodrug MMPi will both neutralize damaging ROS and inhibit degradative metalloproteinases to provide a dual mode of action in the protection of the blood-brain barrier following ischemia.

MEDI 251

Novel metal chelator fragments for the design of metalloenzyme inhibitors

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Anthrax Lethal Factor (LF) is a zinc dependent metalloenzyme which cleaves the N-terminus of mitogen-activated protein kinase kinases (MAPKKs) to disrupt downstream signaling pathways and cause macrophage apoptosis. Resistance to antibiotics makes LF an attractive target for synthetic inhibitors. Matrix Metalloproteinases (MMPs) are zinc dependent endopeptidases that have been implicated in many diseases such as arthritis, inflammation, multiple sclerosis and cancer, which also make them attractive targets for synthetic inhibitors. Quinoline sulfonamide derivatives have been found to be very selective zinc chelators and have been extensively used as fluoresecent zinc sensors. We have therefore started the design of a small fragment library using 8-sulfonamidoquinoline as a zinc binding group (ZBG). Other small fragment libraries were developed using related ZBGs such as the 2-sulfonamidophenylbenzimidazole, 4-sulfonamidobenzimidazole, 4-sulfonamidobenzoxazole, 2-phenyl-4-sulfonamidobenzimidazole, 2-phenyl-4-sulfonamidobenzoxazole and 2-(2-sulfonamidophenyl)quinoline. The potency of these libraries against several MMPs and Lethal Factor is presented

MEDI 252

Synthesis of poly-enolic Zinc-binding compounds, new inhibitors of matrix metalloproteinases and inflammatory mediators for periodotitis and other diseases

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Matrix metalloproteinases (MMPs) are a group of more than 20 structurally related zinc-containing enzymes that play an important role in the degradation of the main components of the extracellular matrix (ECM) and thereby are crucial in cancer and inflammation. Tetracyclines, an old family of drugs, were found to inhibit matrix metalloproteinases by L. Golub *et al.* several decades ago. However, tetracyclines have several disadvantages. They are antibiotic in nature,

which discourages their use for non-infective conditions and they may cause photosensitivity. These side effects limit chronic high dose regimens, so the development of novel inhibitors for MMPs having fewer limitations, is important. Since a β-diketone assembly on the tetracycline molecule is responsible for the MMP inhibition(via zinc binding), this led us to consider Curcumin as a possible lead structure, because it also contains a β-diketone moiety. Curcumin(CM) is the major component in turmeric and has been used to treat a variety of conditions including inflammation. Our investigations have focussed on a series of enolic tricarbonyl compounds derived from CM, with the idea of improving metal binding. The nature of these compounds and their ability to inhibit MMPs will be discussed.

MEDI 253

Synthesis and SAR of potent & selective MMP-12 inhibitors

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Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory lung disease associated with irreversible progressive airflow limitation. The disease ranks among the top five leading causes of death worldwide. Matrix metalloproteinase-12 (MMP-12) has been characterized to be one of the major proteolytic enzymes to induce airway remodeling, destruction of elastin and the aberrant remodeling of damaged alveoli in COPD and asthma. The goal of this project is to develop and identify an orally potent and selective small molecule inhibitor of MMP-12 for treatment of COPD and asthma. A wide variety of potent and selective MMP-12 compounds, which have a tricyclic scaffold with sulfonamide attached to an amino acid, had been synthesized.

MEDI 254

Discovery and characterization of 2-(7-(5-phenyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid derivatives as potent and selective human $S1P_1$ receptor agonists

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$S1P_1$ receptor driven lymphopenia may have utility in the treatment of an array of autoimmune disease states. Herein, we describe a series of 2-(7-(5-phenyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acids which were identified as potent and selective agonists of the human $S1P_1$ receptor. Analogues from within this series possessed desirable safety and ADME profiles, and were efficacious at reducing circulating rodent lymphocytes following administration of an oral bolus. Subsequent lead optimization studies resulted in analogues with dramatically improved *in vitro* and *in vivo* potencies.

MEDI 255

Synthesis and SAR of substituted 7*H*-pyrrolo[2,3-d]pyrimidines as ACK1 inhibitors

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ACK1 (activated Cdc42Hs associated tyrosine kinase), a non-receptor tyrosine kinase, is frequently amplified in human tumors. Overexpression of ACK1 in cancer cell lines can increase the invasive phenotype of these cells both in vitro and in vivo and leads to increased mortality in a mouse model of metastasis. Here a new series of 4-substituted-amino-5,6-disubstituted-7*H*-pyrrolo[2,3-d]pyrimidines were synthesized and evaluated as potent inhibitors of the ACK1. Subsequent structure-activity relationship (SAR) studies led to the identification of several compounds that are potent against ACK1. **Figure 1**

MEDI 256

Imidazoles and other heterocycles as amide bioisosteres for the inhibition of anaplastic lymphoma kinase (ALK)

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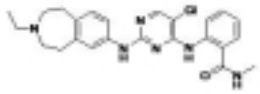
Anaplastic large cell lymphoma (ALCL) is a rare and aggressive type of T-cell lymphoma. Anaplastic lymphoma kinase (ALK), a member of the insulin receptor family, when disregulated acts as an oncogene. Literature supports a role for ALK in malignancies in which constitutively over expressed and activated NPM-ALK fusion proteins drive proliferation of ALCLs prompting the need for potent ALK inhibitors. The synthesis and ALK potency of heterocyclic bioisostere mimics for the carboxamide of **1** will be discussed.



1

MEDI 257

Potent EGFR tyrosine kinase inhibitors as anticancer agents

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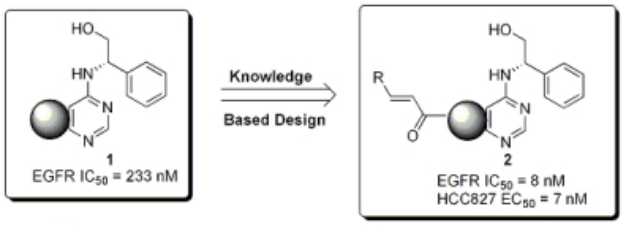
Abnormally elevated EGFR kinase activity can lead to various pathological states, including proliferative diseases such as cancer. Several small-molecule inhibitors of EGFR tyrosine kinase have been developed; however, the drug's resistance has been clinically observed and has been associated with the T790M. The development of selective protein kinase inhibitors has become an important area of drug discovery for the potential treatment of the variety of solid tumors. Through enzyme based screening strategy, **1** which was synthesized as the Aurora kinase inhibitor was also the potent EGFR kinase inhibitor. Further rational-design based on literatures, the introduction of the Michael acceptor group led to the identification of **2**, which inhibited drug's resistance of double mutant EGFR kinase (T790M/L858R). Further structural modification to improve the potency and drug like properties is underway to identify development candidate.



compound	EGFR WT IC_{50} (nM)	HCC-827 EC_{50} (nM)	EGFR DM IC_{50} (nM)
2	7	8	22
Iressa	39	12	2900
BIBW-2992	11	14	15

MEDI 258

Design and synthesis of potent Aurora kinase inhibitors

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Aurora kinases are potential targets for anticancer drug development due to their role in tumorigenesis and cancer progression. Our group found BPR1K0432 as potent Aurora kinase inhibitors, however, BPR1K0432 was inactive in HCT-116 tumor xenograpft model *in vivo*. Here we report introduction of soluble group into molecules to improve drug like properties (Clog P). Several analogs were synthesized and BPR1K0724 in HCT-116 tumor xenograpft mode was found to be active at 20 mpk (bid) while VX-680 was active at 50 mg/kg. Further biological testing of BPR1K0724 is in progress to realize its potential as Aurora kinase inhibitor drug candidate. [**figure1**] **-**

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MEDI 259

Synthesis and structure-activity relationship of novel 4-substituted pyrazolo[1,5-*a*]pyridine analogs as potent MAPKAP-K2 inhibitors

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MAPKAP-K2 (mitogen activated protein kinase-activated protein kinase 2) is a direct substrate of the p38 kinase in MAP kinase pathway and it is believed to be a potentially safer target compared to p38 for anti-inflammatory therapy. We have already reported a new class of pyrazolo[1,5-*a*]pyrimidine analogues as MAPKAP-K2 inhibitors. According to the X-ray co-crystal structure analysis of complex of MAPKAP-K2 with pyrazolo[1,5-*a*]pyrimidine derivative, it was found that there was a space to accommodate a small substituent around 4-position of the pyrazolo[1,5-*a*]pyrimidine scaffold. To introduce a substituent into this space, 4-substituted pyrazolo[1,5-*a*]pyridine derivatives were designed and synthesized. As a result of the exploration of substituents on 4-position of the pyrazolo[1,5-*a*]pyridine, CN group was found to be the most appropriate substituent. We will present the synthesis, the SAR studies and the X-ray co-crystal structure of pyrazolo[1,5-*a*]pyridine analogues.

MEDI 260

Development of selective B-RAF kinase inhibitors

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B-Raf kinase has a central role in the regulation of the MAPK pathway and as such is an enticing target for cancer therapy. Recent clinical data on PLX4032 and GSK2118436 has provided proof-of-concept for mutant selective B-Raf inhibitors in B-Raf mutant melanoma. However, little is known about pan-Raf inhibitors that have the potential for broader clinical activity in B-Raf mutant and wild type cancers. Herein we report the development of a series of substituted purines as pan-Raf inhibitors which show superior kinase selectivity and cell potency relative to Sorafenib (marketed VEGF/Raf inhibitor). *In vivo* pharmacology in rodents and efficacy in a melanoma based xenograft model will be discussed.

MEDI 261

Targeting kinase docking sites: A fluorescence-based assay for p38-α inhibitors targeting a substrate binding site

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Blocking docking interactions between kinase network partners is a promising alternative approach to targeting the ATP-binding sites for selectively inhibiting kinase (and/or phosphatase) signaling. The mitogen-activated protein kinases (MAPKs) are serine/theronine kinases that serve as important mediators of inflammatory cytokines including tumor necrosis factor alpha (TNFα) and interleukin-1 beta (1L-1β). MAPK-substrate specificity has been shown to be mediated through docking interactions involving substrate docking motifs that interact with kinase docking sites. Here we report the identification of a new class of small molecule, covalent p38α MAP kinase docking site probes. We further demonstrate that such probes can be used to fluorescently label p38α both in vitro and in cells via azide-alkyne “Click” chemistry. This serves as the basis of an assay that can be used to identify inhibitors that specifically target the substrate docking site of p38α.

