



Division of Medicinal Chemistry
Scientific Abstracts
For the
244th National Meeting and Exposition
August 19-23, 2012
Philadelphia, PA

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American Chemical Society

Division of Medicinal Chemistry

July 6, 2012

Dear Division of Medicinal Chemistry Members-

Following this letter you will find the scientific program and all abstracts for MEDI programming at the 244th National Meeting of the American Chemical Society (Philadelphia, PA, August 19-23, 2012). Please note that the official publication date for these abstracts is July 6, 2012. As you can see, the MEDI Long Range Planning Committee has organized symposia at the cutting edge of drug discovery research that should be of great interest to all division members.

The meeting in Philadelphia features a number of events that we hope you will plan to attend, including the First Time Disclosures session (Sunday afternoon), the Poster Session and Social Hour (Sunday evening), the MEDI Awards Symposium (Tuesday afternoon) and the Hall of Fame Induction ceremony (Tuesday evening). In addition, the Wednesday evening poster session, co-organized with ORGN, will again feature food and music. Times and locations for these events will be listed in the ACS Meeting booklet.

The Division of Medicinal Chemistry strives to provide you with the most useful programming at each national meeting. If you have suggestions for any future symposia, or any other suggestions, please feel free to contact me or one of the other MEDI officers or Long Range Planning Committee members. The names and contact information of these individuals can be found on the division web site at <http://www.acsmedchem.org>. I look forward to seeing you at the meeting in Philadelphia!

Best regards,

Patrick M. Woster, Ph.D.
2012 Chair, ACS Division of Medicinal Chemistry

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Nominations are Now Being Accepted for the 2013 Bristol-Myers Squibb Edward E. Smissman Award

The ACS Division of Medicinal Chemistry invites nominations for the 2013 Bristol-Myers Squibb Edward E. Smissman Award. This Award is open to a living scientist, in the U.S. or abroad, whose research, teaching, and/or service have had a substantial impact on the intellectual and theoretical development of the field of medicinal chemistry. Normally, the Award is intended for scientists relatively late in their active scientific careers whereupon a substantial body of creative work is available and sufficient time has passed to place their work in perspective. Nominations must include a letter of nomination, up to two seconding letters and a copy of the nominee's most recent curriculum vitae. All materials must be received by 5:00 pm on **Friday, September 21, 2012**. Nomination packets should be submitted electronically as a single file to:

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American Chemical Society
Division of Medicinal Chemistry
244th ACS National Meeting, Philadelphia, PA, August 19-23, 2012

J. Barrish, Program Chair

SUNDAY MORNING

Personalized Health Care In Oncology

K. George, Organizer; K. George, Presiding Papers 1-6

General Oral Session

J. Barrish, Organizer; N. Meanwell, Presiding Papers 7-17

SUNDAY AFTERNOON

First Time Disclosures of Clinical Candidates

A. J. Robichaud, Organizer; A. J. Robichaud, Presiding Papers 18-22

General Oral Session

J. Barrish, Organizer; K. Seley-Radtke, Presiding Papers 23-33

SUNDAY EVENING

General Poster Session

J. Barrish, Organizer Papers 34-194

MONDAY MORNING

New Strategies for Targeting Parkinson's Disease and Other Neurodegenerative Conditions

J. Macor, Organizer; J. Macor, Presiding Papers 195-199

Cellular Targets and Chemical Biology

J. Wanner, Organizer; B. Turunen, Organizer; B. Turunen, Presiding; J. Wanner, Presiding Papers 200-204

MONDAY AFTERNOON

Validating the Glutamatergic Hypothesis: How Far Have We Come?

J. Schwarz, Organizer; J. Schwarz, Presiding Papers 205-210

Peptide Hormones and Therapeutics

L. Yan, Organizer; C. Haskell-Luevano, Organizer; C. Haskell-Luevano, Presiding; L. Yan, Presiding Papers 211-216

MONDAY EVENING

Sci-Mix

J. Barrish, Organizer Papers 33, 36, 38, 44, 46, 54, 56, 61, 67, 70, 73, 89, 91-92, 101, 107, 112, 114, 148, 151, 165, 171, 174-175, 309, 314, 319, 328-331, 335, 353, 369, 374, 377-378, 380, 387, 389-390, 393

TUESDAY MORNING

General Oral Session

J. Barrish, Organizer; J. Barrish, Presiding; W. Ewing, Presiding Papers 217-223

MEDI Predoctoral Awardees: Where Are They Now?

P. Woster, Organizer; J. Macor, Organizer; J. Macor, Presiding; P. Woster, Presiding Papers 224-229

TUESDAY AFTERNOON

A Medicinal Chemist's Toolbox: A Tactical and Strategic Inventory

P. Scola, Organizer; N. Meanwell, Organizer; N. Meanwell, Presiding; P. Scola, Presiding Papers 230-234

MEDI Awards Symposium

J. Barrish, Organizer; J. Zablocki, Presiding; P. Woster, Presiding Papers 235-241, 428

WEDNESDAY MORNING

Drug Delivery Technologies: Getting Your Compounds to the Clinic

J. Higgins, Organizer; J. Lubach, Organizer; J. Lubach, Presiding; J. Higgins, Presiding Papers 242-249

General Oral Session

J. Barrish, Organizer; J. Barrish, Presiding Papers 250-261

Bioisosteres Redux: Strategic Deployment in the Design and Development of Drug Candidates

N. Meanwell, Organizer; J. Butera, Organizer; J. Butera, Presiding; N. Meanwell,

Presiding Papers 262-266

WEDNESDAY AFTERNOON

From Fragments to Leads: Medicinal Chemistry in Fragment-Based Drug Discovery

P. Carter, Organizer; D. Loughney, Organizer; R. Dominique, Organizer; D. Loughney, Presiding; R. Dominique, Presiding Papers 267-273

Small-Molecule Modulation of Cell Stress Response Pathways: From Chemical Design to Clinical Opportunities

G. Wondrak, Organizer; A. Dinkova-Kostova, Presiding; G. Wondrak, Presiding Papers 274-278

Process Chemistry: The Role of Organic Synthesis in Early Clinical Drug Development

A. Abdel-Magid, Organizer; R. Vaidyanathan, Organizer; R. Vaidyanathan, Presiding Papers 279-284

WEDNESDAY EVENING

General Poster Session

J. Barrish, Organizer Papers 285-427

MEDI 1

Personalized healthcare in oncology

Robert Wasserman, *ROBERT.WASSERMAN@ROCHE.COM. Roche Pharma Research and Early Development, Hoffmann-La Roche, Nutley, NJ 07110-1199, United States*

The understanding of cancer biology has increased dramatically over the past decade, in part through the use of sophisticated assays which allow for the unraveling of the complexities of cancer and its subsequent molecular and phenotypic characterization. Although, on a clinical basis, cancer is still generally classified to the organ of origin and the histological pattern, a biological basis for further differentiation “subtyping” is now recognized as being essential to advance cancer therapy. Consequently, a new paradigm has arisen in regard to treatment, such that the clinician is increasingly turning to the results of tissue-based diagnostic assessments to provide treatments that counteract the causal drivers of the malignant state. In this presentation, I will provide an overview of the progress in deciphering cancer biology and how this progress has been translated into breakthrough treatments for patients, many of which are new small molecule chemical entities targeting the underlying abnormalities within the cancer cell.

MEDI 2

Targeting JAK2 pathway mutations for treatment of myeloproliferative neoplasms

Ashok V Purandare, *ashok.purandare@bms.com. Oncology Chemistry, Bristol-Myers Squibb R & D, Princeton, New Jersey 08543, United States*

Myeloproliferative neoplasms (MPNs) are clonal malignancies resulting from hematopoietic progenitors and characterized by overproduction of mature and functional blood cells. Significant medical need exists, as the current standard of care is only palliative and does not change the course of these diseases. Over the past 10 years noteworthy advances have been made toward understanding the role of JAK2 in numerous cancers, particularly in MPNs. Discovery of JAK2V617F as well as JAK2—STAT pathway mutations and their relevance to MPNs have fuelled research in academia and pharmaceutical industry. Success with kinase-targeted therapies, such as imatinib and dasatinib for the BCR-ABL mutation-driven CML, has raised hopes for using this same approach for JAK2 inhibitors. The presentation will review current state of affairs in the area of MPN therapy targeting JAK2; including work leading to discovery of BMS-911543, as a clinical candidate.

MEDI 3

Personalized medicine in action: Invention of crizotinib (PF-02341066)

J. Jean Cui, *jean.cui@pfizer.com. Oncology Medicinal Chemistry, Pfizer, Inc., San Diego, CA 92130, United States*

Crizotinib, a potent c-Met/ALK dual inhibitor, was fast track approved in August 26, 2011 by FDA for late stage lung cancer patients with EML4-ALK fusion gene. The invention of crizotinib starts from a cocrystal structure of c-Met/PHA-665752 complex. The cocrystal structure of **PHA-665752**, bound to c-MET kinase domain, revealed a novel ATP site environment, which served as the target to guide parallel, multi-attribute drug design. A novel 2-amino-5-aryl-3-benzyloxy pyridine series was created to more effectively make the key interactions achieved with **PHA-665752**. In the novel series, the 2-aminopyridine core allowed a 3-benzyloxy group to reach into the same pocket as the 2,6-dichlorophenyl group of **PHA-665752** via a more direct vector, and thus with a better ligand efficiency (LE). Further optimization of the lead series generated the clinical candidate crizotinib (**PF-02341066**), which demonstrated potent *in vitro* and *in vivo* c-MET kinase and ALK inhibition, effective tumor growth inhibition, and good pharmaceutical properties and safety profile.

MEDI 4

Targeting oncogenic BRAF and the development of BRAF resistance

Wayne Spevak, *wspevak@plexxikon.com, Gideon Bollag, Gaston Habets, Peter Hirth, Prabha Ibrahim, Yan Ma, Keith Nolop, Ben Powell, Brian West, Chao Zhang. Plexxikon Inc, Berkeley, CA 94710, United States*

BRAF is a frequently mutated protein kinase in human cancers, with approximately 50% of patients with metastatic melanoma having an activating mutation replacing valine-600. Vemurafenib (PLX4032), a potent inhibitor of oncogenic BRAF kinase, was approved by the FDA in 2011 along with a companion diagnostic for the treatment of patients with BRAF^{V600} mutation-positive inoperable or metastatic melanoma. Paradoxically, it has been found that while BRAF inhibitors block signaling in cells with mutant BRAF, they can enhance signaling in cancer cells with wild-type BRAF. This activation is believed to accelerate the development of cutaneous squamous cell carcinoma, and may also be important in the development of resistance to BRAF inhibitors. Second generation BRAF inhibitors are being developed to address this paradoxical activation of wild-type RAF.

MEDI 5

Putting personalized healthcare in oncology into action: A stakeholder analysis of key issues, risks, and opportunities

Ryan P Million, *rmillion@trinitypartners.com. Trinity Partners, LLC, New York, New York 10017, United States*

Oncology has been the leading therapeutic area to connect bench to bedside innovation in personalized medicine, driven by novel agents and their associated companion diagnostics. From a commercial perspective, although many successful examples exist to date, development of new drugs with associated diagnostics increases the commercial risk and complexity in making new brands successful. As a result, this environment has created a number of challenges and opportunities for the broad set of stakeholders in the health care value chain. Despite these issues, tremendous commercial opportunity exists as best demonstrated by significant investment by drug discovery companies and related recent product launches. In this presentation, we will review how this changing landscape affects physicians, patients, payors, manufacturers and other stakeholders in a variety of ways and discuss the future potential of the marketplace.

MEDI 6

Targeting Imatinib resistance: Progress toward “final generation” inhibitors of BCR-ABL for the treatment of CML

William Shakespeare, *william.shakespeare@ariad.com.ARIAD Pharmaceuticals Inc., United States*

The BCR-ABL inhibitor Imatinib is the exemplar of targeted therapy in CML. Although most patients attain a durable complete cytogenetic response, minimal residual disease persists in nearly all patients. Importantly, discontinuation of imatinib due to intolerance or resistance is necessary in up to 30% of patients within the first five years of therapy. Resistance to imatinib usually involves point mutations in the kinase domain of BCR-ABL that impair inhibitor binding. To address these mutations, second-generation inhibitors nilotinib and dasatinib were developed leading to recaptured response. Despite the effectiveness of these newer agents which successfully target most imatinib failures, pockets of resistance remain and neither compound inhibits the T315I gatekeeper mutant which constitutes 15-20% of all clinically observed mutants. More recently, several next-generation inhibitors including DCC-2036, ponatinib (AP24534) and others have emerged that effectively target T315I and other disease resistant mutations. Critical to the evolution of these next generation inhibitors has been the judicious use of structure to guide design of molecules which either avoid or proactively engage the increased bulk of the isoleucine mutation resulting in potent gatekeeper inhibition. Finally, ponatinib has been shown to abrogate resistance in a cell-based mutagenesis screen revealing no liabilities and suggesting that final-generation inhibitors of BCR-ABL driven CML may become a reality.

MEDI 7

Getting Syk selectively

Matthew C Lucas, *matthew.lucas@roche.com.Department of Discovery Chemistry, Roche, Nutley, NJ 07110, United States*

Inhibition of spleen tyrosine kinase has attracted much attention as a mechanism for the treatment of autoimmune diseases such as asthma, rheumatoid arthritis, and SLE. Fostamatinib, a Syk inhibitor that successfully completed Phase II clinical trials, also exhibits off-target kinase activity that may have contributed both to its efficacy as well as to some of the side effects. These included hypertension, neutropenia, diarrhea, and elevations in transaminase enzymes. More selective Syk inhibitors could offer safer, alternative treatments. We identified Pro455 and Asn457 in the Syk ATP binding site as a rare combination among sequence aligned kinases and hypothesized that optimizing the interaction between them and a Syk inhibitor molecule would impart high selectivity for Syk over other kinases. This presentation will report the structure-guided identification of three series of selective spleen tyrosine kinase inhibitors that support our hypothesis.

MEDI 8

Discovery of potent and selective Syk kinase inhibitors based on an indazole core

Bernat Vidal¹, bernat.vidal@almirall.com, **Joan Carles Fernandez**², **Montserrat Erra**¹, **Nuria Aguilar**¹, **Marta Mir**¹, **Ines Carranco**¹, **Manuel Lopez**¹, **Monica Maldonado**¹, **Adelina Orellana**¹, **Peter Eichhorn**¹, **Cristina Carreño**¹, **Raquel Otaí**¹, **Jorge De Alba**¹, **Montserrat Miralpeix**¹. (1) *Almirall Research Center, Almirall, Sant Feliu de Llobregat, Barcelona 08980, Spain* (2) *Almirall-Barcelona Science Park Unit, Almirall-Barcelona Science Park Unit, Barcelona, Barcelona 08028, Spain*

Syk kinase plays an essential role in immunoreceptor signalling and is considered a promising therapeutic target for the treatment of immune-mediated disorders such as allergy, autoimmune diseases and haematological malignancies.

The presentation will focus on the design and synthesis of indazole based compounds from HTS hits. SAR expansion focussed on improving potency by capturing additional interactions within the ATP binding area of the kinase (X-Ray structures will be disclosed) allowed the identification of advanced leads with good *in vitro* enzymatic potency ($IC_{50} < 10$ nM) as well as cellular activity ($IC_{50} < 100$ nM) blocking LAD2 cell degranulation *in vitro*. Additionally the compounds were optimized to be suitable for inhaled administration. A selected lead compound showed *in vivo* efficacy in a model of the early allergic response in OVA-sensitized BN rats ($ED_{50} < 1$ mg/Kg by intratracheal route).

The results support the potential benefits for Syk kinase inhibitors in the treatment of allergic diseases including asthma and allergic rhinitis.

MEDI 9

Identification of a selective lead series for a PI3K-delta programme by kinase cross-screening

Zoe Harrison, *zoe.x.harrison@gsk.com. Department of Medicinal Chemistry, GlaxoSmithKline, Stevenage, Hertfordshire SG1 2NY, United Kingdom*

Kinases are regulators of a broad range of cellular processes. Deregulated kinase activity is a frequent cause of disease hence kinases are considered attractive targets for drug discovery. As kinase inhibitors mainly share the adenosine triphosphate binding site, an efficient way of finding hits for a new target kinase is by screening a small focussed set of compounds designed to target this pocket. A key issue for translating hits into candidates and medicines for kinases has been that of selectivity over other undesired kinase target activities.

This presentation will discuss how a hit compound for PIM1, found through a focussed set screen, and its potential issues of selectivity over GSK3 led to change in kinase profile and a promising selective lead series for PI3Kdelta.

MEDI 10

Small molecule inhibitors of IL-17A and IL-17F secretion for the treatment of autoimmune diseases

Stefan Tasler, *stefan.tasler@4sc.com. 4SC Discovery GmbH, Planegg-Martinsried, Germany*

Th17 cells have been identified as a major player in autoimmunity. An important transcription factor during Th17 differentiation and responsible for IL-17A and F transcription, which are key cytokines in a Th17 response, is ROR γ t.

We were able to identify inhibitors of IL-17A and IL-17F secretion in a single-digit nanomolar to subnanomolar range which proved to be potent ROR γ t inhibitors.

The potential for treating autoimmune diseases with such inhibitors has been evaluated in an animal model for psoriasis, in which mice bearing a skin-specific vs. ubiquitous I κ B α knockout were used. Topical application of a lead compound in both models resulted in a complete phenotypical recovery in the skin-specific variant and a clearly prolonged survival in the ubiquitous knockout animal.

Within an SLE model in MRL^{lpr/lpr} mice, oral administration of a lead compound resulted in complete survival of all animals within a timeframe resulting in 50% mortality in the control group.

MEDI 11

Hematopoietic prostaglandin D synthase inhibitors for the treatment of inflammatory disorders

Sukanthini Thurairatnam, *sukanthini.thurairatnam@sanofi.com*. Lead Generation to Candidate Realization, Sanofi Pharmaceuticals, Bridgewater, New Jersey 08807, United States

The cyclooxygenases convert arachidonic acid to PGG₂ and then to PGH₂ which is further metabolized to TxA₂, PGI₂ and the prostaglandins PGE₂, PGF₂, and PGD₂. Prostaglandins play a key role in the generation of inflammatory responses and their biosynthesis is significantly increased in inflamed tissue. Production of PGD₂ in the peripheral tissues and in inflammatory cells is catalyzed by H-PGDS, which is a cytosolic, glutathione dependent enzyme. PGD₂ and its metabolites show a range of biological activities mediated through two distinct G-protein coupled receptors, DP1 and CRTH2. Recently a CRTH2 receptor antagonist Setipiprant has shown promising results in Phase II study but until now none of the H-PGDS inhibitors have reached the clinical status. However, growing understanding of the functions of PGD₂ and its metabolites, and studies in animal models indicate the potential use of H-PGDS inhibitors for the treatment of inflammatory disorders.

Identification and optimization of the lead compound resulted in potent, selective and orally bioavailable inhibitors of H-PGDS that suppressed the secretion of PGD₂ *in vitro* and *in vivo*. Our in-house data suggest that H-PGDS inhibitors could provide a novel therapy for the treatment of inflammatory disorders. Structure activity relationship, X-ray crystal structures, pharmacokinetic profile, efficacy in animal models and the therapeutic potential of H-PGDS inhibitors will be presented.

MEDI 12

Design and structure of stapled peptides binding to estrogen receptors

Lee R Roberts¹, *lee.roberts@pfizer.com*, **Chris Phillips**¹, **Markus Schade**¹, **Richard Bazin**¹, **Andrew Bent**¹, **Nichola L Davies**¹, **Rob Moore**¹, **Andrew D Pannifer**¹, **Andrew R Pickford**², **Stephen H Prior**², **Christopher M Read**², **Andrew Scott**¹, **David G Brown**¹, **Bin Xu**³, **Stephen L Irving**¹. (1) *Worldwide Medicinal Chemistry, Pfizer, Sandwich, Kent CT13 9NJ, United Kingdom* (2) *Institute of Biomolecular and Biomedical Sciences, School of Biological Sciences, University of Portsmouth, Portsmouth, Hampshire PO1 2DY, United Kingdom* (3) *CPC Scientific Incorporated, San Jose, California 95112, United States*

Synthetic peptides that specifically bind nuclear hormone receptors offer an alternative approach to small molecules for the modulation of receptor signaling and subsequent gene expression. Here we describe the design of a series of novel stapled peptides that bind the coactivator peptide site of estrogen receptors. Using a number of biophysical techniques, including crystal structure analysis of receptor-stapled peptide complexes, we describe in detail the molecular interactions and demonstrate that all-hydrocarbon staples modulate molecular recognition events. The findings have implications for the design of stapled peptides in general as the addition of the all-hydrocarbon staple not

only conformationally restrains the peptide but can also affect the interactions of the peptide with hydrophobic protein surfaces.

MEDI 13

Removing genotoxicity of aromatic amines? Almost simple – mechanism-based insights into structure-genotoxicity relationships

Igor Shamovsky¹, *igor.shamovsky@astrazeneca.com*, **Lena Ripa**¹, **Peter Hansen**¹, **Christine Mee**², **Nicholas Tomkinson**³, **Christian Tyrchan**⁴, **Mike O'Donovan**², **Peter Sjo**¹. (1) Department of Medicinal Chemistry, R&I iMed, AstraZeneca R&D, Molndal, Sweden (2) Genetic Toxicology, AstraZeneca R&D, Alderley Park, United Kingdom (3) R&D Information, AstraZeneca R&D, Alderley Park, United Kingdom (4) Department of Medicinal Chemistry, CVGI iMed, AstraZeneca R&D, Molndal, Sweden

Fear of potential genotoxicity discourages wide use of aromatic and heteroaromatic amines (ArNH₂) in drug discovery projects. Experimental data suggest that metabolic activation in many classes is linked to the resonance stabilization of the anionic forms. Accordingly, it has been hypothesized that the rate-limiting step of metabolic activation by CYP1A2 as by arylamine N-acetyltransferase is proton abstraction [Shamovsky et al., JACS 2011, 133, 16168]. On the other hand, chemical reactivity of the metabolically activated species (ArNHOH and ArNHOAc) depends on the resonance stabilization of nitrenium ions. Energy profiles of four chemical reactions of the genotoxicity pathway of ArNH₂ are studied by QM calculations and linked to their mutagenicity. The results are generalized using AstraZeneca corporate mutagenicity database. We demonstrate that chemical reactivity of metabolically activated species is maximal if their nitrenium ions are more stable than that of aniline by around 20 kcal/mol. Mutagenic potency of ArNH₂ is proportional to chemical reactivity of metabolically activated species and to the rate of their formation. Strong resonance destabilization of either cationic or anionic form leads to genotoxicity free ArNH₂. In addition, structural elements that make ArNH₂ non-genotoxic by preventing their binding to CYP1A2 in the productive binding mode regardless of ionic stabilization are identified. The attained mechanism-based understanding of structure-genotoxicity relationships leads to three general approaches to design non-genotoxic ArNH₂: (i) to prevent initial proton abstraction in CYP1A enzymes; (ii) to hinder hydrolytic cleavage of N-O bonds of ArNHOH and its bioconjugates; (iii) to force transition of nitrenium ions to neutral imines.

MEDI 14

Discovery of AM-8553: Structure-based design of novel piperidinone inhibitors of the MDM2-p53 interaction

Yosup Rew¹, *yrew@amgen.com*, **Daqing Sun**¹, **Felix Gonzalez Lopez De Turiso**¹, **Michael D Bartberger**⁴, **Hilary P Beck**¹, **Jude Canon**⁵, **Ada Chen**¹, **David Chow**¹, **Jeffrey Deignan**¹, **Brian M Fox**¹, **Darin Gustin**¹, **Xin Huang**⁶, **Min Jiang**³, **Xianyun Jiao**¹, **Lixia Jin**³, **Frank Kayser**¹, **David J Kopecky**¹, **Yihong Li**¹, **Mei-Chu Lo**¹, **Alexander M Long**⁶,

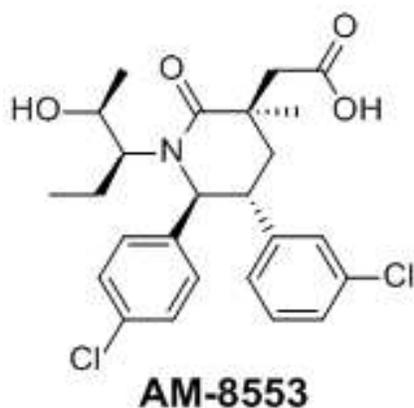
Klaus Michelsen⁴, Jonathan D Oliner⁵, Tao Osgood⁵, Mark Ragains², Anne Y Saiki⁵, Steve Schneider⁶, Maria Toteva², Peter Yakowec⁶, Xuelei Yan¹, Qiuping Ye³, Dongyin Yu⁵, Xiaoning Zhao¹, Jing Zhou¹, Julio C Medina¹, Steven H Olson¹. (1) Therapeutic Discovery, Amgen, South San Francisco, CA 94080, United States (2) Pharmaceuticals, Amgen, South San Francisco, CA 94080, United States (3) Pharmacokinetics and Drug Metabolism, Amgen, South San Francisco, CA 94080, United States (4) Therapeutic Discovery, Amgen, Thousand Oaks, CA 91320, United States (5) Oncology Research, Amgen, Thousand Oaks, CA 91320, United States (6) Therapeutic Discovery, Amgen, Cambridge, MA 02142, United States

The tumor suppressor protein p53 plays a central role in preventing tumor development by upregulating the transcription of numerous genes involved in cell cycle arrest and apoptosis. Inactivation of the p53 pathway in tumor cells provides a strong selective growth advantage, and it has been proposed that elimination of p53 function may be a requisite step in tumor formation.

The MDM2 (murine double minute 2) oncogene is an important negative regulator of p53. MDM2 is transcriptionally activated by p53, and the activity of p53 is regulated by MDM2 through various mechanisms. Wild-type p53 is found in approximately 50% of human cancers, and inhibition of the MDM2-p53 interaction with small-molecule MDM2 inhibitors has been shown to be a tractable mechanism for the activation of the endogenous p53 pathway and the treatment of a variety of wild type p53 tumors.

This presentation will describe the structure-based rational design of novel MDM2 inhibitors, which led to the discovery of a series of 1,3,5,6-tetrasubstituted piperidinone derivatives. The affinity of these compounds for MDM2 was improved through conformational control of both the piperidinone ring and the appended *N*-alkyl substituent.

Further optimization resulted in the discovery of AM-8553 which demonstrated high in vitro potency ($K_D = 0.4$ nM) and significant anti-tumor efficacy in SJSA-1 xenograft studies. AM-8553 is a highly selective and orally bioavailable inhibitor of the MDM2-p53 interaction. In addition, AM-8553 is projected to have low clearance and a long half-life in humans.



MEDI 15

Development of design and selection parameters to accelerate the discovery process of novel CNS PET ligands

Lei Zhang¹, lei.zhang3@pfizer.com, Elizabeth Beck¹, Thomas Bocan², Laigao Chen², Sarah Grimwood³, Steven Heck⁴, Christopher Helal¹, Marc Skaddan², Timothy McCarthy², Kenneth Zasadny², Anabella Villalobos¹. (1) Neuroscience Chemistry, Pfizer Global Research & Development, Groton, CT 06340, United States (2) Precision Medicine, Bioimaging Center, Pfizer Global Research & Development, Groton, CT 06340, United States (3) Neuroscience Biology, Pfizer Global Research & Development, Groton, CT 06340, United States (4) WWMC Data Analytics, Pfizer Global Research & Development, Groton, CT 06340, United States

PET imaging is a non-invasive methodology frequently used in central nervous system (CNS) applications to quantify the concentration of a drug reaching a target by directly measuring receptor occupancy (RO). PET RO data are extremely useful for optimization of clinical dose selection, differentiation of drug candidates and defining clear and translatable clinical Go/No Go criteria. To enable clinical measurement of RO through PET imaging, one would need to make available a PET ligand with suitable attributes. While many factors that determine the success of a CNS PET ligand are similar to those governing the success of a candidate drug, important differences exist. In particular, achieving low levels of non-specific binding is crucial for enabling clinical measurement of RO through PET imaging. To streamline and accelerate the discovery process of novel CNS PET ligands, we aim to define a chemical space that would facilitate compound prioritization and rational ligand design, thereby providing a higher probability of success for novel PET ligand development. Toward this end, we built a database consisting of 62 fit-for-purpose PET ligands, together with 15 radioligands that failed in late-stage as negative controls. Their physicochemical and PK properties were then calculated using a series of *in silico* models developed within Pfizer and the results were analyzed in a Spotfire visualization tool. Based on this systematic analysis, a set of preferred property parameters were defined for physicochemical properties,

permeability, brain penetration and non-specific binding. These preferred parameters have been applied subsequently to several Pfizer programs, which will be exemplified by the successful development of the first PDE2 selective PET ligand [¹⁸F]-0430. The efforts described herein tackled the key hurdles associated with PET ligand discovery process, thereby allowed acceleration of the discovery process with reduced resources and higher success rate.

MEDI 16

Structure based drug design and discovery of iminopyrimidinones as potent renin inhibitors

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Numerous medications such as diuretics, beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin antagonists, calcium channel blockers (CCBs), alpha-blockers, alpha-beta-blockers, and most recently renin inhibitors (aliskiren) are available to treat high blood pressure. Despite this, often two or more drugs are required to regulate BP so there is still an unmet medical need. Direct aspartyl protease renin inhibitors have attracted great interest over the past 40 yrs because renin performs the first and rate-limiting step in the renin angiotensin aldosterone system (RAAS).

We have recently reported^{1,2} the discovery of iminopyrimidinones as novel aspartyl protease inhibitors. Potent inhibitors were identified through structure based design. Herein, the discovery and initial SAR of the iminopyrimidinone core for the development of potent renin inhibitors will be discussed.

Reference:

1. Wang et al. JMC (2010), 53(3), 942-950
2. Zhu et. al, JMC (2010), 53(3), 951-965

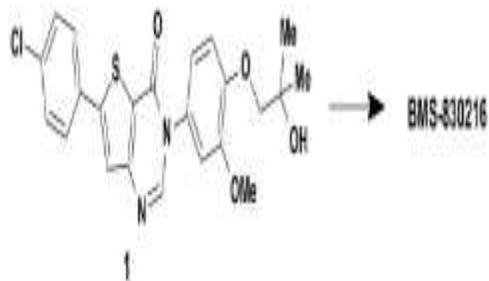
MEDI 17

Evolution of nonbasic thienopyrimidinone containing alcohols as selective MCHR1 antagonists culminating in the discovery of the clinical candidate BMS-830216

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Studies with melanin concentrating hormone (MCH) peptide and both melanin concentrating hormone receptor-1 (MCHR1) and MCH peptide knockout mice indicate that MCH plays a role in energy homeostasis and food intake. Many pharmaceutical groups have pursued development of MCHR antagonists for the treatment of obesity. Identification of compounds that could be safely evaluated in clinical trials has been a major challenge due to the propensity of these compounds to inhibit hERG and other ion channels. Most reported MCHR1 antagonists contain a basic amine functionality which contributes to the off-target ion channel activity.

We had previously disclosed that non-basic thienopyrimidinones such as **1** are selective high affinity MCHR1 antagonists. Herein, we report factors that influenced the SAR evolution from analogs of **1** to the discovery of BMS-819881 and the eventual selection of the corresponding phosphate pro-drug BMS-830216 for clinical trials.



MEDI 18

Discovery of GS-9669, a thumb site II non-nucleoside inhibitor of NS5B for the treatment of genotype 1 chronic hepatitis C infection

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The treatment of chronic hepatitis C virus (HCV) infection is undergoing a radical transformation through the introduction of direct-acting antiviral agents (DAAs). Recent clinical data indicate DAA combinations offer the prospect of curing HCV infection with interferon-free, all-oral regimens with reduced treatment durations. Results of clinical trials with filibuvir and, more recently, VX-222 have demonstrated the value of inhibiting HCV replication via binding to the thumb site II region of the viral polymerase NS5B. Herein we describe the medicinal chemistry analysis of ligands binding to this site and the execution of a project that culminated in the identification of GS-9669, a novel thumb site II inhibitor with improved in vitro potency against both wild-type virus and several known resistance mutants. The structure of GS-9669 will be disclosed, and clinical antiviral and pharmacokinetic data will also be reviewed.

MEDI 19

Discovery of CNV1014802: A novel Na_v1.7 selective state-dependent sodium channel blocker for the treatment of neuropathic pain

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Voltage-gated sodium channel blockade is a clinically precedented mechanism for the treatment of chronic pain, however, current therapies are associated with inconsistent efficacy and are often poorly tolerated. Hence the need for a new agent with an improved pharmacology and safety profile.

Herein we report the design and synthesis of a class of sodium channel ligands based on a glycinamide template. This programme led to the discovery of CNV1014802, a novel, centrally-penetrant state-dependent Na_v blocker which shows selectivity for Na_v1.7 over Na_v1.2, Na_v1.5, Na_v1.6 and TTX-resistant subtypes. CNV1014802 has good oral bioavailability, a half-life that supports BID dosing and shows efficacy across a range of rat models of somatic pain. The compound has an excellent safety and tolerability profile both preclinically and in Phase 1 studies.

CNV1014802 is currently in two Phase 2a studies for pain. Its discovery, preclinical and early clinical profile will be presented and the structure disclosed.

MEDI 20

Discovery of ACT-129968, a potent, selective, and oral CRTH2 receptor antagonist for the treatment of allergic diseases.

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More effective and safer treatment modalities are needed to treat patients suffering from allergic diseases. Recent approaches target the receptors of the lipid mediator prostaglandin D2 (PGD2). PGD2 is involved in allergic responses, for example, released PGD2 activates the G-protein coupled receptor CRTH2 (also known as DP2) and triggers pro-inflammatory signaling in Th2 cells, eosinophils and basophils.

In this presentation we report the SAR leading to the discovery and development of ACT-129968 (setipiprant), a novel CRTH2 receptor antagonist, originating from a screening hit. ACT-129968 was selected for clinical development based on its potency and selectivity for CRTH2, good pharmacokinetic properties and a favorable safety profile. ACT-129968 inhibits *in vitro* key mechanisms of allergic responses, such as PGD2-induced eosinophil activation and migration, as well as cytokine secretion by Th2 cells. Furthermore, ACT-129968 interferes with PGD2-induced lung eosinophilia in rats.