MEDI 262

Synthesis and structure-activity relationship of (1-halo-2-naphthyl) carbamate-based inhibitors of KIAA1363

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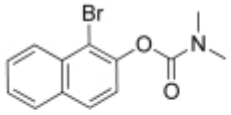
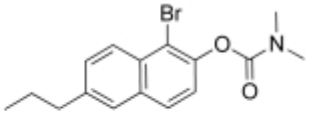
KIAA1363 is a serine hydrolase whose activity has been shown to be positively associated with tumor cell invasiveness. Furthermore, inhibition of KIAA1363 has been shown to decrease alkyl-LPA levels and cancer cell migration in vitro. Thus inhibitors of KIAA1363 represent a novel targeted therapy approach towards cancer. The HTS hit **1** was identified as a KIAA1363 inhibitor with an IC_{50} value of 1100 nM and shown using ESI-MS to carbamylate the catalytic residue Ser^{191}. SAR studies explored both substitution of the 1-bromo group and derivatization of the 6-position. Activity based protein profiling demonstrated **AX13057** inhibited tumor-localized KIAA1363 in SK-OV-3 xenograft-bearing mice.



1
KIAA1363 IC_{50} = 1100 nM



AX13057
KIAA1363 IC_{50} = 130 nM

MEDI 263

7-Benzyl-2-methyl-*N*-substituted-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amines: Design, synthesis and evaluation as receptor tyrosine kinase inhibitors

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Angiogenesis, the process of formation of new blood vessels from existing vasculature, plays a vital role in tumor growth and metastasis. Receptor tyrosine kinases (RTKs) have been identified to play a crucial role in cellular signaling cascades that regulate growth, differentiation and proliferation of cells. Tumor growth suppression by inhibiting blood supply via inhibition of angiogenesis is a well documented concept. The importance of designing single agents targeting multiple RTKs is widely recognized. Using a general pharmacophore model developed by Gangjee *et al.* and previous findings in our group we have designed and synthesized 7-benzyl-2-methyl-*N*-sustituted-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amines for evaluation of RTK inhibitory activity and antiangiogenic activity. The design, synthesis and biological activities of these analogs will be presented.

MEDI 264

Tyrosinase inhibitor activity of citronellol type compounds and their derivatives: The study of structure activity relationship

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Several citronellol type compounds and their derivatives have strong anti-tyrosinase activity. The strongest inhibitors are the aliphatic alcohols, with primary alcohols showing the best.

MEDI 265

Novel and potent calcium sensing receptor antagonists: Discovery of TAK-075 as an orally active bone anabolic agent

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Calcium-sensing receptor (CaSR) antagonism has been recognized as a promising target of anabolic agents for treating osteoporosis. We first discovered a novel structural class of tetrahydropyrazolopyrimidine derivatives containing an adamantyl group with potent CaSR antagonistic activity as a lead series. However this compound did not stimulate transient PTH secretion due to poor pharmacokinetic profiles. In order to address the issue, we introduced the *gem*-dialkyl benzyl group as a bioisostere of the adamantyl group. Further optimization led to the discovery of TAK-075, which stimulates transient PTH secretion, as a potent and orally available CaSR antagonist. The design, structure-activity relationship (SAR) and in vivo animal studies will be presented.

MEDI 266

Correlation between cardiorespiratory fitness, blood lipid profile and glucose according to insulin resistance in abdominal obesity men

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The purpose of the current study was to investigate correlation between insulin resistance and cardiorespiratory fitness (CRF), and change of blood lipid profile and glucose during exercise in order to improve obesity and insulin resistance of abdominal obesity men. A total of 82 abdominal obesity men (25.1±3.01; range: 21~32years) were recruited in this study. The participants were divided into 4 groups (quartile 1, 2, 3, and 4) by homeostasis model assessment of insulin resistance (HOMA-IR) level. As expected, we found that the insulin resistance is correlated with CRF, obesity indices, high density lipoprotein cholesterol (HDLC), and insulin significantly. Also, interaction effects between group and blood collecting time on triglyceride (TG), free fat acid (FFA), and glucose concentration during exercise and recovery were significant. In conclusion, the current findings suggest that CRF and insulin resistance should be need to be considered in exercise prescription for 20~30years abdominal obesity men individually.

MEDI 267

Scaffold extension-based discovery of novel, highly potent and selective small molecule farnesoid X receptor (FXR) agonists

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2-Aryl-4,5,6,7-tetrahydro-2*H*-indazoles are a novel class of non-steroidal FXR agonists. Starting from recently identified 2-aryl benzimidazoles, scaffold extension led to the identification of pyrazolo[1,5-*a*]pyridine-, imidazo[1,2-*a*]pyridine- and 2*H*-indazole-based FXR agonists. Further evolution of the 2*H*-indazole subseries provided 2,4,5,6-tetrahydro-cyclopentapyrazoles, 4,5,6,7-tetrahydro-2*H*-indazoles and 2,4,5,6,7,8-hexahydro-cycloheptapyrazoles exhibiting excellent *in vitro* potencies. Subsequent lead optimization efforts on the 4,5,6,7-tetrahydro-2*H*-indazoles guided by structure-based design culminated in the discovery of FXR ligands with excellent physicochemical properties and *in vitro* safety profiles. In addition, they show favorable pharmacokinetic properties as well as potent plasma lipid lowering effects in $LDLR^{-/-}$ mice after oral administration. The identification, synthesis, structure-activity relationship and overall profile of the 2-aryl-4,5,6,7-tetrahydro-2*H*-indazoles will be described.

MEDI 268

WITHDRAWN

MEDI 269

Discovery and evaluation of second generation pyrimidine agonists of the endocrine orphan receptor GPR119

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GPR119 is a recently discovered rhodopsin-like class A GPCR highly expressed in pancreatic beta-cells and incretin releasing cells in the gastrointestinal tract.

Small molecule GPR119 agonists have been reported to promote postprandial incretin and insulin secretion and therefore, could provide a new therapeutic approach for the treatment of type 2 diabetes in a glucose dependent fashion. Herein we present the discovery and characterization of second generation tri-substituted pyrimidine agonists that contain nitrogen heteroatoms in the C4 linked aromatic motif. We will describe synthesis and structure-activity relationships, and present additional *in vitro* and *in vivo* profiling data, showing improvements in key parameters over earlier GPR119 agonist prototypes.

MEDI 270

Comprehensive analysis of zinc binding groups using the protein data bank

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Many inhibitors that target zinc-dependent enzymes have zinc binding groups (ZBGs), which play an important part in their activity. A hydroxamic acid moiety is such a potent ZBG that it is widely used for the inhibitors of such enzymes. To date, in addition to a hydroxamic acid moiety, various functional groups have been reported as ZBGs. However, we thought that there should be other functional groups capable of binding zinc in proteins. In the present study, by computational methods, we tried comprehensively to discover the potential ZBGs by using protein-ligand complexes from entries in the protein data bank (PDB). The method with which we identified ZBGs was based on the Euclidean distance between the zinc ion and a corresponding functional group of the ligand. As a result, we obtained various ZBGs such as hydroxamic acid, carboxylic acid, thiol, phosphonate, diol, carbamate, boronic acid, etc. We also investigated the distribution of interaction distances to reveal the preferred distances between zinc and the nearest heteroatoms. The results obtained in this study could help medicinal chemists design new drug candidates for zinc-dependent enzymes.

MEDI 271

Extraction and organization of chemical information from public sources

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One of the most significant challenges for drug discovery informatics in the coming years is in the merger of public data with proprietary information to develop the comprehensive knowledge base need to effectively advance drug discovery projects. Here we introduce a tool that saves time when trying to build

chemical databases from web information or chemical literature, including patent information. ChemDox technology provides an automated avenue to quickly extract and transform compound names and images from document sources into editable molecular structures. The extraction of chemical information is just the first step. We apply the tools developed to compare the chemical content of different patents and databases. We combined them with the ability to carry out Boolean operations at the chemotype level that would enable the identification of novel information when time is of the essence.

MEDI 272

Novel multi-component approaches towards dimeric epidithiodiketopiperazines as anti-cancer agents

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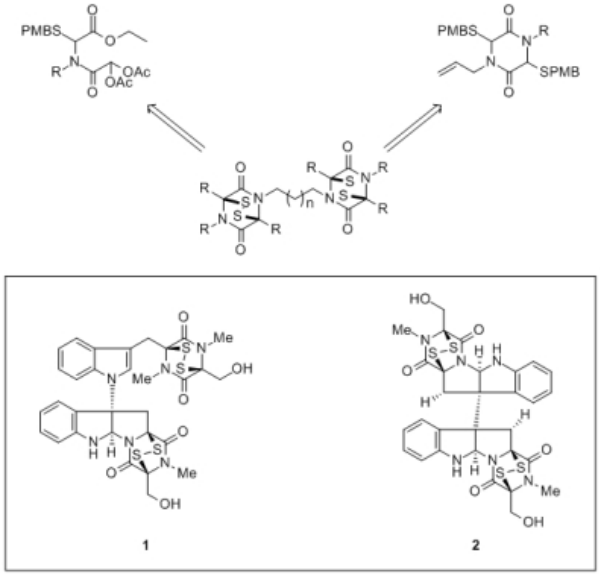
Epi-3,6-dithio-2,5-diketopiperazines (ETPs), are a group of diverse natural products that display potent biological activity related to their disulfide bridge. Examples include Chetomin (**1**) and Chaetocin (**2**). Dimeric ETPs are synthetically challenging and our 4-step multi-component approach towards these and more substituted members will be described.



With this new methodology, we can now develop a library of compounds with varying functionality, allowing us to evaluate their biological activity against a range of cancer cell lines.

MEDI 273

Diversity from simplicity: A common precursor approach towards natural products

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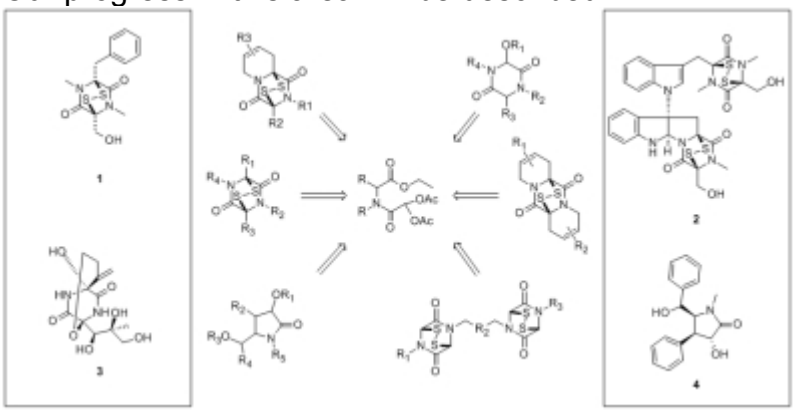
The piperazine-2,5-dione motif occurs in a number of biologically active natural products such as hyalodendrin (**1**), chetomin (**2**) and bicyclomycin (**3**). Previous approaches have encountered stereoselectivity and regioselectivity problems rendering these compounds inaccessible from a Medicinal Chemistry perspective. However, using a common synthetic precursor, we are able to synthesise the natural products, their related monomeric/dimeric counterparts and other natural products such as clausenamide (**4**) in a short number of steps. Our progress in this area will be described.