MEDI 21

Discovery of GS-6620: C-Nucleoside HCV polymerase inhibitor

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Nucleotide inhibitors (NIs) of the hepatitis C virus (HCV) have illustrated pan-genotype activity, a high barrier to the selection of resistance and the potential for potent antiviral activity. NIs tested clinically are all *N*-nucleoside derivatives. GS-6620 is a nucleotide prodrug of *C*-nucleoside analog. GS-6620 shows potent activity (EC₅₀ of 67.8 to 427 nM

in replicon assays for GT1a-6a) and a high barrier to resistance in vitro. The active triphosphate metabolite serves as a chain-terminator of RNA elongation by NS5B and is an effective inhibitor in enzymatic assays (IC_{50} of 0.29 μ M (GT1b) and 0.39 μ M (GT2a) and K_i/K_m of 0.11 (GT1b)). Oral administration of GS-6620 to animals resulted in efficient delivery of the triphosphate metabolite into the liver. The chemical structure of GS-6620 will be disclosed for the first time. In addition, SAR and Phase 1 clinical results will be presented.

MEDI 22

Identification of a brain penetrant, highly selective phosphodiesterase 2A inhibitor for the treatment of cognitive impairment associated with schizophrenia (CIAS)

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While treatments exist for positive symptoms of schizophrenia in the form of atypical antipsychotics, no approved therapies exist for the concomitant negative symptoms or cognitive impairment associated with schizophrenia (CIAS). The key second messenger molecules cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) have been implicated as playing a major role in cognitive processes. Phosphodiesterase 2A (PDE2A), which hydrolyzes both cGMP and cAMP, has highest levels of expression within limbic and basal ganglia brain circuitry found to be dysfunctional in schizophrenia. Inhibitors of PDE2A would increase cyclic nucleotide levels in these key brain regions and could thus potentially improve cognitive processes. This presentation will detail the identification of a hit series via high-throughput screening (HTS), and the strategic application of parallel synthesis, fragment and structure-based design to improve potency, selectivity, ADME and safety to yield a clinical candidate. The pre-clinical biological profile and first-in-human pharmacokinetic data will be presented.

MEDI 23

Inactivation of HIV-1 nucleocapsid NCp7 with a small molecule scaffold: In vitro mechanism and in vivo efficacy

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The HIV-1 nucleocapsid protein, NCp7, is composed of two highly conserved zinc-binding domains and is important throughout the virus replication cycle. We have developed a class of small molecule inhibitors of NCp7, based upon an S-acyl-2-mercaptobenzamide thioester scaffold (SAMT). These compounds display antiviral activity without evidence of cytotoxicity. We investigated the mechanism of viral

inactivation, demonstrating that SAMTs covalently modify NCp7 within the Gag polyprotein in treated cells. Moreover, we observed that the thiol released by reaction of the SAMT with NCp7/Gag is re-acetylated intracellularly to form an active thioester. Thus, a SAMT is able to be recycled, suggesting that a single molecule of SAMT could inhibit more than one molecule of NCp7/Gag. A direct consequence of the recycling mechanism is the development of pro-drugs that show improved stability while maintaining antiviral activity. We have systematically characterized different pro-drug molecules as to their activity and stability, identifying two lead molecules.

MEDI 24

HIV inhibitors targeting entry, fusion, and integrase

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The AIDS chemotherapy involving HAART has brought a great success. However, it is still desirable to develop new categories of anti-HIV agents. We have had multiple targets to develop HIV inhibitors on the first receptor of an HIV entry, CD4, the co-receptor, CXCR4, an HIV envelope protein, gp41 and integrase. Small CD4 mimics and CXCR4 antagonists such as T140 that function as entry inhibitors have been developed. These CD4 mimics induce a conformational change in another HIV envelope protein, gp120, exposing its co-receptor-binding site. CD4 mimics and CXCR4 antagonists show synergistic effects on anti-HIV activity. Furthermore, we have developed compounds mimicking trimer structures of gp41. The native structure mimics of the gp41-N36 and C34 trimers were proven to be useful for HIV vaccines and fusion inhibitors. In addition, Vpr-derived peptides have been found to have integrase inhibitory activity. Taken together, these HIV inhibitors represent novel avenues for future AIDS therapy.

MEDI 25

New ionic derivatives of betulinic acid as potent anti-HIV and anticancer agents

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As a naturally occurring pentacyclic triterpenoid, betulinic acid has exhibited several attractive biological functions including anti-HIV and anti-cancer activities. Due to its natural origin, this compound has very low toxicity to healthy cells. However, the *in vivo*

application of this compound has been challenged by its low solubility in aqueous solutions. To overcome this bottleneck, we have prepared a number of ionic derivatives of betulinic acid through straightforward synthetic routes, and found improved water solubilities of these new derivatives. Subsequently, we observed that some new compounds are much more inhibitory to the activities of HIV-1 protease and HIV-1 reverse transcriptase than betulinic acid itself. In addition, we also found these new ionic derivatives have much higher inhibitory effects against different cancer cell lines such as melanoma A375, neuroblastoma SH-SY5Y and breast adenocarcinoma MCF7.

MEDI 26

Discovery and in vivo activity of sphingosine kinase 2 selective inhibitors

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Sphingosine 1-phosphate (S1P) is a pleiotropic lipid mediator involved in numerous cellular and physiological functions such as cell survival and migration as well as lymphocyte trafficking. S1P, a ligand for five GPCRs, is formed by the action of two sphingosine kinases (SphKs), which are important drug targets for diseases characterized by hyperproliferation such as cancer and fibrosis. We recently discovered a novel SphK2 selective inhibitor with a K_i of 1 μ M, which is currently the most potent and selective compound to date. In the course of characterizing this compound in wild type and SphK null mice, we discovered that administration of the inhibitor resulted in a rapid increase in blood S1P, which is in contrast to SphK1 inhibitors, which drive circulating S1P levels down. The increase in response to SphK2 inhibition was observed only in wild type mice. We will discuss the SAR and in vivo characterization of this compound.

MEDI 27

Monitoring in vitro response of photosensitized human LNCaP prostate cancer cells by NMR and mass spectrometry

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Metabolomics involves measurement of metabolites present within cells. In this study, NMR and mass spectrometry were utilized as metabolic profiling tools to monitor variation in metabolite levels of photosensitized prostate cancer (PCa) cells. Photosensitizers (PSs), CAS and TAS, were synthesized. Fluorescence microscopy of CAS-sensitized cells showed more apoptosis than TAS. Necrotic cells were observed at

higher concentration and prolonged light exposure. NMR spectra were collected on CAS- or TAS-incubated PCa cells exposed to 650 nm light. CAS-sensitized apoptotic cells showed higher levels of choline, taurine, sugars and creatine, but lower levels of lactate-lipid. Metabolite levels in necrotic cells decreased due to loss of structural integrity. Mass spectral data showed presence of low MW (<500) region corresponding to metabolites responsible for physiological functions, while mass range 700-800 is observed for cells under stress. NMR and Mass spectral data of intact cancer cells can provide information on the biochemical processes of cells.

MEDI 28

Attenuation of ischemia/reperfusion-induced remote organ injury in rat using novel indole-tempol conjugates

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We synthesized a series of new indole-tempo conjugates that were predicted to have anti-inflammatory properties. The latter was confirmed in a murine model of xylene-induced ear edema. Moreover, we observed that these conjugates could attenuate multiple organ injury induced by intestine ischemia/reperfusion injury. We propose that the pharmacological profile of our novel indole-tempo conjugates involves convergent roles, including the ability to decrease free radical production via lipid peroxidation coupled to a concomitant decrease in ROS (reactive oxygen species)-mediated activation of the inflammatory process.

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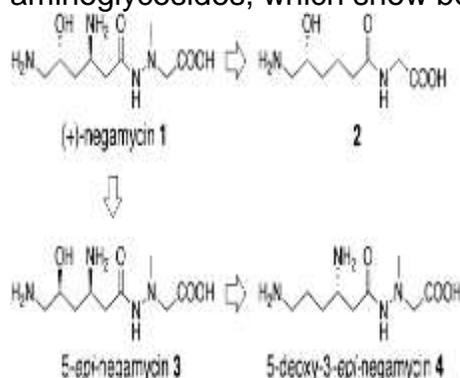
MEDI 29

Identification of negamycin analogs with readthrough-promoting activity as potential drug candidates for Duchenne muscular dystrophy

*Akihiro Taguchi¹, Shigenobu Nishiguchi², Masataka Shiozuka³, Thanigaimalai Pillaiyar¹, Yuri Yamazaki¹, Fumika Yakushiji¹, Yoshiaki Kiso², Yoshiaki Nonomura³, Ryoichi Matsuda³, **Yoshio Hayashi¹**, yhayashi@toyaku.ac.jp. (1) Department of Medicinal Chemistry, Tokyo University of Pharmacy and Life Sciences, Hachioji, Tokyo 192-0392, Japan (2) Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Kyoto,*

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A series of (+)-negamycin **1** analogs were synthesized and their readthrough-promoting activity was evaluated for nonsense mutations in Duchenne muscular dystrophy (DMD). A SAR study indicated that analog **2** was one of the potent compounds. Treatment with **2** restored dystrophin expression and decreased serum creatine kinase levels in *mdx* mice, a DMD mouse model. Moreover, **2** demonstrated lower toxicity than **1**. Thus, **2** could be a useful candidate for long-term treatment of DMD (ACS Med. Chem. Lett., **2012**, 3, 118). In addition, 5-*epi*-negamycin **3** exhibited the similar activity to **1** *in vitro*. Hence, we synthesized a 5-dehydro analog, 5-deoxy-3-*epi*-negamycin **4**, which is a natural product reported with little antimicrobial activity. Surprisingly, **4** exhibited more potent readthrough-promoting activity than **1**. This result suggests that Mother Nature independently evolved readthrough compounds like suppressor tRNA in distinction from aminoglycosides, which show both antimicrobial and readthrough-promoting activities.



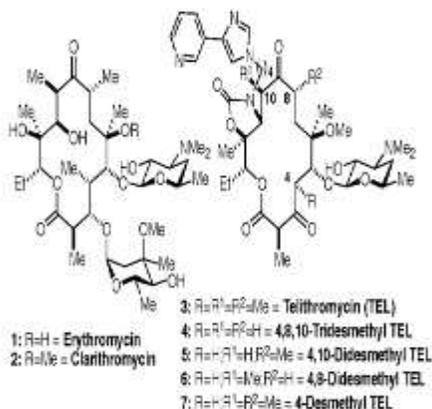
MEDI 30

Discovery of novel macrolide antibiotics: Synthesis and evaluation of desmethyl analogs of telithromycin

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New sources of antibiotics are required to keep pace with the inevitable onset of bacterial resistance. Herein we discuss the rationale and results derived from our novel desmethylation strategy (i.e., replacing specific methyl groups with hydrogen) for addressing target-based (i.e., ribosomal) mechanisms of resistance, specifically A2058G mutations and erm-mediated N6 methylation of A2058. Said mutations render erythromycin (**1**) and 6-O-methyl congener clarithromycin (**2**) ineffective, in addition to compromising the activity of telithromycin (**4**). We have prepared various desmethyl

congeners of the FDA approved ketolide antibiotic telithromycin (**4**) by total synthesis, evaluated them against various bacterial strains using MIC assays, and performed molecular modeling to better understand the consequences of desmethylation on the macrolactone scaffold.

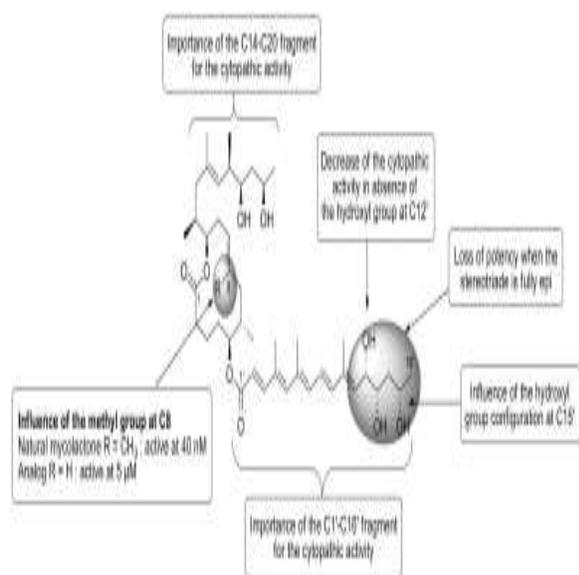


MEDI 31

First structure activity relationship of the mycolactones analogs

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Buruli ulcer, a severe necrotizing skin disease caused by mycolactones, toxins secreted by *Mycobacterium ulcerans*, is one of the most neglected tropical diseases. Mycolactones are the first polyketides to be a human pathogen, and have immunosuppressive properties. Our objective is to provide several analogues and to develop the first structure-activity relationship (SAR) study of mycolactones aiming at better understanding their mode of action. A diverted total synthesis approach of mycolactones has been designed.



This modular strategy allowed a rapid synthesis of a panel of analogs which have been evaluated. The cytopathicity results of the variants already obtained seems to be promising for the establishment of the first complete SAR study of this toxin.

MEDI 32

Systematic discovery and optimization of novel DNMT inhibitors: Structure- and ligand-based approaches

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DNA methylation which is a covalent chemical modification of DNA catalyzed by DNA methyltransferases (DNMTs) plays a crucial role in epigenetic modification. DNMT inhibition is a promising strategy for the treatment of cancer and other diseases. Docking studies of established DNMT1 inhibitors with the crystal structure of human DNMT1 gave rise to a structure-based pharmacophore model that suggests key interactions of the inhibitors with the catalytic binding site. We also report a chemoinformatic-based approach to explore the potential to identify novel inhibitors in large screening collections of natural products and synthetic commercial libraries. The results of this work highlight the value of rational approaches using structure- and ligand-based approaches for the systematic discovery of novel inhibitors targeting DNMT1.

MEDI 33

Design, synthesis, and characterization of picomolar selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor inhibitors

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The brain neuronal nicotinic receptors, particularly $\alpha 4\beta 2$ subtypes in the mesolimbic dopaminergic system, are now acknowledged in the acquisition of behavior reinforcement of nicotine in nicotine addiction. Recently, much interest has been aimed in developing novel and selective compounds to target $\alpha 4\beta 2$ subtype nicotinic acetylcholine receptors with partial agonist or desensitization effects. The proposed prevention and intervention strategies could provide new effective treatments for nicotinic addiction. Herein we report a new series of nAChR ligands which display picomolar selectivity for $\alpha 4\beta 2$ receptor subtype compared to other CNS receptors. The most potent compounds showed high radio ligand binding affinity for $\alpha 4\beta 2$ subtype receptors in the range from 0.031-0.26 nM. The compounds have good ligand binding efficiency for $\alpha 4\beta 2$ receptor, ideal CNS drug like properties suggesting a high chance to cross the blood brain barrier. VMY-2-95 blocks the functional activity of desensitized state of $\alpha 4\beta 2$ receptor and significantly reducing nicotinic self-administration in vivo rat model at 3 mg/kg, which did not appear to be secondary to sedative effects. Moreover, VMY-2-95 strongly binds to the in vitro rat brain tissue and does not affect on p-glycoprotein (MDR-1). The overall results suggest further characterization of VMY-2-95 for overcoming nicotine self-administration.

MEDI 34

Design and synthesis of potent IAP antagonists bearing an octahydropyrrolo[1,2-a]pyrazine scaffold as a novel proline mimetic

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To develop novel IAP antagonists, we designed a bicyclic octahydropyrrolo[1,2-*a*]pyrazine scaffold as a novel bioisostere of proline based on the co-crystal structure of *N*-terminal AVPI four amino acid residues of second mitochondria-derived activator of caspase in complex with XIAP. After lead optimization of this scaffold to improve low metabolic stability and oral absorption, we found compound **A** which showed potent cIAP1 (IC₅₀, 1.7 nM)/XIAP(IC₅₀, 340 nM) binding inhibitory activity and tumor growth inhibitory activity (GI₅₀, 4.8 nM) against human breast cancer MDA-MB-231 cells. Reflecting these activities, compound **A** showed tumor regressive efficacy against MDA-MB 231 tumor xenograft model in mice (T/C= -53%). The co-crystal structure of compound **A** with both XIAP and cIAP1 revealed that the key different interactions of binding mode contribute to higher affinity of compound **A** against cIAP1 over XIAP. The design, synthesis and characterization of compound **A** will be discussed in detail.

MEDI 35

Design, synthesis, and biological evaluation of small molecule inhibitors of 14-3-3 proteins

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By interacting with different proteins, 14-3-3 proteins play a vital role in regulating the cellular biological pathway at each stage of cancer development. 14-3-3 ζ protein and other isoforms, over-expressed in most tumor cell lines, have been evaluated as a new anti-cancer drug target. Natural products, Blapsin A and B, isolated from beetle *Blaps japonesis*, were identified as a new class of small-molecule inhibitors of 14-3-3 proteins. By using Blapsin A and B as our lead compounds, we designed and synthesized a series of compounds as small-molecule inhibitors against 14-3-3 protein. Fluorescence polarization (FP) assay and enzyme-linked immunosorbent assay (ELISA) showed that these small molecules can inhibit 14-3-3 proteins potently. Our research also showed that, at the concentration of 20 nM, compound A17 can completely disrupt the interaction between Raf-1 and 14-3-3 protein. Further modification of A17 may lead to a type of new anti-cancer agents.

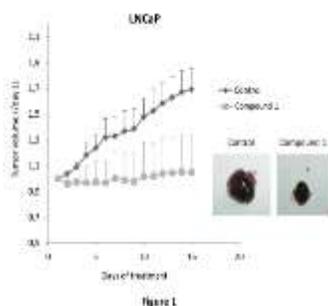
MEDI 36

Quinone derivatives of chromenopyrazoles as cannabinoid ligands with antitumor activity in vivo

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Due to the variety of biological processes involved in the pathogenesis of cancer, combined therapies are usually used. In this context, targeting different anticancer modes of action in a single molecule is a challenge. Our interest in cannabinoid ligands and antiproliferative agents lies in developing molecules which structure includes cannabinoid and quinone features. Antineoplastic effects of quinones have been widely reported. On the other hand, increasing evidence showed that cannabinoids can modulate tumor growth, apoptosis and angiogenesis in various types of cancer. Herein, we report the synthesis of quinone derivatives of chromenopyrazoles. Their ability to bind to cannabinoid receptors was assessed through radioligand competition binding assays. Their antitumor activity was evaluated in vitro by human cancer cell cytotoxicity assays. In vivo human hepatocellular carcinoma and prostate cancer proliferation studies in mice are reported of one of them.



MEDI 37

Determination of the substrate specificity of dual-specificity phosphatase VHR and discovery of a novel substrate-binding mode

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Vaccinia H1-related (VHR) phosphatase is a dual-specific phosphatase (DSPs). VHR is a potential drug target as it is upregulated in cervical and prostate cancer cells.

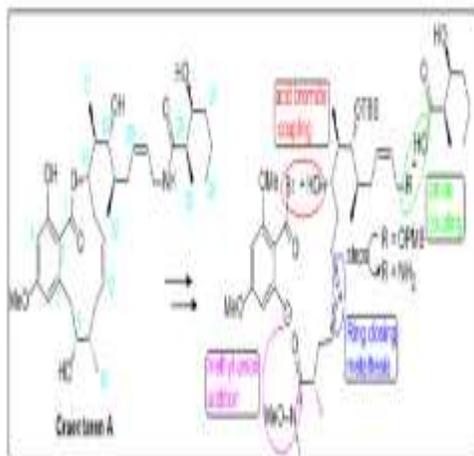
However, the comprehensive study on the substrate specificity of VHR has not been explored. In this work, the substrate specificity of VHR has been determined by using one-bead-one-compound (OBOC) phosphotyrosine peptide libraries. The library screening reveals two distinct types of peptide substrates, which have been confirmed by solution-phase kinetic analysis. Mutagenesis studies and molecular dynamics simulation have been performed to identify the binding interactions of the selected peptides and VHR. The specificity profile may be useful to predict their physiological substrates in signaling pathways.

MEDI 38

Stereoselective total synthesis of cruentaren A: An HSP90 inhibitor?

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Cruentaren A, an antifungal benzolactone produced by the myxobacterium *Byssovorax cruenta*, proved to be highly cytotoxic against various human cancer cell lines and also a highly selective inhibitor of mitochondrial F-ATPase (F-type adenosine triphosphatase). Because of the interesting biological profile manifested by cruentaren A, an efficient synthetic route was pursued. Our approach is based on a stereoselective aldol reaction, Soderquist asymmetric allylation and an asymmetric reduction and ring-closing metathesis (RCM) reaction.



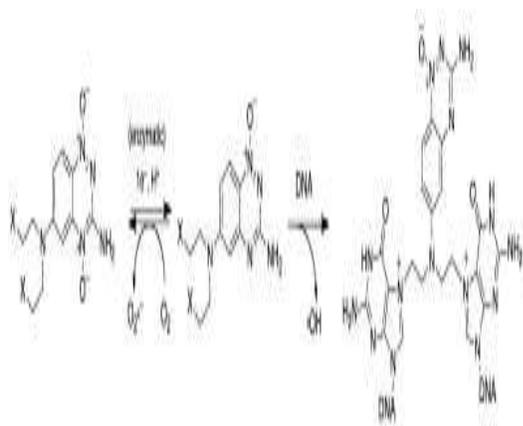
MEDI 39

Tirapazamine as a molecular switch for cellular hypoxia: Grafting nitrogen mustard chemistry onto the 1,2,4-benzotriazine 1,4-dioxide core

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Compounds containing the 3-amino-1,2,4-benzotriazine 1,4-dioxide core are hypoxia selective bioreductively-activated drugs that kill oxygen-poor cells found in solid tumors. In the parent drug tirapazamine, the one-electron reduced drug radical mediates oxidative DNA damage, while the two-electron reduced mono-N-oxide is an inactive

metabolite. Here we describe tirapazamine analogues in which the mono-N-oxide metabolite is an activated DNA cross-linking agent. Agents of this type potentially possess increased hypoxia-selective cell killing properties.



MEDI 40

Role of epigallocatechin-3-gallate as an anticancer agent in A431 cells

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Epigallocatechin-3-gallate (EGCG), the major component of polyphenols in green tea, is a potent antioxidant that has many therapeutic applications including the treatment of cancers and inflammations. In this study, we examine the effect of EGCG and its hydrophobic derivative on cell biology of human epidermoid carcinoma A431 cells with the use of the quartz crystal microbalance with dissipation monitoring (QCM-D). The QCM-D detection is based on changes in mass and viscoelastic property of cells. We are particularly interested in the effect of these molecules on epidermal growth factor receptor-mediated cell signaling, the pathway that is essential to cell growth, survival, differentiation, and migration. Our study will shed light on why EGCG is an effective cancer-preventative agent.

MEDI 41

Synthesis of pyrrole derivatives for selective inhibition of Wip-1 phosphatase

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The enzyme Wip-1 is a serine/threonine phosphatase with oncogenic properties. Over expression of Wip-1 has been observed in several cancers, including breast cancer,

neuroblastoma, and ovarian clear cell adenocarcinoma. The phosphatase Wip-1 indirectly suppresses the activity of protein p53, a protein that functions as a tumor suppressor and is frequently described as the “guardian of the genome.”

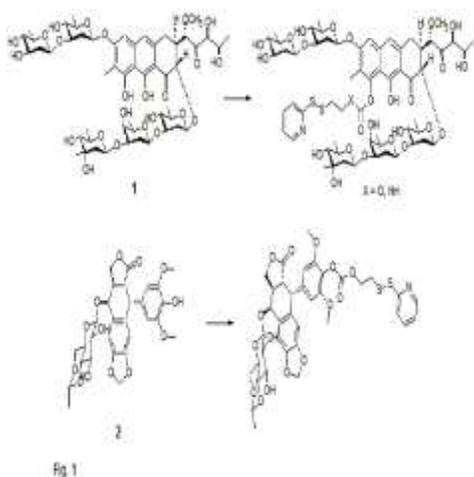
Targeting Wip-1 with small molecule inhibitors represents a novel approach to restore tumor suppressor function and subsequent cancer cell arrest/apoptosis. We recently reported the design, solid-phase synthesis, and inhibition data of a series of selective Wip-1 inhibitors bearing a penta-substituted pyrrole core. To further establish the structure-activity relationships (SARs) and to identify potent inhibitors for crystal structure studies, a synthetic route amenable for large-scale solution phase synthesis was designed. The synthesis is based on Knoevenagel-Stetter-Paal-Knorr sequence, and features stepwise incorporation of substituents. The inhibition data against Wip-1 phosphatase will be described along with an analysis of the selectivity of the molecules for Wip-1 over other phosphatases.

MEDI 42

***Regio*-selective activation of mithramycin and etoposide for synthesis of their folate conjugates**

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Mithramycin (**1**) and Etoposide (**2**, Fig 1) are very well known chemotherapy for years. Mithramycin (plicamycin) is an anti-neoplastic antibiotic. It inhibits RNA synthesis and is used in testicular tumor, disseminated neoplasms and hypercalcaemia. Etoposide is an inhibitor of the enzyme topoisomerase II. It is used as chemotherapy for diseases such as Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, non-lymphocytic leukemia, and glioblastoma multiform. Mithramycin and Etoposide were used as warhead for our proprietary Small Molecule Drug Conjugate (SMDC) technology. Folate conjugates of these drugs were synthesized which are directed to the cancerous cells with over-expressed folate receptors. Herein we report the efficient regio-selective synthesis of folate conjugates via direct activation of the phenolic hydroxyl group of Mithramycin and Etoposide. No additional protection of other hydroxyl groups, presented in the drug molecules, was required.



MEDI 43

Targeting conserved water molecules: Design of 4-aryl-5-cyanopyrrolo[2,3-d]pyrimidine Hsp90 inhibitors using fragment-based screening and structure-based optimization

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Inhibitors of the Hsp90 molecular chaperone are showing promise as anti-cancer agents. Here we describe a series of 4-aryl-5-cyanopyrrolo[2,3-d]pyrimidine ATP competitive Hsp90 inhibitors that were identified following structure-driven optimization of purine hits revealed by NMR based screening of a proprietary fragment library. Ligand-Hsp90 X-ray structures combined with molecular modeling led to the rational displacement of a conserved water molecule leading to enhanced affinity for Hsp90. This displacement was achieved with a nitrile group, presenting an example of efficient gain in binding affinity with minimal increase in molecular weight. Some compounds in this chemical series inhibit the proliferation of human cancer cell lines in vitro and cause depletion of oncogenic Hsp90 client proteins and concomitant elevation of the co-chaperone Hsp70. This work demonstrates the power of structure-based design for the rapid evolution of potent Hsp90 inhibitors and the importance of considering conserved water molecules in drug design.

MEDI 44

Identification of a novel series of highly potent and selective inhibitors of the class I phosphatidylinositol 3-kinases for treatment of cancer

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Phosphoinositide 3-kinases (PI3Ks) are lipid kinases recognized as being involved in several critical regulatory cellular processes. Genomic aberrations in the PI3K pathway have been closely linked to the development and progression of a wide range of cancers. Thus, inhibition of the PI3K pathway has emerged as an attractive anticancer strategy in drug discovery. A highly selective series of class I PI3Ks inhibitors has been developed starting from a benzimidazole-triazine dual PI3K / mTOR inhibitor identified via a high throughput screen. Lead optimization through structure-based drug design led to the discovery of a highly potent class I PI3K inhibitor, 4-(2-((6-methoxypyridin-3-yl)amino)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine, which exhibited excellent selectivity over mTOR, related phosphatidylinositol kinases, and a wide range of protein kinases. This lead was orally bioavailable and suppressed tumor growth in a mouse U87 MG xenograft model.

MEDI 45

Fragment-based drug design of novel STAT3 inhibitors as potent and orally bioavailable anticancer agents

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Signal transducer and activator of transcription 3 (STAT3) regulates the expression of many critical genes that are involved in proliferation, survival, angiogenesis and immune evasion of cancer cells. STAT3 represents a promising drug target for developing new therapies for human cancers with constitutively activated STAT3. In this poster, we will present a systematic drug design, chemical synthesis and pharmacological evaluation of novel STAT3 inhibitors with enhanced pharmacokinetic properties using the fragment-based drug design (FBDD) strategy and molecular modeling. A number of small molecules with new scaffolds have been identified with low-micromolar to nanomolar potency inhibiting the proliferation of various human breast cancer and pancreatic cancer cells. The identified **HJC0152** compound significantly suppresses tumor growth and induces apoptosis in breast cancer xenografts at the doses of 2.5 and 7.5 mg/kg, respectively.

MEDI 46

Dual PI3K/ERK inhibitor AEZS-136, a potent antitumor compound under preclinical development

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Dysregulated signalling pathways have been implicated to promote cancer cell survival and growth. RAF/MEK/ERK and the PI3K/Akt cascades are among the best characterized cancer related signalling pathways.

The use of dual pathway inhibitors may provide advantages over single pathway inhibitors or combination therapy. Specifically, simultaneous blockage of the RAF/MEK/ERK and the PI3K/Akt pathways may result in enhanced anti-tumor potency and improved drug tolerability. Further, in comparison to combination therapy, a dual inhibitor may provide reduced toxicity and improved patient compliance.

Here we present AEZS-136, a unique orally available dual PI3K / Erk inhibitor.

AEZS-136 was identified during a medicinal chemistry program to optimize derivatives of the pyrido[2,3-b]pyrazines structure class. Presented are the synthesis, pharmacological activity in the nanomolar range (i. e. ERK 1/2: IC₅₀ ~ 50nM and PI3K: IC₅₀ ~ 100nM), physicochemical and ADME data of AEZS-136, together with promising *in vivo* data.

Encouraged by the favorable *in vitro*, ADME and *in vivo* profiles, AEZS-136 is under development for clinical phase I trials.

MEDI 47

Discovery of a novel class of tubulin polymerization inhibitors by virtual and biological screening

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The development of small molecule modulators that interfere with microtubule dynamics through the interaction with the tubulin is a particularly valid approach in cancer chemotherapy. First, it was carried out a virtual screening with a series of substances synthesized from Morita-Baylis-Hillman adducts using three different types of program: GOLD, SURFLEX and AUTODOCK. After detailed evaluation of the complementary geometric 25 compounds were selected for biochemical assays. The cyclopenta[b]indole derivatives showed great potential of modulation of microtubule functions, with a significant decrease in the tubulin polymerization rate, a similar effect found for positive control colchicine. The molecular modeling suggested that the cyclopenta[b]indoles are held in colchicine-binding site by interaction of the indole nucleus with the side chain of ASN 249 and the hydroxyl group seems to be important to increasing activity and this data is in accordance with experimental assays.

References

INCA, Instituto Nacional de Câncer, 2011.

MEDI 48

Development of novel C-4 analogs of JG-03-14 as antitubulin agents

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Drugs that target microtubules have a vital role in the treatment of cancer. Despite the efficacy and success of such analogs, there have been increasing efforts to design new inhibitors due to multi-drug resistance to tubulin-binding antimetabolic agents. JG-03-14 (3,5-dibromo-4-(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester) is a promising antitubulin lead agent that targets the colchicine site of tubulin. The integrated synthesis, microtubule inhibitory and antiproliferative effects and the electronic, hydrogen bonding and hydrophobic characteristics of substituent's at C-4 position of JG-03-14 will help in enriching our understanding of the SARs.

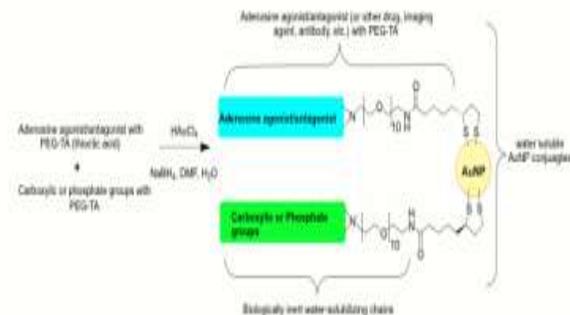
MEDI 49

Design of adenosine receptor agonist- and antagonist-conjugated gold nanoparticles for therapeutic applications including cancer

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Surface-functionalized gold nanoparticles (AuNPs) are being developed as cancer therapeutics and imaging agents to target affected cells/organs and by minimizing the side effects. G protein-coupled receptors (GPCRs) belong to a superfamily of cell surface signaling receptors having important roles in many physiological functions and disease states. The four subtypes of adenosine (ARs) receptors, A₁, A_{2A}, A_{2B} and A₃, are GPCRs with therapeutic potential for a wide range of diseases including cancer.

We have tethered to the functionalized gold surface specific ligands, agonists and antagonists, of ARs, as models for cell surface GPCRs, and found retention of the biological properties. These adenosine ligands conjugated AuNPs were in average diameters of 2-4.5 nm range and showed excellent water solubility. Pharmacological studies on these AuNP conjugates were performed in mammalian cells expressing CHO cells (A₁ and A₃) or HEK293 cells (A_{2A}) stably expressing a hAR subtype. This is the first prototypical application to gold carriers of small molecule GPCR ligands that are under investigation for treatment of cancer and inflammatory diseases.



MEDI 50

CoMFA analysis of 6-5 bicyclic inhibitors of human and *Toxoplasma gondii* thymidylate synthase

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Thymidylate synthase (TS) is a crucial enzyme that catalyzes the reductive methylation of 2'-deoxyuridine-5'-monophosphate to 2'-deoxythymidine-5'-monophosphate. Inhibition of TS has been an attractive strategy in the development of agents against cancer. Though the dihydrofolate reductase of pathogens such as *Toxoplasma gondii* (tg) have been attractive targets, TS from tg (tgTS) is a potential novel target for inhibition to treat *T. gondii* infections. We have previously published the design, synthesis and biological evaluation of pyrrolo[2,3-*d*]pyrimidines and thieno[2,3-*d*]pyrimidines as potent inhibitors of human (hTS) and tgTS. A dataset of 85 inhibitors reported from our laboratory was used to develop 3D QSAR models that correlate chemical structure and inhibitory potency for hTS and tgTS using CoMFA. The details of these models, their predictive power and their utility to explain selectivity for hTS and tgTS will be reported.

MEDI 51

Development of water-soluble prodrug of diketopiperazine-type antitumor agent "Plinabulin" by a skeletal transformation to monolactim

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Plinabulin (**1** ; NPI-2358), a diketopiperazine derivative, is a new vascular disrupting agent (VDA), which induces selective vascular collapse based on the microtubule depolymerization to prevent blood supply to the tumor tissues, resulting in tumor regression, and worldwide Phase II clinical trials with intravenous injection have been undertaken. Despite the potent antitumor activity, its water solubility was very low (<0.1 µg/mL). Hence, to improve the water solubility, new water-soluble prodrugs were developed with skeletal transformation to monolactim followed by click chemistry. Prodrug **2** with a serine-type water-solubilizing moiety showed tremendously higher water solubility than **1**. This prodrug was able to reproduce **1** *in vitro* by the treatment of porcine esterase under physiological conditions with a $t_{1/2}$ value of 59.9 min. Further structural modification at the water-solubilizing moiety could develop prodrugs with diversified $t_{1/2}$ values, which would be applicable to the study to understand the appropriate conversion time *in vivo*.

MEDI 52

Synthesis and biological evaluation of FUDR monophosphate prodrugs as anticancer agents

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Nucleoside analogues, such as the fluorinated pyrimidines are widely used for the treatment of cancer. The highly charged nature of the 5'-phosphates means they are not able to penetrate the cell membrane, which can limit their direct therapeutic potential. We have developed ProTide technology, that allows 5'-monophosphates to cross biological membranes, bypassing active transport. The family of compounds were tested for their anti-proliferative effects in different cancer cell lines, with or without thymidine kinase.

FUDR ProTides were synthesised using phosphorochloridate chemistry.

The majority of the compounds retained the high potency of FUDR. They showed nanomolar IC₅₀ values against different tumor cell lines and partially bypass the high dependence of the parent nucleoside on kinase-mediated activation and on cell transporter-mediated uptake.

The ability of the ProTides to overcome several sources of resistance associated with FUDR in the clinic suggests that these agents should be further progressed towards clinical trials.

MEDI 53

New substituted 4H-chromenes as anti glioma agents

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Glioblastoma multiforme (GBM) is the most common primary brain tumor and is a highly aggressive malignancy with a very poor prognosis. Post-surgical therapy consisting of chemotherapy in combination with radiotherapy is currently the standard of care for glioma. Several chemotherapeutic agents including temozolomide are used to treat GBM. However, this treatment remains suboptimal with most patients dying within the first year of diagnosis despite aggressive therapy. This highlights the urgent need to develop new chemotherapeutic agents to treat GBM. We have identified **SP-6-27** as a potent anti glioma agent. The chromene **SP-6-27** is active against four human glioma cell lines (T98, A172, LN18, and U87) and was particularly effective against A172 cell (IC₅₀: 7.4 nM). Overall anticancer activity was verified by one of the selected chromenes (**SP-6-19**) through the NCI 60 cell line screen. Our data suggest that these novel chromenes should be further developed as potential therapeutic agents against GBM.

MEDI 54

Peptides containing tryptophan and arginine as Src kinase inhibitors

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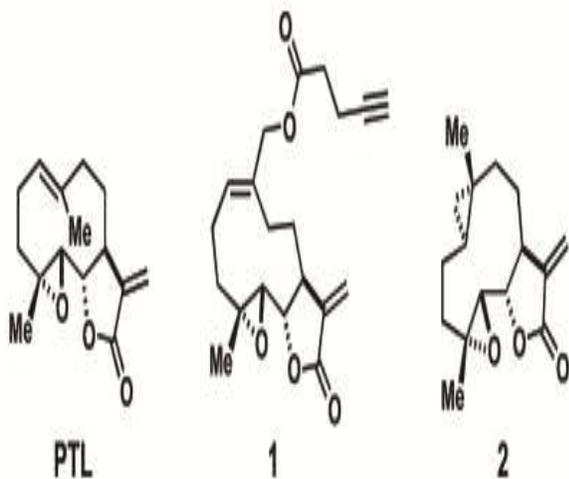
Src tyrosine kinase mutations and/or overexpression have been implicated in development of different cancers. Thus, designing Src kinase inhibitors is a subject of major interest. Fourteen peptides containing tryptophan and arginine and their methylated counterparts were synthesized using Fmoc solid-phase peptide synthesis and evaluated as Src kinase inhibitors. Three dipeptides W-R(Me), W(Me)-R(Me), and W-R(Me)₂ exhibited IC₅₀ values of 510 nM, 916 nM, and 1 μM, respectively. The presence of both tryptophan and arginine and methyl substitution were critical for Src kinase inhibition. These peptides did not show any significant cytotoxicity after 72 h incubation with human ovarian adenocarcinoma (SK-OV-3), and human leukemia (CCRF-CEM) cancer cells at a concentration of 50 μM, possibly because of their limited cellular uptake. The structure–activity relationship data provide insights for further optimization of tryptophan-arginine scaffold with improved cellular permeability and/or discovery of Src kinase inhibitors.

MEDI 55

Synthesis and evaluation of parthenolide analogs: Chemical probes and therapeutic agents

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Parthenolide (PTL) is a plant-derived natural product from feverfew and a well-established active component of many natural medicines. Previous studies have demonstrated that PTL selectively targets the cancer stem cell population in acute myeloid leukemia (AML) without destroying normal hematopoietic stem cells. The selectivity for targeting cancer stem cells versus normal stem cells by a small molecule has generated excitement in the drug discovery community. Notably, cancer stem cells are highly resistant to chemotherapeutic drugs and treatment regimens that allow cancer stem cells to survive therapy may ultimately result in disease relapse. Our laboratory at the University of Minnesota has synthesized PTL pull-down probes (such as **1**) to elucidate the mechanism of AML CSC toxicity by PTL. In addition, we prepared a number of novel PTL analogues (such as **2**) and studied their activities with *in vitro* and *in vivo* models of AML. Our progress in both areas will be presented.



MEDI 56

Design and synthesis substituted 2,4-diaminopyrimidine-5-amides as novel Mer inhibitors for the treatment of acute lymphoblastic leukemia (ALL)

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A series of novel compounds, substituted 2,4-diaminopyrimidine-5-amides, were designed and synthesized based on X-Ray co-structure of pyrazolopyrimidine on Mer kinase. The Structure Activity Relationships (SAR) on this new scaffold has been studied; lead compounds with nanomolar to subnanomolar IC₅₀ activity against Mer kinase in both enzymatic and cell-based assays were identified for further development. Structure modification for further improvement of the DMPK of the lead compounds is currently ongoing.

MEDI 57

Chemoenzymatic synthesis of novel cryptophycin anticancer agents

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The cryptophycin family of cyanobacterial peptolides contains exceptionally potent antimitotic anticancer agents. Active at levels significantly lower than currently approved cancer therapies, cryptophycin 52 was also effective against multi-drug resistant (MDR) cancers. Phase II clinical trials revealed minor peripheral neurotoxicity, making synthetic derivatization a priority for development of safe, effective cryptophycins for the treatment of cancer. Specifically, incorporation of heterocycles on unit A of cryptophycin will likely increase the solubility and stability, as well as reduce toxicity of the parent drugs. To this end, an efficient and divergent synthetic route to unit A analogues was developed and optimized, and is joined with complementary enzymatic processing to produce fully elaborated cryptophycins. In addition to potent microtubule suppression, cryptophycins also display extraordinarily tight binding to tubulin polymers and will therefore be utilized to construct powerful affinity probes for mechanism of action studies.

MEDI 58

Design and synthesis of sphingosine kinase 2 inhibitors

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Sphingosine 1-phosphate (S1P) is an endogenous signaling molecule that regulates many cellular processes, including cell growth, survival, and movement, upon binding to S1P1-5. It is produced from the phosphorylation of sphingosine by two sphingosine kinase isoenzymes (SphK1 and SphK2). Compared to the well characterized SphK1 little is known of SphK2. The production of S1P is up-regulated in hyperproliferative diseases such as cancer. Our lab is working towards synthesizing three different inhibitors: a dual SphK1 and SphK2 inhibitor as well as SphK1- and SphK2-selective inhibitors to elucidate the different roles each kinase plays within the cell and in disease states. Thus far, we have developed potent SphK1-selective inhibitors as well as a potent dual SphK inhibitor. It is necessary to synthesize a SphK2-selective inhibitor to evaluate its effects on cellular processes. Progress toward the development of SphK2-selective inhibitors is described.

MEDI 59

Selective dual inhibitors of the cancer-related deubiquitylating proteases USP7 and USP47

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Inhibitors of the cancer-related cysteine isopeptidase human ubiquitin-specific proteases 7 (USP7) and 47 (USP47) are considered to have potential as cancer therapeutics owing to their ability to stabilize the tumor suppressor p53 and to decrease DNA polymerase β . A new class of dual small molecule inhibitors of these enzymes has been discovered. P005091, a selective inhibitor of USP7 and USP47 with moderate potency, demonstrates inhibition of USP7 in cells and induces elevated p53 and apoptosis in cancer cell lines. P005091 demonstrates activity in human xenograft multiple myeloma and B-cell leukemia *in vivo* models. This activity may be the result of dual inhibition of USP7 and USP47. To address issues regarding potency and developability, P005091 analogs have been synthesized and tested, leading to improvements in potency, solubility, and metabolic reactivity profile. Further optimization is expected to yield preclinical candidates and, ultimately, clinical candidates for the treatment of certain cancers.

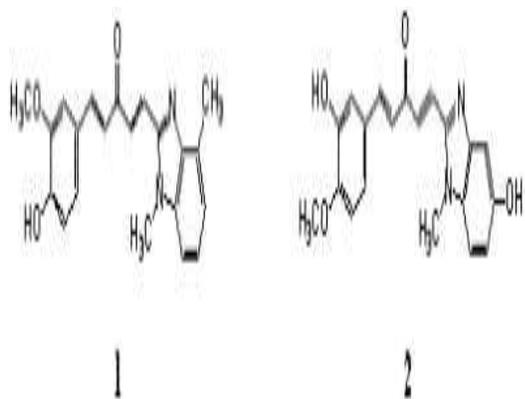
MEDI 60

Synthesis of substituted benzimidazolyl curcumin mimics and their anticancer activity

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A novel curcumin mimic library possessing variously substituted benzimidazole groups was synthesized through the aldol reaction of (E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one or (E)-4-(3-hydroxy-4-methoxyphenyl)but-3-en-2-one with diversely substituted benzimidazolyl-2-carbaldehydes. The cytotoxic activities of synthesized compounds against cancer cells MCF-7, SH-SY5Y, HEP-G2, and H460 showed that compound **1** with IC₅₀ of 1.0 and 1.9 μM has a strong inhibitory effect on the growth of SH-SY5Y and Hep-G2 cells, respectively, and that compound **2** with IC₅₀ of 1.9 μM has a strong inhibitory effect on the growth of MCF-7 cancer cells.



MEDI 61

Backbone alignment modeling on the binding modes of HSP90 inhibitors

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Determining the binding mode of a ligand at its target is a key step for the computational drug design. Currently there are many ways to deal with this issue and most of them belong to the energy-calculation based category. Due to limitation involved in current computational theory and practice, the predicted binding modes resulting from these types of methods are often ambiguous and even contradictory. Here we wish to introduce a non-computational way for this purpose. Our approach is based on a novel backbone alignment concept, which was developed in our recent modeling studies on opioid ligands (PMID: 21488692).

In addition to opioid ligands, we realized that the backbone alignment concept is also applicable to the other types of ligand-protein interactions. In this presentation, we will use HSP90 inhibitors as examples to illustrate how the binding modes of various HSP90 ligands can be determined with this approach. The results as shown here demonstrate that this approach is straightforward and effective.

MEDI 62

Design and synthesis of novel bis-mitomycins and their folate conjugates for targeted cancer therapies

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Mitomycin C (MMC), a DNA-alkylating agent, is an antitumor drug. Synthetic MMC-based dimers have been designed with the expectation that enhanced levels of DNA cross-linkage would result in higher potency. Further, conjugating MMC dimers with target-specific ligands, such as folic acid (FA), might improve selectivity and efficacy of the parent drug.

Here we report the synthesis of a series of bis-MMCs, which utilized symmetric triamines to separate the two MMC base drugs. The distance between the two MMC units ranges from five to eleven C-, N-, and/or O-atoms to allow both MMCs the flexibility for best DNA binding and subsequent alkylation. The third amino group on the core aromatic ring was introduced as attachment site and was tethered to FA via a water-soluble carbohydrate-based spacer unit and a disulfide-base self-immolative linker system. Such molecular architecture will allow for release of intact bis-MMC-based alkylating agent inside of targeted cancer cell.

MEDI 63

Aziridine aldehyde-driven cyclization of RGD peptides for $\alpha_v\beta_3$ integrin targeting

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Targeting peptide research is shifting towards the use of analogues possessing secondary conformations constrained by cyclization. Here we show the aziridine aldehyde-driven cyclization of RGD-peptides and the development of a modification strategy whereby the aziridine ring was used as a conjugation handle. Cysteamine was attached to this handle and fluorescein was then conjugated by NHS-chemistry with no need for backbone modifications. Modeling studies showed that this cyclization

chemistry modulated the geometry of the RGD-motif within peptides of different lengths. The pentapeptide cPRGDA contained a β -turn at the RGD-motif while the hexapeptide cPRGDAA did not. *In vitro* studies showed that cPRGDA and cPRGDAA both selectively bound to $\alpha_v\beta_3$ -overexpressing U87 glioblastoma cells, and that cPRGDA had a better binding affinity compared to cPRGDAA. This suggests that the stabilized β -turn in cPRGDA was responsible for improving the binding affinity of the RGD sequence compared to cPRGDAA.

MEDI 64

Development of second generation atypical RAMBAs for triple negative breast cancer therapy

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Retinoic Acid Metabolizing Enzyme Blocking Agents (RAMBAs) are being developed in attempts to overcome retinoid resistance by our laboratory and others. Our RAMBAs are considered 'atypical RAMBAs' because they are endowed with multiple anticancer activities along with high binding affinity towards CYP26A1. We have discovered two lead candidates VN/14-1 and VN/66-1 for breast and prostate cancer therapy. Here we describe systematic optimization of leads by substituting different privileged moieties in hydrophobic, alkene spacer and carboxylic acid regions. We prepared VN/14-1 by convergent synthesis starting from α -ionone. Synthesis of oxadiazole derivative was accomplished by coupling of amidoxime with VN/14-1. Different retinamides were prepared using aromatic and heterocyclic amines. Aromatic RAMBAs were synthesized by aldol condensation ionone intermediate with aromatic aldehydes. These compounds were evaluated for their abilities to inhibit growth of drug-resistant MDA-MB 231 and MDA-MB-468 triple negative breast cancer cells lines. Exciting results for promising compounds will be presented.

MEDI 65

Azepine inhibitors of JAK2

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A novel set of azepine compounds were designed and synthesized as small-molecule inhibitors of JAK2. Further optimization of the azepine lead led to the discovery of INCB016562, an orally bioavailable and JAK2 selective inhibitor. Treatment with once daily doses of INCB016562 in a MPLW515L-dependent murine model of essential thrombocytosis (ET) and primary myelofibrosis (PMF) demonstrated normalized white blood cell counts and platelet counts while improving myelofibrosis and survival compared to vehicle controls.

MEDI 66

Synthesis and evaluation of cell-penetrating peptide-doxorubicin conjugates

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We previously reported a cyclic peptide containing alternative tryptophan and arginine [WR]₄ that enhanced the non-covalent cellular delivery and intracellular retention of doxorubicin (Dox). Herein, cyclic [WR]₄ and the corresponding linear peptide (WR)₄ were conjugated with Dox through an appropriate linker to afford cyclic C[WR]₄-Dox and linear L(WR)₄-Dox conjugates. All derivatives inhibited the cell proliferation of human leukemia (67-72%), colorectal carcinoma (61-66%), ovarian adenocarcinoma (33-73%), and breast carcinoma (74-78%) cells at a concentration of 1 μM after 24-120 h of incubation. The conjugate inhibited topoisomerase II at 30 nM. Flow cytometry showed 4-fold higher cellular uptake of C[WR]₄-Dox than Dox alone in SK-OV-3 cells after 24 h incubation. The cellular hydrolysis study showed that 99% of C[WR]₄-Dox was hydrolyzed intracellularly within 72 h and released Dox. These data suggest that C[WR]₄-Dox can be used for improving the cellular delivery of Dox.

MEDI 67

Discovery of novel STAT3 small molecule inhibitors via in silico site-directed fragment-based drug design

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Constitutive activation of STAT3 has been found in a wide variety of cancers, and it has been validated as an attractive therapeutic target. STAT3 SH2 domain inhibitors could compete with the native phosphotyrosine (pTyr) peptide to block both STAT3 activation and dimerization.

We have built enrichment libraries from existing STAT3 inhibitors according to their binding poses using fragment-based drug design (FBDD) strategy. Fragments selected

from the library were recombined and linked together computationally. Four of the five selected and synthesized compounds have IC₅₀ lower than 5µM for cell line U2OS; among which, LY5 has IC₅₀ range in 0.5~1.4µM in various cancer cell lines. The fluorescence polarization (FP) assay also confirmed that LY5 strongly binds to STAT3 SH2 domain biochemically. The study has proved the feasibility of *in silico* site-directed FBDD for STAT3 drug discovery.

MEDI 68

Mechanism and inhibition of human O-GlcNAc transferase

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Glycosyltransferases are implicated in a number of human diseases including cancer. Cell-permeable inhibitors of glycosyltransferases have long been sought as tools for understanding their biological functions. Success has been limited because of challenges in designing inhibitors that mimic the negatively charged diphosphate substrates. Here we present the mechanism of action of a small molecule that inhibits O-linked N-acetylglucosamine transferase (OGT), an essential human enzyme that modulates cell signaling pathways by catalyzing a unique intracellular post-translational modification. The molecule contains a dicarbamate core that functions as a neutral diphosphate mimic and reacts with OGT active-site residues through an unprecedented mechanism by forming a carbonyl crosslink. Furthermore, crystal structures of ternary substrate and product complexes of human OGT, together with biochemical studies have revealed major factors that contribute to enzymatic catalysis. Understanding the mechanism of OGT will assist us in the design of new inhibitors with improved potency and selectivity.

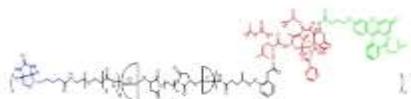
MEDI 69

Synthesis of a novel asymmetrical bow-tie PAMAM dendrimer-based drug conjugate bearing biotin and a second-generation taxoid

Tao Wang¹, *wangtaonkchem@gmail.com*, Gary Y.-H. Teng¹, Iwao Ojima^{1,2}. (1) *Department of Chemistry, Stony Brook University, Stony Brook, New York 11790, United States* (2) *Institute of Chemical Biology & Drug Discovery, Stony Brook, New York 11790, United States*

PAMAM dendrimer has been studied as a macromolecular carrier to deliver drug resulting in accumulation within the tumor tissue due to EPR effect. By applying its derivatives with cleavable cystamine core, different half dendrons covalently modified with different functionalities could be assembled into one conjugate. It is also reported that vitamin receptors are over-expressed in various tumor cell lines. To exploit these favorable properties, a novel asymmetrical bow-tie PAMAM dendrimer-based conjugate

through a bis-(imido)-alkene linking a vitamin, a second generation taxoid (SB-T-1214), a fluorescent probe and a disulfide linker was designed and synthesized. The synthesis and biological evaluation of the novel dendrimer-based drug conjugate will be presented.

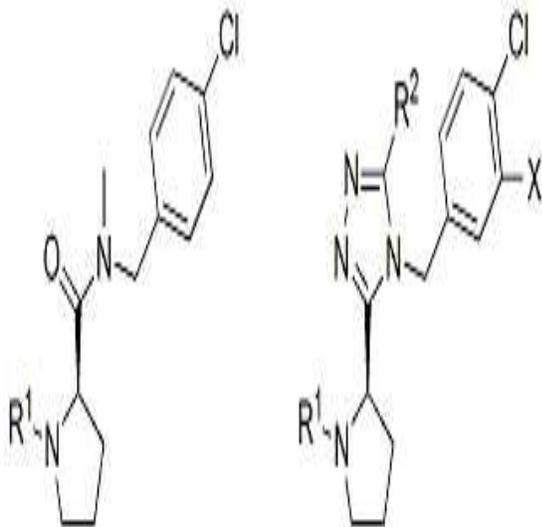


MEDI 70

Synthesis and evaluation of pyrrolidine derivatives as CCR1 antagonists for in vitro inhibition of multiple myeloma

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Multiple myeloma (MM) is an incurable cancer resulting from malignant transformation of plasma cells, terminally differentiated B cells that reside in the bone marrow (BM). The BM allows reciprocal interactions between the different components of the BM microenvironment and the MM cells necessary for migration, differentiation, proliferation and survival of the malignant plasma cells leading to osteolytic bone disease. The chemokine CCL3 appears to play a role in promoting differentiation and increased activity of osteoclasts. Expressed by both myeloma cells, and osteoclasts, CCR1 and CCR5 are the primary chemokine receptors for CCL3. This study focused on synthesis and evaluation of more than twenty novel small molecules via competitive binding assays that utilized membranes prepared from a MM cell line. These molecules were based on a previously published series of CCR1 antagonists defined by a unique pyrrolidine motif. Compounds inhibiting binding of ¹²⁵I-CCL3 were further evaluated using functional cell based assays.



MEDI 71

Discovery and synthesis of cyclopentyl derivatives as CCR1 antagonists

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CCR1 (CC Chemokine receptor 1) is a G protein-coupled receptor target expressed on leukocytes. It is implicated in initiating and exacerbating inflammatory conditions and thus is viewed as a good target for treating autoimmune and inflammatory disorders. This poster will describe the design, synthesis, and structure activity relationships of cyclopentyl based CCR1 antagonists.

MEDI 72

Identification of potent and selective pyrazole based agonists of sphingosine-1-phosphate 1 (S1P1)

Alaric J. Dyckman, dyckmana@bms.com, **Ling Li**, **Scott H. Watterson**, **Jagabandhu Das**, **Tianle Li**, **Dana Banas**, **Mary Ellen Cvijic**, **Richard Liu**, **Suzanne Suchard**, **Ding Ren Shen**, **Melissa Yarde**, **Kathleen Gillooly**, **Kim McIntyre**, **David Shuster**, **Tracy Taylor**, **Xiaoxia Yang**, **Georgia Cornelius**, **Celia D'ariento**, **Anthony Marino**, **Praveen Balimane**, **Luisa Salter-Cid**, **Murray McKinnon**, **Joel C. Barrish**, **Percy H. Carter**, **William J. Pitts**,

Jenny Xie. Research and Development, Bristol-Myers Squibb, Princeton, NJ 08543-4000, United States

Sphingosine-1-phosphate (S1P) is the endogenous ligand for the sphingosine-1-phosphate family of G-protein coupled receptors (S1P1-5). The interaction of S1P with the S1P receptors plays a fundamental physiological role in a number of processes including proliferation, angiogenesis, cytoskeletal rearrangement, vascular development, and lymphocyte trafficking. Agonism at S1P1, in particular, is immunomodulatory via a unique mechanism involving impaired lymphocyte egress from the thymus and secondary lymphoid organs. Clinical validation of S1P receptor modulation therapy was recently achieved with the approval of fingolimod (FTY720), the phosphorylated metabolite of which is a non-selective S1P receptor agonist, as the first oral disease modifying treatment for relapsing remitting multiple sclerosis. This presentation will detail the discovery and SAR of a potent and selective series of pyrazole based agonists of S1P1. Compounds in this series were highly active in a pharmacodynamic model (suppression of circulating lymphocytes) and demonstrated impressive efficacy when administered orally in rodent models of arthritis and multiple sclerosis.

MEDI 73

Novel S1P1 receptor agonists

Zhongyu Wang, zhongyu.wang@bms.com, Robert J. Cherney, Ding Ren Shen, Melissa Yarde, Mary Ellen Cvijic, Kathleen Gillooly, Tracy Taylor, Kim W. McIntyre, Anthony Marino, Praveen Balimane, Luisa Saltercid, Joel C. Barrish, Percy H. Carter, Jenny Xie, Alaric J. Dyckman. Research and Development, Bristol-Myers Squibb, Princeton, NJ 08543-4000, United States

Sphingosine-1-phosphate (S1P) is a lipid signaling molecule that is involved in multiple biological processes. In order to elicit a functional response, S1P can bind to any of five specific G protein-coupled receptors (GPCRs), numbered S1P1 through S1P5, which are differentially expressed across a variety of tissues. Agonists of the S1P1 receptor have been shown to be immunosuppressive through inhibition of lymphocyte egress from the thymus and lymph nodes. As a result, agonists of this type hold promise as therapeutics for autoimmune disorders. In this communication, we report the discovery of novel S1P1 receptor agonists.

MEDI 74

Synthesis and characterization of nitrogen oxide adducts with nonsteroidal anti-inflammatory drugs

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Non-steroidal anti-inflammatory drugs (NSAIDs) are used frequently to treat symptoms of pain and inflammation. Although NSAIDs are effective in treatment of these symptoms, they can be responsible for serious side effects, in particular, gastrointestinal ulceration. Second generation NSAIDs overcome these side effects, but chronic use can lead to an increase in the risk of heart attack and stroke. HNO (nitroxyl) and NO (nitric oxide) donors have demonstrated cardioprotective effects, and thus adducts with NSAIDs may prove to be safer and more effective than NSAIDs alone. A small library of NO/HNO releasing derivatives of NSAIDs were synthesized for the treatment of pain, inflammation and cancer. These compounds were characterized in their effectiveness as HNO/NO donors. The mechanism of decomposition and NO/HNO release were compared to the parent donors. Analysis showed that our prodrugs were releasing NO and HNO more effectively than their ionic precursors.

MEDI 75

Dual β_2 -adrenoceptor agonists-PDE4 inhibitors for the treatment of respiratory disease: I. Pyrazolopyridine PDE4 series

Joshua A. Kaplan¹, *joshua.kaplan@gilead.com*, **William R. Baker**⁴, **Shaopei Cai**¹, **Musong Kim**¹, **Leena Patel**¹, **Lafe J. Purvis**¹, **Marcin Stasiak**³, **Kirk L. Stevens**¹, **Josh Van Veldhuizen**¹, **Terry Gentzler**², **Michael Salmon**², **Rick Sorensen**², **Stacey Tannheimer**², **Gary Phillips**¹. (1) Department of Respiratory Medicinal Chemistry, Gilead Sciences, Inc., Seattle, WA 98102, United States (2) Department of Biology, Gilead Sciences, Inc., Seattle, WA 98102, United States (3) Pall Corporation, Port Washington, NY 11050, United States (4) Department of Chemistry, University of Washington, Seattle, WA 98195, United States

Combination therapy of an inhaled corticosteroid and a bronchodilator is a frontline treatment for asthma and chronic obstructive pulmonary disease (COPD). With the recent approval of roflumilast, phosphodiesterase 4 (PDE4) has received attention as a promising target for the treatment of COPD. Presented will be the design, synthesis, and biological activity of novel bifunctional compounds derived from a pyrazolopyridyl PDE4 inhibitor and a β_2 -adrenoceptor agonist, connected by a stable linker.

MEDI 76

Dual β_2 -adrenoceptor agonists-PDE4 inhibitors for the treatment of respiratory disease: (II) Quinoline PDE4 series

Lafe J Purvis¹, *lafe.purvis@gilead.com*, **Joshua A Kaplan**¹, **Leena Patel**¹, **Jennifer Loyer-Drew**¹, **Stephane Perreault**¹, **Kirk Stevens**¹, **Josh Van Veldhuizen**¹, **Bill Baker**³, **Marcin Stasiak**⁴, **Rick Sorensen**², **Stacey Tannheimer**², **Michael Salmon**², **Gary Phillips**¹. (1) Respiratory, Medicinal Chemistry, Gilead Sciences, Inc., Seattle, Washington 98102, United States (2) Respiratory, Biology, Gilead Sciences, Inc., Seattle, Washington 98102, United States (3) Chemistry, University of Washington,

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Combination therapy of an inhaled corticosteroid and a bronchodilator is a frontline treatment for asthma and chronic obstructive pulmonary disease (COPD). PDE4 inhibition has been recognized as an approved approach to managing COPD. We will present the design and synthesis of compounds containing both a quinoline PDE4 inhibitor and β_2 adrenergic agonist activity in a single molecule. The data will illustrate that the activity of each pharmacophore can be attenuated independently via structural changes.

MEDI 77

Dual β_2 -adrenoceptor agonists-PDE4 inhibitors for the treatment of respiratory disease: (III) Discovery of GS-9759

Musong Kim¹, *Musong.Kim@gilead.com*, **Leena Patel**¹, **Lafe J Purvis**¹, **Zhi-Hua Cu**², **Terry Gentzler**², **Michael Salmon**², **Rick Sorensen**², **Stacey Tannheimer**², **Gary Phillips**¹. (1) Respiratory medicinal Chemistry, Gilead Sciences, Inc., Seattle, WA 98102, United States (2) Respiratory Biology, Gilead Sciences, Inc., Seattle, WA 98102, United States

Combination therapy of an inhaled corticosteroid and a bronchodilator is a frontline treatment for asthma and chronic obstructive pulmonary disease (COPD). PDE4i has been recognized as an approved approach to managing COPD. We will present data for GS-9759 a novel bifunctional compound that has both PDE4i and β_2 -agonist activity in a single molecule. Data will illustrate the advantages of PDE4i and LABA combination therapy.

MEDI 78

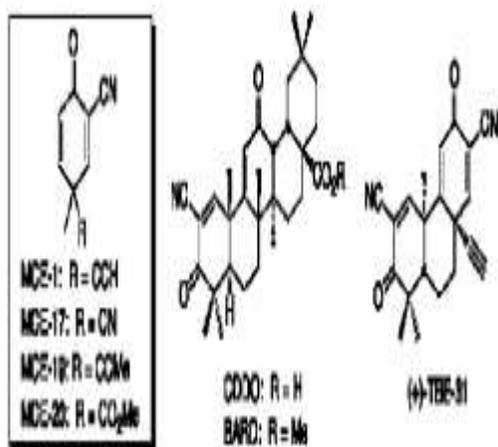
Synthesis, biological evaluation, and molecular modeling study of diclofenac analogs

Tasneem Islam², *tislam@roosevelt.edu*, **Kang-Yeoun Jung**¹, *kyjung@gwnu.ac.kr*, **Tae-Woo Kim**¹, **Jonathan Derouin**². (1) Department of Biochemical Engineering, Gangneung-Wonju National University, Gangneung, Gangwondo, Republic of Korea (2) Department of Biological, Chemical and Physical Sciences, Roosevelt University, Chicago, IL, United States

Rapid and efficient synthesis of a library of diclofenac analogs enabled cost effective biological testing of a range of novel NSAIDs with potential for improved drug efficacy and toxicity profiles. Utilizing click chemistry and Arbuzov reactions, a series of phosphonate and carboxylic acid derivatives of diclofenac were synthesized from 2-aminobenzyl alcohol. Anti-inflammatory properties of the products were tested with xylene induced ear edema in mice and compared to a diclofenac standard. Four of the

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Novel monocyclic cyanoenones (MCEs) examined to date display unique and interesting features with respect to both chemical reactivity as Michael acceptors and biological potency. Remarkably, the simple monocyclic structure is more potent than pentacycles (e.g., CDDO and BARD) and tricycles (e.g., TBE-31) in some of the bioassays related to inhibition of inflammation and carcinogenesis. Some of MCEs function as very reactive Michael acceptors with thiol nucleophiles. Interestingly, the reactivity of these Michael acceptors is closely related to the biological potency.

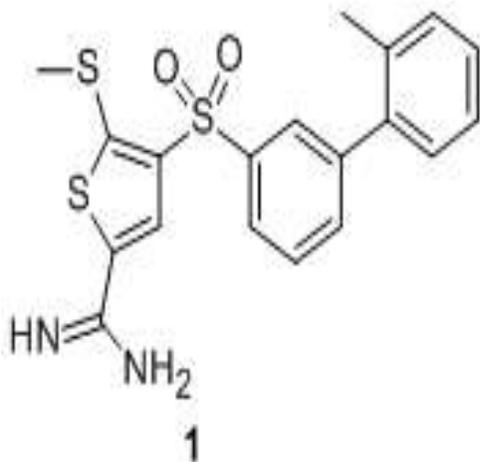


MEDI 81

Design and synthesis of polyethylene glycol-modified biphenylsulfonyl-thiophene-carboxamide inhibitors of the complement component C1s

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The complement cascade is a major component of the innate immune system in mammals and other vertebrate species. It plays a major role in the destruction of invading microorganisms and the clearance of immune complexes. However, unregulated complement activation leading to acute inflammation and tissue damage has been implicated in the pathology of many disease states. Here we describe the synthesis, in vitro potency, and in vivo pharmacokinetic properties of pegylated arylsulfonylthiophene-2-carboxamide inhibitors (**1**) of the complement component C1s.



MEDI 82

Discovery and SAR studies of (imidazolylmethyl)chroman, a potent and selective α_2C agonist, as a treatment of nasal congestion

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The α -adrenergic receptors belong to a class of G-protein-coupled receptors. They are further divided into several subtypes α_1 -(1A, 1B, 1D) and α_2 -(2A, 2B, 2C). Nasal congestion is a symptom induced by the swelling of venous sinusoids and mucosal engorgement. Nasal congestion is treated by constricting the nasal vasculature and decreasing the blood flow through the nasal mucosa. Standard oral decongestants pseudoephedrine (PSE) and phenylephrine (PE) are non-selective α -adrenergic receptor agonists, with side-effects such as hypertension, stroke and abuse potential. Selective activation of the α_2C adrenergic receptors has been shown to constrict the venous nasal vasculature and produce decongesting activity in animal model, suggesting that peripheral-acting, selective α_2C agonists have great therapeutic value

for the treatment of decongestion with potentially improved side-effect profile over current marketed drugs. Herein, we disclose the synthesis and SAR study of two novel series of α_2C agonists based on the chroman and tetrahydroquinoline core. The urea analog from chroman series exhibits in vivo efficacy at 1 mg/kg in our cat decongestion model.