MEDI 274

Application of robust nonlinear regression techniques for unraveling quantitative structure activity relationships in drug design

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The quantitative structure-activity relationship (QSAR) has received great attention in the field of medicinal chemistry and drug discovery for predicting the biological activities of compounds. The main aim of the present work is using different nonlinear regression methods such as artificial neural networks (ANN) and multivariate adaptive regression splines (MARS) for investigating relationships between the structure of the molecules and their biological

activities. The activities of a diverse set of CCR5 modulators, integrin antagonists, histamine and ACC1 inhibitors were predicted by ANN and MARS algorithms. The values of correlation coefficient between the predicted and experimental activities were in the range of 0.78 ~ 0.94, which reveals the robustness of the developed models. These models are useful for designing novel drugs and clarifying of the inhibitory activity of considered compounds. Maximum negative charge, number of rotatable bounds and spanning tree number were found to be important parameters for describing the activity of compounds.

MEDI 275

Beyond filters: ADMET risk for multi-objective drug development

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We examined the distributions of values predicted for over 20 relevant ADMET properties across a subset of the World Drug Index, and we have identified relevant thresholds for each property, enabling us to calculate the ADMET Risk for any molecule. ADMET Risk is analogous to Lipinski's “Rule of 5” [1] in that points are added for any prediction that violates a threshold value, but ADMET Risk incorporates many more potential liabilities, and it provides codes that identify each potential liability, providing the chemist a truly multidimensional view of potential problems in a single number. We believe this is a powerful tool to guide early steps in the multiobjective optimization process required to produce a successful drug. 1. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J. Adv. Drug Deliv. Rev. 1997, 23, 3-25

MEDI 276

New approach for in silico genotoxicity testing of impurities and degradants

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According to FDA Guidance for Industry, assessment of genotoxicity/carcinogenicity by computational methods is sufficient for impurities in drug products present at levels below the ICH qualification thresholds. This study presents a novel approach to aid this assessment based on a probabilistic predictor of Ames genotoxicity, and a knowledge-based system of structural

alerts. The list of potentially hazardous structural fragments was compiled from various literature sources and refined by analyzing their performance on data from different assays detecting point mutational and/or clastogenic mechanisms of DNA damage (Ames test, in vitro chromosomal aberrations, micronucleus test, mouse lymphoma assay). Finally, the expert system was tested on the Carcinogenic Potency Database to ensure detection of common non-genotoxic carcinogens. Selected structural alerts achieved >90% sensitivity for recognizing positive compounds in Ames and Chromosomal Aberrations data sets showing that the absence of alerting groups is a reliable criterion for identifying impurities not posing significant genotoxic/carcinogenic risk.

MEDI 277

In silico identification of metabolic soft spots: Case study using ACD/ADME Suite software

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Metabolic stability, as determined in liver microsomes, is one of the primary assays used in early drug discovery. A key factor limiting compound half-life is the CYP mediated metabolism. High clearance by cytochrome P450 enzymes implies a higher and more frequent dosing as well as poses a risk for individual variations in exposure. Experimental identification of metabolic soft spots during lead optimization is a time and resource consuming task as it requires separation of individual metabolites and elucidation of their structure. Here we present a case study illustrating how this workflow can be facilitated by in silico regioselectivity prediction tools. Presented examples involve analysis of the detailed metabolite identification studies for recently published novel compounds and demonstrate the performance of the ACD/ADME Suite software in identification of their most likely metabolites, thus providing an insight on the structural modifications needed to achieve optimal metabolic stability.

MEDI 278

QSAR model of regioselectivity of metabolism in human liver microsomes: Development, validation, comparison and adaptation to novel compounds

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A probabilistic model predicting sites of human liver microsomal metabolism in a molecule has been developed using experimental data for 873 compounds and recently introduced GALAS modeling methodology. It involves calculation of the Reliability Index (RI) values which are shown to reflect the accuracy of predictions for the test set, thus serving as a basis for the Model Applicability Domain assessment. The main emphasis is made on the model evaluation using newly published data for >40 novel drug-like compounds. At least one metabolism site was found for more than 80% of compounds, and more than 60% of them had majority of metabolites identified correctly. High RI values again successfully identified correct predictions. After training procedure previously not recognized metabolism sites could be identified as well illustrating the straightforward expansion of the Applicability Domain for GALAS method based models. Analogously the developed model can be adapted for cytochrome P450 isoform profiling.

MEDI 279

Design and application of computational tools for the rational design and discovery of Autotaxin inhibitors

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Autotaxin (ATX) has been shown to play important roles in normal physiology, as well as in diseases such as cardiovascular disease, cancer, and chronic pain. Due to these roles, the identification and characterization of ATX inhibitors is becoming recognized as an important therapeutic goal. To help focus our experimental screening program we have compiled a database of published and internally characterized ATX inhibitors and inactive structural analogs. This effort was recently expanded to include data from a 10,000 compound diversity screen. Our database has been used to develop ligand-based pharmacophores, as well as quantitative structure-activity relationship (QSAR) models for ATX inhibition. In order to validate and apply these models we have generated conformational libraries from commercial sources (>1 million compounds to date) that allows identification and prioritization of commercial leads. This approach allows us to focus experimental screening efforts on the most promising subset of inhibitor candidates.

MEDI 280

Molecular modeling as a tool in the evaluation of a site-targeted micelle system containing anacardic acid and hydroxymethylnitrofurazone (NFOH)

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Introduction and Purpose. Chagas´ disease and leishmaniasis are important neglected diseases with lack of effective drugs. A preliminary study of aggregates composed by units of covalently bound thiomannopyranoside, anacardic acid, and NFOH (Mon1) was made by applying molecular modeling. This study aims future developments of site-directed micelle. Methodology. **Mon1 model was constructed,** energy-minimized (MM+), and AM1 partial atomic charges were calculated (HyperChem 7.51). A relaxation warming–up scheme of molecular dynamics simulations was performed (MOLSIM 3.2), and the lowest-energy conformer (300 K) used as starting unit model to generate aggregates of up to 13 units. **Preliminary Results and Conclusions.** Aggregates of 11 units or less presented heat of formation (DH) values from 3026.59 to 3983.67 kcal/mol. With the addition of more monomers DH increased almost 300 kcal/mol and total potential energy values changed approximately 36 kcal/mol. A small DH difference (3 kcal/mol) was observed for the 12 and 13 unity.

MEDI 281

Ligand supported homology modeling of the human protease activated receptor: Insights into molecular recognition

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p { margin-bottom: 0.08in; } G-Protein coupled receptors (GPCRs) are important proteins for drug design as a large number of current drug targets are from GPCRs. The human thrombin receptor (h-PAR) is a member of the family of rhodopsin-like G-protein coupled receptors (GPCRs). The inhibition of protease-activated receptors (PARs) is an important strategy in designing of the potent and safe anti-platelet agents with significantly reduced side effects. In order to elucidate the receptor's molecular recognition, a homology model of h-PAR1 was constructed and refined by a multistep ligand-supported model refinement protocol which involved initial docking of a PAR1 specific antagonist in the putative binding site, followed by iterative energy minimizations and molecular dynamics simulations of the ligand receptor complex. The finally derived model was validated based on its correlation with several structure-activity relationships and site-directed mutagenesis data. These studies reveal the important characteristics of h-PAR1 binding site and the role of electrostatic and hydrophobic interactions in ligand recognition which may be useful for

understanding the ligand's potency for facilitating the structure based drug design of novel and more potent h-PAR1 ligands.

MEDI 282

Procedural developments in molecular docking methods via novel substituted aurones

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Cyclooxygenase-2 selective agents have been intensively evaluated for their ability to treat cancer. Unfortunately, the most promising class of COX-2 specific inhibitors evaluated as anticancer agents also exhibited adverse and sometimes fatal side effects. Therefore, it is critical to develop a new class of agents with superior COX-2 specific inhibition and fewer side effects. Flavonoids are naturally-occurring compounds that have anti-cancer properties. Reports indicate that inhibition of tumor development by flavonoids is mediated through inhibition of the COX-2 enzyme. Using rational drug design methods, docking studies were performed to model novel structurally-modified flavonoids, particularly aurone derivatives, at the COX-2 active site. Presented herein are docking studies of key interactions between derivatives and the enzyme binding pocket. Furthermore, binding free energy and inhibitory concentration (IC_{50}) values were calculated and compared against known inhibitors. Results of these docking studies provided promising results thereby leading to the synthesis of the most promising derivatives.

MEDI 283

Dehydroepiandrosterone esters and lactones as antiandrogens

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Testosterone is generally regarded as a proandrogen and under the influence of the enzyme 5 alpha-reductase is reduced to dihydrotestosterone which causes prostate cáncer, benign prostatic hyperplasia, acné and other androgen dependent diseases. It follows that inhibition of dihydrotestosterone formation by antiandrogens represents an important requirement for the development of improved forms of treatment. In view of the fact that dehydroepiandrosterone has some antiandrogenic activity, in this paper we describe the synthesis of

several new derivatives of dehydroepiandrosterone having an ester moiety at C-3(acetoxy, propanoyloxy, butanoyloxy), a double bond at C-5 and a lactone function in ring-D. The biological evaluation of these compounds in vitro indicated that the compounds containing a butanoyloxy and propanoyloxy ester group at C-3 and a lactone function in ring-D exhibited much higher 5- alpha reductase inhibitory activity than the commercially available drug finasteride. A new mechanism is proposed for the inhibition of this enzyme

MEDI 284

Process developments for the practical synthesis of eldecalcitol [1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3] by linear synthesis, convergent synthesis and biomimetic synthesis

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Eldecalcitol [1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3, **1**], an analog of active vitamin D_3, calcitriol (1α,25-dihydroxyvitamin D_3, **2**), possesses a hydroxypropoxy substituent at the 2β-position of **2**. **1** has potent biological effects on bone and is now in preparation for approval for the treatment of osteoporosis as a new drug in Japan. Considering the potential clinical applications of **1** in the near future, we have been investigating a practical synthesis of **1** for industrial scale production. **1** was initially synthesized in a linear manner in which the 1,2α-epoxide, prepared from lithocholic acid *via* 25-hydroxycholesterol, served as a key intermediate for the introduction of the characteristic hydroxypropoxy substituent. The 27-step linear sequence was, however, suboptimal due to its lengthiness and low overall yield (ca. 0.03%). We developed a convergent approach based on the Trost coupling reaction, in which A-ring part (ene-yne, 10.4% overall) and C/D-ring part (bromomethylene, 27.0% overall) are coupled to produce triene system of **1** (15.6%). Although the overall yield of convergent synthesis was better than linear synthesis, significant improvements are still demanded, therefore, further biomimetic investigations on microbiological 25-hydroxylation of steroidsl side chain using cholesterol as a starting material are ocgoing. Process development for the practical production of **1** between linear, convergent and biomimetic syntheses will be discussed.

MEDI 285

Asymmetric synthesis of 6-cyanoindoles as nonsteroidal glucocorticoid receptor modulators

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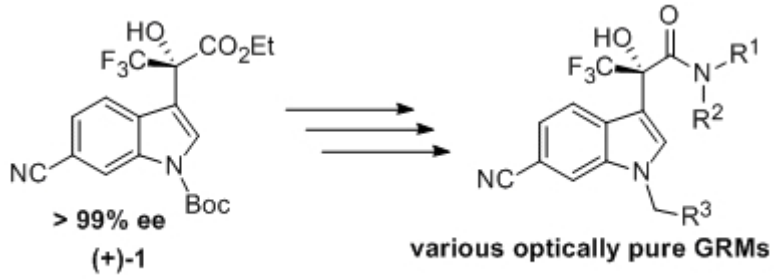
Glucocorticoids (GCs) are the most commonly used anti-inflammatory drugs for a variety of inflammatory diseases. However, their outstanding therapeutic effects are often accompanied by severe side effects. To date, several researches have explored glucocorticoid receptor modulators (GRMs) having the profile of both decrease in severe side effects and maintenance of the anti-inflammatory and immunosuppressive effects. In the course of our GRM program, we discovered a series of compounds with a 6-cyanoindole scaffold which show dissociation between anti-inflammatory effects and side effects *in vitro*. Furthermore, to obtain the optically pure 6-cyanoindoles, we have optimized the asymmetric synthesis of 6-cyanoindole (**1**) as a key intermediate. In this report, we describe the efficient synthesis of the optically pure (+)-**1** (>99% ee) and our GRMs. In addition, we provide structure analyses of 6-cyanoindoles as a new structural class of nonsteroidal GRMs.



[figure1]

MEDI 286

Examination of significance of measurement of free amino acid in the blood in pregnancy and diabetes

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This study suggests that branched chain amino acid covers importantwork as glucose metabolism adjustment factor such as glucose loweringeffect. In case values of blood sugar and hemoglobin A1c of diabetic pregnant womenare normalized in relatively early stage, value of serum freeamino acid, especially branched chain amino acid which increased aftera meal, are not normalized until third pregnancy trimester, however(Fig.1). I took blood samples from five normal and diabetic pregnant women eachwhen they were hungry in early morning and one hour after breakfast aswell. I researched fluctuation between

early stage of pregnancy (13th week) and after birth (41st week) of serum free amino acid, bloodsugar, hemoglobin A1c, fructosamine, insulin, glucagon, C-peptide, and human growth hormone of the samples.

MEDI 287

Photochemical modulation of Ras-mediated signal transduction using caged farnesyltransferase inhibitors: Activation via one- and two-photon excitation

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The creation of caged molecules involves the attachment of protecting groups to biologically active compounds such as ligands, substrates, and drugs that can be removed under specific conditions. Photoremovable caging groups are the most common due to their ability to be removed with high spatial and temporal resolution. Here, the synthesis and photochemistry of two caged inhibitors of protein farnesyltransferase, BHQ-FTI and Bhc-FTI will be described. We will then show that these molecules can be photolyzed with UV light to release FTI that inhibits Ras farnesylation (observed via Western blot analysis), Ras membrane localization (detected by confocal microscopy), and downstream signaling (fibroblast morphology). Finally, we will show that Bhc-FTI can be uncaged by two-photon excitation to produce FTI at levels sufficient to inhibit Ras localization.

MEDI 288

Purification in drug discovery with flash chromatography techniques

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Separation and identification of biologically active compounds is critical during drug discovery and development. Chemical synthesis or crude extraction towards a lead compound plays a dominant role in the development of new drugs for medicinal purposes. The process requires multiple steps that are tedious and time consuming. Additional steps including guesswork becomes a barrier and poses a challenge towards productivity. As drug development approaches a

more lean process with cost reduction, the objective is to make the purification step more efficient and faster. Traditional flash chromatography with only UV detection, conventional columns, and/or low capacity separation media is often not enough during purification. Here we discuss how to overcome some of the challenges using flash chromatography for chromophoric and non-chromophoric compounds present at low levels with speed and greater recovery. Applications based on the isolation of drug compounds, extraction of natural products, and compounds with lipids and carbohydrate entities will be discussed.

MEDI 289

Aripiprazole derivatives for once-monthly-injection: Effect of tail-length on absorption rate, injection site reactions, crystal packing, and physical properties

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A series of Aripiprazole (**ARP**) derivatives has been prepared with the goal of increasing the absorption rate and reducing injection site reactions caused by crystalline **ARP** monohydrate. The lactam ring of **ARP** was modified with a linker group to allow attachment of hydrocarbon tails. The derivatives are cleaved following dissolution *in vivo* and the linker group hydrolyzes rapidly at pH 7 to regenerate the parent. The dissolution and cleavage rates vary as a function of tail length, allowing the team to balance parameters including: plasma vs. time profiles; exposure to intact derivatives; and buildup of **ARP** monohydrate at intramuscular injection sites in rats. Tail lengths shorter than C6 allow buildup of **ARP** monohydrate at injection sites. Physical property (melting point, melting enthalpy, and solubility in oils) dependence on tail length is not a simple, monotonic function. Instead, physical properties appear to be related to molecular arrangement into one of two dramatically different crystal packing motifs.

MEDI 290

Peptide nucleic acid (PNA) agents for anthrax detection

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Current DNA detection techniques require the confines of a well-equipped laboratory which are not suited for first-hand responders in bio-terrorism attacks

or in a military battlefield in case of anthrax infection. Robust probes are required that can function properly under harsh conditions. Successful probes should be specific for the anthrax gene, stable to biochemical degradation, and possess low background signal. Our lab is interested in investigating and developing a class of synthetic nucleic acids called peptide nucleic acids (PNAs) as agents for use in genomic detection, and in particular for developing a technology for anthrax detection. PNAs are synthetic DNA mimics in which the phosphate sugar backbone of DNA is replaced with an amino ethyl glycine (aeg) pseudo peptide moiety [1]. PNA probes are more advantageous and robust than DNA probes in that they are resistant to enzymatic degradation have greater sequence specificity to complementary DNA, and higher stability when bound with complementary DNA. Our group has already developed a sandwich-hybridization DNA detection system that uses PNA to detect anthrax DNA [2]. In this presentation, we describe the design and synthesis of PNA agents for anthrax detection, and our effort towards improvements in detection limit. The probes are constructed with cyclopentane-modified PNA and multi-biotin labeled PNA sequences that are specific to anthrax DNA. Detection is achieved when two PNA oligomers, one that is surface-immobilized and the other linked to biotin, form a DNA-PNA hybridized sandwich complex. The probes are assayed using an avidin-horseradish peroxidase conjugate (HRP-avidin) in an Elisa assay in a 96-well plate format to give a colorimetric readout. Herein, we discuss covalent crosslink method as well as a non-covalent method of using PNA agents for anthrax detection. Refs:[1] Nielsen, PE et al. Science, **1991***,254,* 1497-500 [2] Zhang, Ning and Appella, Daniel. *JACS*, **2007***,129,* 8424-8425

MEDI 291

Opportunities for drug development at the biomedical advanced research and development authority

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The Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies. BARDA manages Project BioShield, which includes the procurement and advanced development of medical countermeasures for chemical, biological, radiological, and nuclear agents, as well as the advanced development and procurement of medical countermeasures for pandemic influenza and other emerging infectious diseases that fall outside the auspices of Project BioShield. In addition, BARDA manages the Public Health Emergency

Medical Countermeasures Enterprise (PHEMCE).From its inception, BARDA has been committed to creating a robust and dynamic pipeline of medical countermeasures through advanced development of new and improved medical countermeasures. The goal of medical countermeasure development is to provide multiple product candidates in each program to both account for attrition in medical countermeasure development and to establish multi-product/multi-manufacturer portfolios for sustainability and redundancy. One area in which BARDA supports advanced pharmaceutical research is in the development of mitigators or treatments for subsyndromes associated with Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE), arising from exposure to ionizing radiation. Treatments that have efficacy when administered no earlier than 24 hours post irradiation are of particular interest. Subsyndromes of interest include: Neutropenia Thrombocytopenia Gastrointestinal Skin (Cutaneous) Lung (Pulmonary) Kidney (Renal) Brain (central nervous system)

MEDI 292

Potential CRF_1R PET imaging agents: *N*-fluoroalkyl-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethyl-*N*-alkylpyrazolo[1,5-*a*][1,3,5]triazin-4-amines

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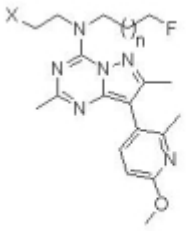
A series of *N*-(3-fluoroalkyl)-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethyl-*N*-alkylpyrazolo[1,5-*a*][1,3,5]triazin-4-amines **1** were prepared and evaluated as potential CRF_1R PET imaging agents. Optimization of their CRF_1R binding potencies and octanol–phosphate buffer phase distribution coefficients resulted in discovery of analog **2** (IC_{50} = 6.5 nM, logD = 3.5).



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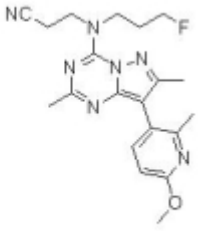

2

MEDI 293

T3P®: Reagent of choice for amide bond formation and many other applications

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Propane Phosphonic Acid Cyclic Anhydride (T3P®) is an exceptional reagent for amide/peptide bond formation. It is very easy to use and provides excellent selectivity, low epimerization and high yields with simple product isolation by extraction. Because of its properties, hazardous additives such as explosive HOBt, are not required. Additionally, the T3P® reagent is really “green” - nontoxic, non-allergenic/non-sensitizing, and the by-products are non hazardous and completely water soluble, in sharp contrast to most other coupling reagents. These salts are readily removed via an aqueous wash at the conclusion of the reaction. Numerous examples of the formation of amide bonds and peptide couplings, particularly challenging couplings (sterically hindered substrates, free OH groups), will be presented, wherein the inherent advantages of T3P® will be highlighted. Further, examples of the utilization of T3P® in the preparation of other functional groups, such as nitriles, isonitriles and aldehydes will be presented.

MEDI 294

WITHDRAWN

MEDI 295

Load bearing capacity of cartilage: Ionic interactions

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To elucidate the differences between healthy cartilage and changes associated with degeneration requires the knowledge of the relationships between molecular and tissue-level properties. Increased hydration and loss of proteoglycans are the earliest signs of cartilage degeneration during osteoarthritis. To recover load-bearing and lubrication functions lost through disease or injury, the micro-structure, biochemical composition, and physical properties of the healthy tissue must be restored. The matrix of articular cartilage has a highly specific structural

arrangement consisting of successive zones from the articular surface to the subchondral bone interface. Both the structural organization and chemical composition vary through the depth of the matrix. In the present study atomic force microscopy and osmotic swelling pressure measurements are used to determine the depth-dependent mechanical and osmotic properties of bovine cartilage. Elastic and osmotic modulus maps are constructed for cartilage layers located at different distances from the joint surface.