MEDI 83

Design of de novo glucocorticoid receptor agonist: Chemical manipulation to transform indole derivatives from antagonist into agonist

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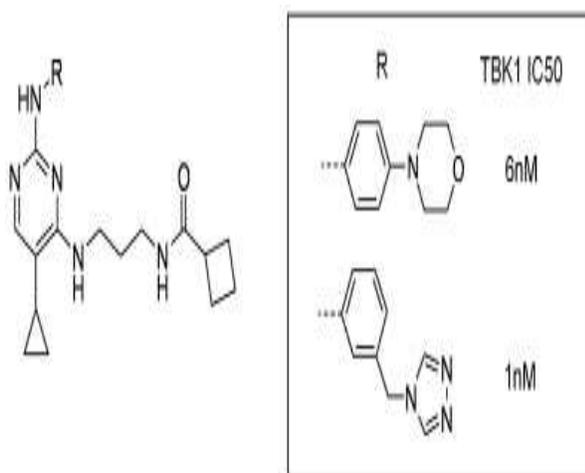
Glucocorticoid receptor (GR) agonists are one of the most widely prescribed for the treatment of inflammatory diseases such as rheumatoid arthritis and asthma. However their therapeutic usages are limited by their severe side effects. We identified a novel series of indole-based GR ligands with trifluoromethylcarbinol moiety which has been introduced as a key structural motif on non-steroidal GR agonists. Our prototype ligands showed moderate binding affinities and antagonistic activities. Further extensive structural characterizations succeeded in converting from antagonists into agonists by installing the substituted cyclic amine moiety, which could interact with Gln642 and Thr739 in GR ligand binding pocket. Our de novo design strategy with the insights of computational docking simulations will be described in detail.

MEDI 84

Synthesis and SAR of a novel series of 2,4-diamino-5-cyclopropyl pyrimidines as selective inhibitors of TBK1/IKK ϵ

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TANK-Binding Kinase (TBK1) and I κ B kinase epsilon (IKK ϵ) play a key role in the activation of the innate immune system [1,2,3]. We describe the development of a novel series of 2,4-diamino-5-cyclopropyl pyrimidines as potent inhibitors of TBK1, with good kinase selectivity and drug-like properties. These compounds have been evaluated in a range of cellular and *in vivo* assays, enabling us to probe the putative role of the TBK1/IKK ϵ pathway in inflammatory diseases and cancer [4,5].



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MEDI 85

Discovery and optimization of novel purines as potent and selective CB2 agonists

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A focused screening strategy identified a thienopyrimidine as a hCB2 cannabinoid receptor agonist with modest selectivity over the hCB1 receptor. This initial hit suffered from poor *in vitro* metabolic stability and high *in vivo* clearance. Structure activity relationships described here outline the optimization and modification to a more polar purine core. Examples from this novel purine series were found to be highly potent and fully efficacious agonists of the human CB2 receptor with excellent selectivity against CB1. Some of these molecules have attractive rat and dog pharmacodynamic (PK) profiles and have demonstrated robust oral activity in rodent models of joint pain.

Herein we report on the discovery and structure activity relationships of this new structural class of selective CB2 agonists.

MEDI 86

Discovery of novel monoaryl CCR2 antagonists

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During the course of our CCR2 research program we discovered a series of novel 3-amino-azetidiny glycinamides with potent antagonist activity. Replacement of the terminal benzoyl amide bond with a quinazoline led to a divergence in the SAR from the original series. Not only were carbinol substituents on the cyclohexane ring equipotent with their des-oxy analogs but we also found that the (hetero)aryl substituents on that position were not necessary for potent antagonist activity. This observation launched a comprehensive medicinal chemistry campaign encompassing both a range of heterocyclic quinazoline surrogates and investigation of non aromatic substituents on the distal region of the pharmacophore which will be detailed herein.

MEDI 87

Discovery and structure-activity relationships of a novel series of fused piperidines as potent TRPM8 antagonists

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The transient receptor potential melastatin 8 (TRPM8) is a non-selective cation channel expressed in a subset of sensory neurons and their peripheral terminals. TRPM8 is activated by a variety of stimuli, including voltage, cold temperatures (< 25° C), and exogenous ligands such as menthol and icilin. Mouse knockout studies suggest that TRPM8 may play an important role in certain types of cold-induced pain. Antagonism of the TRPM8 channel is currently under investigation as a new approach for the treatment of pain. As a result of our screening efforts, we identified *N*-(4-chlorophenyl)-4-propyl-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-carboxamide as an inhibitor of icilin-induced calcium influx in CHO cells expressing recombinant rat TRPM8. We undertook a detailed structure-activity relationship investigation aimed at improving potency as well as increasing metabolic stability of this compound. These efforts led to the identification of (1*R*)-*N*-(4-fluorophenyl)-1-(4-(trifluoromethyl) phenyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxamide. This compound demonstrated potent in vitro activity [rTRM8 (Icilin) IC₅₀ = 56 nM] and a suitable PKDM profile for in vivo oral dosing. This compound also successfully blocked icilin-induced wet-dog shakes (WDS) in rats, an on-target biochemical challenge model. This poster will present a detailed structure-activity

relationships that led to the discovery of a new series of potent and orally bioavailable TRPM8 antagonists.

MEDI 88

Discovery of aminooxazoline xanthenes as potent CNS penetrable BACE inhibitors

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The proteolytic cleavage of amyloid precursor protein (APP) to generate toxic A β fragments occurs via a sequence that is initiated by the aspartyl protease BACE1. It has been proposed that this event plays an early and critical event in the pathogenesis of Alzheimer's disease (AD). BACE1 knockout mice developed normally and displayed no profound phenotype, suggesting BACE inhibition as a disease modifying therapy for the treatment of AD. As a membrane-bound aspartyl protease highly expressed in the central nervous system, the site of action makes effective inhibition of BACE1 in vivo a substantial challenge. This poster will describe our structure- and property-based approach in discovering novel aminooxazoline xanthenes as potent BACE inhibitors. These compounds demonstrate good selectivity against other aspartyl proteases and are orally available. Special emphasis was placed on modulating physiochemical properties to maximize CNS penetration. A set of potent BACE1 inhibitors which demonstrate robust efficacy in a rat pharmacodynamic model will be presented.

MEDI 89

Design, synthesis, and evaluation of brain-penetrant thromboxane (A₂) receptor antagonists as potential candidates for Alzheimer's disease

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Alzheimer's disease (AD) brain is characterized by the presence of proteinaceous aggregates comprised of hyperphosphorylated tau proteins and amyloid- β (A β) peptides. Recent studies demonstrated that activation of the thromboxane-prostanoid receptor results in enhanced amyloid precursor protein mRNA stability with increase in A β production and deposition. These findings indicate that TP receptor antagonists may be therapeutically useful for the treatment of AD. However, most of existing TP receptor antagonists exhibit poor blood-brain barrier permeability, which may be caused by the presence of a carboxylic acid moiety. Hence, we designed, synthesized and evaluated analogues of known TP-receptor antagonists wherein the carboxylic acid moiety was replaced by an isostere or masked as an ester or amide. Evaluation of these compounds for brain penetration and activity in the functional assays resulted in the identification of candidates that can readily access the CNS of mice and antagonize the TP receptor with IC₅₀ values in the nM range.

MEDI 90

Synthesis of 2-phenethyl-8-phenyl-1,2,3,4-tetrahydroisoquinolines as potent and selective 5-HT₇ receptor ligands

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In previous study, a series of 8-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives, which possessing the ABD partial structure of aporphine alkaloids, was synthesized and demonstrated significant 5-HT₇ receptor binding affinity. These compounds could be the leads for the discovery and development of highly potent and selective 5-HT₇ receptor ligands as potential treatment for 5-HT₇ receptor-related disorders. Further structure-activity relationship studies were conducted and novel series of 8-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and pharmacologically evaluated. The 5-HT₇ receptor binding affinity and selectivity to other 5-HT receptor subtypes for these novel compounds have been determined. In the series, 2-phenethyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives exhibited the most potent and selective binding affinity for 5-HT₇ receptor.

MEDI 91

Discovery of a novel, potent, selective, and orally active corticotropin-releasing factor 1 (CRF₁) receptor antagonist, E2009, for the treatment of stress-related disorders such as anxiety and depression

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Corticotropin-releasing factor 1 (CRF₁) receptor has been of considerable interest for the development of stress-related disorder treatment. We will describe the discovery

and preclinical development of our clinical candidate, E2009, for the treatment of anxiety and depression.

MEDI 92

Discovery of a novel, potent, selective, and orally active corticotropin-releasing factor 1 (CRF₁) receptor antagonist, E2508, for the treatment of stress-related disorders such as anxiety and depression

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Corticotropin-releasing factor 1 (CRF₁) receptor has been of considerable interest for the development of stress-related disorder treatment. We will describe the discovery and preclinical development of our clinical candidate, E2508, for the treatment of anxiety and depression.

MEDI 93

PF-04995274: A 5-HT₄ partial agonist developed as a potential treatment for cognitive dysfunction associated with learning and memory disorders

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Evidence suggests that 5-HT₄ receptor agonists act as pro-cognitive agents and may provide therapeutic relief for cognitive impairments resulting from the decline in cholinergic function commonly seen in Alzheimer's Disease (AD). Acting to increase brain acetylcholine (ACh) levels, 5-HT₄ receptor agonists have been shown to reverse memory deficits induced by cholinergic antagonists in behavioral studies. In addition, 5-HT₄ receptor agonism is reported to increase hippocampal theta activity; a response that is modulated by ACh and linked to several cognitive, memory and attentional processes. Herein we describe the discovery and characterization of the 5-HT₄ receptor agonist PF-04995274.

MEDI 94

Discovery and profile of cyclopentylamines as inhibitors of chemokine receptor CCR2

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Inhibition of chemokine receptor CCR2 has been implicated in alleviating a variety of inflammation associated diseases including rheumatoid arthritis, multiple sclerosis, type II diabetes, atherosclerosis, asthma and COPD. The discovery and SAR of a novel series of cyclopentylamines will be discussed. The *in-vitro* and *in-vivo* profiles of a lead compound in inflammation and diabetes pharmacology models will also be detailed.

MEDI 95

Hit to lead studies on pyrazoles as novel N-type calcium channel inhibitors

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N-type calcium channels (Ca_v2.2 channels) are implicated to play a pivotal role in pain sensation, particularly in neuropathic pain. There is a marketed drug, the peptide ziconotide (Prialt®), that is a potent blocker of N-type calcium channels. Prialt® is indicated for the management of severe chronic pain, although its intrathecal route of administration and side effect profile have limited its use. Presented here is the synthesis and SAR of 2 series of novel pyrazoles that achieved low nanomolar potency for inhibition of the N-type calcium channel.

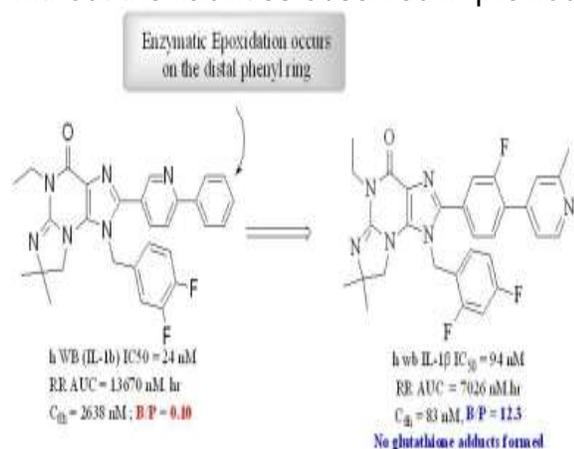
MEDI 96

Design and synthesis of potent P2X₇ antagonists for the treatment of neuropathic pain

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Novel P2X₇ antagonists were developed using a purine-based scaffold. These analogues were potent and selective P2X₇ receptor antagonists as assessed in human and rodent *in vitro* assays, as well as efficacious in rodent pain models. SAR studies were conducted to eliminate glutathione conjugation at the purine C-2 position. This led to the identification of analogues with improved brain penetration, better solubility, and

without the liabilities observed in previously reported efforts.



MEDI 97

Biaryl indolines and phenylmorpholines as potent and selective α_{2c} adrenoceptor agonists

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Novel selective α_{2c} agonists have been discovered by the introduction of a heteroaryl group at the 6-position of the central core (phenylmorpholine and indoline). Compounds active in vitro and in vivo have been identified in both the neuropathic pain and the decongestion models. Selected biaryl agonists exhibit an improved pharmacokinetic profile and in vivo efficacy in several neuropathic pain models compared to compounds with N-substituted central cores. The main issue in this series of compounds have been CYP450 inhibition and 1A1 enzyme induction in the rat. However, this liabilities has been overcome by selecting the right heterocycle-central core combination and by the introduction of *ortho*-substituents (alkyl and amino groups) on the heterocycle at the 6-position.

MEDI 98

3-Hydroxy-pyridazin-4(1H)-one derivatives as novel D-amino acid oxidase inhibitors

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D-amino acid oxidase (DAAO) catalyzes the oxidation of D-amino acids including D-serine, which is a co-agonist of N-methyl-D-aspartate receptor. We have identified a series of 3-hydroxy-pyridazin-4(1H)-one derivatives as novel DAAO inhibitors using Fragment Based Drug Design.

Comparison among complex structures determined in in-house fragment hits and those deposited in PDB, revealed that the hydrophobic sub-pocket was formed perpendicular to the flavin ring by flipping Tyr224 in the compound-dependent manner. We developed compounds to fill this sub-pocket with the aid of this complex structure information. Several compounds exhibited the predicted binding mode and demonstrated high inhibitory activity for human DAAO. We found that they also had substantial cell permeability and were effective in the MK-801-induced cognitive deficit in the Y-maze. We will report the synthesis, the SAR and the pharmacological properties of 3-hydroxy-pyridazin-4(1H)-one derivatives.

MEDI 99

Mitoxantrone-antisense conjugates: Molecular clasps for the regulation of tau alternative splicing

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Mutations in the gene encoding the microtubule-associated protein tau can cause tau aggregation, neurodegeneration and dementia. A number of these mutations destabilize a hairpin structure in the tau pre-mRNA that regulates alternative splicing of exon 10. We seek compounds that bind to and stabilize the hairpin structure as a potential therapeutic strategy and have pursued two approaches: small molecules and bipartite antisense oligonucleotides. We identified mitoxantrone (MTX) as a small molecule hairpin stabilizer as well as bipartite DNA, RNA and peptide-nucleic acids (PNA) that bind the sequences flanking the hairpin. Here we describe efforts to combine these two approaches to identify bipartite PNA antisense molecules conjugated to MTX. We have dubbed such tripartite molecules "molecular clasps", as they can simultaneously bind to the tau pre-mRNA hairpin structure, the 5' flanking region and the 3' flanking region. The design, synthesis and evaluation of these compounds will be reported.

MEDI 100

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 Frontotemporal Dementia (FTD). 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. Identification of a cyclohexyl diamine "war-head" provided compounds with sub-nanomolar activity, but poor PK profile. Attenuation of the basicity of the amine optimized potency, PK, selectivity and appropriate physical properties. MARK inhibition was validated as a method for reducing both phosphorylated and total soluble Tau species, but may also result in hemodynamic effects.

MEDI 101

Pyrrolidine-fused iminoheterocycles as BACE1 inhibitors for the treatment of Alzheimer's disease

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Alzheimer's disease is characterized by amyloid plaques and neurofibrillary tangles in the brain leading to debilitating dementia. The beta-site APP cleaving enzyme (BACE1) has emerged as one of the primary targets to test the amyloid hypothesis of Alzheimer's disease. We have found that the pyrrolidine-fused class of iminoheterocycles are potent binders to the BACE1 enzyme. This conformationally rigid bicyclic system displays substitution in the S1 and S2' pockets of the enzyme active site. The synthesis and SAR of this previously undisclosed bicyclic iminoheterocycle series will be covered.

MEDI 102

SAR and optimization of the pharmacokinetic properties of 2-aryl-4-aryloxypyrimidines, a novel class of δ -opioid receptor agonists

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Agonists of the delta opioid receptor (DOR) have the potential to treat pain without the respiratory depression and dependence liability associated with the use of morphine and other mu opioids. Delta opioid agonists exhibit enhanced efficacy during inflammation, likely resulting from increased expression and/or plasma membrane translocation of DOR following tissue injury.

A high-throughput screen of our proprietary compound library identified a bis-aryloxy pyrimidine derivative as a partial DOR agonist, with an EC₅₀ value of 1.1 μ M in a cell-based agonist-stimulated GTP γ S functional assay. This chemical template contained four common recognition moieties for opioid agonists: a protonatable nitrogen atom, two hydrophobic groups and the centroid of an aromatic ring. In this presentation, syntheses and systematic SAR studies of three of the four moieties will be discussed in detail. Optimization of the pharmacokinetic profile and in vivo efficacy of the lead compound in an inflammatory pain model will also be presented.

MEDI 103

Novel series of pyrazolylpiperidine N-type calcium channel blockers

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Selective blockers of the N-type calcium channel have proven to be effective in animal models of chronic pain. Even though intrathecally delivered synthetic ω -conotoxin MVIIA from *Conus magnus* (ziconotide [Prialt®]) has been approved for the treatment of chronic pain, its mode of delivery and narrow therapeutic window have limited its usefulness. Therefore, the identification of orally active, small-molecule N-type calcium channel blockers would represent a significant advancement in the treatment of chronic pain. A novel series of pyrazole-based N-type calcium channel blockers was identified by structural modification of a high-throughput screening hit and further optimized to improve potency and metabolic stability. Here we describe the synthesis, and *In vivo* efficacy of this series of compounds.

MEDI 104

Design and synthesis of novel benzothioephene-sulfones: Transient receptor potential melastatin 8 (TRPM8) antagonists

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TRPM8 is a temperature-gated ion channel that is activated by moderately cold temperatures in the range of \sim 8-26 °C. Also known as the cold/menthol receptor, it can be activated by chemical stimulation with menthol or icilin and is likely responsible for the therapeutic cooling sensation that these agents provoke. TRPM8 is located on primary nociceptive neurons, and modulation of this channel represents a potential strategy for the treatment of various pain states, such as cold hyperalgesia and cold allodynia. We have reported the discovery and optimization of a series of benzothioephene-phosphonate esters that are potent and selective TRPM8 antagonists. Herein we will describe the further progression of the TRPM8 program to a series of benzothioephene-sulfones, potent antagonists of the TRPM8 receptor with favorable ADME profiles. Selected sulfones were shown to be efficacious in preventing icilin-induced behaviors *in vivo*.

MEDI 105

Arylglycine derivatives as potent antagonists of transient receptor potential melastatin 8 (TRPM8)

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Transient receptor potential melastatin 8 (TRPM8) is a cationic channel that is activated by cool to cold temperatures as well as chemical stimuli, such as menthol and icilin. The localization of TRPM8 on primary nociceptive A δ - and C-fiber neurons suggests a role in the cold hypersensitivity that is often observed in certain clinical disorders in which such neurons are injured. Thus, there is a strong scientific rationale to support the use of TRPM8 antagonists in the treatment of cold allodynia and cold hyperalgesia, conditions commonly associated with neuropathic and inflammatory pain. A series of arylglycine-based compounds was discovered to be TRPM8 antagonists. Successive structure-activity relationship studies produced a large number of analogs with potent TRPM8 antagonist activity *in vitro*. Several compounds were subsequently evaluated in an *in vivo* icilin-induced “wet-dog” shakes model in rats in which they demonstrated good to excellent efficacy. Herein, we report the synthesis of this series of arylglycine-based TRPM8 antagonists and their corresponding pharmacologic activities.

MEDI 106

Discovery of novel 1-(Piperidin-4-yl)-1H-indoles as novel H3 receptor antagonists for the treatment of cognitive disorder

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H3 receptor modulators may serve as therapeutic agents for various diseases related to abnormal release of neurotransmitters in the nerves. We have identified a novel series of 1-(piperidin-4-yl)-1H-indole derivatives as potent H3 receptor antagonists. However, these compounds generally have potent hERG affinities. Displacement of the benzene ring at the terminal of the compounds with pyridine ring retains potent H3 receptor binding affinity with improved hERG properties. (R)-(6-Methylpyridin-3-yl)(4-(5-(3-(2-methylpyrrolidin-1-yl)propoxy)-1H-indol-1-yl)piperidin-1-yl)methanone shows good bioavailability and *in vivo* efficacy in rat social recognition model. Details of the structure activity relationships (SAR) of these compounds will be presented.

MEDI 107

1,3-Dihydro-2H-indol-2-one derivatives as novel vasopressin V1b antagonists: Lead optimization and pharmacological effects of the potent V1b antagonists in animal models

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Arginine vasopressin (AVP) is a neuropeptide that plays a primary role in the neuroendocrine and behavioral responses to stressors. Previous reports have indicated that an AVP receptor subtype V1b receptor antagonist elicited antidepressant- and anxiolytic-like effects in animal model. In order to clarify the potential role of selective V1b receptor antagonists, we performed optimization of a 1,3-dihydro-2*H*-indol-2-one scaffold to identify original tool compounds for pharmacological evaluation. The compounds showed excellent antagonistic activity against the V1b receptor and have favorable pharmacokinetic profiles. A representative compound exhibited antidepressant- and anxiolytic effects in several animal models including forced swimming and social interaction test. We will present the synthesis and SAR study of 1,3-dihydro-2*H*-indol-2-one derivatives, and in addition, the *in vivo* effects of the representative compounds in these animal models.

MEDI 108

Discovery and structural modification of 3,4-dihydroquinolin-2(1*H*)-ones as novel histamine H3 receptor antagonists

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Histamine H3 receptors are present in the presynaptic membrane as autoreceptors controlling the synthesis and release of histamine. Histamine regulates the circadian rhythm in the brain and is responsible for maintaining a balance between waking and sleeping states. Thus, a possible target disease for H3 receptor antagonists is sleep disorder. We have identified a novel series of 3,4-dihydroquinolin-2(1*H*)-one derivatives as highly potent and selective H3 receptor antagonists with a good pharmacokinetic properties. The synthesis, SAR and *in vivo* efficacy of these promising compounds will be presented.

MEDI 109

Asymmetric synthesis of potential siderophores di-alkylated piperazine analogs

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Substituted piperazines are found in a large variety of drugs such as antidepressants, anxiolytics, anthelmintic agents, antibiotics and antihistamines and possess very low acute toxicity in mammals.¹ We are interested by the synthesis of Rhodotorulic acid (RA) analogues. RA is a tetradentate piperazine siderophore produced by *Rhodotorula pilimanae*² that possesses two hydroxamate ligands with a (3S, 6S) stereochemistry to chelate ferric iron. In continuation of precedent work concerning the development of efficient and stereoselective di-substituted 2-oxopiperazines,³ we present here the stereoselective synthesis of 3,5 and 3,6 di-alkylated piperazine substituted by hydroxamate or catechol moieties.

(1) (a) Foguet, **1989**, US: 4859675. (b) Colglazier, M. L. *et al. The Journal of Parasitology* **1960**, 46, 267–270. (c) Coban, A. Y. *et al. Current Microbiology* **2010**, 62, 508.

(2) Müller, G. *et al. Journal of Biological Chemistry* **1985**, 260, 13916.

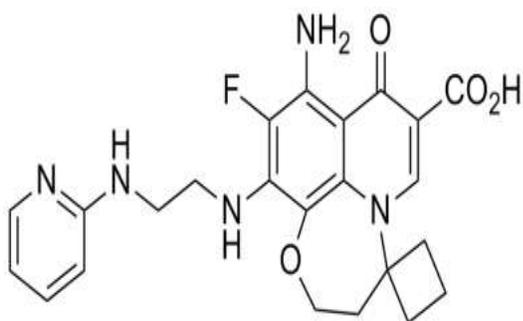
(3) Lencina, C. L. *et al. Tetrahedron: Asymmetry* **2008**, 19, 1689.

MEDI 110

Quinolone derivatives containing strained spirocycle as orally active glycogen synthase kinase 3 β (GSK-3 β) inhibitors for type 2 diabetics

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Glycogen synthase kinase 3 β (GSK-3 β), a serine/threonine protein kinase, is an attractive target for the treatment of type 2 diabetes, etc. We will disclose our SAR effort to increase the GSK-3 β inhibitory activity in both cell-free and cell-based assays by synthesizing 6-6-7 tricyclic quinolones containing a strained spirocycle moiety (e.g., IGB-13). Additionally, based on the in vitro data, selected analogues were further tested to evaluate in vivo characteristics, including mice pharmacokinetic (PK) experiments and oral glucose tolerance testing.



IGB-13

GSK-3 β (Cell-free): IC₅₀ = 36 nM

GSK-3 β (Cell-based): EC₅₀ = 3 μ M

MEDI 111

Strategies to reduce Log P to improve pharmaceutical properties of a series of CB1 receptor antagonists

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CB1 (cannabinoid-1 receptor) antagonists have been studied for over a decade as treatments for obesity. They have been demonstrated to decrease food intake and body weight in obese patients. However, the development of CB1 antagonists has been halted because of the side effects, such as psychiatric AEs, depression, and nausea/vomiting.

Log P is known to have important correlation with favorable pharmaceutical properties. Our early series of triazolo[4,3-b]pyridazin-3(2H)-one CB1 antagonists were highly lipophilic with undesired off-target activities. With modifications to both the core and the substituents, we were able to lower the Log P of the chemotype. These changes led to improvements in pharmaceutical properties such as solubility, improved off-target profile, and reduced hERG activity while maintaining good *in vivo* weight loss potential.

MEDI 112

Discovery of triazolopyridazines as CB1 antagonists

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Pharmacologic blockade with CB1 (cannabinoid-1 receptor) antagonists results in hypophagia and decreased body weight in animal models. These observations have stimulated the search for potent and selective CB1 antagonists as a treatment for obesity. Several CB1 antagonists have demonstrated sustained weight loss in obese patients. Unfortunately, the long term safety profiles, e.g. the risk of psychiatric side effects, have halted the development of many centrally acting CB1 antagonists. However, there is continuing interest in exploring the CB1 blockage mechanism for therapeutic applications through other approaches, including the peripheral system.

We discovered a series of novel [1,2,4]triazolo[4,3-b]pyridazin-6(5H)-ones as potent CB-1 antagonists. These CB-1 antagonists are orally bioavailable and show efficacy in a 4-day chronic rat model. An efficient procedure to form the triazole ring of the triazolo[4,3-b]pyridazin-6(5H)-one is the important step to the synthesis of these compounds. The synthesis, SAR and pharmacology along with chronic efficacy data of this series CB-1 antagonists will be presented.

MEDI 113

Synthesis and biological evaluation of novel pyrrolidine acid analogs as potent dual PPAR- α /g agonists

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Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that function as transcription factors. PPAR α agonists (e.g. fibrates and fatty acids) stimulate the β -oxidation of fatty acids and decrease triglyceride synthesis in the liver. PPAR γ agonists (e.g. thiazolidinediones) promote adipogenesis, increase insulin sensitivity & decrease hyperglycemia in rodents and humans. Combining PPAR α and PPAR γ agonist activity simultaneously increase insulin sensitivity and decrease triglyceride levels. Our goal was to identify a clinical candidate structurally different from our lead clinical PPAR α / γ dual agonist muraglitazar with: 1) more potent and balanced *in vitro* PPAR α and γ functional activity, and 2) comparable or better *in vivo* efficacy (glycemic and lipid effects). The discovery of several series of novel N-substituted pyrrolidine acid analogs II as PPAR ligands is outlined. The SAR and *in vivo* activities of analogs from these series will be discussed.

MEDI 114

Indazole-based ligands for estrogen-related receptor α as potential antidiabetic agents

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Estrogen-related receptor α (ERR α) is an orphan nuclear receptor that has been functionally implicated in the regulation of energy homeostasis, and the effects of selective modulation of this receptor *in vivo* have been described in diet-induced models of obesity as well as in overtly diabetic rat models. We have identified and optimized a series of indazole-based thiazolidinediones, which function *in vitro* as selective ligands for this receptor. In the monogenic *ob/ob* mouse model of obesity, hyperlipidemia, insulin resistance and type 2 diabetes, chronic administration of an ERR α modulator resulted in improvements in glucose tolerance and evidenced dose-dependent reductions in %HbA1c. In the *fa/fa* rat, which serves as a monogenic model of prediabetes, chronic administration of the ERR α modulator improved glucose tolerance and favorably impacted other metabolic parameters such as fed insulin, fed glucose, triglycerides and free fatty acids. A summary of SAR, ADME properties, and efficacy data from this series will be presented.

MEDI 115

GPR142 agonists for the treatment of type II diabetes

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GPR142 is a novel G Protein-coupled receptor highly enriched in the pancreas . Because GRP142 only stimulates insulin secretion under conditions of high blood

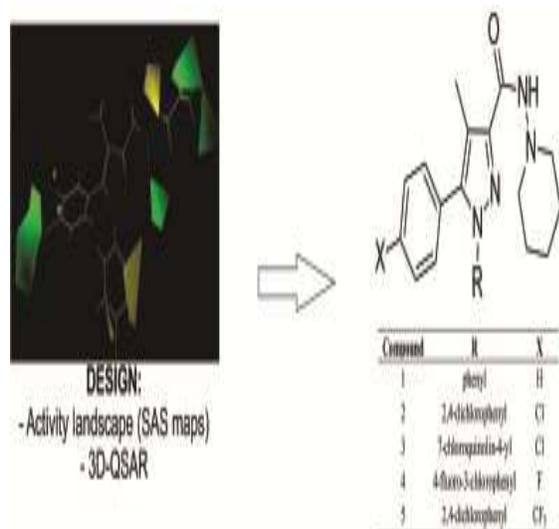
glucose, we hypothesized that GPR142 agonists could provide a benefit over existing therapies due to a greatly reduced risk of hypoglycemia. Assays to measure GPR142-mediated Ca^{2+} influx, IP_3 accumulation, and insulin secretion from pancreatic islets have been developed to support SAR (Structure Activity Relationship) efforts. In this presentation we report SAR studies that lead to potent GPR142 agonists and approaches to solve liabilities involving CYP inhibition and metabolic instability. Islet assays in WT and KO mice using tool compounds demonstrated that glucose-dependent insulin secretion was mediated by GPR142. These compounds were efficacious in reducing glucose and increasing insulin levels in lean C57BL6 male mice after oral glucose challenge.

MEDI 116

Design, synthesis, and antihyperglycemic activity of potent 1,5-diarilpyrazole derivatives

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As an effort towards the development of useful and potent agents for the treatment of metabolic syndrome and related diseases, high predictable models were derived employing the CoMFA and CoMSIA 3D-QSAR methodologies. Generated by these models, five 1,5-diarilpyrazole derivatives were synthesized. The compounds were evaluated for in vivo antihyperglycemic activity using a streptozotocin-nicotinamide rat model.



Three compounds demonstrated an important antihyperglycemic activity, by lowering glycemia ranging from 31% to 42%. The design, synthesis, characterization and biological data will be presented.

MEDI 117

Discovery of a novel series of indazoles as ketohexokinase inhibitors through a pyrazole hit from FBDD

Xuqing Zhang, *xzhang5@its.jnj.com*, Fengbing Song, Gee-Hong Kuo, Amy Xiang, Alan C Gibbs, Marta C Abad, Weimei Sun, Lawrence C Kuo, Zhihua Sui. Janssen Research & Development, LLC, Spring House, PA 19477, United States

Ketohexokinase (KHK, also known as fructokinase) catalyzes, with adenosine triphosphate (ATP) and potassium ion (K^+), the conversion of furanose form of D-fructose to fructose-1-phosphate. It initiates the intracellular catabolism of a large proportion of dietary carbohydrate and is an important regulator of hepatic glucose metabolism. Due to its role in dietary fructose metabolism, inhibition of KHK's activity would suppress carbon supply for fatty acid and very low density lipoprotein synthesis. Hence, modulation of KHK will help relieve the aforementioned metabolic disturbances making KHK an important target in drug discovery. We described herein a novel series of indazoles as KHK inhibitors from a pyrazole hit identified through fragment-based drug discovery (FBDD). The optimization process guided by both X-ray crystallography and solution activity resulted in lead-like compounds with good pharmaceutical properties.

MEDI 118

Discovery and application of a fluorescent RXR antagonist to fluorescence polarization assay

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RXR ligands are candidate agents for the treatment of type 2 diabetes, because they can control lipid- or glucose-metabolic controlling nuclear receptor functions (PPARs, LXRs etc.). However, since current methods for screening of RXR ligands need cost and complicated handling. First screening for RXR ligands remains inefficient. These backgrounds prompted us to create a simple and inexpensive RXR ligand screening system such as fluorescence polarization (FP) assay using fluorescent ligands. Though we have reported fluorescent RXR agonists, their fluorescent properties and RXR binding potencies remain unsatisfied. In this research, we discovered 6-[N-ethyl-N-(5-

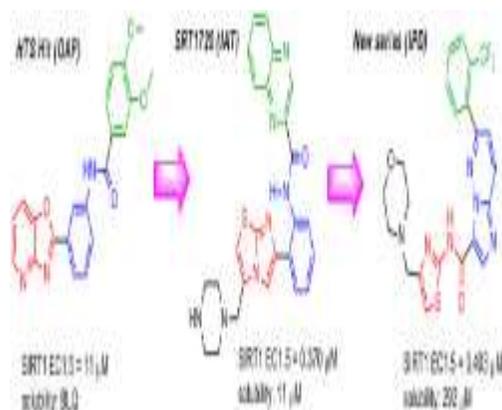
isobutoxy-4-isopropyl-2-(*E*-styrylphenyl)amino]nicotinic acid (NEt-SB) as a fluorescent RXR antagonist (Ex: 299 nm, Em: 435 nm). In addition, we performed FP assay using NEt-SB (100 nM) in the presence of RXR (0.1 mg/mL) and evaluated the RXR binding affinities of several RXR ligands. As a result, the correlation between FP assay employing NEt-SB and reporter gene assay was observed.

MEDI 119

Optimization of Imidazo[1,2-*b*]pyridazine based SIRT1 activators

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Sirtuins are a highly conserved family of NAD⁺ dependent deacylases that may have evolved as cellular energy regulators. SIRT1 is the most studied of the seven mammalian sirtuins that have been identified (SIRT1-7). SIRT1 regulates key metabolic and inflammatory pathways by deacetylation of several endogenous substrates, including PGC-1 α , P65 and FOXO. In recent years, SIRT1 has increasingly gained relevance as a potential small molecule drug target. Of the scaffolds identified through high-throughput screening Oxazolopyridines (OAP) were chosen for initial optimization. Early efforts led to the discovery of SRT1720, an imidazo[2,1-*b*]thiazole (IAT) based SIRT1 activator that has demonstrated efficacy in rodent diabetes models. Further lead optimization has resulted in new SIRT1 activating scaffolds that have significantly improved physicochemical properties over the earlier series. In this presentation, we describe optimization of the potency, stability, and solubility of the imidazo[1,2-*b*]pyridazine (IPD) based series



MEDI 120

4-Arylphthalazin-1(2H)-one derivatives as potent antagonists of the melanin concentrating hormone receptor 1 (MCH-R1)

Chae Jo Lim, *chemlcj@kriict.re.kr*, Byung Ho Lee, Kwang-Seok Oh, Kyu Yang Yi, Division of Drug Discovery Research, Korea Research Institute of Chemical Technology, Daejeon, Republic of Korea

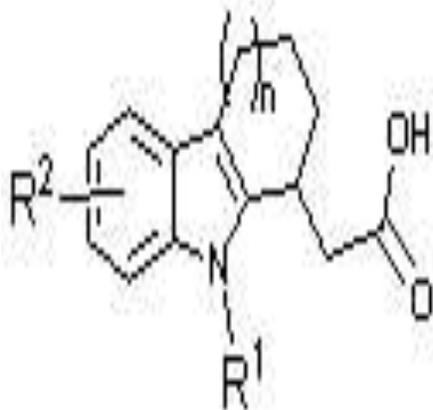
MCH is expressed predominantly in the lateral hypothalamus of the brain and is known to be involved in both regulation of feeding and energy homeostasis. The effects of MCH are mediated by G protein-coupled receptor, MCH receptor-1 (MCH-R1). The results of previous genetic and pharmacological studies demonstrated that MCH-R1 plays an important role in the control food intake and body-weight and suggested that this receptor is one of the most promising targets for the obesity treatment. As part of a continuing drug discovery program aimed at the development of potent MCH-R1 antagonists, we found that a novel series of 4-arylphthalazin-1(2H)-one linked to arylpiperidines display highly potent binding affinities to MCH-R1. The results of an extensive SAR study probing the effects of substituents on the 4-arylphthalazin-1(2H)-one C-4 aryl group led to the identification of the 4-(3,4-difluorophenyl) derivative as a highly potent MCH-R1 inhibitor with an $IC_{50} = 1$ nM.

MEDI 121

Discovery of 1,2,3,4-tetrahydrocarbazolo-1-yl-acetic acids as fatty acid binding protein 4/5 (FABP4/5) inhibitors

Songnian Lin¹, *songnian.lin@merck.com*, Qiaolin Deng¹, Lihu Yang¹, Kevin Chapman¹, Changqing Wei², Fuzhi Zhang², Zhigang Jiao², Ji Song², Jinyuan Li², Hao Wu², Sajjad A Qureshi¹, Joel P Berger¹, Joe Becker¹, Paula Fitzgerald¹, Gino Salituro¹, Nandani Sharma¹, Serena Xu¹, Ruoqing Yang¹, Xiaodong Yang¹, Bei B Zhang¹. (1) Department of Discovery & Preclinical Science, Merck Research Laboratories, Rahway, NJ 07065, United States (2) Department of Medicinal Chemistry, WuXi AppTec, Shanghai, Shanghai 200131, China

Metabolic syndrome is a constellation of disorders related to glucose and lipid metabolism that predispose humans to diabetes, obesity and cardiovascular diseases. Fatty acid binding proteins (FABP) are intracellular proteins that bind fatty acids and have been implicated in fatty acid trafficking. Animals lacking FABP4 or 4&5 have been shown to have a diminution of HFD-induced insulin resistance and resistance to development of atherosclerosis. Therefore pharmacological inhibition of FABP4/5 using small molecules could be beneficial for the treatment of diabetes and related metabolic diseases. This presentation will describe the discovery of a novel series of 1,2,3,4-tetrahydrocarbazolo-1-yl-acetic acids as FABP4/5 inhibitors. The synthesis, structure-activity relationship, crystal structure of a lead compound with FABP4, as well as chronic studies in young and established diet induced obese mice will be discussed.

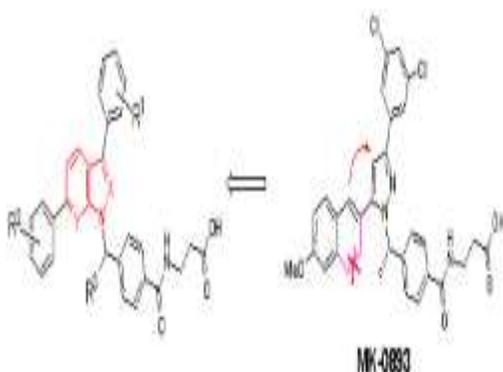


MEDI 122

Novel indazole-/indole-based glucagon receptor antagonists for treatment of type II diabetes

Songnian Lin, songnian.lin@merck.com, Fengqi Zhang, Guoqiang Jiang, Sajjad A Qureshi, Xiaodong Yang, Gary G Chicchi, Laurie Tota, Alka Bansal, Edward Brady, Maria Trujillo, Gino Salituro, Corey Miller, James R Tata, Bei B Zhang, Emma Parmee. Department of Discovery & Preclinical Science, Merck Research Laboratories, Rahway, NJ 07065, United States

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 anti-diabetic agents. This presentation will describe the synthesis and biological evaluation of a novel series of GRAs bearing an indazole- / indole core, designed based on the pyrazole GRA lead MK-0893.



MEDI 123

Design and synthesis of potent and selective acyl-CoA:diacylglycerol acyltransferase (DGAT1) inhibitor: novel indole and benzomorpholine derivatives

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Diacylglycerol O-acyltransferase, also known as diglyceride acyltransferase (DGAT), is a key enzyme in triglyceride synthesis. DGAT1 catalyzes the final and rate-limiting step in the triacylglycerol synthesis from 1,2-diacylglycerol (DAG) and long chain fatty acyl CoA as substrates. Thus, DGAT plays an essential role in the metabolism of cellular diacylglycerol and is critically important for triglyceride production and energy storage homeostasis. Herein we report the design and development of several series of bicyclic carboxylic acid derivatives as potent and selective DGAT1 inhibitors. In vivo mouse postprandial triglyceridemia studies have shown these DGAT1 inhibitors reduce plasma triglyceride levels significantly following a lipid challenge.

MEDI 124

Iminotetrahydropyrimidinones as renin inhibitors: A foray into the S3sp of renin

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Hypertension affects over one billion adults across the world with a majority in economically developing countries. Over the past four decades the development of orally active renin inhibitors for the treatment of hypertension has been a tremendous

challenge for the pharmaceutical industry. In this time frame only aliskiren, in 2007, was approved by the FDA. Our studies into the optimization of iminotetrahydropyrimidinones as orally active renin inhibitors by their elaboration into the S3sp of renin will be detailed.

MEDI 125

Novel heterocycles as renin inhibitors

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Although numerous treatments for hypertension are available, (ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics) hypertension still affects approximately one billion people and is the cause of seven million deaths per year worldwide. It is estimated that 20-30% of patients can not control their blood pressure even with three or more drugs. Therefore, there is a need for more efficacious therapies. The direct inhibition of renin, an enzyme responsible for the rate-limiting step in the renin-angiotensin system, has been a desirable approach to treat hypertension. Despite nearly four decades of research, only aliskiren has been approved by the FDA for treatment of hypertension. Our early studies of the synthesis and structure-activity relationships of several novel heterocycles as direct renin inhibitors will be detailed.

MEDI 126

Discovery of small molecule P2Y₁ antagonists: N-1 and C-3 indole carboxamides as novel antiplatelet agents

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Two distinct G protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂ which are present on platelets mediate ADP driven platelet activation and as such are important regulators of thrombosis and hemostasis. P2Y₁₂ receptor blockade is a well-established strategy for antithrombotic therapy. Recent preclinical data suggests that P2Y₁ and P2Y₁₂ inhibition provides similar antithrombotic efficacy, while targeting P2Y₁ may have the potential for reduced bleeding liability. We previously described a series of t-butylphenoxy pyridinyl urea analogs as small molecule P2Y₁ antagonists. In this poster,

we will describe our SAR efforts focused at identifying t-butylphenoxy replacements, which led to the discovery of novel N-1 and C-3 indole carboxamides as novel antiplatelet agents.

MEDI 127

Discovery of small molecule P2Y₁ antagonists: Amino-heterocycles as urea mimetics in the spiropiperidine indoliny series

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Two distinct G protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂, mediate ADP driven platelet activation. The clinical effectiveness of P2Y₁₂ blockade is well established. Recent preclinical data suggests that P2Y₁ and P2Y₁₂ inhibition provide equivalent antithrombotic efficacy, while targeting P2Y₁ has the potential for reduced bleeding liability. We previously identified a series of spiropiperidine indolinyldiaryl urea analogs as small molecule P2Y₁ antagonists. In this poster, we will present our efforts to replace the urea moiety with heteroaryls, which led to the discovery of novel amino-heterocycle analogs in the spiropiperidine indoliny series as potent P2Y₁ inhibitors.

MEDI 128

Identification of BMS-816106, potent P2Y₁ antagonist as a novel antiplatelet agent

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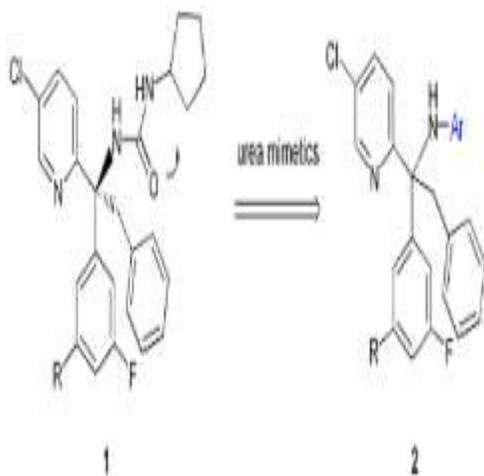
Two related but distinct G-protein coupled purinergic receptors, P2Y₁ and P2Y₁₂, have been shown to exhibit significant reduction in ADP-induced platelet aggregation. Inhibition of the P2Y₁₂ receptor has resulted in several important marketed antithrombotic agents. Our recent preclinical studies have shown that inhibition of P2Y₁ or P2Y₁₂ provides equivalent antithrombotic efficacy. However, targeting P2Y₁ antagonism has shown the potential benefit of providing a reduced bleeding liability. We have previously disclosed a series of spiropiperidinyldiaryl ureas as small molecule P2Y₁ antagonists. This poster describes the further optimization of this series which gave rise to a series of spiropiperidine analogs with improved potency in the platelet aggregation assay. This work culminated in BMS-816106, a novel potent antiplatelet agent. The SAR leading to this compound, synthesis, and in vivo data will be described.

MEDI 129

Exploration of aminoheterocycles as cholesterol ester transfer protein inhibitors

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Abstract. Epidemiology studies have demonstrated an inverse relationship between HDL-C and the risk of developing cardiovascular diseases. CETP is a plasma glycoprotein secreted predominantly by liver which mediates the net transfer of cholesterol ester from HDL to LDL and VLDL (pro-atherogenic) in exchange for TG. Pharmacological inhibition of CETP raises HDL-C in humans in clinical studies and should therefore be anti-atherosclerotic. Previously, identification of the DPPE (DiPhenylPyridylEthanamine) series compound **1** as a lead CETP inhibitor through optimization of a high-throughput screening hit was reported. To improve the metabolic stability of the cyclopentyl urea in compound **1**, various aminoheterocycles were surveyed as the urea mimetics. The synthesis and SAR of these aminoheterocycles as CETP inhibitors will be presented.

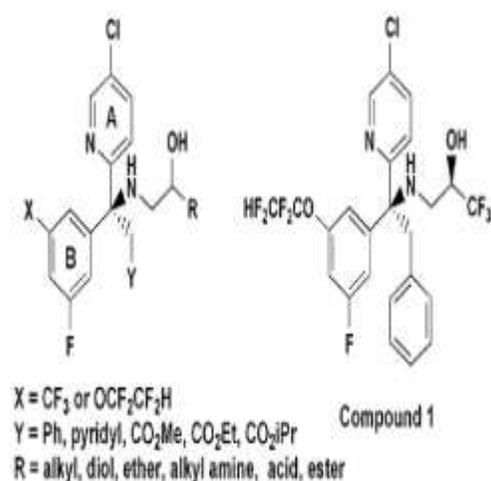


MEDI 130

Hydroxyl 1,2-diphenylethanamine analogs as potent cholesterol ester transfer protein inhibitors

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Hydroxyl 1,2-diphenylpyridineethanamine analogs are disclosed as potent cholesterol ester transfer protein (CETP) inhibitors. SAR for the B-ring, Y position and for the amine substitution will be described leading to the discovery of the lead analog in this series (1) which demonstrated robust efficacy in CETP/apo-B-100 dual transgenic mice. Compound 1 did not produce blood pressure effects in telemetry rats at 30 mpk.



MEDI 131

General concept for the design of allosteric regulators of coagulation enzymes

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Proteins that recognize heparin/heparan sulfate play critical roles in several biological responses including coagulation, angiogenesis, and immune regulation. We describe a general, design concept for discovering allosteric modulators of heparin/heparan sulfate-binding proteins. This concept relies on recruiting the hydrophobic domains typically found adjacent to most heparin binding sites to engineer affinity and specificity of interaction. The highly cationic heparin binding site serves as the initial recognition point for sulfate group(s) on the non-saccharide mimetic. In combination, the hydrophobicity and anionic character of non-saccharide mimetics result in discovery of allosteric modulators of proteins. To test this concept, a library of variably sulfated quinazolinones was synthesized and screened against coagulation proteins. Several

structurally distinct quinazolinones were identified as potent and selective inhibitors of factor XIa that allosterically modulated enzyme activity. By the very design, the strategy promises to be significant value in the design of allosteric anticoagulants with potentially minimal bleeding complications.

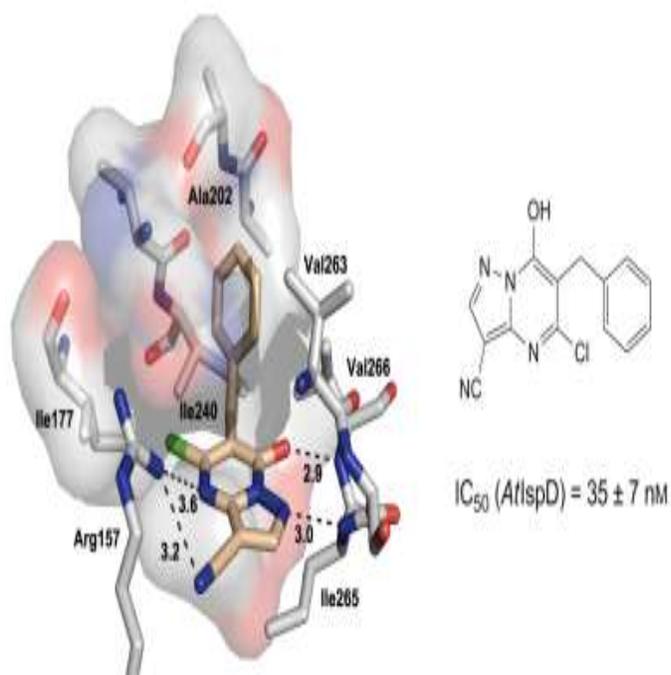
MEDI 132

Lead discovery and optimization for IspD

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IspD (4-Diphosphocytidyl-2C-methyl-D-erythritol Synthase, EC 2.7.7.60) is an enzyme of the non-mevalonate pathway of isoprenoid biosynthesis. This pathway occurs in many bacteria, some algae, plants, and in certain protozoa such as the malaria parasite *Plasmodium*, but is absent in humans. Thus, these enzymes are highly interesting drug targets for antimalarials, antibiotics or herbicides. The rising emergence of multi-drug resistant pathogens and weeds underline the necessity of new drug development with novel mode of action.

In a combined approach of high throughput screening and computer-assisted drug design, we published the first inhibitors for IspD [*Angew. Chem. Int. Ed.* **2011**, 50, 7931–7935]. We revealed an allosteric binding site in IspD from *Arabidopsis thaliana* and could proof the binding mode by co-crystal structure analysis (Figure below: PDB code 2YC5, 1.6 Å resolution). Lead optimization by molecular modeling and distinct water replacement resulted in an improved IC₅₀ value of 35 ± 7 nM.



MEDI 133

Synthesis and antibacterial activity of 2'-deoxy macrolide derivatives

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Dimethylation of A2058 residue in bacterial ribosome by erm-type methyltransferases dramatically decreases its affinity to macrolides making bacteria cross-resistant to all known types of macrolide antibiotics. The molecular mechanism of the disappearance of antibacterial activity is unknown and may involve either non-bonding interactions between methyl group and desosamine ring of macrolide derivatives or changes in conformation of 23S RNA of the ribosome resulting in substantial alteration or complete loss of the macrolide binding pocket.

We report on our studies to discriminate between these two possible mechanisms using new macrolide derivatives with chemically modified desosamine sugar. We synthesized derivatives of erythromycin, clarithromycin, telithromycin, and cethromycin possessing 2'-deoxygenated or 3'-demethylated desosamine and determined their antibacterial activity against native and erm-resistant *S. aureus* strains. New chemical compounds were found to possess moderately decreased antibacterial activity on native strains and were inactive against erm-resistance ones. These results suggest that change in conformation of 23S RNA is the likely mechanism of the erm resistance.

MEDI 134

Novel 8-modified 2'-C-methyl-6-O-methylguanosine nucleosides and phosphoramidates for the treatment of hepatitis C virus

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Millions of people worldwide are affected by the hepatitis C virus (HCV). The current treatment is not only long but has limited efficacy and causes numerous side effects¹; hence the need of more efficient therapies. The recent discovery of INX-189, a phosphoramidate of 2'-C-methyl-6-O-methylguanosine, targeting the RNA dependant RNA polymerase (RdRp) and showing nanomolar potency ($EC_{50}=0.008 \mu\text{M}$), led to nucleobase modifications of the poorly active parent nucleoside ($EC_{50}=3 \mu\text{M}$) in order to investigate potential inhibitory activity against RdRp² by delivering inside the cells a new nucleoside analogue.

A range of new 8-modified nucleosides was synthesised, and their anti-HCV activity evaluated. The ProTide approach developed in our lab was then applied to improve the cellular uptake and to by-pass the first phosphorylation step required for delivery of the nucleoside monophosphate. Inhibitory activity in HCV replicon assay and toxicity are reported.

¹ M.P. Walker & *al.*, *Antivir. Chem. Chemother.*, 2003, 14, 1-21.

² C. McGuigan & *al.*, *BMCL*, 2010, 4850-4854.

MEDI 135

Novel bisbenzimidazoles with improved antiplasmodial activities

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Previous results demonstrated that bis-1*H*-benzimidazoles represent promising leads as novel drug candidates against *Plasmodium falciparum* (Biorg Med Chem 2011, 19, 7493-7500). Whereas some of the reported derivatives are characterized by high selectivity indexes against the parasite, a major drawback is their poor hydrophilicity

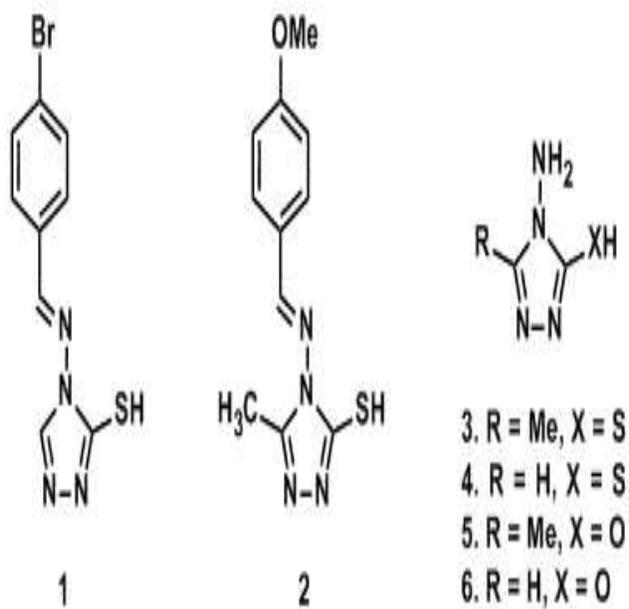
thus precluding further *in vivo* studies. We now describe the design, preparation, and *in vitro* evaluation of novel analogs with improved solubility in water.

MEDI 136

Development of 1,2,4-triazole-3-thiol based inhibitors of APOBEC3G cytosine deaminase

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Human Immunodeficiency Virus-1 (HIV-1) remains a serious threat to public health initiatives due to the continued spread and emergence of drug resistant strains. The rapid accumulation of HIV-1 genomic mutations has been largely attributed to the promiscuity of viral replication enzymes, such as HIV-1 reverse transcriptase. We propose, however, that APOBEC3G (A3G), a single-stranded DNA cytosine deaminase, also promotes rapid evolution of the HIV-1 genome. A3G contributes to innate immune defense mechanisms against viral infection and completely restricts HIV-1 infection in cells that are deficient in Vif, or HIV-1 virion infectivity factor. Vif is a virally encoded protein that interacts with A3G to signal ubiquitination and proteasomal degradation of A3G. Although Vif can overcome A3G, viral sequences from patients often show G→A hypermutations. Therefore, we hypothesize that A3G continues to mutate HIV-1 genomes to a sub-lethal extent and provides fuel for virus evolution. Small molecule inhibition of A3G activity may therefore yield hypomutated HIV-1 genomes and reduced viral fitness, which would translate to HIV-1 elimination by normal immune clearance mechanisms and/or currently available chemotherapeutics. We have performed high-throughput screening and identified potential inhibitors of A3G, including a large class of heterocyclic thiols that are currently being developed as chemical probes of A3G enzymatic activity. The synthesis of a library of 1,2,4-triazole-3-thiol based A3G inhibitors, their *in vitro* biochemical testing against A3G and A3A enzymes and their proposed mechanism(s) of action will be presented.



MEDI 137

Tryptanthrin derivatives as *Toxoplasma gondii* inhibitors: Structure-activity-relationship of the 6-position

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The intracellular parasite *Toxoplasma gondii* (*T. gondii*) is an obligate intracellular parasite in the phylum Apicomplexa. Although its life cycle can only be completed in cats, it infects a wide variety of intermediate mammalian hosts. In humans, acute infections with *T. gondii* (toxoplasmosis) are usually mild, however serious complications occur during pregnancy or in individuals with compromised immune system. Currently, the most effective pharmacotherapies for toxoplasmosis are characterized by limited efficacy, teratogenicity and haematological toxicity. Thus, there is a need to develop non-toxic, well-tolerated alternative treatment options. We recently showed that D-ring substituted derivatives of the natural product tryptanthrin (indolo[2,1-b]quinazoline-6,12-dione) are potent inhibitors of the lifecycle of *T. gondii*, while also displaying low host cell cytotoxicity. The current work describes the structure-activity relationship of analogs of tryptanthrin in which the 6-keto group has been modified in order to increase solubility and bioavailability.

MEDI 138

Antimalarial thioacetal trioxanes in the artemisinin family

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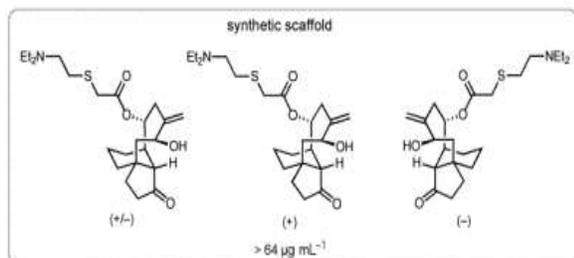
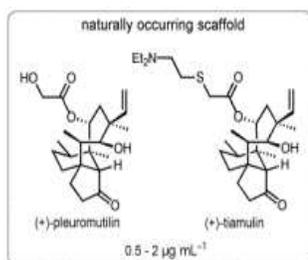
One goal of antimalarial researchers is to chemically manipulate the artemisinin parent molecule to increase its antimalarial potency while still maintaining the endoperoxide unit, crucial for its activity. New derivatives are typically combined and tested with a traditional antimalarial alkaloid such as mefloquine or chloroquine, a method known as Artemisinin Combination Therapy (ACT). Using ACT, malaria parasites are less likely to develop resistance toward artemisinin. We have prepared a new class of C-10 artemisinin-derived thioacetal trioxanes as efficacious antimalarials against *Plasmodium berghei*-infected mice. A C-10 thioacetal alcohol and a C-10 thioacetal carboxylic acid displayed high efficacy, and these analogs have been functionalized further in one chemical step to produce a variety of derivatives, many of which also are efficacious antimalarials. Finally, a series of C-10 thioacetal pro-drugs have been synthesized and tested *in vivo* to demonstrate potent antimalarial activity by slow release of the active drugs.

MEDI 139

Importance of the hydrophobic substituents on pleuromutilin family of antibiotics

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Pleuromutilin, a naturally occurring diterpene containing a unique 5-8-6 tricyclic skeleton, displayed a moderate activity against Gram-positive bacterial strains. This antibacterial activity could be enhanced by semi-synthetic modifications on the natural product. The pleuromutilin family of antibiotics are able to bind to bacterial ribosomes, which are intrinsically different from human ribosomes, and hence selectively inhibit bacterial protein syntheses. Inspired by the reported binding hypothesis based on X-ray analysis, we designed and synthesized a structurally simplified scaffold to further study the role of the hydrophobic substituents on pleuromutilin. Compared to the natural pleuromutilin, the synthetic scaffold maintains the essential functional groups responsible for the proposed hydrogen bonds with bacterial ribosomes, but does not contain the hydrophobic substituents. It was found that absence of those hydrophobic groups on the pleuromutilin compounds greatly decreased their antibacterial activity against many bacterial stains. This result demonstrated the importance of the hydrophobic groups to maintain the antibacterial activities of pleuromutilin compounds.



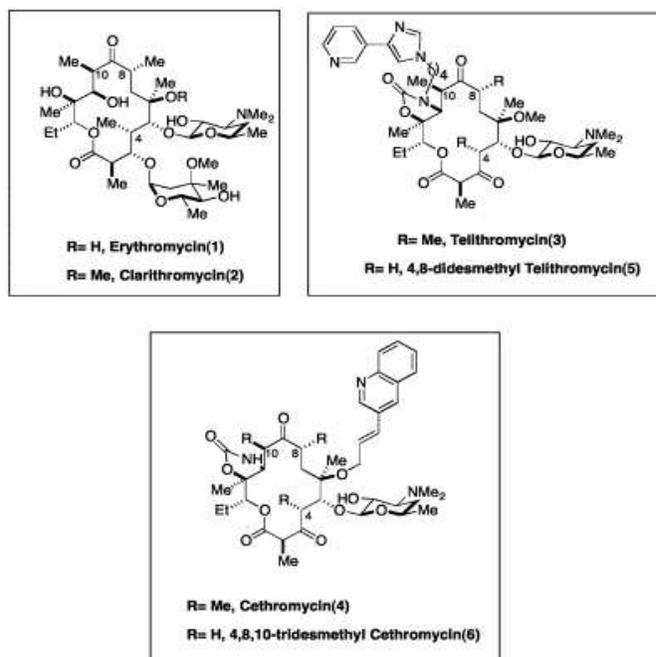
MIC against: *S. aureus*, *S. pseudintermedius*, *A. pleuropneumoniae*, *S. agalactiae*, *S. suis*

MEDI 140

Synthesis and biological evaluation of 4,8-didesmethyl telithromycin(5) and 4,8,10-tridesmethyl cethromycin(6): An effort toward addressing antibiotic resistance

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Antibiotic resistance is an inescapable problem in the current world of pharmacology. All antibiotics have theoretically limited lifespans, as bacteria can pass modes of resistance both vertically to their progeny & horizontally to their neighbors. To address this pressing issue, there is an urgent need to discover new drugs. Working towards this goal, we have applied the paradigm of natural product structure simplification (i.e., desmethylation) to the third generation macrolide antibiotics Telithromycin (3) & Cethromycin (4), which are FDA-approved semisynthetic analogs of erythromycin (1). The rationale behind the desmethylation strategy is grounded in the structural data obtained by Steitz and co-workers who successfully co-crystallized (1), (2) & (3) bound to ribosomal subunits, their studies corroborating the biochemical mechanisms of antibiotic resistance. Toward this end we have accomplished the *de novo* synthesis of 4,8-didesmethyl telithromycin (5) & 4, 8, 10-tridesmethyl cethromycin (6), which were found to be mildly biologically active [attached table] against both wild type and mutant bacterial strains, thus giving a positive footing for attempting more complex desmethyl analogs. Synthesis & the biological data of analogs (5) & (6) would be presented.



Strain	Bacteria	wt/mutant	MIC(3)	MIC(5)	MIC(6)
SQ171/2058G	E.Coli	A2058G	>512	>256	>256
DK/pKK3535	E.Coli	w.t	0.5	8	2
DK/2058G	E.Coli	A2058G	1	16	1
UCN14	S.aureus	A2058T	>256	>256	>256
ATC33591	S.aureus	ermA	>128	>256	>128

MEDI 141

Hydroxy-pyrrolopyridine-trione based HIV-1 integrase inhibitors

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HIV-1 integrase (IN) is a validated therapeutic target for the treatment of AIDS. The first FDA-approved HIV-1 integrase (IN) inhibitor, Merck's Isentress™ (MK-0518 or Raltegravir), shares key structural features with other IN inhibitors. These features include a co-planar arrangement of heteroatoms that chelate magnesium ions and halogen-substituted aromatic functionality linked to the chelating portion of the molecule that interacts with a region formed between a viral DNA base and the protein in the IN•DNA complex. The emergence of Raltegravir-resistant IN mutants demonstrates a need to develop new IN inhibitors that can overcome this resistance. A co-crystal of Raltegravir bound to the Prototype Foamy virus (PFV) IN complexed with DNA provides insights into the basis for the resistance caused by mutations in IN. Based on our previously reported 4,5-dihydroxy-1*H*-isoindole-1,3(2*H*)-diones, which are structurally simple IN inhibitors that exhibit good potency and strand transfer selectivity *in vitro* in the presence of Mg²⁺ cofactor, a series of bicyclic and tricyclic hydroxy-pyrrolopyridine-trione-containing analogues were prepared by insertion of a nitrogen into the original ring system. This simultaneously combines structural features of our original inhibitors with Merck's pyrimidinone IN inhibitors. The efficient synthesis of these compounds relies on the application of a "Pummerer cyclization deprotonation cycloaddition" cascade of imidosulfoxides as well as [3+2] cycloaddition of isomünchnones. Nitrogen substituent introducing into the catechol ring to give the 2(1*H*)-pyridone moiety reduces collateral cytotoxicity and improves potency against IN mutants resistant to Raltegravir. The biological evaluation of these agents, including activity profiles against mutant forms of IN that are resistant to raltegravir will be presented.

MEDI 142

Structural analysis of inhibitors of the *Mycobacterium tuberculosis* biotin-protein ligase BirA

Todd W. Geders¹, Teresa De la Mora-Rey¹, dela0174@umn.edu, Benjamin P. Duckworth², Riccardo Petrelli², Alvin S. Kalinda², Courtney C. Aldrich², Barry C. Finzel¹. (1) Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455, United States (2) Center for Drug Design, University of Minnesota, Minneapolis, MN 55455, United States

Biotin is an essential cofactor that is necessary for the synthesis of essential membrane phospholipids, cell-wall mycolic acids, and important virulence factors in *Mycobacterium tuberculosis* (*Mtb*). The first committed step of fatty acid biosynthesis is catalyzed by Acetyl-Coenzyme A Carboxylase, a multimeric complex that requires the covalent ligation of biotin to the Biotin Carboxyl Carrier Protein (BCCP) domain in order to become functionally active. In *Mtb*, this step is catalyzed by the biotin protein ligase BirA. Biotinylation proceeds through a two-step reaction wherein biotin is first activated to 5'-biotinyl-AMP before transfer to the ε-amino group of a target lysine residue of the BCCP domain. BirA is the only biotin protein ligase detected in the *Mtb* genome and has

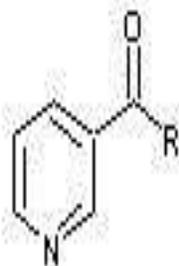
been shown to be essential for fatty acid biosynthesis in *Mycobacterium smegmatis*. Inhibitors of BirA are under investigation as potential novel antibacterial agents for the treatment of tuberculosis and other pathogenic microorganisms.

MEDI 143

Synthesis and antiprotozoal activity of nicotinamide derivatives

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As a part of our actual antiprotozoal lead optimization project, five new nicotinamide derivatives were synthesized and in vitro tested against *Plasmodium berghei*, *Trypanosoma cruzi*, *Giardia intestinalis* and *Leishmania mexicana*. Although all compounds showed moderate antiparasitic activity and low cytotoxicity, three of them presented interesting antiplasmodial activity. These compounds would interact with SIR2, a protein identified in *Plasmodium berghei* as a novel target for the design of antiprotozoal agents. The synthesis, spectroscopic data and biological tests will be presented.