MEDI 296

Multi-receptor strategies io improve management of ailments of mental origin

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Diseases of mental origin are among the most complex to manage because of the involvement of multiple receptors and their widespread distribution in the brain. Improved understanding of brain function following advances in imaging techniques and molecular biology has given rise to multi-targeting of newer drugs with improved therapeutic profile. Atypical antipsychotic drugs have fewer side effects than neuroleptics partially because they bind to dopamine D_2 receptors with lower affinity, and also modulate serotonin 5-HT_{2A} receptor subtype among others; whereas neuroleptics have high affinity to D_2 receptors. Older anti-depressants are mainly MAO inhibitors while newer agents target reuptake of serotonin and norepinephrine and blockage of 5-HT_{1A} receptors. In this study, we designed and synthesized arylalkyl linked 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol, 1-(4-chlorophenyl)-1,4-diazepane, and 1,2,3,4-tetraisoquinoline with multi-receptor modulating abilities. Binding assays indicate that several of these compounds have potential atypical antipsychotic and anti-depressant properties.

MEDI 297

WITHDRAWN

MEDI 298

Programmable RNA nanoring as a novel siRNA packaging nanoparticle

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RNA interference (RNAi) offers tremendous promise as a selective means to silence gene expression and become a whole new class of therapeutics. However, the nature of short interfering RNA (siRNA) presents significant obstacles that need to be overcome. Currently, challenges involving short-term efficacy, stoichiometric control over the simultaneous delivery of several siRNAs, as well as their premature degradation constitute significant technical challenges preventing a more widespread clinical use. Here, we discuss the potential of packaging multiple siRNAs into a single all-RNA nanoparticle through the self-assembly of six specific Watson-Crick kissing-loop interactions. The RNA nanoring previously reported has been shown to offer increased ribonuclease resistance while maintaining the ability to be processed by the enzyme Dicer to produce siRNAs. Extensive characterization of the biophysical, structural, and biochemical properties of the programmable nanorings provides support for their potential use in siRNA packaging and delivery. This work was funded by the National Institutes of Health (RO1 GM079604-01) to Luc Jaeger.

MEDI 299

Investigation of the redox stability of radiopharmaceutical $M(CO)_3$ (M = Re, Tc-99m) amino acid complexes in physiological aqueous solution

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Radioactive complexes have been utilized for decades for diagnostic or therapeutic applications in nuclear medicine. Group VII congeners, technetium (Tc-99m, γ, 6.02 h, 140 keV) and rhenium (Re-186, β-, 17 h and Re-188, β-, 3.7 d) provide a synergistic imaging and therapeutic medicinal combination, respectively. Several $M(CO)_3(L)$ (M = Re, Tc-99m) complexes with biological targeting agents for cancer detection and therapy have been reported in recent years, however, limited information about the radiation-stability of these complexes under physiological conditions that would simulate clinical dose conditions is known. Here we have performed a fundamental study on model $Re(CO)_3(L)$ complexes prepared from amino acids, using electron pulse radiolysis to replicate free radical conditions found in the kit formulation.

Activation energies for the reactions of oxidizing hydroxyl radicals and hydrated electrons over a range of temperatures have been determined and used to elucidate the dominant mechanisms of these radicals' reactions with these complexes.

MEDI 300

Pyridinium-sulfonamides as efficient inhibitors of carbonic anhydrases

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Carbonic anhydrase is a zinc enzyme responsible for the reversible hydration of carbon dioxide to bicarbonate, being involved in respiration and CO_2 transport between the metabolizing tissues and the lungs, pH and carbon dioxide homeostasis, electrolyte secretion, biosynthetic reactions, etc. In mammals 16 isozymes have been described to date, with different catalytic activity, sub-cellular localization, and tissue distribution. Its inhibitors were exploited for more than five decades in the treatment of edema, glaucoma, obesity, cancer, epilepsy and osteoporosis. Of recent interest is the development of selective inhibitors against membrane-bound isozymes, which will leave untouched the cytosolic ones, thus reducing the side effects associated with existing drugs on the market. We will present our efforts towards generation of membrane-impermeant CA inhibitors through conjugation of known potent CA inhibitors with positively charged pyridinium moieties. Structure-activity correlations will be made, emphasizing the impact of different structural elements towards inhibition of various CA isozymes.

MEDI 301

Research on the moisturizing effect of dragon fruit extract produced through various methods of extraction

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This study investigates the moisture found in dragon fruit extract. Test extracts were produced from the flesh of fresh dragon fruit and the extracts were divided

into two groups: water extraction and ethanol extraction. Researchers used a Conway's dish to test the water absorption rate and water retention rate of the extracts and prepared separate aqueous solutions containing 1 %, 0.1 %, and 0.01 % of dragon fruit extract. These solutions were applied to the skin of 20-30 year old subjects, after which the moisture absorption and retention of the skin were tested. Experimental results indicated that the water absorption rate and water retention rate of dragon fruit extract exceeded those of the control group hyaluronic acid.Skin test results showed that higher concentrations of dragon fruit extract in the solutions implied higher moisture absorption and retention of skin.These results could form the basis of an evaluation into the feasibility of using dragon fruit extract as a skin moisturizer in medicinal products or cosmetics, for the purpose of relieving symptoms such as tightness, roughness, irritation or itching of the skin. *Keywords:* dragon fruit, water absorption rate, water retention rate, Conway's dish.

MEDI 302

Microwave accelerated three-component fluoroalkylations: Expeditious routes to fluoropharmaceuticals and PET ligands

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One pot three-component coupling methods have been developed to allow in situ preparation of fluoroalkylated arenes and hydrocarbon chain analogs. We have been investigating means to develop efficient coupling methodologies which (1) allow effective coupling of functionalized hydrocarbon chains onto readily available arenes (2) where chain length and hybridization can be modified at ease and (3) where the ^{18}F can be introduced *in situ* at the final stage of the process. The methodology, which is accelerated under microwave irradiation gives access to w-fluorinated alkyl, alkenyl, and alkynyl substituted arenes from readily available precursors. The methodology involves late stage introduction of the fluorine and is well suited to application in the synthesis of ^{18}F labeled PET imaging agents.

MEDI 303

Lead optimization studies of N-(2-[1,1'-biphenyl]-4-ylethyl)-8-CAC

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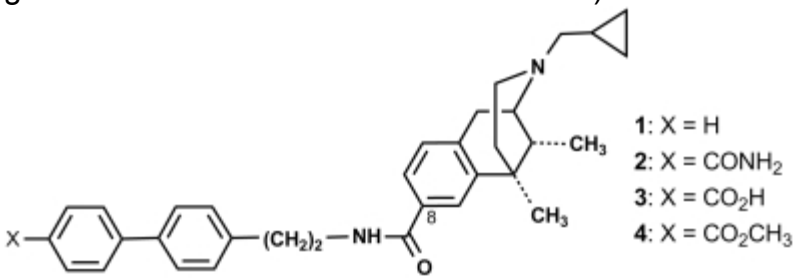
We recently reported the high binding affinity [K_i = 0.30 nM (mu)] of lead compound N-(2-[1,1'-biphenyl]-4-ylethyl)-8-CAC (**1**) to opioid receptors. In order to further explore the SAR of this lead as well as increase its aqueous solubility (clop*P* = 7.3), we have prepared and characterized the opioid receptor binding properties of derivatives **2-4** having polar substituents in the distal phenyl ring. K_i values as low as 0.005 nM was observed for the mu receptor. We also prepared derivatives of **1** where each CH of the biphenyl group was individually replaced by N where K_i values as low as 0.064 nM (mu) were seen. (Supported by NIDA grants R01 DA012180 and K05-DA00360)



MEDI 304

Synthesis and RP-HPLC monitored hydrolysis of non-natural glucosinolates

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Studies have shown that diets rich in the *Brassica* vegetables are associated with reduced risks of cancer. These vegetables contain chemopreventive precursors, called glucosinolates, that undergo a myrosinase-dependent hydrolysis when digested in the body. The goal of this project was to synthesize two non-natural glucosinolates and monitor their hydrolysis using RP-HPLC. The glucosinolates were successfully synthesized in 11% and 19% yields over five steps. A RP-HPLC assay is currently being developed as a method to compare the ability of synthetic glucosinolates to serve as myrosinase substrates.

MEDI 305

Chemical analysis of the cytotoxic plant *croton discolor*

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In Puerto Rico, some plants have been used to treat diseases including colds, coughs, diarrhea, respiratory infections, and skin lesions among others. Unfortunately, it is estimated that only a few group of endemic and native plants with potential medical applications have been studied. Our team has been focused on the study of endemic and native plants from Puerto Rico and the Caribbean. The objective of this study is to identify and discover new metabolites and evaluate its biological activity against breast cancer cell lines from the medicinal plant *Croton discolor*, a native plant of the Antilles, belonging to the Euphorbiaceae family. In a preliminary screening using brine shrimp lethality test, we found that the crude extract showed significant cytotoxicity with a LC_{50} of <150 µM. Based on this result, different extracts will be examined and their active constituents identified and evaluated. The results will be presented and discussed.

MEDI 306

NMR paramagnetic relaxation enhancement study of the binding of ligands to cytochrome P450 eryF

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One mechanism of drug-drug interactions involves multiple drug molecules binding to the same cytochrome P450 enzyme, where addition of a second molecule influences metabolism of the first. It is important to understand how binding of a second molecule could influence binding and metabolism of the first. Our novel approach uses NMR paramagnetic relaxation enhancement (PRE) experiments to measure the position of ligands within P450 eryF (S93C/C154S) chemically labeled with a methanethiosulfonate ligand (MTSL). We present the results of our chemical labeling experiments using liquid chromatography-mass spectrometry, and the results of NMR experiments demonstrating the PRE effect of the heme iron on the NMR resonances of ligand 4-chlorophenylimidazole. Combining the two techniques will allow measurement of the location of various ligand binding sites within or near the P450 active site, and allow testing of the influence of a second ligand (of different type) on the position of the first.

MEDI 307

Synthesis and biological evaluation of fluoroalkyl-substituted 1,4-bis(2-amino-ethylamino)anthraquinones as potential P-Glycoprotein function imaging agents

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Overexpression of P-glycoprotein (P-gp) is a likely mechanism causing multidrug resistance (MDR) of human cancers, which remains one of the most significant impediments to successful cancer chemotherapy in clinic. Thus, an imaging agent that could quantitatively determine P-gp function would be valuable for predicting the outcome of cancer chemotherapy for individual patient, and development of novel anti-cancer drugs and chemotherapeutic treatment strategies. Fluoroalkyl-substituted 1,4-bis(2-amino-ethylamino)anthraquinone derivatives were designed and synthesized as potential probes for P-gp function. With a fluoro-substituent, these compounds could be labeled with [18F] as potential positron emission tomography (PET) imaging agents. Several compounds have been shown to be sensitive to the expression and function of P-gp. These ligands could be accumulated in P-gp-deficient cancer cells in concentrations significantly higher than that in P-gp-highly-expressed cancer cells. These fluoroalkyl-substituted anthraquinones are promising for the development of [18F]-labeled PET imaging agents for evaluation of P-gp function *in vivo*.

MEDI 308

Synthesis and evaluation of non-aminoglycosides as potential readthrough compounds

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A Structure-Activity Relationship (SAR) study was carried out to identify novel therapeutic compounds that allow readthrough of premature termination codons (PTCs) for treating genetic diseases resulting from nonsense mutations, such as

Duchenne's muscular dystrophy (DMD) and ataxia-telangiactasia (A-T). It has been demonstrated that certain compounds can induce readthrough of PTCs, resulting in translation of full-length functional protein. Our research group has recently developed non-aminoglycoside readthrough compounds (RTCs) showing excellent readthrough activity. Current efforts are focused on compound optimization by preparing and identifying molecules with improved activity and pharmacokinetic properties. The successful development of novel RTCs is anticipated to demonstrate chemical-induced readthrough of PTCs and therefore, potentially resulting in an efficient strategy for treating A-T and DMD genetic diseases.

MEDI 309

Synthesis of heterocyclic glucosinolates and sulforaphane

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L-Sulforaphane is a chemopreventive isothiocyanate (ITC) that is metabolically-derived from glucoraphanin, the natural glucosinolate found in broccoli. Synthesis of D,L-sulforaphane was pursued as well as exploration of synthetic routes to obtain 2-(3-pyridyl)ethanal, a key intermediate in the synthesis of 2-(3-pyridyl)methylglucosinolate. Problems in the sulforaphane synthesis yields lead to development of a new synthetic pathway. The synthesis of 2-(3-pyridyl)ethanal was approached by both TEMPO oxidation and nitrile reduction. The nitrile intermediate in the new sulforaphane pathway was more amenable to purification. Acquisition of 2-(3-pyridyl)ethanal is still being pursued.

MEDI 310

Strategies for palladium(II) catalyzed cyclization reactions

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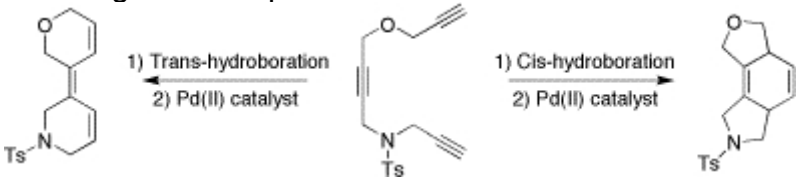
Palladium(II) catalysis is an efficient and operationally simple strategy for cyclization reactions employing bis(pinacol vinylboronate ester) substrates. This protocol is much more synthetically efficient than typical palladium(0) catalyzed cyclizations of substrates which have the end-groups differentiated into both electrophilic and nucleophilic moieties. We will report applications of this strategy to the synthesis of small, medium, and large ring products, as well as compounds

involving insertion processes and trans annular Diels Alder reactions.



MEDI 311

Characterization of medicinal plants of Mojave Desert: GC-MS analysis and HPLC-UV fractionation of evening primrose (*Oenothera biennis*) extracts

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Oenothera biennis (Common Evening Primrose or Evening Star) is a species of *Oenothera* native to eastern and central North America and widely naturalized elsewhere in temperate and subtropical regions including Southwest Deserts. Native residents of Nevada have been using local plants for medicinal use for centuries. The Evening Primrose leaves, also known as *Oenothera biennis* were obtained from Bonnie Springs, Las Vegas, NV. The leaves were dried and extracted with a series of solvents with varying degrees of polarity (H2O-MeOH, Dichloromethane, and Hexane). The Extracts are analyzed by a GC-MS system. The identification of compounds is based on the NIST library searches and comparisons with other literature, followed by chromatogram based quantitation of eluted compounds. HPLC-UV is also used for separation and fractionation of plant extract for further characterization and analysis.

MEDI 312

Efficient LC-MS/MS method for the determination of D^9-Tetrahydrocannabinol in biological fluids with excellent selectivity and sensitivity

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The analysis of D^9-tetrahydrocannabinol by Liquid Chromatography-Tandem Mass Spectroscopy (LC-MS/MS) is really difficult due to the absence of functional groups such as amine and carboxylic acid, which normally allow for good sensitivity. The fragmentation of these compounds in MS/MS, often results in a loss of water leading to a decrease in the accuracy of compounds quantification. SiliCycle has developed a new C18 stationary phase that can be used to extract these drugs in biological fluids. The uniform grafting on silica

surface combined to an optimal end-capping methodology provide excellent recovery and reproducibility. LC-MS/MS analysis can then be achieved by derivatization with dansyl-chloride and Girard's reagent T, allowing for a significant increase in the sensitivity and selectivity for these drugs. This poster presents the uses of this new C18 silica and the results obtained with this new methodology developed in our laboratories for the determination of D^9-Tetrahydrocannabinol in biological fluids using LC-MS/MS analysis.

MEDI 313

Establishment of *in vitro* cultures of *Pyrostegia venusta* and analysis of secondary metabolites

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The use of synthetic estrogen to decrease the symptoms of menopause causes side effects on female such as obesity, headache and insomnia. It has been associated with an increase in several types of cancer. It is important to seek new alternatives with natural estrogenic activity and minimal side effects. In recent years, the tea from the plant *Pyrostegia venusta* has been used to reduce the symptoms of menopause. However, the active ingredients in this extract are found in rather low concentration. Plant tissue culture represents an alternative for the generation of plant extracts with higher concentrations of metabolites without affecting wild plant populations. In this study, *in vitro* callus cultures of plant leaves were establish. Furthermore, an increment in the concentration of steroids and flavonoids was achieved by subjecting the cultures to a biotic, hydric and osmotic stress.

MEDI 314

Progress toward ingenane skeleton via IMDA reaction involving cycloheptadiene

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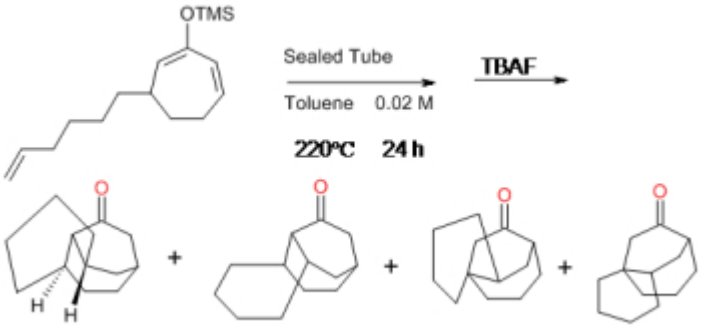
A particular derivative of ingenol is an anti-leukemic agent. This particular poster presents the synthetic methodology towards the ingenane skeleton with the crucial inside, outside-intrabridgehead stereochemistry. The IMDA reaction (scheme) was carried out with success showing after a subsequent transformation that ingenane skeleton with inside, outside-stereochemistry could have been formed along with three other products. We have only the GC trace

with mass from GC-MS. However, it is clearly evident from the GC trace that one of the products should be the desired. The retrosynthetic analysis towards ingenane skeleton and the results will be presented



MEDI 315

Synthesis and investigation of novel direct thrombin inhibitors

Elizabeth A Girnys[(1)]*, girnyse@umich.edu, 428 Church Street, Ann Arbor MI 48109, United States ; Katarzyna Sobczyk-Kojiro*[(1)]*; Henry I Mosberg*[(1)]*. (1) Department of Medicinal Chemistry, University of Michigan, Ann Arbor Michigan 48109, United States*

The serine protease thrombin is the main clotting enzyme in the hemostatic system, in addition to being an effective platelet activator. Thrombin has two G protein-coupled receptor substrates on platelets, PAR1 and PAR4, which upon thrombin activation stimulate platelet aggregation. Thus, the development of a direct thrombin inhibitor offers an approach for the treatment of acute coronary syndromes through modulation of the hemostatic system. Previous studies have shown that the pentapeptide Arg-Pro-Pro-Gly-Phe, a bradykinin breakdown product, inhibits the function of thrombin by interacting with its active site in a retro-binding fashion, as well as binding to PAR1 to prevent thrombin activation. SAR studies led to the development of a lead compound, FM19, and the x-ray structure of FM19 in the active site of thrombin has revealed modification sites to improve binding, resulting, thus far, in several peptides with improved inhibition. Additional modifications are underway, to improve both inhibition and bioavailability.

MEDI 316

Use of *para*-methoxybenzyl-protected urea scaffolds for the discovery of novel Factor Xa inhibitors

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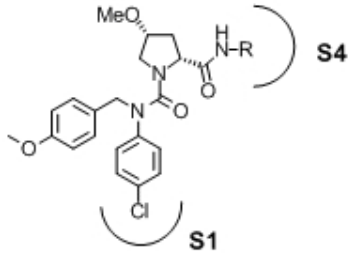
Edmunds[(1)]. (1) CVMED Chemistry, Pfizer-PharmaTherapeutics, Groton CT 06340, United States

During investigations into the syntheses of proline-based, Factor Xa (FXa) inhibitors containing amino-heterocyclic P4 pharmacophores, difficulties were encountered during a key amide coupling step due to the formation of intramolecular cyclization by-products. In order to circumvent these issues, scaffolds were discovered that utilized a fully elaborated chlorophenyl urea P1 pharmacophore that was protected by a *para*-methoxybenzyl group. Using novel urea-protected templates, allowed us to increase the diversity of FXa inhibitors discovered in our program.



MEDI 317

Discovery of novel phenylpropanoic acid analogs as potent and selective EP3 receptor antagonists

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Prostaglandin E_2 (PGE_2) is an oxidative metabolite of arachidonic acid and plays important roles to maintain homeostasis in the living body. The multiple physiological actions of PGE_2 are mediated by four specific receptor subtypes, namely EP1, EP2, EP3, and EP4. Many studies suggest that stimulation of the EP3 receptor causes a variety of responses such as pyrexia, hyperalgesia, uterine contraction, gastric acid secretion, and platelet aggregation. Thus, antagonism of the EP3 receptor is expected to be useful for the treatment of various diseases. This presentation will be focused on the discovery of novel potent and selective EP3 receptor antagonists consisting of phenylpropanoic acid scaffold with a characteristic carboxyamide side chain. Synthesis, SAR studies,

pharmacokinetic profiles, and pharmacological properties of this series will be described.