Compound 5

R=7-chloro-4-hydrazinylquinoline

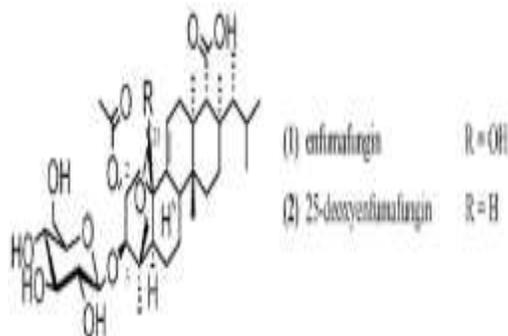
IC₅₀ = 2 μM

MEDI 144

Novel enfumafungin derivatives: Orally active β-1,3-glucan synthase inhibitors

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The inhibition of β -1,3-glucan synthase (GS) reduces the β -1,3-glucan content of the fungal cell wall, which alters the cell wall composition and leads to cell lysis. The clinical success of the echinocandin class of antifungal agents has demonstrated the effectiveness of GS inhibition as a target. The candins are well tolerated, broad spectrum agents but are limited to intravenous administration because of poor oral bioavailability. Enfumafungin (**1**), a triterpene natural product, is a broad spectrum GS inhibitor that was isolated from *Hormonema carpetanum* by the Natural Products Department at Merck. Synthetic modifications were performed on the 2- and 3- positions of a previously reported 25-deoxyenfumafungin analog (**2**). The replacement of the 2-acetoxy group with heterocyclic substituents in conjunction with the removal of the 3- β -glucoside moiety in favor of various amino ethers produced a potent, broad spectrum class of antifungal agents that were efficacious upon oral dosing in a mouse model of disseminated candidiasis.

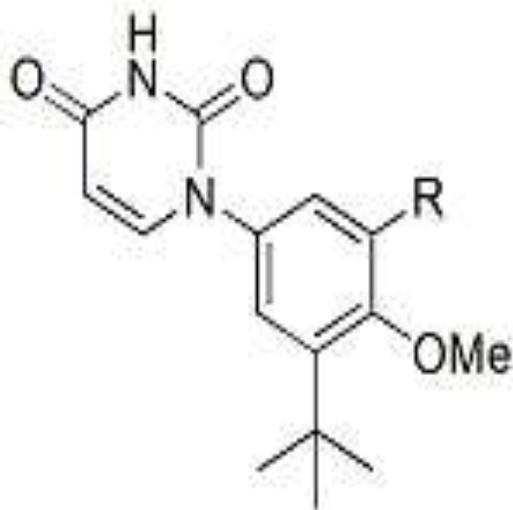


MEDI 145

Aryluracil inhibitors of Hepatitis C virus NS5B polymerase: Synthesis and characterization of analogs with a fused 5,6-bicyclic ring motif

Allan C Krueger¹, a.chris.krueger@abbott.com, John T Randolph², David A DeGoey², Pamela L Donner¹, Charles A Flentge², Douglas K Hutchinson², Dachun Liu², Christopher E Motte², Todd W Rockway², Rolf Wagner¹, David WA Beno², Gennadiy Koev², Hock B Lim², Jill M Beyer², Rubina Monda², Yaya Liu², Warren M Kat², Kenton L Longenecker², Akhteruzzaman Molla², Kent D Stewart², Clarence J Maring². (1) Department R4DH, Abbott Labs, Abbott Park, Illinois 60064, United States (2) Abbott Labs, Abbott Park, Illinois 60064, United States

This poster reports the synthesis and structure-activity relationships of a novel aryluracil series of inhibitors of the HCV NS5B polymerase. More specifically, we describe a number of potent aryluracil analogs which contain a fused 5,6-bicyclic ring unit and bind in the palm site of HCV NS5B. Several of these analogs inhibit the replication of the genotype 1 HCV replicon at single digit nanomolar concentrations and additionally have excellent pharmacokinetic properties.

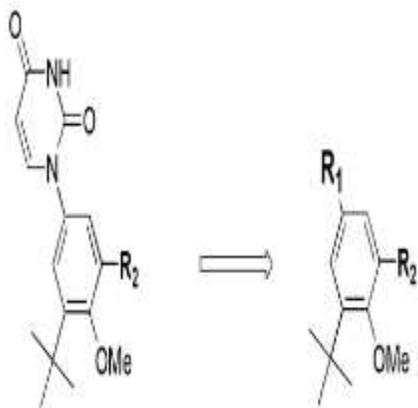


MEDI 146

Aryl 1-uracil inhibitors of HCV genotype 1 NS5B RNA-dependent RNA polymerase: Uracil ring replacements

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Resistance studies of novel, uracil-based HCV polymerase inhibitors such as ABT-333 suggested important interactions between the uracil ring of the inhibitor and the polymerase palm initiation binding site. Our investigations focused on understanding these protein-inhibitor interactions with a goal of improving the anti-viral potency and physical-chemical properties of the series. Several derivatives (**R**₁) displayed single digit nanomolar potency in HCV polymerase biochemical and replicon assays. The poster will highlight syntheses, virology data and limited PK.

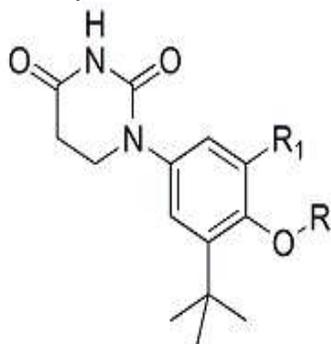


MEDI 147

Discovery of a potent HCV NS5B polymerase inhibitor developed from an aryl-dihydro-uracil screening hit

Pamela Donner¹, pamela.l.donner@abbott.com, John T Randolph¹, Peggy Huang¹, Doug Hutchinson¹, Qinghua Xie¹, Rolf Wagner¹, Hock Ben Lim¹, Lynn Colletti¹, Gennadiy Koev¹, Yaya Liu¹, Rubina Mondal¹, Jill Beyer¹, Kennan Marsh², David Beno², Kenton Longenecker², Tami Pilot-Matias¹, Warren Kati¹, Akhter Molla¹, Clarence Maring¹. (1) Department of Antiviral Research, Abbott Laboratories, Abbott Park, IL 60064, United States (2) Abbott Laboratories, Abbott Park, IL 60064, United States

Described herein is the development of a non-nucleoside, small molecule inhibitor of genotype 1 HCV NS5B Polymerase. We discovered a 23 μM analog that is active against HCV polymerase. This small fragment was elaborated into a potent single digit nanomolar inhibitor of HCV NS5B polymerase by manipulation of the R and R₁ substituents. Subsequent modifications to improve physical properties were made in an attempt to achieve an acceptable pharmacokinetic profile.



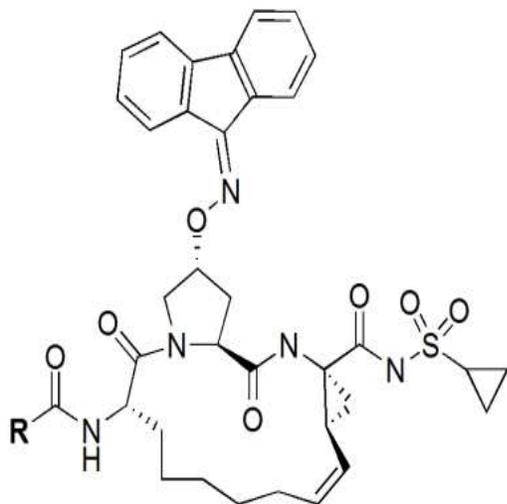
IC₅₀ 23 μM → IC₅₀ 0.022 μM

MEDI 148

Novel HCV protease inhibitors: The effect on activity and stability of P3-capping groups on macrocyclic HCV protease inhibitors

Jason P Shanley¹, jason.shanley@abbott.com, Hui-Ju Chen¹, Brian Green¹, Keith McDaniel¹, Dale Kempf¹, Tim Middleton¹, Tami Pilot-Matias¹, Liangjun Lu¹, Tatyana Dekhtyar¹, Luciana Godzicki¹, David Beno¹, Lisa Hernandez¹, Zhe Wang². (1) Department of Anti-Viral Research, Abbott Laboratories, Abbott Park, IL 60064, United States (2) Enanta Pharmaceuticals, Watertown, MA 02472, United States

Recent efforts in the field of Hepatitis C research have focused on the discovery of new direct acting antiviral (DAA) drug combinations, which can be used in combination with or to replace pegylated interferon/ribavirin, the current standard of care. Several classes of DAAs are being developed, including inhibitors of the viral NS3 protease. This poster examines modification of the P4 group (**R**) of the macrocyclic HCV protease inhibitor **1** focusing on the examination of amide analogs. These structural changes produced compounds with excellent antiviral activity against wild type and mutant virus and unexpectedly led to improvement in the metabolic stability of the compounds. Application of these modifications, discussion of the syntheses and selected pharmacokinetic profiles will also be presented.



MEDI 149

Identification and evaluation of influenza RNA-dependent RNA polymerase (RdRp) inhibitors

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Vincent A. Boyd¹, Thomas R. Webb¹. (1) Department of Chemical Biology and Therapeutics, St Jude Children's Research Hospital, Memphis, TN 38105, United States (2) Department of Structural Biology, St Jude Children's Research Hospital, Memphis, TN 38105, United States (3) Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, TN 38105, United States

There is a need to develop new anti-influenza agents due to limitations and viral resistance to current influenza treatments. Influenza RNA-dependent RNA polymerase (RdRp), which consists of three subunits (PA, PB1 and PB2), is necessary for virus transcription and is a promising target for the development of inhibitors. To facilitate the discovery of new RdRp inhibitors targeting the PA subunit, we have developed a fluorescent polarization binding assay to screen fragments and analyze follow-up targeted libraries for SAR purposes. High affinity compounds that exhibited no cellular cytotoxicity were found to inhibit viral plaque formation ($IC_{50} = 12-18 \mu M$) compared to a Merck PA inhibitor ($IC_{50} = 3 \mu M$). Evaluation of ADME properties of our initial inhibitors along with insight provided from inhibitor-protein co-crystal structures directed structural alterations which resulted in the generation of compounds with superior ADME properties and higher plaque inhibition efficacy.

MEDI 150

Development of tripeptide-type SARS coronavirus 3CL protease inhibitors with an electrophilic 2-benzothiazole ketone structure

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On the development of effective drug against severe acute respiratory syndrome (SARS), we focused on the causative corona viral cysteine protease (SARS-CoV 3CL^{Pro}), which is essential for its replication, and developed tripeptide-type inhibitors from the native substrate sequences based on two strategies; i) chemical modification at the P1 position (Gln) and ii) introduction of the chemical warhead; an electron-withdrawing arylketone. As a result, Z-Val-Leu-Ala(pyrrolidone-3-yl)-2-thiazole (**1**) exhibited a strong inhibitory activity. According to the molecular modeling study of **1**, it was predicted that there was a large space in the S1' pocket. Therefore, a benzothiazole unit was introduced into the warhead part, resulting in the five-fold increase of the inhibitory activity than **1**. Furthermore, hydrophilic modification of the P4 position, which stuck out from the binding pocket of the protease, was afforded more potent inhibitors than **1**. These inhibitors would be promising lead compounds to develop more potent inhibitors.

MEDI 151

Fragment-based drug design and X-ray crystallography towards the optimization of potent ethionamide boosters as a new strategy to fight MDR-tuberculosis

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Tuberculosis is the main cause of mortality and morbidity due to a single infectious agent. Ethionamide, a second-line antibiotic, is widely used to treat multidrug resistant tuberculosis. EthR, a mycobacterial transcriptional repressor, has been shown to limit the bioactivation of ethionamide and thus its activity. With the design of potent inhibitors we recently validated EthR *in vitro* and *in vivo* as a new drug target to boost the sensitivity of *M. tuberculosis* to ethionamide.¹⁻⁴ In the current study we combined, SPR assay, X-ray crystallography, *in silico* design and medicinal chemistry for the rapid discovery and optimization of new structurally diverse EthR inhibitors based on two fragment-based drug design approaches. The design, synthesis, *in vitro* and *ex vivo* activity of these compounds will be discussed.

1 Willand, N. *et al. Nat. Med.* **15** , 537-544 (2009).

2 Willand, N. *et al. ACS Chem. Biol.* **5** , 1007-1013 (2010).

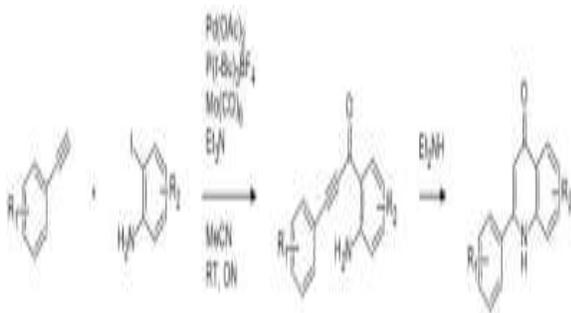
3 Flipo, M. *et al. J. Med. Chem.* **54** , 2994-3010 (2011).

4 Flipo, M. *et al. J. Med. Chem.* **55** , 68-83 (2012).

MEDI 152

Mild and efficient protocol for the synthesis of functionalised quinolones via a carbonylative Sonogashira cross-coupling

Linda Nilsson Möllers, *linda.nilsson_mollers@orgfarm.uu.se*, Matyas Wejdemar, Patrik Nordeman, Mats Larhed. Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, Uppsala, Uppsala SE-751 23, Sweden



Quinolones represent an important class of compounds in medicinal chemistry *e.g.* as substructures in antibacterial agents. Here, we present a mild and efficient protocol for the synthesis of functionalised quinolones. A carbonylative Sonogashira cross-coupling reaction using $\text{Mo}(\text{CO})_6$ as a solid source of carbon monoxide provides the non-cyclised precursor. By the addition of diethylamine to the reaction mixture the cyclised compound can be obtained.

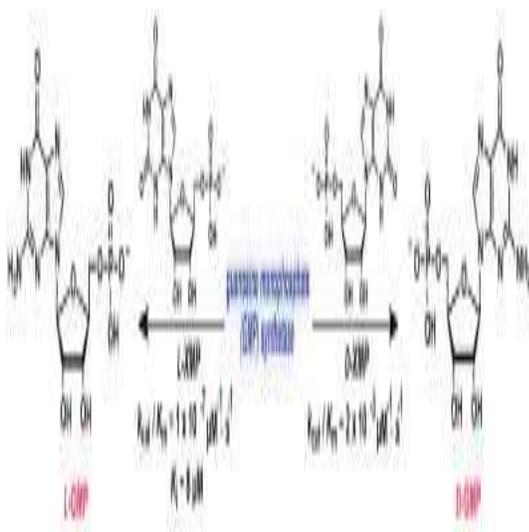
The quinolone scaffold can be used in the synthesis of potent inhibitors of *Mycobacterium tuberculosis*.

MEDI 153

Inhibition of guanosine monophosphate synthetase by the substrate enantiomer L-XMP

Nicholas B Struntz, *stru0157@umn.edu*, Tianshun Hu, Brian R White, Daniel A Harki. Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55414, United States

Recent studies with “mirror-image” L-enantiomer nucleosides have yielded efficacious antiviral drugs with enhanced *in vivo* stabilities and pharmacokinetics, as well as less off-target toxicity. These properties are largely attributable to differences in the enantioselectivities of viral versus cellular enzymes. Although the tolerances of viral polymerases to recognize and utilize L-nucleotides as substrates has been well studied, the abilities of enzymes involved in *de novo* nucleotide biosynthesis pathways to utilize L-nucleotides as substrates is significantly less developed. We have recently characterized the enantioselectivity of GMP Synthetase (GMPS), a key enzyme in the *de novo* synthesis of GMP. The synthesis of L-xanthosine monophosphate (L-XMP) and its kinetics of incorporation and inhibition of GMPS will be presented.



MEDI 154

Antibacterial bipyridinium amphiphiles with conventional, bicephalic, and gemini architectures

*Melissa C. Grenier, Jacob W. Black, Robert W. Davis, **Kevin P.C. Minbiole**, kevin.minbiole@villanova.edu. Department of Chemistry, Villanova University, Villanova, PA 19085, United States*

The continued development of new antimicrobial structures is crucial for slowing the spread of bacterial disease and resistance. Our group is working towards the preparation and antimicrobial assessment of a series of alkylated bipyridium compounds. Such compounds are widely employed for their useful reduction-oxidation properties, and are commonly known as viologens due to their coloration upon reduction. We have prepared a series of mono- and bis-alkylated analogs of bipyridines to investigate structure-activity relationships in their inhibition of Gram positive and Gram negative bacteria. The cationic compounds prepared were conventional (one cationic head, one non-polar tail), bicephalic (two heads, one tail), or gemini (two heads, two tails) in their amphiphilic structure. The rapid synthesis of antimicrobials with low micromolar MIC levels portends well for continued optimization.

MEDI 155

Antimicrobial and lytic activities of squalamine analogs: Effect of stereochemistry at C3 and C7

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Squalamine (3 β -N-1-{N-[3-(4-aminobutyl)]-1,3-diaminopropane}-7 α ,24R-dihydroxy-5 α -cholestane-24-sulfate), an aminosterol from the dogfish shark *Squalus acanthias*, is a potent antimicrobial compound believed to act through plasma membrane lysis. In this report, the synthesis of a series of squalamine analogs is described, and their antimicrobial activity characterized using two different assays. The synthesized analogs vary in the stereochemistry at the 3- and 7- substituents, and also in the length and composition of the polyamine added at C-3. The antimicrobial activity of the analogs was assessed against four bacterial strains. Membrane lytic activity was assayed using large unilamellar vesicles encapsulating a fluorescent calcein dye. Both vesicle lysis and antimicrobial activity of the aminosterols are shown to improve with a longer polyamine chain at C-3. Also, analogs with a 7 α -OH substituent are more potent than their 7 β -OH analogs. The results suggest that the stereochemistry of the C7-OH group is important in aminosterol activation at the membrane surface.

MEDI 156

Synthesis and antimicrobial activity of a series of (3 β -N-1,3-diaminopropyl) bile acids

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Squalamine is a naturally occurring aminosterol antibiotic found in the tissues of the dogfish shark *Squalus acanthias*. In this study, a series of aminosterols are synthesized from bile acid methyl esters, and the minimal inhibitory concentrations of the aminosterol derivatives are measured against a series of bacteria. The aminosterols were synthesized from the methyl esters of cholic acid, deoxycholic acid, chenodeoxycholic acid, and hyodeoxycholic acid; the 3-OH of each was oxidized to the 3-oxo compound using silver carbonate, followed by the addition of 1,3-diaminopropane to the oxosterol by reductive amination. The minimum inhibitory concentrations were determined against *E. coli*, *S. aureus*, *P. aeruginosa*, and *E. faecalis*, using a cell viability assay with resazurin dye. Resazurin is an oxidation-reduction indicator that is originally blue but is reduced to a pink, fluorescing color when around viable cells. The relationship between aminosterol structure and minimal inhibitory concentration for the aminosterols will be discussed.

MEDI 157

Synthesis of new antibacterial siderophores derived from pyoverdine

Natacha Farvacques, Viviane Silva Pires - Antonietti, Christine Cézard, **Alexia Jonet**, alexia.jonet@u-picardie.fr, Pascal Sonnet. UFR Pharmacie, Université Picardie Jules Verne, Amiens Cedex 1, France

Pseudomonas aeruginosa is an opportunistic pathogen and represents one of the biggest challenges in the treatment of hospital-acquired infections. This Gram negative

bacteria has been able to quickly develop resistance to practically every antimicrobial drug currently in use. *P.aeruginosa* needs iron, present in low quantity in biological media, for its development and absorbs it *via* specific receptors (FpvA) or uptake mechanisms. *P.aeruginosa* synthesizes siderophores belonging to the pyoverdine family, which possess hydroxamate amino-acids and catechol moieties acting as iron chelator groups. Our objective is to mimic this siderophore by synthesizing analogues which can antagonize the FpvA receptor or/and carry antibiotics. At first we want to synthesize modified amino acids from lysine, ornithine and aspartic acid, then the synthesis of simplified chromophore² will be established from L-DOPA and dopamine. This synthesized chromophore will be coupled to the different amino acids to give potential antibacterial peptids.

MEDI 158

Asymmetric synthesis of new bacterial efflux-pump inhibitors

Sylvain Fardeau, Catherine Mullie, Alexandra Dassonville-Klimpt, Aexia Jonet, alexia.jonet@u-picardie.fr, Nicolas Audic, Pascal Sonnet. UFR Pharmacie, Université Picardie Jules Verne, Amiens Cedex 1, France

Many cases of multidrug-resistant bacteria are correlated with the decrease of the permeability of bacterial membrane toward antibiotics due to change of absorption mechanisms or bacterial efflux pump systems. In the last case, these proteinaceous transporter efflux pumps are able to extrude antibiotics outside the bacteria cytoplasm. Research done on this system has shown that its inhibition allows better sensibility of resistant bacteria toward antibiotics. For instance Phe-Arg- β -naphthylamide (PA β N) and 1-(1-naphthylmethyl)-piperazine (NMP) have shown strong inhibition of efflux system within Gram negative bacteria.

Our goal is to synthesize new pure enantiomer piperazine derivatives and study their efflux pump inhibition potential. Herein we describe an enantiopure synthetic and straightforward route to prepare pure enantiomer (*S*) or (*R*)-piperazinylarylethanol derivatives from a regio and enantioselective ring-opening of chiral aryloxirane with a piperazine. Their inhibitor activities have been evaluated by measuring their impact, compared to NMP, to restore the ciprofloxacin activity on *Pseudomonas aeruginosa*.

MEDI 159

Computational study of a possible binding site of benzimidazoles to β -tubulin of *Trichinella spiralis*

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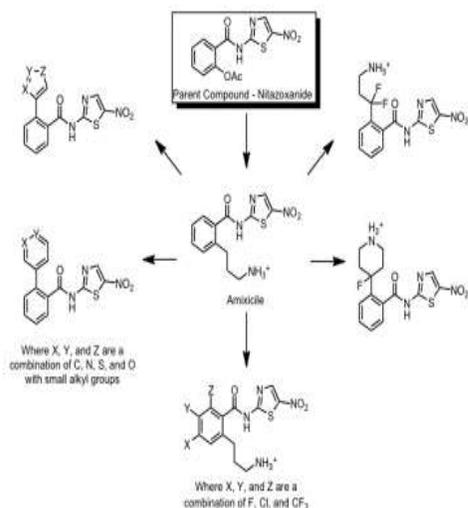
Carbendazim (methyl 1*H*-benzimidazol-2-ylcarbamate) derivatives are among the most important broad-spectrum anthelmintic drugs for the treatment of nematode infections. The mode of action of these benzimidazoles is through the inhibition of microtubule polymerization by binding selectively to the β -tubulin monomer. Because of the lack of a crystallographic structure corresponding to parasite tubulin, we used homology modeling techniques to build a tridimensional structure of this protein. We were able to identify a possible binding site for benzimidazoles based on the molecular docking and molecular dynamics of several carbendazim derivatives. Results are in good agreement with the most common amino acid mutations associated with drug resistance (F167Y, E198A and F200Y), and competitive inhibition of colchicine binding to tubulin. Also, the T165 in this model stands as an important amino acid that may explain the differences in affinity between organisms, i.e. humans and parasites.

MEDI 160

Synthesis and evaluation of second generation nitrothiazolide antibiotics

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Clostridium difficile infections (CDIs) have overtaken MRSA as the leading cause of death among hospital acquired infections. Nitrothiazolide derivatives of Nitazoxanide have been designed and synthesized to improve efficacy and bioavailability against pyruvate-ferredoxin oxidoreductase (PFOR), a metabolic enzyme in anaerobic bacteria including *C. difficile*. The library of NTZ derivatives target PFOR inhibition by withdrawing electron density from the aromatic ring to increase *in vitro* activity and adding positive charge at the *ortho* substituent on the aromatic ring to maximize bioavailability.



MEDI 161

Synthesis of 2-[¹¹C]methoxy-3,17β-O,O-bis(sulfamoyl)estradiol as a new potential PET agent for imaging of steroid sulfatase (STS) and carbonic anhydrase II (CAII) in cancers

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The enzyme steroid sulfatase (STS) catalyzes the hydrolysis of steroid sulfates to estrones, the main source of estrogens in tumors. The enzyme carbonic anhydrase II (CAII) is highly expressed in red blood cells through a coordination of the monoanionic form of the sulfamate moiety to the zinc atom in the enzyme active site, and CAII is highly expressed in several tumors. 2-Methoxy-3,17β-O,O-bis(sulfamoyl)estradiol is a potent irreversible STS inhibitor, and also a highly active reversible CAII inhibitor. This compound exhibited potent antiproliferative activity with mean graph midpoint value of 87 nM in the NCI 60-cell-line panel, and antiangiogenic in vitro and in vivo activity in an early-stage Lewis lung model as well. The compound has been recently developed as a multitargeted anticancer agent by Leese et al. STS and CAII are attractive targets for cancer treatment and molecular imaging of cancer. Here we report the first design and synthesis of 2-[¹¹C]methoxy-3,17β-O,O-bis(sulfamoyl)estradiol as a new potential imaging agent for biomedical imaging technique positron emission tomography (PET) to image STS and CAII in cancers. The authentic standard 2-methoxy-3,17β-O,O-bis(sulfamoyl)estradiol was synthesized from β-estradiol by published procedures in 5 steps with 40% overall chemical yield. The precursor 2-hydroxy-3,17β-O,O-bis(sulfamoyl)estradiol for radiolabeling was synthesized from β-estradiol in 10 steps with 5% overall chemical yield. The target tracer 2-[¹¹C]methoxy-3,17β-O,O-bis(sulfamoyl)estradiol was prepared from the precursor with [¹¹C]CH₃OTf through O-[¹¹C]methylation and isolated by HPLC combined with solid-phase extraction (SPE) purification in 40-50% radiochemical yields based on [¹¹C]CO₂ and decay corrected to end of bombardment (EOB), with 370-740 GBq/mmol specific activity at EOB.

MEDI 162

Synthesis of [¹¹C]OMAR and its analog radioligands for PET imaging of CB1 receptor in brain diseases

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Cerebral cannabinoid receptor subtype 1 (CB1) is predominantly expressed in the central nervous system, and involved in a variety of brain functions and disorders such as schizophrenia and depression, obesity, drug addiction and alcoholism, and traumatic brain injury. [¹¹C]OMAR ([¹¹C]JHU75528) is a promising radioligand for positron

emission tomography (PET) imaging of CB1 receptor, originally developed and characterized at the John Hopkins University. Wishing to study this compound in our PET center, we investigated the synthesis of [^{11}C]OMAR and its analog radioligands by following the literature methods. The published method for the synthesis of OMAR and its analogs, and their corresponding desmethylated precursors gave poor yields. Therefore, alternate synthetic approaches and modifications were studied. OMAR analogs including 4-cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (OMAR), 4-cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide, 1-(2-bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, and 1-(2-bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide; and their corresponding desmethylated precursors 4-cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, 4-cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide, 1-(2-bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, and 1-(2-bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide were synthesized from substituted anilines either in 4 and 5 steps with 27-32% and 24-31% yield, or in 3 and 4 steps with 21-30% and 19-28% yield, respectively. [^{11}C]OMAR and its analog radioligands including 4-cyano-1-(2,4-dichlorophenyl)-5-(4-[^{11}C]methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide ([^{11}C]OMAR), 4-cyano-1-(2,4-dichlorophenyl)-5-(4-[^{11}C]methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide, 1-(2-bromophenyl)-4-cyano-5-(4-[^{11}C]methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, and 1-(2-bromophenyl)-4-cyano-5-(4-[^{11}C]methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide were prepared from their desmethylated precursors with [^{11}C]CH₃OTf through O-[^{11}C]methylation and isolated by HPLC combined with solid-phase extraction (SPE) in 50-65% radiochemical yields based on [^{11}C]CO₂ and decay corrected to end of bombardment (EOB), with 370-740 GBq/ μmol specific activity at EOB.

MEDI 163

Synthesis, SAR, and tissue distribution of novel $^{99\text{m}}\text{Tc}/\text{Re}(\text{CO})_3$ labeled benzenesulfonamide conjugates for molecular imaging of carbonic anhydrase IX

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Carbonic anhydrase IX (CA-IX) is upregulated in cancer cells in response to the hypoxic tumor microenvironment making it an attractive molecular target for the development of radiopharmaceuticals to detect hypoxic solid tumors. A series of small molecule benzenesulfonamide (BzSA) CA-IX inhibitors containing novel tridentate chelates with the $\text{M}(\text{CO})_3$ core (M = Re or $^{99\text{m}}\text{Tc}$) were synthesized from a BzSA moiety tethered through a linker to pyridylmethylamine, functionalized *bis*-imidazolylmethylamine or functionalized *bis*-triazolylmethylamine derived chelates. The binding affinity to CA-IX expressing HeLa cells was measured for the BzSA $\text{Re}(\text{CO})_3$ complexes ($\text{IC}_{50} = 3\text{-}280$

nM). An effect of the linker length and composition of the linker between BzSA and the chelators was observed. One of the most potent compounds, ^{99m}Tc -MIP-1505, exhibited high tumor uptake (15% ID/g) and low accumulation in non-target tissues in HEK-293/CA-IX xenograft tumors. These compounds have the potential to significantly impact diagnosis, staging, and treatment selection of hypoxic solid tumors.

MEDI 164

Magnetic nanostructures for potential theranostics

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Magnetic nanostructures (MNS) are a class of promising theranostic agents by virtue of their unique applicational approaches, such as magnetic resonance (MR) imaging and thermal ablation. Furthermore, MNS can be functionalized for selective surface recognition elements for *in vitro* and *in vivo* targeting, diagnosis, and therapy. Here we describe a new methodology for iron oxide nanostructure surface functionalization and applications thereof. Specifically, due to the extraordinary stability of the new MNS in all types of biological media and their elevated R_2 contrast for MRI they are a promising new agent for cancer theranostics. Cellular incubation of MNS was characterized with transmission electron microscopy, showing that MNS reside in vesicles throughout the cell. *In vitro* cellular studies with U251 human glioblastoma, UT197 bladder cancer, and MDA-MB-468 Human Breast Cancer cells demonstrated that the MNS are nontoxic at elevated concentrations and exhibit a high efficacy in thermal ablation therapy.

MEDI 165

Radiosynthesis of [^{11}C]CNS 1261, a positron emission tomography radiotracer for imaging the phencyclidine site of the *N*-methyl-D-aspartate receptor

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Over-activation of *N*-methyl-D-aspartate (NMDA) receptors has been indicated in neurodegenerative conditions such as Alzheimer's, Parkinson's, and Huntington's disease. However, a radiotracer capable of quantifying activated NMDA receptors in human brain *in vivo* is still lacking. The most successful radiotracer to date is the high-affinity SPECT radioligand [^{123}I]CNS 1261 (K_i , 4.65 nM). Here we report our radiosynthesis of [^{11}C]CNS 1261, a PET analogue of [^{123}I]CNS 1261. The des-methyl precursor was successfully synthesized in 70% yield from the guanidinylation of 3-iodoaniline hydrochloride with *N*-(naphthalen-1-yl)cyanamide. Treatment of this precursor with [^{11}C]MeOTf or [^{11}C]MeI gave [^{11}C]CNS 1261 after HPLC separation from

labeled regioisomer in 21% and 46% decay-corrected radiochemical yields, respectively. The ratio of [^{11}C]CNS 1261 to labeled regioisomer was 1:1.6 from [^{11}C]MeOTf and 1.6:1 from [^{11}C]MeI. This labeling methodology is now being applied to other high-affinity analogs of CNS 1261 to provide new candidate radiotracers with improved imaging properties.

MEDI 166

Binding of the anti-HIV drug Efavirenz to human serum albumin: A ^{19}F -NMR study

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Efavirenz is a non-nucleoside reverse transcriptase inhibitor used against HIV-1. Its major drawback is neurotoxicity, though it also causes skin rash and hepatotoxicity. Thus, efficient monitoring of efavirenz and its metabolites in human serum is essential to establish reliable correlations between exposure and disease biomarkers.

Taking advantage of the presence of fluorine in efavirenz we optimized a ^{19}F -NMR experiment allowing clean direct detection of the drug and its major metabolites in complex matrices. We then applied the technique to investigate the mode of efavirenz binding to human serum albumin (HSA). Competition experiments, using drugs with well-characterized binding to HSA (ibuprofen, warfarin, and benzocaine), indicated that efavirenz interacts with multiple HSA sites. Moreover, the presence of competitors affected efavirenz concentration in solution. Our data demonstrate that co-administration of warfarin and efavirenz, frequent in anti-HIV therapies, can mutually influence their pharmacokinetic parameters, potentially leading to adverse effects.

Supported by FCT (PTDC/QUI-QUI/113910/2009; PEst-OE/QUI/UI0100/2011).

MEDI 167

Synthesis of calcium carbonate nanoparticles using agar gel via polymer mediated growth route for biomedical and other industrial applications

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One among the many techniques of synthesizing nanoparticles developed is the 'Polymer Mediated Growth (PMG)' technique. In this route, ions of one of the reactants are allowed to diffuse from an external solution into a polymer matrix where the other reactant is complexed and bound. The exact role of ionic diffusion in the formation of nanoparticles has been investigated in the current study. Typically calcium carbonate nanoparticles have been formed by PMG route using agarose gel. The agarose

concentration used to form the gel and reaction temperature affect the size of the particles formed due to change of diffusivity of ions into the polymer matrix. Particle size was calculated using Scherrer's formula on X-ray Diffraction plots and was reconfirmed with Field Emission Scanning Electron Microscope and Transmission Electron Microscope images. Energy Dispersive X-ray analysis and FTIR spectroscopic techniques are used to study the composition, allotropic forms and purity of nanoparticles formed. Also, their biocompatibility is studied using ROS and MTT assays. Through this knowledge we have optimized the above parameters to obtain smaller particles as they are more suitable for applications in biomedical, polymer and plastic industries. Also, we have confirmed that this technique can be used to synthesize and control the size of nanoparticles.

MEDI 168

Preparation and evaluation of new 1,5-diarylpyrazoles as potential probes for imaging cyclooxygenase-2 (COX-2) expression in the brain

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Inflammation and related disorders are highly prevalent and affect millions of people every year. Inflammation, a complex, biological and defensive response to harmful stimuli or irritants, is often associated with other pathological processes, including Alzheimer's and Parkinson's disease, many cancers and atherosclerosis. Cyclooxygenase-2 (COX-2) is expressed during inflammatory conditions and is responsible for the biosynthesis of the prostaglandins (PGs) required by inflammatory cells. Quantification of COX-2 expression in the brain could potentially be useful for the diagnosis and monitoring of disease progression, as well as a measure of efficacious treatment. To date, no suitable yet specific probe for imaging COX-2 expression has emerged. On this premise, our aim was to develop an optimal probe to provide images of COX-2 expression in the brain. Thus, a series of 1,5-diarylpyrazoles were prepared and evaluated in vitro for their ability to block the activity of the cyclooxygenase-1 and -2 (COX-1 and -2) enzymes.