MEDI 318

Structure-based design, structure-conformation and structure-activity relationship studies of D-Phe-Pro-D-Arg-P1'-CONH2 tetrapeptides noncovalent inhibitors of thrombin

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By employing in silico structure-based design approaches, novel beta-turn tetrapeptides were designed, that may be used as additives in the treatment of acute coronary diseases (ACD). The new compounds were tested for their ability to reversible inhibit alpha thrombin using kinetics, thermodynamics, and thrombin mediated platelets aggregation assays. A structure-activity relationship (SAR) for the tetrapeptides D-Phe-Pro-D-Arg-P1'-CONH2, reversible inhibitors of thrombin is reported. The significant differences between their inhibitory constants (Kis) support the hypothesis that the interaction between the amino acid at the P1' position and the S1' pocket in thrombin is very specific: only small hydrophobic (Ala, Val, Gly) and polar (Ser, Thr, Cys) amino-acids were found to be favorable at P1', and their inhibitory constants are in the 0.8-15 micromolar. In addition, switching the configuration from L- to D- for some amino acids in P1' position (such as for Ala, Cys, Gln, and Thr) resulted in at least eight fold increase in their affinity for thrombin. These differences in the binding affinities were confirmed both kinetically and through isothermal titration calorimetry (ITC). Circular dichroism analysis showed that the D-Arg- at the (i+2) position followed by D-amino acids (polar and neutral like D-Thr, D-Gln, D-Ser and D-Ala) at the (i+3) position favors beta turn and beta hairpin structures in solution at low and neutral pH. The SAR supports the view that the tetrapeptides which adopt beta turn or beta hairpin conformation in solution are more potent as noncovalent inhibitors for thrombin.

MEDI 319

New approach for protein protein interaction antagonists

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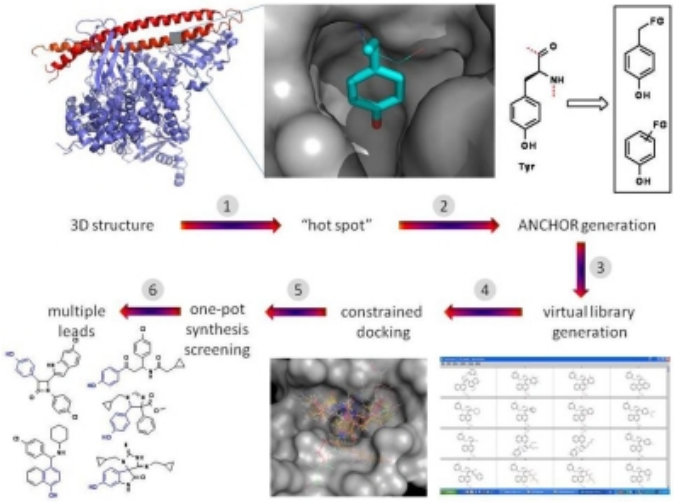
Burriedness of amino acid side chains in a receptor protein, in a first approximation, is indicative for their role in the protein protein interaction (PPI). Deeply buried amino acid side chains thus comprise a starting point for the discovery of antagonists of PPIs. We propose (Fig. 1) to excavate the amino acid with the highest burriedness from the PPI interface and to rename this amino acid side chain “ANCHOR”. Next we impose this fragment on efficiently chemical-accessible scaffolds (multicomponent reaction chemistry - MCR)[1] and to create virtual libraries based on several MCR scaffolds. These compound libraries are then docked into the PPI interface whereby the compounds “anchor” align with the protein “anchor” as a starting pose. Manual inspection of the docking results or automatic scoring functions are then used to choose compounds for synthesis and screening.[2] This novel approach is validated by the discovery of several (!) new classes of HDM2 and the first HDM4 antagonists as well as by dual-action HDM2/4 antagonists with nM potency and cell activity and appropriate PKPD.[3] A web-based highly interactive tool will be introduced (http://anchorquery.ccbb.pitt.edu/).[4]



References [1] A. Dömling *Chem. Rev.* **2006**, *106,* 17. [2] A. Czarna et al. *Angew. Chem. Intl. Ed. Engl.* **2010**, *49*, 5352. [3] G. Popowitz et al. *Cell Cycle* **2010**, *6*, 1104. [4] C. Camacho, A. Dömling et al. submitted.

MEDI 320

Deuterated telaprevir: Process via an efficient deuteration and a novel epoxidation condition

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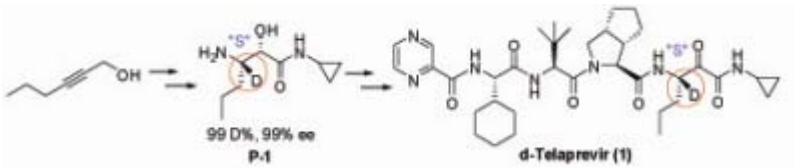

Telaprevir, a novel protease inhibitor, in combination with pegylated interferon alfa-2a/ribavirin, is being investigated for chronic HCV infection. Deuteration has been proposed to increase exposure of the active telaprevir conformer. Achieving high deuterium content on the chiral center, and preparing diastereomerically pure preparations were challenging. Herein, we report a practical, efficient process for preparing (**1**) that yielded >99D% isomer. We employed a novel epoxidation condition of the unprotected a,b-unsaturated enamide. D-telaprevir and telaprevir were comparatively tested for activity and stability.

MEDI 321

Novel apogossypol and apogossypolone derivatives as Pan Bcl2 antagonists for the treatment of cancer

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Gossypol, a natural product derived from cotton, is currently in phase III clinical trials as an apoptosis-based anti-cancer drug candidate. Because of its toxicity, Apogossypol (ApoG) and Apogossypolone (ApoG2), have been developed as non-toxic Gossypol derivatives. However, anti-cancer activities of ApoG and apoG2 are moderate and Structure-activity relationships studies (SAR) of ApoG and ApoG2 have never been explored. We have recently developed novel synthetic schemes and successfully synthesized several libraries of 5, 5' substituted ApoG and ApoG2 derivatives. Our findings demonstrated that installation of suitable amide, ketone or alkyl groups at 5, 5' position of ApoG and ApoG2 have significantly improved their anti-cancer activities in numerous cancel cell lines and different mice models, such as transgenic mice and xenograft model. 5, 5' substituted amide ApoG derivatives also improved chemical stability of ApoG. A natural product, Hemigossypol, a monomer of Gossypol, and its analogs were also synthesized to explore SAR of Gossypol at 7 position.

MEDI 322

Identification of new topoisomerase type II inhibitors for the treatment of multi-drug resistance *Staphylococcus aureus* through computer-aided drug design

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have increased in hospital and community settings. They are involved in skin cellulites, bacteremia, endocarditis, osteomylitis, and septic shock. We are applying computer-aided drug design (CADD) tools to identify new lead compounds expected to inhibit ATP hydrolysis at the ATP-binding sites of gyrase (GyrB) and topoisomerase IV (ParE). We have used Shape Signatures, a novel computational method developed in our laboratory, to scan a large chemical library of readily available compounds (the ZINC database) for molecules similar in shape to known inhibitors. Top hits from this initial scan were further validated by molecular docking using the GOLD and GLIDE docking tools. The docking results were further validated with molecular dynamics simulations to refine and rationalize predicted variations in binding affinity. The most promising compounds are being acquired and tested for activity by determining their minimal inhibitory concentrations, with Novobiocin as a positive control.

MEDI 323

ß-Dicarbonyl enolates: A new class of neuroprotectants

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We have discovered that simple β-diketones are neuroprotective and have identified a compelling structure activity relationship between flexible 1,3-dicarbonyl compounds and the amelioration of oxidative stress. Acetylacetone (AcAc) and analogous dicarbonyl compounds protected rat striatal synaptosomes from acrolein induced dysfunction and a neuronal cell line (MN9D) from acrolein toxicity. Analogs with conformational flexibility, particularly 2-acetylcyclopentanone (2-ACP), also provided cytoprotection against toxicity induced by H_2O_2 in a cell culture model of oxidative stress. In an animal model of oxidative stress induced by CCl_4 orally administered 2-ACP reduced markers of liver injury 36%. Initial chemical investigations indicated 1,3-dicarbonyl analogs do not scavenge free radicals but metal ion chelation is, as expected, a significant property of both AcAc and 2-ACP. Since 1,3-dicarbonyl compounds decreased the rate of thiol sulfhydryl loss caused by acrolein in cell free systems and also protected protein sulhydryl groups from acrolein adduction in

synaptosomes, a molecular mechanism involving the formation of soft enolate nucleophiles acting as surrogate thiol targets is presumed. To support this contention enolate ions were characterized using HSAB parameters derived from quantum mechanical computations. A nucleophilic index calculated from the enolate parameters provided a method for predicting the in vitro potency of the respective 1,3-dicarbonyl compounds. The combined data suggest that enolates formed from 1,3-dicarbonyl compounds represent a new class of neuroprotectants that scavenge or prevent the formation of cytotoxic electrophiles. As such, 2-ACP, AcAc and analogs are potential candidates for treatment of neurodegenerative conditions that have oxidative stress as a molecular etiology. NIEHS grant ES03830-24.

MEDI 324

Synthesis of anticancer agents that selectively target drug resistant cancer

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Multidrug resistance (MDR) is a phenomenon in which administration of a single chemotherapeutic agent can cause cross-resistance to a variety of other therapies. Development of MDR against current therapies is a major challenge in the treatment of cancer. Previously, we have demonstrated the ability of sHA 14-1 to mitigate drug resistance and synergize with a variety of chemotherapeutic agents. This presentation will describe a thorough structure-activity relationship study of sHA 14-1 leading to the identification of CXL017, which is 23-fold more potent than sHA 14-1. CXL017 can selectively target MDR cell lines cross-resistant to a variety of known chemotherapeutic agents *in vitro*. In addition, CXL017 shows significant anti-tumor acitivity against drug resistant tumors *in vivo*. Importantly, MDR cell lines continously treated with CXL017 over a period of six months fail to develop resistance. These results suggest that CXL017 is a promising candidate for treatment of cancer with MDR.

MEDI 325

Targeting truncated mu opioid receptor splice variants: Toward pain relief without side-effects

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Opiates have been the subject of intense research as agents acting through opiate receptors in the CNS for pain relief. Three families of opiate receptors have been isolated: mu, kappa and delta. There remains a need for alternative drug targets capable of providing pain relief without atypical opioid side-effects. The mu receptor gene (Oprm1) encodes a number of MOR-1 splice variants. One set of variants are generated from a promoter associated with exon 1 yield traditional 7 transmembrane G-protein-coupled receptors while a second set are produced from the exon 11 promoter and predict primarily truncated variants with only 6 transmembrane domains. The novel radioligand ^{125}I-BNtxA, synthesized in our laboratory, labels a novel opioid binding site in brains of wildtype and a series of knockout (KO) mice. Disruption of exon 1 variants has no effect upon the binding, but loss of exon 11 eliminates it. Its binding selectivity is quite distinct from traditional mu, delta and kappa$_1$ receptors. In vivo, IBNtxA is 10-fold more potent analgesic than morphine. The analgesia is not reversed by selective mu, delta and kappa$_1$ antagonists, but is antagonized by the morphinan levallorphan. As with the binding site, IBNtxA analgesia is present in opioid KO mice lacking the exon 1 variants, delta and kappa$_1$ receptors, but is lost in mice with a disruption of exon 11. Despite its profound analgesic potency, detailed pharmacological evaluation failed to observed evidence of respiratory depression, constipation, physical dependence or reward in the conditioned place preference test. It also showed no cross tolerance to morphine and U50,988H. Thus, we have no identified a promising target for the development of potent opioid analgesics lacking side effects. Design, synthesis of novel analgesics and implications in opioid drug discovery will be discussed.

MEDI 326

Potent and selective small molecule in vitro inhibitors of cdc2-like (CLK) and dual specificity tyrosine-phosphorylation-regulated (DYRK) kinases

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Many human diseases are caused by improper mRNA splicing by the splicesome protein complex. The cdc2-like kinase (CLK) family, capable of auto-phosphorylation and phosphorylation of exogenous proteins, is proposed to alter the function of the splicesome by targeting serine-arginine-rich proteins used in splicesome assembly. It is hypothesized that manipulation of the splicesome by inhibiting CLK4 will eliminate splicing abnormalities allowing the process of gene translation to be controlled and mRNA disease-causing phenotypes to be

corrected. DYRK1A is a dual-specificity tyrosine-phosphorylation regulated kinase distantly related to members of the CLK family that is proposed to play a critical role in the development of Down Syndrome. Herein we report a series of 6-arylquinazolin-4-amines that show both excellent inhibition of CLK1, CLK4, DYRK1A and DYRK1B as well as high selectivity over the rest of the human kinome. These inhibitors provide a starting point for potentially important future chemotherapeutics for a variety of genetic diseases.

MEDI 327

Synthesis, biological evaluation, molecular modeling and 3D-QSAR studies of 3-keto salicylic acid chalcones as novel HIV-1 integrase inhibitors

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HIV-1 integrase is one of the three most important enzyme required for viral replication and is therefore an attractive target for antiretroviral therapy. We herein report the design and synthesis of 3-keto salicylic acid chalcone derivatives as novel HIV-1 integrase inhibitors. The most active compound, 5-bromo-2-hydroxy-3-[3-(2,3,6-trichloro-phenyl)-acryloyl]-benzoic acid, was selectively active against strand transfer with IC_{50} of 4 μM. Selected potent compounds also inhibited HIV replication with potencies comparable with their integrase inhibitory activities. Docking conformations and PHASE pharmacophore-derived molecular alignments were used for 3D-QSAR modeling. The resulting CoMFA and CoMSIA models had q^2 values up to 0.57 and 0.52 respectively. The CoMSIA model from docking pose-2 alignment performed the best with a predictive r^2 of 0.50 for a prospectively synthesized external validation test set. This model can thus be used to guide the rational design of more potent novel 3-keto salicylic acid integrase inhibitors.

MEDI 328

Synthesis of macrocycles with embedded carbohydrates for peptidomimetic research

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Over the past 20 years, new concepts in peptidomimetic chemistry have been developed with the aim of transposing structural and functional requirements from peptide targets onto metabolically more stable and drug like scaffolds. Carbohydrate templates or scaffolds are one example that have found wide application in bioactive compound discovery as they contain functional groups to which pharmacophores can be grafted. These multifunctional scaffolds have been applied to generate compounds of interest in peptidomimetic research.[1] The design of peptidomimetics to mimic a specific conformation of SST14, the somatostatin hormone and endogenous ligand of the SST1-5 receptors has been of broad interest.[2] Herein, polyfunctional analogues of natural polyketide derived macrolides have been synthesized, providing a basis for their development as peptidomimetic scaffolds. The strategy involved combining a carbohydrate and macrolactone and the side chains of the Trp-Lys dipeptide fragment, which are important for the recognition to somatostatin receptors, were installed onto the scaffold. The results of binding assays to SSTRs are reported. 1. (a) Hirschmann, R.F., et al., *The beta-D-Glucose Scaffold as a beta-Turn Mimetic.* Accounts of Chemical Research, 2009. **42**(10): p. 1511-1520. (b) Murphy, P.V., *Peptidomimetics, glycomimetics and scaffolds from carbohydrate building blocks.* European Journal of Organic Chemistry, 2007(25): p. 4177-4187. 2. Seebach, D. and J. Gardiner, *beta-Peptidic Peptidomimetics.* Accounts of Chemical Research, 2008. **41**(10): p. 1366-1375.

MEDI 329

Design, synthesis, and biological evaluation of novel diazide-containing pyrazole- and isoxazole-based HDAC probes

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In this presentation, we describe the design, synthesis, and biological evaluation of active and selective HDAC3 and HDAC8 diazide isoxazole-based and pyrazole-based probes suitable for photolabeling experiments in cells. We also performed a closely related small SAR study focused on a novel pyrazole-based scaffold and optimized the synthetic procedures for gram scale synthesis. Both the isoxazole- and pyrazole-based probes exhibit excellent low double digit nanomolar inhibitory activity against HDAC3 and HDAC8, respectively. The cell-based experiments show that these probes are cell permeable and exert an anti-

proliferative activity towards HepG2, Hela, and SH-SY5Y cell lines, and neuroprotective activity in SH-SY5Y cell lines at micromolar concentrations. The presence of an azide or a diazide group does not interfere with the neuroprotection properties, or enhance cellular cytotoxicity, or affect cell permeability, making these probes excellent candidates for cell-based photolabeling experiments.

MEDI 330

Fragment based drug discovery in teams of medicinal and computational chemists

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Lead discovery often starts from small fragment binders for which experimental evidence has been found in an active site. These fragment binders can then be developed into leads with improved affinity by a) Developing them into the depth of the active site, exploiting pharmacophore points on the protein side b) Linking two or more fragment binders from subpockets of the active site c) Merging small molecules where they coincide in the pocket to form one molecule with improved properties These tasks can now be accomplished with a novel software tool, LeadIT, which was primarily designed for mixed medicinal and computational chemistry teams. The approach uses an indexed 3D fragment database which is interactively searched. The medicinal chemist can give immediate feedback on the synthetic feasibility of the results, interesting compounds can be saved and further elaborated on. We will show the basic principles of this approach as well as a few retrospective examples which show the usefulness of this approach.

MEDI 331

Bile acid signaling and control of metabolism

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Bile acids are natural detergents, facilitating the intestinal absorption of dietary lipids and fat-soluble vitamins. In addition to this function, bile acids have emerged as important signaling molecules that can coordinate diverse metabolic pathways. A number of these bile acid-mediated effects involve the activation of the nuclear hormone receptor farnesoid X receptor (FXR) and include the transcriptional control of the synthesis and recycling of bile acids as well as the regulation of hepatic lipid and glucose production. Recently, we found that bile acids can also exert metabolic effects via an FXR independent pathway thereby

protecting mice against diet-induced obesity. Bile acid-mediated increase in energy expenditure was shown to be mediated by the membrane receptor TGR5, also known as GPR131, and involves the induction of the thyroid hormone activating enzyme deiodinase 2. We also provide evidence that bile acids improve glucose tolerance through the stimulation of the release of the incretin, glucagon like peptide 1, from enteroendocrine L cells. Together our data suggest that bile acids are important signaling molecules, with activities, which clearly extend beyond nuclear receptor activation and involve activation of the GPCR, TGR5.

MEDI 332

From orphan nuclear receptor libraries to farnesoid X receptor agonists: The GSK story

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As part of a systems-based drug discovery strategy, a series of combinatorial nuclear receptor ligand-biased libraries were prepared and screened against a panel of orphan nuclear receptors. A partial agonist hit was identified for the farnesoid X receptor (FXR) from a stilbene carboxylate library. Further screening of a discrete, focused library, synthesized around this isoxazole hit, led to the identification of the potent, selective, full FXR agonist GW 4064. Although this chemical tool has been instrumental in probing the physiological roles of FXR, GW 4064 has several limitations for further development, including light instability and low oral bioavailability. Medicinal chemistry efforts to improve the drug properties of GW 4064, leading to the discovery of the FXR clinical candidates GSK8062 and GSK2324, will be discussed.

MEDI 333

Discovery of novel, highly potent and selective small molecule farnesoid X receptor (FXR) agonists

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A novel class of small molecule farnesoid X receptor (FXR) agonists based on the benzimidazolyl acetamide scaffold was identified by high-throughput screening of the Roche compound library. Hit to lead optimization led to the establishment of a robust structure-activity relationship (SAR) that resulted in the identification of potent compounds with good *in vitro* and *in vivo* activity. Subsequent lead optimization efforts guided by structure-based design focused on improving bioavailability and reducing hERG inhibition while maintaining the high potency of the initial lead structures. The identification of an exit vector which permitted the introduction of polar substituents led to the discovery of compounds endowed with excellent physicochemical and ADME properties that also displayed potent plasma lipid lowering effects in LDLR receptor knockout mice after oral administration. The presentation will describe the synthesis, SAR and structure-property relationships of this novel class of non-steroidal FXR agonists.

MEDI 334

Deconstructing bile acid signaling pathways

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Recent years are seeing an ever growing interest in bile acids (BAs) as versatile signaling molecules. Through the activation of nuclear and G-protein-coupled receptors, BAs regulate diverse signaling pathways of metabolic functions. Accordingly, natural and synthetic modulators of BA receptors have been developed to provide novel drug candidates for common metabolic diseases. In this framework, we have previously reported the design and synthesis of INT-747 and INT-777 as potent and selective ligands of FXR and TGR5, respectively. These compounds are on track for preclinical and clinical assessments in a number of metabolic disorders such as primary biliary cirrhosis (PBC) and type 2

diabetes, with INT-747 having successfully reached phase III of clinical studies in PBC. In this presentation, further developments in the chemistry and biology of BA derivatives will be reported. Moreover, the results of computational studies on the hitherto hidden conformational aspects of BAs will be presented and discussed.

MEDI 335

Synthesis, SAR, and anti-diabetic potential of TGR5 receptor agonists

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The TGR5 receptor is being studied as a potential target for more effective treatment of patients with type II diabetes and its associated complications. Use of 7TM focused cross-screening as well as high-throughput diversity screening identified multiple small molecule agonists of the TGR5 receptor. During the hit-to-lead optimization phase, key structure-activity relationships (SAR) were rapidly identified, and key exemplars of the more promising chemotypes were progressed to in vivo studies to evaluate their effect on GLP-1 secretion, as well as insulin and glucose levels. Details of the early exploratory efforts using these small molecule TGR5 agonists, including SAR, synthesis, and in vivo results, will be presented.