MEDI 169

Investigation of the binding of UDP-galactopyranose mutase inhibitors by saturation transfer difference NMR spectroscopy and molecular dynamics simulations

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Galactofuranose (Gal_f), absent in mammals, is the building block of the galactan chain in *Mycobacterium tuberculosis* cell wall. The biosynthesis of this chain is essential for the growth and survival of *M. tuberculosis*, thus the corresponding biochemical pathway provides attractive drug targets for the treatment of tuberculosis. One of the enzymes involved in this pathway is UDP-galactopyranose (Gal_p) mutase (UGM), crucial for the viability of *M. tuberculosis*, and we have identified several structurally different inhibitors against *M. tuberculosis* UGM (mtUGM). Herein, an approach combining saturation transfer difference NMR and molecular dynamics was employed to study the binding modes and dynamics of mtUGM inhibitors as well as the natural substrate UDP-Gal_p. The results provided further insights into the interactions between mtUGM and its ligands, which will facilitate the design of novel drug candidates for tuberculosis.

MEDI 170

Development of long lived luminescent probes for ultrasensitive detection of biopolymers

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Lanthanide luminescent probes are attractive alternatives to radioisotopic and fluorescent labeling due to extremely high detection sensitivity. The probes include antenna fluorophore that absorbs the excitation light and transfers the energy to a lanthanide ion coupled to an antenna through a chelating group as well as crosslinking group for the attachment to a biomolecule of interest. The excited lanthanide state is long-lived that allows to avoid short-lived background fluorescence using time-gated detection. We developed new efficient strategies for the synthesis of lanthanide probes, which makes them available for variety of biological, biomedical and technical applications. The synthesized probes were 50-100 times more sensitive comparing to conventional fluorescent labels in the context of molecular beacon hybridization probes and allowed highly contrast microscopic imaging of bacterial and mammalian cells. The probes with Eu³⁺, Tb³⁺, Dy³⁺, and Sm³⁺ lanthanide ions were characterized using fluorescent, NMR, light absorption as well as laser pulsed spectroscopy.

MEDI 171

Re/^{99m}Tc complex: Towards the conception of diagnostic probes for optical/nuclear bimodal imaging

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Molecular imaging allows the *in vivo* detection and follow-up of biological processes at the cellular and molecular levels, using modalities as MRI, nuclear or optical imaging. These modalities present, however, specific imaging properties like high sensitivity (nuclear or optical imaging) or high resolution (MRI). Bimodal imaging, an attractive concept mixing strengths of two modalities, should improve diagnostic accuracy.

The evolution of bimodal techniques requires bimodal contrast agents. Among the available bimodal small molecules, our group synthesized the first dinuclear Re/^{99m}Tc complex, a potential probe for SPECT (^{99m}Tc) and optical imaging (Re). Following a similar synthetic pathway based on Click chemistry, we developed a new Re/^{99m}Tc functionalized system, which may be graft to a biomolecule to target the imaging probe. In this communication, the synthesis of this complex is reported as well as the photophysical and the stability studies. Cytotoxicity and cells uptake will be also presented.

MEDI 172

Exploiting the Syntheverse: Discovery and assessment of new leads from synthetically tractable virtual libraries

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The Syntheverse is a synthetically accessible region of virtual compound space that can be readily assembled using available starting fragments and tractable reaction schemes. Virtual assembly of structures that exhibit sufficient three-dimensional similarity to known bioactive molecules enables rapid scaffold hopping into lead series not precedented in the literature. We have generated a small Fragment Space (32 million structures) from our unique collection of building blocks and queried it with existing kinase inhibitors to retrieve focused libraries of compounds which are simultaneously highly similar to the query and not previously described for the target kinases. The emphasis on synthetic viability and availability has enabled the facile translation of docking hits into early lead compounds. Examples of the scope and utility of this method will be presented.

MEDI 173

Fragment based approaches to GPCRs

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G-protein coupled receptors (GPCRs) play a crucial role in many diseases and are the site of action of 25-30% of current drugs; as such they represent a major area of interest for the pharmaceutical industry. Fragment based screening using biophysical approaches is very challenging for G-protein-coupled receptors (GPCRs) due to their inherent instability outside of the cell membrane.

Heptares has developed a technology that dramatically stabilizes GPCRs; the new stabilized human receptors (StaRs) are much more robust than the corresponding wild type proteins. StaR proteins can be readily purified and are amenable to crystallography, biophysical/fragment screening and for raising monoclonal antibodies.

This poster will focus on the potential of the technology for structure-based drug design and fragment screening of GPCR targets. Biophysical screening results from both TINS-NMR and Surface Plasmon Resonance (SPR) binding studies and high-concentration fragment screening using an agonist StaR protein with libraries of fragments will be shown.

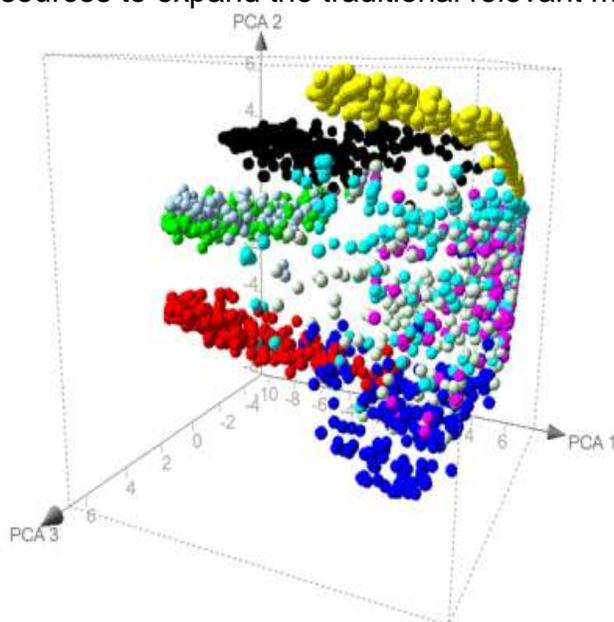
MEDI 174

Interrogating novel regions of chemical space with complex molecular libraries

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Recent analysis of marketed drugs and commercial vendor libraries commonly used in high-throughput screening suggest that the medicinally relevant chemical space may be expanded to unexplored regions. Novel regions of the chemical space can be conveniently explored with structurally unique molecules with increased complexity, as compared to commonly used screening libraries, and balanced physicochemical properties. In light of the recent studies showing that more complex compounds have better chances to succeed at various stages of the drug discovery process, herein we report a comprehensive comparison of a large in-house collection assembled from 30 small-molecule combinatorial libraries with emphasis on assessing molecular complexity. We used a well-established and intuitive approach to quantify stereochemical and shape complexity. The combinatorial libraries analyzed in this work have been successfully used over the past 20 years to identify novel bioactive compounds across different therapeutic areas. We also analyzed the complexity, distribution of physicochemical properties and structural diversity of the Traditional Chinese Medicine (TCM) database, a large publicly available collection of natural products, approved drugs, and other commonly used screening collections. We show that in-house combinatorial libraries and natural products from TCM are suitable

sources to expand the traditional relevant medicinal chemistry space



MEDI 175

Combinatorial quantitative structure-activity relationship (QSAR) modeling of oral bioavailability

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Conducting Adsorption, Distribution, Metabolism, and Excretion (ADME) experiments *in vivo* or on humans is costly and time consuming. The Quantitative Structure-Activity Relationship (QSAR) ADME models attract great attention as alternatives. However, the current computational bioavailability models were developed based on limited data and have little applicability to predict external compounds. In this project, we compiled a large bioavailability database of 1,263 orally administered drugs. Using the commercial MultiCASE® bioavailability module to predict these compounds resulted in poor predictions. In this study, we endeavor to use the combinatorial QSAR method to develop predictive models for oral bioavailability drugs. The utilization of the applicability domain could be included to balance the prediction accuracy with the chemistry space coverage based on the requirement of the users with respect to the error tolerance level. The resulting models could be used to virtually screen new compounds and greatly benefit the drug design procedure.

MEDI 176

Computational study on the inhibition of cruzain by purine-carbonitriles

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Cruzain has been identified as the major cysteine protease of *Trypanosoma cruzi*, thus many efforts have been undertaken to design new inhibitors against this enzyme. Molecules with a nitrile moiety susceptible to a nucleophilic attack by the enzyme have been identified as good inhibitors. Although it is known that the nitrile group binds covalently to Cys25, there are no reports about the reaction mechanism of this process. Quantum calculations were carried out to study this mechanism. Also, to gain an insight into the structural requirements that can lead to the improvement of the activity and reactivity of these molecules, we report the CoMFA and CoMSIA studies of a series of purine-carbonitriles as cruzain inhibitors. High predictive models were obtained and contour maps show important structural requirements for inhibitory activity.

MEDI 177

Finally, a user-friendly way of computing and presenting individual group contributions to polyprotic ionization of drugs

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It is tempting to "assign" the macroscopic ionization constants of molecules to specific ionizable groups; however, this is exact only in the case of monoprotic molecules. An extreme example is benzene hexacarboxylic acid where the six measured pK_a 's range from 1.4 to 7.0 - spanning 6.6 orders of magnitude. Assigning each pK_a to a specific group is absurd in this case, since the six carboxylic acid groups are completely equivalent! This potentially confusing situation is clarified by considering microscopic ionization equilibria replacing the inaccurate and misleading "one group = one pK_a " paradigm. We have explored microequilibria theory in detail and have developed novel concepts: the pH-dependent Average Single Proton Acidity (ASPA), and the pH-dependent Average Atomic Protonation Profiles (AAPP). The ionization midpoint of the latter - the pK_{50} - is pH-independent and closely related to concepts from the physical chemistry of proteins. We show that the pK_{50} , unlike macroscopic pK_a , is a transferable property of an individual ionizable group, illustrating its inherent acidity in the absence of intergroup interactions. For example, we calculate a chemically realistic $pK_{50} = 3.92$ for each carboxyl group in the benzene hexacarboxylic acid. In the case of monoprotic molecules as well as molecules with well-separated ionization patterns, the pK_{50} 's correspond to macroscopic pK_a 's exactly and approximately, respectively. An added bonus is a direct determination of individual site occupancies from the calculated AAPP at any pH of interest, which eliminates the need to deduce these quantities from pK_a .

MEDI 178

Exploring the chemical space of histamine receptor ligands using drug discovery tools at mcule.com

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Mcule.com provides a large database of purchasable compounds from multiple chemical suppliers. This large, carefully curated database is integrated with many searching and screening tools providing a powerful resource for drug discovery tasks. In this presentation we show how mcule.com can be used to identify novel histamine receptor ligands by means of ligand- and structure-based approaches available at mcule.com. Similarity searches with different descriptors by using known H1 and H4 reference ligands were able to recover several active classes. In particular, by applying linear molecular fingerprints close analogs of H1 and H4 ligands were found. Such searches and hits can be very valuable when exploring chemical space around HTS hits. On the other hand, more fuzzy descriptors were able to identify scaffolds significantly differing from those of the reference ligands. These latter searches are therefore more useful for scaffold hopping purposes. Docking into the recently discovered X-ray structure of histamine H1 receptor combined with the pharmacophore constraint optimizer feature of mcule also yielded good hit rates. It is also demonstrated how to filter out molecules with undesirable pharmacokinetic properties to keep only the most valuable hits.

Since the applied tools are integrated with the high quality mcule database, the outcoming hits can be ordered directly on the website.

MEDI 179

Functionalized 1,2,3-triazoles as analogs of purine nucleobases

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The discovery of novel nucleoside analogues is limited, in part, by the availability of scaffolds able to imitate purine or pyrimidine bases. 1,2,3-Triazole rings, if appropriately functionalized with a sugar off N1 and a hydrogen bonding group off C4, bear a striking resemblance to purine nucleosides. Several triazole-based nucleoside analogues have been prepared through either an azide-enol ether or azide-alkyne cycloaddition. Details on the synthetic procedures and preliminary screening results will be presented.

MEDI 180

Rational design of functional peptide nucleic acids for the direct and ultrahigh sensitive detection of HIV-1 DNA and RNA with a sandwich-hybridization assay

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One of the great challenges in human immunodeficiency virus (HIV) diagnosis and prevention today is to develop technologies for early and direct detection of HIV nucleic acid sequences in patient tissue or blood samples. Enzymatic amplification of conserved sequences of the HIV-1 genome by PCR has been the subject of a large number of studies. However, the direct biochemical test used for PCR-based molecular diagnosis of HIV-1 infection is usually time consuming, is not quantitative and requires molecular biology facilities. So, direct detection methods that eliminate the requirement for a PCR step could afford faster and simpler devices that can be used outside of a laboratory. Here, a convenient, universal, colorimetric, nucleic acid-responsive detection system that uses two short peptide nucleic acids (PNAs) is demonstrated for the ultrahigh sensitive detection of HIV-1 gag DNA and RNA on a 96-well plate based on the sandwich-hybridization strategy. This protocol eliminates the requirement for a PCR step. Using PNA probes instead of traditional DNAs can improve the detection devices for the following reasons: resistance to degradation by enzymes, increased sequence specificity to complementary DNA and RNA, and higher stability when bound with complementary DNA or RNA. Furthermore, the design of a 3-cyclopentane modified surface probe and a 16-biotin containing reporter probe impart extraordinarily high sensitivity. This sandwich-hybridization assay is convenient, universal and colorimetric with a qualitative detection limit of 6 molecules for both of HIV-1 gag DNA and RNA, and a quantitative detection limit of 576 molecules for HIV-1 gag DNA, 493 molecules for HIV-1 gag RNA. These properties should make this device suitable for early detection of HIV virus in remote settings. In principle, this assay can also be used to detect any kind of infectious disease by simply changing the PNA sequences of the specific probe.

MEDI 181

Discovery of indazole and benzoisoxazole containing 4-azetidiny-1-aryl-cyclohexanes as CCR2 antagonists

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The CC chemokine receptor 2 (CCR2) and its primary ligand, monocyte chemoattractant protein-1 (MCP-1), play key roles in attracting monocytes to sites of inflammation. Inhibiting this receptor could impart beneficial outcomes in many disease states. We discovered an azetidiny cyclohexane bis-amide scaffold bearing two consecutive amide bonds as potent CCR2 antagonists with good selectivity versus hERG. However, this type of functionality is prone to rapid metabolism in vivo, which

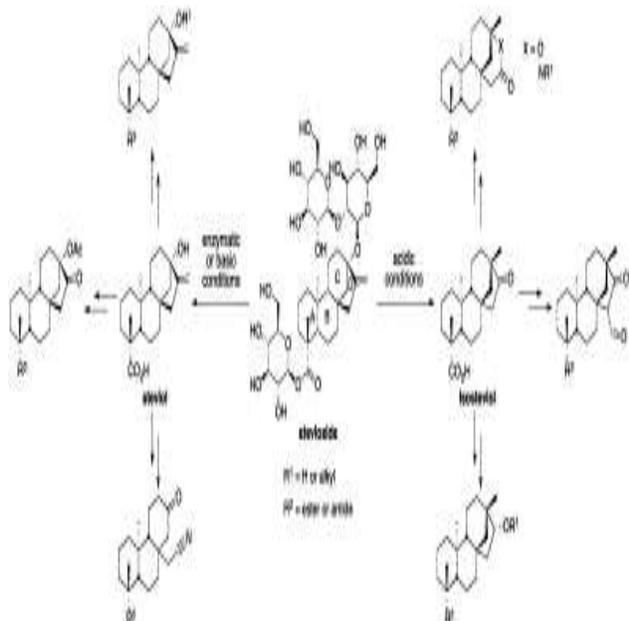
might lead to low exposure. We describe herein our exploration on amide replacement by 5-membered heterocycle into 5/6-fused ring system such as indazole or benzoisoxazole to afford a novel series of CCR2 antagonists. Optimization of this series according to divergent SARs on both CCR2 and hERG generated a lead compound with potent CCR2 activity and good selectivity over hERG. Furthermore, the PK profile proved to be amenable with moderate clearance and volume distribution and high oral bioavailability in dogs, which is suitable for further development.

MEDI 182

Design and synthesis of Stevioside analogs for diterpene scaffold development

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Stevioside, a natural product from the *Stevia rebaudiana* Bertoni plant, contains a diterpene carbon skeleton that provides a novel template for scaffold development. Hydrolysis of the glycosidic bonds of stevioside under enzyme-mediated or basic conditions produces the steviol aglycone while acidic conditions yield the Wagner-Meerwein rearranged product isosteviol. Both stevioside analogs, along with their parent molecule, have been shown to possess pharmacological activity. The aglycone structures provide the initial templates to explore diversity-oriented reactions of the different rings in the diterpene system and various functionalities of the core structure. With multiple scaffolds in hand, small molecule libraries were designed and synthesized for biological evaluation.

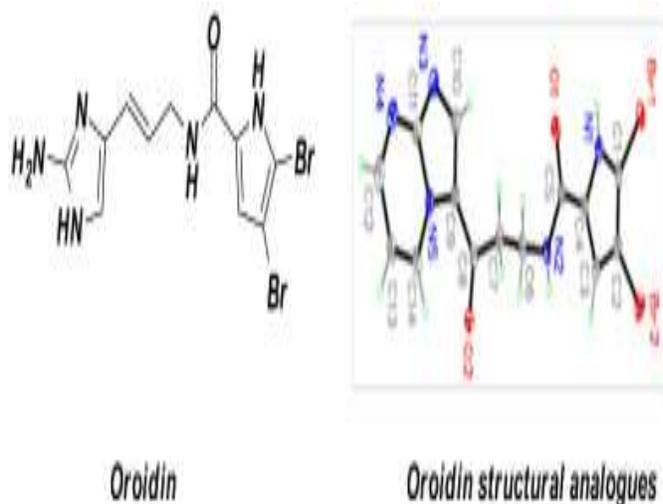


MEDI 183

Synthesis of novel 3-acylimidazo[1,2-a]pyrimidine cores and their unusual chemistry and antibacterial activity

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Guanidine alkaloids are widely distributed in nature and include many biologically important molecules. Marine sponges produce a plethora of fascinating, structurally diverse guanidine secondary metabolites usually containing 2-aminoimidazole or 2-aminoimidazolidine. Since the discovery of the first alkaloid of this family, Oroidin, in 1971 many hundreds of such compounds have been isolated. Oroidin has been shown to be a potential anti-bacterial lead molecule. We have developed structural analogues of Oroidin for the SAR studies through imidazopyrimidine chemistry, and the anti-bacterial activity data of the same was established towards various strains, and the results will be presented.



MEDI 184

FM 19 analogs for direct thrombin inhibition

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The serine protease thrombin is the main clotting enzyme in the hemostatic system, in addition to being an effective platelet activator. 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. SAR studies have led to the development of the pentapeptide lead compound FM 19, and the x-ray structure of FM 19 in the active site of thrombin has revealed modification sites to improve inhibitor binding. Alterations to the C-terminus, N-terminus, and center residues of the peptide were explored individually, resulting in several peptides with superior thrombin inhibition, including new compounds which have the potential to improve oral bioavailability in addition to potency.

MEDI 185

Benzosuberenes as cytotoxic tubulin binding agents

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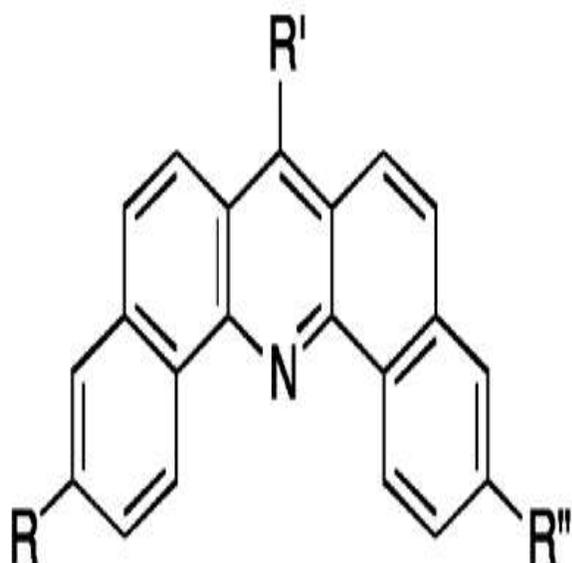
Benzosuberenes belong to a class of tubulin polymerization inhibitors that possess remarkable potency against a variety of cancer cell lines. Herein, an efficient synthetic route for benzosuberene analogs is described featuring a Claisen rearrangement/RCM sequence and a late stage Suzuki coupling as the key steps. Based on the established synthetic route a number of analogs were designed and synthesized and their biological activities were evaluated. The structure activity relationship of benzosuberene analogs is discussed and presented.

MEDI 186

Synthesis and biological evaluation of substituted dibenz[c,h]acridines

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The G-quadruplex structure, putatively identified in the human telomere, has been associated with telomerase activity. G-Quadruplex selective ligands are known, but vary greatly in their ability to inhibit telomerase through association and stabilization of the quadruplex. Using computer modeling, we have identified a series of dibenz[c,h]acridines that exhibit a good fit with the G-quadruplex structure common to human telomeric sequences. The synthesis of these compounds, and initial evaluation of their biological activity, will be described.



MEDI 187

Nanocapsule that delivers their payload by interaction with a DNA trigger

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Hollow colloidal capsules were filled with the payload and sealed with a DNA zipper based mechanism trapping the payload inside. The capsules were opened by the detection of a specific DNA trigger sequence. The interaction of the capsule with the trigger sequence resulted in the release of the drug. The construction protocols of the DNA zippers and the capsules are presented together with SEM, DLS and Fluorescence data.

MEDI 188

Design, synthesis, and structure-activity-relationship of a novel series of GluN2C selective potentiators

*Sommer S. Zimmerman*¹, sshelle@emory.edu, *Alpa H. Khatri*², *Jing Zhang*², *Phuong Le*², *Stephen F. Traynelis*², *Dennis C. Liotta*¹. (1) Department of Chemistry, Emory University, Atlanta, GA 30322, United States (2) Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322, United States

N-Methyl-D-aspartate (NMDA) receptors are tetrameric assemblies of GluN1 and GluN2A-D subunits. These receptors mediate excitatory synaptic transmission and are

implicated in several neurological diseases. We have evaluated a novel series of pyrrolidinones as positive allosteric modulators of NMDA receptors that contain the GluN2C subunit. These compounds do not have agonist activity, but potentiate the response to maximally effective concentrations of the co-agonists glutamate and glycine. The most selective analogues show over 100-fold selectivity for recombinant GluN2C-containing receptors over GluN2A/B/D-containing NMDA receptors, AMPA receptors and kainate receptors. These compounds represent the first class of allosteric potentiators that are selective for NMDA receptors that contain the GluN2C subunit.

MEDI 189

Finding the sweet spot - the role of nature and nurture in medicinal chemistry

Gyorgy M. Keseru², *gy.keseru@richter.hu*, **Michael M. Hann¹**. (1) *Computational and Structural Chemistry, GSK Medicines, United Kingdom* (2) *Discovery Chemistry, Gedeon Richter plc, Hungary*

Given its position at the heart of small-molecule drug discovery, medicinal chemistry can have a key role in tackling the well-known productivity challenges in pharmaceutical research and development. In recent years, extensive analyses of successful and failed drug compounds have improved our understanding of the role of physicochemical properties in drug attrition, and clarified the difficulties in finding the 'sweet spot' in lead discovery and optimization. Here, we discuss scientific, strategic, organizational and cultural considerations that could help transform present medicinal chemistry practices by promoting the more effective use of what is already known and wider appreciation of the risks of pursuing sub-optimal compounds.

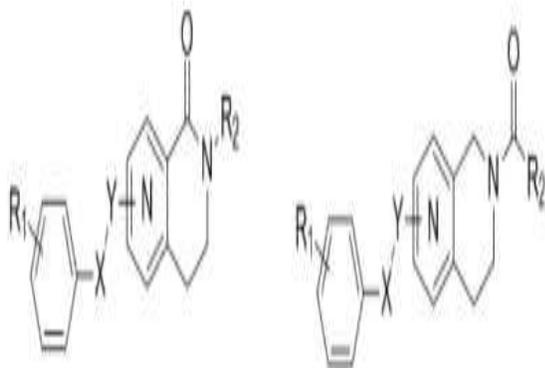
MEDI 190

Bicyclic tetrahydronaphthridine and dihydronaphthridinone ethers as positive allosteric modulators of mGlu5

Jason Manka^{1,2,3}, *jason.manka@vanderbilt.edu*, **John Jacobs^{1,2,3}**, **Ya Zhou^{1,2,3}**, **Paige N. Vinson^{1,2}**, **Satya Jadhav^{1,2}**, **Elizabeth J. Herman^{1,2}**, **Hilde Lavreysen⁶**, **Claire Mackie⁷**, **Jose M. Bartolome⁶**, **Gregor J. MacDonald⁶**, **Thomas Steckler⁶**, **J. Scott Daniels^{1,2,3}**, **C. Dave Weaver⁵**, **Colleen M. Niswender^{1,2,3}**, **Carrie K. Jones^{1,2,3}**, **P. Jeffrey Conn^{1,2,3}**, **Craig W. Lindsley^{1,2,3,4}**, **Shaun R. Stauffer^{1,2,3,4}**. (1) *Department of Pharmacology, Vanderbilt University, United States* (2) *Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, United States* (3) *Vanderbilt Specialized Chemistry Center for Probe Development, United States* (4) *Department of Chemistry, Vanderbilt University, United States* (5) *Vanderbilt Institute of Chemical Biology, Vanderbilt University, United States* (6) *Neuroscience, Janssen Research and Development, Belgium* (7) *CREATE ADME/Tox, Janssen Research, Belgium*

Schizophrenia is a disease in which the function of the NMDA receptor is compromised. The disease manifests a number of complex behavior disorders including deficits in

associative learning, working memory, behavioral flexibility, and attention. Activation of metabotropic glutamate receptor 5 (mGlu5) enhances the function of NMDA and is a promising non-dopamine based approach for potential therapeutic intervention. We have identified a series of bicyclic tetrahydronaphthridine and dihydronaphthridinone ethers as positive allosteric modulators (PAMs) of mGlu5. In contrast to related monocyclic ether series, these 6,6-bicyclic modulator scaffolds appear to exhibit shallow SAR and a higher propensity for pharmacological 'mode switching'. SAR across multiple sub-series and the profile of an optimized PAM VU0405372 will be described.



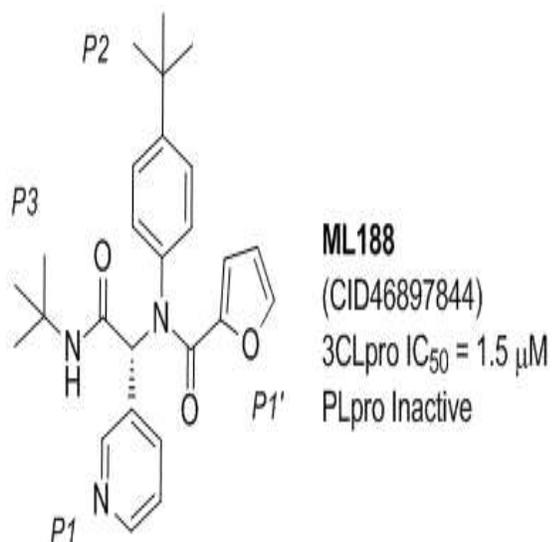
MEDI 191

Discovery of the noncovalent SARS-CoV 3CLpro proteinase inhibitor ML188 and further optimization of the N-anilido P2 sub-group

Aspen Chun^{1,2,3}, aspen.chun@vanderbilt.edu, Jon Jacobs^{1,2,3}, Ya Zhou^{1,2,3}, Valeri Tokars⁷, S. Adrian Saldanha⁵, Peter Chase⁵, Aimee Eggle⁶, Eric S. Dawson^{1,2,3}, Yahira Baez⁶, Craig W. Lindsley^{1,2,3,4}, Peter Hodder⁵, Andrew Mesecar⁶, Shaun R. Stauffer^{1,2,3,4}. (1) Department of Pharmacology, Vanderbilt University, United States (2) Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, United States (3) Vanderbilt Specialized Chemistry Center for Probe Development, United States (4) Department of Chemistry, Vanderbilt University, United States (5) Scripps Research Institute Molecular Screening Center, United States (6) Department of Biological Sciences, Purdue University, United States (7) Department of Molecular Pharmacology and Biological Chemistry, Northwestern University, United States

A high-throughput screen of the NIH molecular libraries sample collection and subsequent chemical optimization at the Vanderbilt Specialized Chemistry Center (VSCC) around a lead series of severe acute respiratory syndrome coronavirus (SARS-CoV) main proteinase 3CLpro inhibitors led to the identification and declaration of probe compound ML188 (Pubchem CID: 46897844). ML188 is a selective, non-covalent SARS-CoV 3CLpro inhibitor with moderate MW and good inhibitory activity. Using X-ray crystallography, a ML188-bound 3CLpro structure was instrumental in guiding

subsequent rounds of chemistry optimization. Efforts to further refine and improve the inhibitory activity of ML188 analogues and in particular within the S2 pocket will be described.



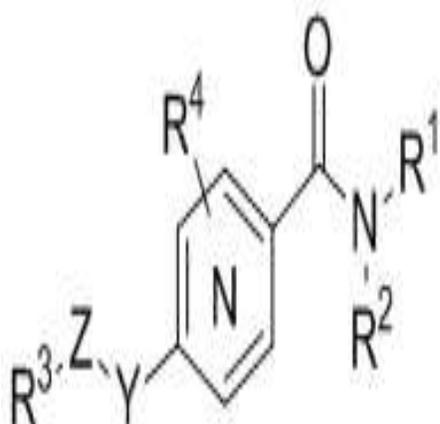
MEDI 192

Investigation of monocyclic ethers as positive allosteric modulators of mGlu5

Chrysa F, Malosh^{1,2,3}, *chrysa.malosh@vanderbilt.edu*, Jason Manka^{1,2,3}, Ya Zhou^{1,2,3}, Rich Williams^{1,2,3}, Paige N. Vinson^{1,2}, Karen J. Gregory^{1,2}, Satya Jadhav^{1,2}, Elizabeth J. Herman^{1,2}, Hilde Lavreysen⁶, Claire Mackie⁷, Jose M. Bartolome⁶, Gregor J. MacDonald⁶, Thomas Steckler⁶, J. Scott Daniels^{1,2,3}, C. Dave Weaver^{1,5}, Colleen M. Niswender^{1,2,3}, Carrie K. Jones^{1,2,3}, P. Jeffrey Conn^{1,2,3}, Craig W. Lindsley^{1,2,3,4}, Shaun R. Stauffer^{1,2,3,4}. (1) Department of Pharmacology, Vanderbilt University Medical Center, United States (2) Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, United States (3) Vanderbilt Specialized Chemistry Center for Probe Development, United States (4) Department of Chemistry, Vanderbilt University, United States (5) Vanderbilt Institute of Chemical Biology, Vanderbilt University, United States (6) Department of Neuroscience, Janssen Research and Development, Belgium (7) CREATe ADME/Tox, Janssen Research and Development, Belgium

Schizophrenia is a disease in which the function of the NMDA receptor is compromised. The disease manifests a number of complex behavior disorders including deficits in associative learning, working memory, behavioral flexibility, and attention. Activation of metabotropic glutamate receptor 5 (mGlu5) is known to increase the function of NMDA and is a promising non-dopamine based target for potential therapeutic intervention. In an investigation of mGlu5 positive allosteric modulators (PAMs) derived from an HTS

screen, we have identified a series of monocyclic ethers with various heterocyclic core structures bearing an amide substituent and an aliphatic ether linkage. Strategies to improve physicochemical properties, functional potency, and selectivity will be presented.



MEDI 193

(Imidazolylmethylene)chroman, a potent, selective, and conformationally restricted α_2c agonist, for the treatment of neuropathic pain

Junying Zheng, junying.zheng@merck.com, Jianhua Chao, Walter Won, Younong Yu, Christopher Boyce, Kevin McCormick, Robert Aslanian, Cynthia Aki, Salem Fevrier, Manuel De Lera Ruiz, Brian Salisbury, Gitali Mukhopadhyay, Tony Priestley, Rosalia Bertorelli, Silva Freduzzi, Angelo Reggiani, Andrea Houghton, Jairam Palamanda, John Hunter. Merck Research Library, Merck & Co., Rahway, NJ 07065, United States

Adrenergic receptors, belong to the G-protein coupled receptors (GPCRs) super family, which mediate the actions of endogenous catecholamines (epinephrine and norepinephrine). They are categorized into α_1 , α_2 , and β receptors. α_2C receptors (a subtype of α_2) are broadly present in both the CNS and peripheral organs. It's known for many years that non-selective α_2 agonists such as clonidine and dexmedetomidine can produce clinically effective analgesia. α_2C receptors are located primarily on primary afferent terminals and interneurons in lamina I and II. They are positioned to reduce transmitter release and central sensitization as well as enhance inhibition of pain perception. Biological studies suggest that selective and brain-penetrating α_2C agonists can be a potential treatment for neuropathic pain without α -adrenergic receptor mediated adverse effect. Herein, we disclose the synthesis and SAR studies of the conformational restricted chroman series. Analogs from the chroman series display excellent in vivo efficacy in our rat spinal nerve ligation (SNL) model.

MEDI 194

Metabolism of a potent neuroprotective hydrazide

Chandramouli Chiruta, *cchiruta@salk.edu*, David Schubert, Yanrong Zhao, Fangling Tang, Tao Wang. Cellular Neurobiology Laboratory, SALK Institute for biological studies, La Joalla, CA 92037, United States

Using a drug discovery scheme for Alzheimer's disease (AD) that is based upon multiple pathologies of old age, we identified a potent compound with efficacy in rodent memory and AD animal models. Since this compound, **J147**, is a phenyl hydrazide, there was concern that it can be metabolized to one or more aromatic amines/hydrazines that are potentially carcinogenic. To explore this possibility, we examined the metabolites of **J147** in human and mouse microsomes and mouse plasma. It was found that **J147** is not metabolized to aromatic amines or hydrazines, that the scaffold is exceptionally stable, and that the oxidative metabolites are neuroprotective in a manner similar to the parent compound. It is concluded that the metabolites of **J147** are likely safe and may contribute to its biological activity in animals.

MEDI 195

Critical targets in Parkinson's disease research

Sonal S. Das, *sdas@michaeljfox.org*, Audrey Dufour, Brian Fiske, Kuldip Dave, Mark Frasier, Maurizio Facheris, Marco Baptista, Jamie Eberling, Todd Sherer. Research Programs, The Michael J. Fox Foundation for Parkinson's Research, New York, NY 10018, United States

As the world's largest private funder of Parkinson's research, The Michael J. Fox Foundation (MJFF) is dedicated to accelerating a cure for Parkinson's disease (PD) and improved therapies for those living with the condition today. Identification and validation of targets involved in PD pathogenesis is integral to ultimately developing and optimizing therapeutics. Working with academic and industry partners, MJFF has supported the validation and therapeutic development efforts of over 100 targets including those that may have symptomatic benefit and putative targets with disease modifying potential. This talk will provide an overview of the most critical targets identified to date, with an eye to the horizon and MJFF's endeavors to validate novel targets with therapeutic potential.

MEDI 196

Discovery of preladenant, an adenosine A_{2A} antagonist for Parkinson's disease treatment

Andrew W Stamford, *andrew.stamford@merck.com*. Discovery Chemistry, Merck Research Laboratories, Rahway, NJ 07065, United States

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by loss of dopamine-producing cells in the substantia nigra, which results in a syndrome of movement disorders. Adenosine A_{2A} antagonists have potential as a non-dopaminergic treatment to control the motor symptoms of PD without inducing troublesome dyskinesias. Commencing with a poorly soluble, modestly selective lead that lacked oral bioavailability, we have developed a novel class of high affinity, highly selective and orally active A_{2A} receptor antagonists culminating in the discovery of preladenant. This presentation will describe the discovery and pharmacological profile of preladenant in preclinical rodent and primate models of PD in support of its selection as a development candidate. Based on its promising preclinical and clinical profile, preladenant recently entered Phase 3 trials for the treatment of PD.

MEDI 197

Progress on allosteric modulation of mGluR5 and mGluR4: Towards new treatment paradigms in Parkinson's disease

Sylvain Célanière, sylvain.celanire@addexpharma.com. Medicinal Chemistry, Addex Pharmaceuticals S.A., Plan-les-Ouates, Geneva, Switzerland

Allosteric modulation of mGluR1-8 has been shown to offer an attractive strategy to develop oral small molecule therapeutics that can be administered orally and that readily cross the blood-brain barrier. Allosteric modulators of both mGluR5 and mGluR4 are emerging as a novel and highly desirable approaches to the treatment of Parkinson's disease. mGluR5 negative allosteric modulation (NAM) is a clinically proven mechanism for Parkinson's disease levodopa-induced dyskinesia (PD-LID). The discovery, pharmacological profiling and preclinical validation of dipraglurant will be presented. mGluR4 positive allosteric modulation (PAM) has been extensively characterized as a valuable mechanism for motor and non-motor symptoms improvement in PD. The identification and drug discovery efforts of novel mGluR4 PAM chemotypes towards proof of concept in relevant preclinical models of PD will be described. Profiling of ADX88178, the first nanomolar, selective, brain penetrant and orally active mGluR4 PAM will be discussed.

MEDI 198

NNR therapeutics for Parkinson's disease

Jon-Paul Strachan¹, jstrachan@targacept.com, Ronald J Heemstra¹, Balwinder S Bhatti¹, Srinivasa Akireddy¹, Srinivasa Murthy¹, Lan Miao¹, Anatoly A Mazurov¹, David C Kombo¹, Jason D Speake¹, Sharon R Letchworth², Kristen G Jordan², Jenny Zhang², John D Graef², Ken T Szeliga², John W James², Tom H Johnston³, Philippe Huot³, Susan H Fox⁴, Michael Hill³, Jonathan M Brotchie³. (1) Department of Discovery Chemistry, Targacept, Winston-Salem, NC 27101, United States (2) Department of Preclinical Research, Targacept, Winston-Salem, NC 27101, United States (3) Atuka,

Inc., Toronto, Ontario, Canada (4) Movement Disorder Clinic, Toronto Western Hospital, Toronto, Ontario, Canada

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by a general dysfunction of the nervous system with a loss of nigrostriatal dopaminergic neurons. The primary nAChR populations in the nigrostriatal pathway, $\alpha 4\beta 2$, $\alpha 6\beta 2^*$ and $\alpha 7$, appear to be important for nicotine-mediated reduction in levodopa-induced dyskinesias (LIDs) or abnormal involuntary movements (AIMs) in parkinsonian animal models. We synthesized a novel series of compounds targeting $\alpha 4\beta 2$ and $\alpha 6\beta 2^*$ nAChRs that bound with very high affinity, partial to full agonists, and were potent desensitizers at both High Sensitivity $\alpha 4\beta 2$ and $\alpha 6/\alpha 3\beta 2\beta 3$. Members of the lead series demonstrated desirable in vitro potency and efficacy for dopamine release assays in rat striatal synaptosomes. The lead compound from this series was assessed in both levodopa-treated unilateral 6-hydroxydopamine lesioned rats and in the MPTP-lesioned nonhuman primate model of PD. This lead compound decreased AIMs or LIDs in both animal models, and is progressing toward clinical studies.

MEDI 199

mGlu₄ PAMs for the treatment of Parkinson's disease

Craig Lindsley, *craig.lindsley@vanderbilt.edu. Vanderbilt Center for Neuroscience Drug Discovery, United States*

Metabotropic glutamate receptor 4 (mGlu₄) is a group III GPCR and has been demonstrated to play a major role in a number of therapeutic areas within the CNS. As the orthosteric site of all glutamate receptors is highly conserved, modulating mGlu₄ via allosteric modulation has emerged as a very attractive mode-of-action and has been validated preclinically in a number of animal models for Parkinson's disease (PD), anxiety, pain and neuroinflammation. A diverse array of mGlu₄ PAM chemotypes have now been reported in the primary and patent literature with robust efficacy in multiple preclinical rodent PD models as well as good PK/PD relationships. However, SAR is often challenging. Moreover, studies with mGlu₄ PAMs have demonstrated true synergy with very low dose L-DOPA as well as with A2A antagonists, broadening the therapeutic potential of selective mGlu₄ potentiation. This talk will provide an overview of the mGlu₄ PAM field, a survey of chemotypes, SAR and efficacy in multiple preclinical models of PD (both alone and in combination with other PD therapeutics).

MEDI 200

Chemical probes to enable epigenetics research and drug discovery

Aled Edwards, *aled.edwards@utoronto.ca. Structural Genomics Consortium, University of Toronto, Toronto, Canada*

The SGC, its six pharmaceutical partners and a network of academics are collaborating to generate tool compounds (chemical probes) for human proteins that regulate epigenetic signaling using a protein-family based approach. The probes are being made available without restriction (open access) to expedite characterization of potential drug targets [e.g. Nature 468:1067 (2010); Nature Chem Biol. 7:648 (2011)]. The current foci are protein methyltransferases, protein demethylases, bromodomains and methyl-lysine and methyl-arginine binding domains. I will describe 3-5 new chemical probes and their use in biological systems.

MEDI 201

Application of chemoproteomics for the discovery of a new druggable epigenetic target class and potential therapeutic utility

Jason Witherington, Jason.Witherington@gsk.com. Immuno & Inflammatory Centre of Excellence for Drug Discovery, Medicines Research Centre, Epinova DPU, Stevenage, Herts SG1 2NY, United Kingdom

Bromodomain proteins constitute a large class of context-dependent epigenetic “readers” present in many developmental and transcriptional regulators. While the biological characterisation of many bromodomain containing proteins has advanced considerably, the therapeutic tractability of this protein family is hitherto undemonstrated. This presentation will describe the discovery and molecular characterisation of potent (nM) small molecule inhibitors that disrupt the function of the BET family of bromodomains (Brd2, 3, 4). Using a combination of phenotypic screening, chemoproteomics, biophysical and structural studies we reveal for the first time that the protein-protein interactions between bromodomains and chromatin can be antagonised effectively by selective small molecules that bind at the acetylated lysine recognition pocket and result in profound pharmacology. The development of a *Bromosphere* chemoproteomics platform has enabled the breadth and depth of clinical opportunity in this novel target class to be appreciated.

MEDI 202

Integrating novel technologies to identify small-molecules that drive translational research and therapeutics in cardiovascular disease

Michelle Palmer, mpalmer@broadinstitute.org. Chemical Biology Platform, Broad Institute, Cambridge, MA, United States

Advances in human genetics have led to new drug discovery strategies that may lower the rate of attrition when translated to human trials. Molecular characterization of patient derived samples is providing new insights into the root cause of many diseases. Many of these insights point to targets that have traditionally been challenging for small-molecule therapeutics, such as transcription factors and protein-protein interactions. Identification of drugs to modulate targets where knowledge of the targets function in

disease is poorly understood requires innovation in chemistry, phenotypic cell-based assays and target identification studies. At the Broad Institute, we have integrated technology across all aspects of lead identification in an effort to realize the benefit of the genes to drugs approach in cardiovascular disease. Using the insights derived from genome-wide association studies (GWAS) in up to 100,000 individuals, we have identified multiple genetic loci associated with LDL-C, HDL-C, and/or triglycerides. The causal genes for two of these loci—*SORT1* and *TRIB1*, are also strongly associated with coronary artery disease, making them highly compelling therapeutic targets. Additional experiments in mice and supporting human genetic data indicate that pharmacological upregulation of hepatic *TRIB1* expression would result in decreased LDL-C, increased HDL-C, and decreased triglycerides, together resulting in decreased risk of MI in humans. We have identified novel scaffolds from our diversity oriented synthesis compound collection using a phenotypic cell based screening strategy that upregulate *TRIB1* expression as well as a decrease in PCSK9 expression in liver cells. The unique properties of this screening collection have facilitated rapid SAR and a fast entry into target ID. Progress on this novel drug discovery target will be presented.

MEDI 203

Chemical approach to understanding cell division

Ulrike Eggert, *ulrike.eggert@kcl.ac.uk*. Department of Chemistry and Randall Division of Cell & Molecular Biophysics, King's College London, London, United Kingdom

How cells regulate and execute cytokinesis, the final step in cell division, remain major unsolved questions in basic biology. It has been challenging to study cytokinesis by traditional methods because it is a very rapid and dynamic process that occupies only a small portion of the cell cycle. New approaches are needed to overcome these barriers to deeper understanding, one of which is to develop probes that act rapidly and with high temporal control. We are in the process of creating a toolbox of small molecules that inhibit different proteins and pathways in cytokinesis, using technologies we developed that integrate chemical and genomic methods to target specific signaling pathways. In addition to being useful tool compounds, our small molecules may also catalyze the development of therapeutics.

MEDI 204

Small molecule control of targeted protein degradation

Craig M. Crews, *craig.crews@yale.edu*. Departments of MCDB, Chemistry, Pharmacology, Yale University, New Haven, CT 06511, United States

Since less than 20% of the proteome has enzymatic activity and current drug development efforts rely heavily on the identification of enzymatic inhibitors, a significant fraction of the proteome, aka 'The Undruggable Proteome', is currently being ignored. Given the lack of active sites to inhibit, one possible solution to this problem is to induce

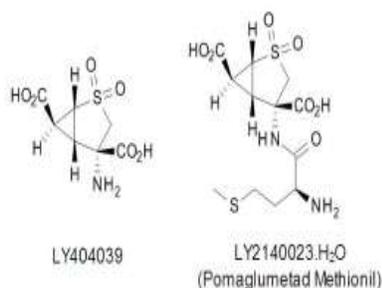
the degradation of these proteins with a small molecule. Using heterodimeric ligands to recruit target proteins to the intracellular protein degradation machinery, my lab has been able to selectively knock down intracellular levels of specific proteins, thus allowing one to target those proteins that are currently not '*pharmacologically vulnerable*'.

MEDI 205

Activation of metabotropic glutamate 2/3 receptors as a new approach for the treatment of schizophrenia

James A Monn, *monn@lilly.com*. Discovery Chemistry Research and Technologies, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

Targeting glutamate neurocircuitry as a means to identify new drugs for the treatment of schizophrenia has drawn considerable attention. We have investigated small molecule agonists that act at metabotropic glutamate receptors mGlu2 and mGlu3 to normalize aberrant glutamate neurotransmission thought to be associated with this disease. From this work, we identified LY404039, a potent, selective mGlu2/3 receptor agonist and a suitable oral prodrug, LY2140023.H₂O (Pomaglumetad methionil). Preclinical and clinical findings associated with these molecules will be presented.



MEDI 206

Crystallographic studies on glutamate receptor ligand binding domains

Mark L Mayer, *mayerm@mail.nih.gov*. Laboratory of Cellular & Molecular Neurophysiology, NIH, Bethesda, MD 20892, United States

Crystal structures for the ligand binding domains of ionotropic glutamate receptors offer a unique selection of targets for pharmaceutical research compared to other drug targets for which the atomic structure of the ligand binding site is not known. Despite high overall amino acid sequence identity, structures of AMPA and kainate receptor subtypes in particular reveal diverse structural features which underlie the selective binding of ligands. The structures also reveal diverse mechanisms for binding of naturally occurring and synthetic allosteric modulators. High resolution crystal structures for kainate receptor GluK1 antagonist complexes which reveal diverse and unexpected modes of binding, highlighting the continued need for experimentally determined receptor ligand complexes.

MEDI 207

Subunit-selective potentiation of NMDA receptors: Tools to test the glutamatergic hypothesis

Stephen F Traynelis¹, *strayne@emory.edu*, **Rose M Santangelo**², **Katie L Strong**², **Kevin K Ogden**¹, **Katie M Vance**¹, **Kasper B Hansen**¹, **Hongjie Yuan**¹, **Dennis C Liotta**². (1) Pharmacology, Emory University, Atlanta, GA 30322, United States (2) Chemistry, Emory University, Atlanta, GA 30322, United States

NMDA receptors are tetrameric assemblies of GluN1 and GluN2 subunits. There are four different GluN2 types (A-D) that are differentially expressed throughout the CNS. Several new classes of GluN2-selective modulators have recently been described. A class of tetrahydroisoquinolines acts as positive allosteric modulators of NMDA receptors that contain the GluN2C or GluN2D subunits. The most potent members of this series show submicromolar EC50 values and have minimal activities at other receptor systems. One member of this class is brain permeable and can enhance the function of synaptic NMDA receptors that contain the GluN2D subunit. These allosteric potentiators appear to interact with both the first transmembrane helix of GluN2 as well as a short adjacent region that may be a helix in the plane above the membrane. This class of compounds provides an opportunity to test the hypothesis that some of the symptoms of schizophrenia reflect NMDA receptor hypofunction.

MEDI 208

Therapeutic potential of GluN2B subtype selective NMDA receptor antagonists: Progress and prospects

John A. Kemp, *john.kemp@vtxmail.ch*. Neuroscience Therapeutic Area, Janssen Research & Development, Beerse, Beerse B-2340, Belgium

While the therapeutic potential of NMDA receptor antagonists has been recognised for several decades, the mechanism-related side-effects of non-selective antagonists has limited this potential. Nevertheless, memantine, a low-affinity, channel blocker is approved and marketed for the treatment of Alzheimer's disease.

The discovery that the “cerebrovascular agent”, ifenprodil, was a selective antagonist of GluN2B (NR2B) subunit containing receptors, coupled with its relatively benign side-effect profile, stimulated considerable interest in the development of novel GluN2B antagonists with cleaner off-target profiles.

Progress in the development of orally available GluN2B antagonists, several of which have made it through to clinical testing, will be discussed, along with preclinical findings on the role of GluN2B subunit containing NMDA receptors. Hopefully, these newer compounds will have profiles sufficient to adequately test the hypothesis in man that antagonism of GluN2B NMDA receptors has therapeutic potential in conditions such as, major depressive disorder, Alzheimer's disease and neuropathic pain.

MEDI 209

AMPA receptor modulators: Improving the concept to get to the clinic

Simon E Ward, simon.ward@sussex.ac.uk. School of Life Sciences, University of Sussex, Brighton, East Sussex BN1 9QJ, United Kingdom

The AMPA receptor subtype of ionotropic glutamate receptors is responsible for mediating the majority of fast, excitatory signalling within the central nervous system. Re-instating full glutamatergic function by positive modulation of AMPA receptors could address the hypoglutamatergic state underling the symptoms of many disease states, including schizophrenia.

A number of chemically diverse AMPA receptor positive modulators have been identified that have reached Phase II clinical trials. As yet though, none has successfully progressed further. This presentation outlines work to identify a chemically distinct series of AMPAR positive modulators which addresses the difficulties created by heterogeneous AMPA receptor populations and the development of structure activity relationships driven by homomeric, recombinant systems on high throughput platforms. In particular, a description will be given of the role played by X-ray crystallography in guiding selection and prioritisation of targets through the lead optimisation process, ultimately delivering a novel drug candidate for clinical evaluation.

MEDI 210

Bitopertin (RG1678), a potent and selective glycine re-uptake inhibitor for the treatment of schizophrenia

Emmanuel Pinard, *emmanuel.pinard@roche.com*, Daniela Alberati, Edilio Borroni, Dominik Hainzl, Jean-Luc Moreau, Joseph G Wettstein. *Pharmaceutical Research Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland*

Various lines of evidence suggest that hypofunction of glutamatergic transmission via NMDA receptors plays a role in the pathophysiology of CNS disorders such as schizophrenia. One strategy to normalize the reduced function of NMDA receptor neurotransmission is to increase the availability of the obligatory co-agonist glycine at its modulatory site on the receptor through inhibition of glycine transporter type 1 (GlyT1). We have discovered bitopertin (RG1678), a potent compound highly selective for GlyT1 that has shown a promising effect when added to a stable dose of an antipsychotic in a Phase II trial in patients with schizophrenia characterized by predominant negative symptoms. We will present the discovery and the pharmacological profile of bitopertin as well as the relationship between target receptor occupancy, exposure and efficacy.

MEDI 211

Opportunity and challenges of developing peptide drugs in the pharmaceutical industry

Waleed Danho, *waleeddanho@gmail.com*. *DANHO Associates Inc., Del Mar, CA 92014, United States*

The peptide market is growing nearly **twice** as fast as overall pharmaceuticals due to increased number of therapeutic targets, and improved delivery methodologies. Important factors and questions need to be considered before starting peptide based project. Is there an unmet medical need for the indication of interest? What is the market size? Is this target amenable for small molecule approach? What are the de-risking approaches vs. small molecules and monoclonal antibodies? What are the delivery methods? Is the starting material available in the amount needed? What is the cost of good? These considerations will be discussed in the presentation illustrated in one example (Y2R agonist program) from research carried out at Hoffmann-La Roche Inc. in the field of Diabetes. Strategies to increase peptide half-life will be addressed. Pro's and cons of different peptide deliveries like Parenteral, Nasal, Transdermal, Pulmonary, and oral will be discussed.

MEDI 212

Enhanced drug discovery: The direct in vivo use of combinatorial libraries

Richard A. Houghten, *houghten@tpims.org*. *Torrey Pines Institute for Molecular Studies, United States*

Drug discovery typically involves target based *in vitro* biochemical and/or cell-based assays to search for active compounds. The animal testing stage is the point that the vast majority of compounds fail (toxicity, lack of efficacy, poor bioavailability, et cetera).

Our working hypothesis is that direct *in vivo* screening of very large mixture-based combinatorial libraries (10s of thousands to millions of compounds) will yield more “advanced” therapeutic candidates, decreasing both the time and costs inherent in the drug discovery process.

We are now in the process of identifying highly active individual compounds that have the promise to be highly active opiate based pain killers lacking the deleterious effects of the classic opiates. If successful, the direct *in vivo* testing of our libraries will have broad implications for the identification of compounds that suppress appetite, modify blood pressure, insulin or glucose levels, tumor growth, et cetera.

MEDI 213

Multifunctional peptides targeting metabolic disease

Richard DiMarchi, rdimarchi@indiana.edu. Department of Chemistry, Indiana University, United States

Glucagon, Glucagon-like Peptide-1 (GLP-1), and Glucose-dependent Insulinotropic Polypeptide (GIP) are regulatory hormones responsible for maintaining control of metabolism, most notably glucose homeostasis. We have developed a series of novel peptides which exhibit high potency and balanced activity across these three receptors. The quest for combinatorial efficacy across the traditional large/small molecule medicinal boundary has been explored through the use of incretin-based peptide conjugates with nuclear hormones. In metabolically-challenged non-diabetic mice, a fully active GLP-1 agonist with a stably-linked estrogen consistently proved to be more efficacious in lowering body weight than the comparable individual GLP-1 and estrogen controls. In addition, highly potent GLP-estrogen conjugates were found to be devoid of uterine hypertrophy. The molecular mechanism by which these beneficial effects are achieved remains a focus of our ongoing studies.

MEDI 214

Optimization of a long-acting PEGylated GLP-1 agonist LY2428757

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The introduction of the GLP-1 incretins presents an important therapeutic option for patients with type-II diabetes (T2D). In addition to maintaining effective glycemic control, these agents offer a unique weight-lowering benefit which is particularly desirable in this patient population¹ As part of our effort to develop long-acting GLP-1 agonists which

combine these benefits with the convenience of once-weekly subcutaneous dosing we utilized an optimized GLP-1 sequence modified at its C-terminus with polyethylene glycol (PEG). To achieve a sufficient half-life we evaluated a series of PEG conjugates of the optimized backbone which differed with respect to size, number of PEGylation sites and utilizing either linear or branched PEG polymer. Pharmacodynamic studies of LY2428757 confirmed potent dose-related insulinotropic activity in stepped glucose infusion studies in the rat. Pharmacokinetic evaluation of the candidate peptide in the cynomolgus monkey indicated a half-life of 2.6 days and a bioavailability of 75 % following subcutaneous administration.

¹ Peters, A. The Am. J. Med (2010) 123, S28–S37

MEDI 215

Pharmaceutical protein and peptide engineering

Jesper Lau, jela@novonordisk.com. Diabetes Protein & Peptide Chemistry, Novo Nordisk A/S, Malov, Denmark

The development of biotechnology has given access to novel peptides and proteins (NBEs) for treatment of various diseases. However, clinical trials of native NBEs have frequently resulted in limited success due to low efficacy or low duration of action due to either enzymatic degradation or high renal clearance of the NBEs. Another general challenge is drug product stability due to low chemical or physical stability or low aqueous solubility.

Protein engineering has emerged as the technology used to optimize key properties of native NBEs to more stable and efficacious drugs with improved pharmaceutical profiles. The presentation will discuss these matters and exemplify how the interface of organic chemistry and protein chemistry can generate solutions to improve the pharmaceutical properties of peptides and proteins using glucagon like peptide 1 and insulin as case stories.

MEDI 216

Peptidic drugs with tailored duration of action

Claudio D. Schteingart, Claudio.Schteingart@ferring.com. Ferring Research Institute, United States

Therapeutic peptides can generally be designed to have very high potency and exquisite selectivity for their molecular targets. Peptides also offer a relative safety advantage over small molecules as they are confined to the extracellular space and tend to be used in small doses. However, the design of peptidic drugs with dosing intervals appropriate to the clinical indication and route of administration is challenging. Examples of tailoring this interval by manipulation of their physicochemical properties

and clearance will be discussed. Degarelix, a GnRH antagonist currently on the market for the treatment of prostate cancer is injected s.c. at monthly intervals. FE 203799, a novel GLP-2 analogue has been designed for weekly or biweekly dosing by the subcutaneous route. FE 202158, a selective V1a agonist currently in Phase II for the treatment of vasodilatory hypotension was purposely designed with short half life for rapid up and down titration by intravenous infusion.

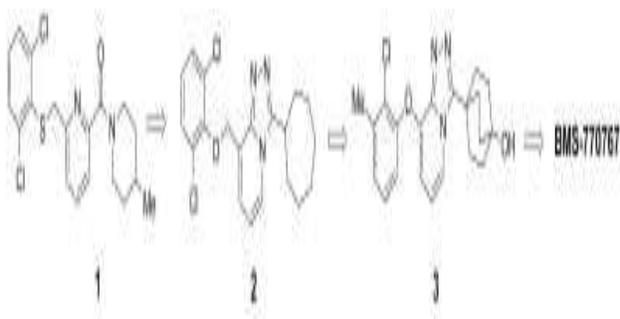
MEDI 217

Optimization of triazolopyridine based 11 β -hydroxysteroid dehydrogenase type-1 (11 β HSD-1) inhibitors leading to the discovery of the clinical candidate BMS-770767

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11 β -Hydroxysteroid dehydrogenase- type 1 (11 β HSD-1) is an enzyme that catalyzes the conversion of inert cortisone to the active glucocorticoid hormone cortisol. Thus, 11 β HSD-1-mediated *in situ* production of cortisol represents a pathway by which glucocorticoid tone may be modulated in tissues. In the liver, glucocorticoids directly upregulate the rate limiting enzymes in both the glycogenolysis and gluconeogenesis pathways thereby providing a mechanism for increased hepatic glucose output. In the adipose tissue, glucocorticoids dampen insulin signaling thereby reducing the ability of insulin to stimulate glucose uptake. Preventing excess glucocorticoid tone in these tissues may therefore be beneficial in addressing glucose homeostasis and hyperglycemia in patients with type 2 diabetes. As such, numerous groups have reported generating highly potent and selective 11 β HSD-1 inhibitors, with several compounds having been advanced to clinical trials.

We have recently reported on a series of triazolopyridine based inhibitors such as **2** and **3** that were derived from the simpler pyridyl amide lead **1** . Further optimization of this series culminated in the discovery of BMS-770767, a compound which was subsequently advanced to phase 2 clinical trials. The genesis of BMS-770767 will be presented as well as a description of its synthesis, development properties, pharmacokinetics, and pre-clinical pharmacology profile.



MEDI 218

Discovery of ABT-072, a potent inhibitor of HCV NS5B polymerase in clinical trials

John T Randolph, john.randolph@abbott.com, Allen C Krueger, Pamela L Donner, Christopher E Motter, John K Pratt, Dachun Liu, Todd W Rockway, Rolf Wagner, Lisa E Hernandez, David W A Beno, Hock B Lim, Jill M Beyer, Rubina Mondal, Neeta Mistry, Lynn Colletti, Yaya Liu, Gennadiy Koev, Warren M Kati, Kenton L Longenecker, Kent D Stewart, Akhteruzzaman Molla, Clarence J Maring. *Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, United States*

HCV NS5B is an RNA-dependent RNA polymerase that plays an essential role in HCV replication. Research at Abbott has identified aryluracil analogs that are potent inhibitors of NS5B activity, and as such represent a novel structural class of HCV antivirals. Early hit-to-lead efforts identified a series of arylamide-substituted analogs that gave >1000-fold improvement in activity in both enzyme inhibition and replicon assays relative to initially identified high-throughput screening hits. However, these potent inhibitors suffered from low oral bioavailability in rat due to poor physical properties. Medicinal chemistry efforts to find a suitable replacement for the amide linkage resulted in the identification of trans-stilbene analogs that provided further improvement in both enzyme and replicon inhibition assays (genotype 1), as well as good plasma exposures in rat following oral dosing. Lead optimization identified a compound that gave a serum-adjusted $EC_{50} \leq 2$ nM in both 1a and 1b replicon assays, good oral bioavailability in both rat (F = 44%) and dog (86%), and high liver/plasma ratios following oral dosing in rat (L/P = 71 at 12 h) and dog (L/P = 11 at 12 h). Following the successful completion of GLP toxicology studies in multiple species, this compound was designated ABT-072. The structure of this compound and the medicinal chemistry enabling its potency and favorable PK will be presented. A summary of preclinical efficacy studies and Phase I and Phase IIa clinical findings will be included.

MEDI 219

Structure-based design of potent and specific non-peptide small-molecule inhibitors of Bcl-2 and Bcl-XL as new anticancer agents

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The anti-apoptotic proteins, Bcl-2 and Bcl-xL, are key regulators of apoptosis and attractive new cancer therapeutic targets. Using a structure-based strategy, we have designed and optimized a new class of potent, specific and efficacious Bcl-2/Bcl-xL inhibitors to target the interactions of Bcl-2/Bcl-xL with their pro-apoptotic binding partners. Our best lead compounds bind to Bcl-2 and Bcl-xL proteins with subnanomolar affinities and function as potent and specific Bcl-2/Bcl-xL antagonists in cell-free functional assays. They inhibit cancer cell growth with IC₅₀ values of 1 nM and are 10-100 times more potent than ABT-737 and ABT-263. They induce robust apoptosis in tumor cells at concentrations as low as 10 nM. The best inhibitors induce rapid and complete tumor regression in animal models of human cancer at dose-schedules that show minimal toxicity to animals. High-resolution crystal structures of our inhibitors in complex with Bcl-xL provide a structural basis for their high affinity binding to their targets. Taken together, our potent and specific Bcl-2/Bcl-xL inhibitors represent exciting lead compounds for advanced preclinical development.

MEDI 220

Discovery of a novel CCR2 antagonist as development candidate via divergent SARs of CCR2 and hERG

Xuqing Zhang, *xzhang5@its.jnj.com*, Cuifen Hou, Heather Hufnagel, Thomas Markotan, James Lanter, Chaozhong Cai, Monica Singer, Evan Opas, Sandra McKenney, Carl Crysler, Dana Johnson, Zihua Sui. *CVM Research, Janssen Research & Development, LLC, Spring House, PA 19477, United States*

Monocyte chemo-attractant protein (MCP-1/CCL2) is a CC chemokine and binds to chemokine receptor 2 (CCR2), which is expressed on the majority of blood born monocytes. CCR2 antagonism has been suggested as a viable approach for the treatment of a variety of inflammatory and autoimmune diseases including rheumatoid arthritis, multiple sclerosis and atherosclerosis. We describe herein a novel series of 4-azetidiny-1-aryl-cyclohexanes as CCR2 antagonists. A divergent SAR studies on hCCR2 and hERG activities led to the discovery of a lead compound as potent CCR2 antagonist with low nM affinity for CCR2 on human monocytes and low nM in the chemotaxis assay. Moreover, it exhibited high selectivity for CCR2 over hERG and had a clean CV safety profile as evaluated in guinea pigs and dogs. It also had amendable oral bioavailability in preclinical species and demonstrated efficacy in multiple animal models. Detailed SAR, in vivo proof of concept studies as well as other preclinical properties of the lead compound will be discussed.

MEDI 221

Identification of a novel series of orexin receptor antagonists with a distinct effect on sleep architecture

Samuel Hintermann¹, samuel.hintermann@novartis.com, Claudia Betschart¹, Dirk Behnke¹, Simona Cotesta¹, Markus Fendt², Christine Gee², Laura Jacobson², Grit Laue³, Silvio Ofner¹, Vinod Chaudhari⁴, Sangamesh Badiger⁴, Chetan Pandit⁴, Juergen Wagner¹, Hoyer Daniel². (1) Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Basel, Switzerland (2) Department of Neuroscience, Novartis Institutes for BioMedical Research, Basel, Switzerland (3) Metabolism and Pharmacokinetics, Novartis Institutes for BioMedical Research, Basel, Switzerland (4) Department of Chemistry, Aurigene Discovery Technologies, Bangalore, India

Orexin A & B (hypocretin 1 & 2) are two neuropeptides produced in discretely localized neurons in the hypothalamus with widespread projections to various brain regions. These peptides activate two G-protein coupled receptors Ox1 and Ox2, generally leading to excitatory postsynaptic effects. The orexin system plays a major role in the regulation of the sleep-wake cycle, feeding and reward seeking. It was therefore suggested that orexin receptor antagonists could be useful for the treatment of related disorders, in particular insomnia. Positive proof of concept clinical studies in primary insomnia were reported with four structurally diverse dual orexin receptor antagonists (Almorexant, Suvorexant, SB-649868 and MK-6096).

Here, we present the discovery, optimization and preclinical characterization of a novel class of orexin receptor antagonists that induce sleep in rodents. Interestingly, they exhibit a remarkably distinct effect on the sleep architecture determined by EEG when compared to previously reported clinical candidates.

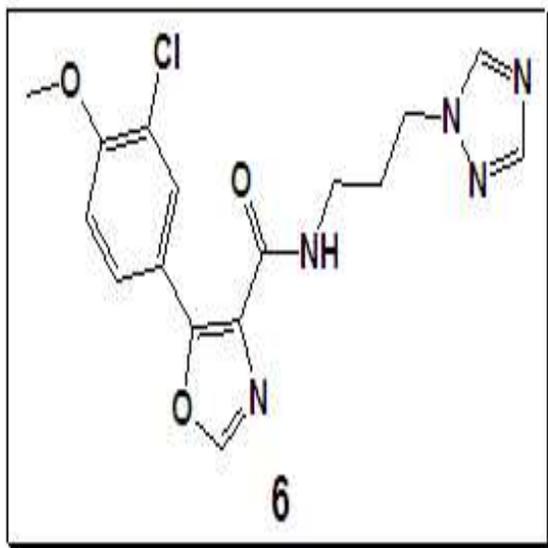
MEDI 222

Oxazole GSK-3b inhibitors for Alzheimer's disease: From HTS hit to efficacious lead

Ravi Kurumbail¹, Susan Andrie¹, Jeff Asbill¹, Jim Boyd¹, Greg Cadelina¹, George Chang¹, Jeanne Chang¹, Ye Che¹, Ed Conn¹, Jim Cook¹, Pat Cosgrove¹, Michael DePasquale¹, Rob Durham¹, Brad Enerson¹, Bruce Lefker¹, Hang Nguyen¹, Lorraine Lanyon¹, Lori Lopresti-Morrow¹, Mark Noe¹, Charlie Nolan¹, Kim Para¹, Jose Perez¹, Justin Pine¹, Mark Plummer¹, Karl Richter¹, Ron Sarver¹, Joel Schachter¹, Sridharan Sundaram¹, Veer Shanmugasundaram¹, Christine Taylor¹, Patrick Trapa¹, Hong Wang¹, Jane Withka¹, Panos Zagouras¹, Rujiang Zhou², Liqiang Qu², Yan Xu², Surkati Sreenivas Reddy³, Reddy A Seetharam³, Chhanda Rarhi³, Brijesh Tiwari³, Rumum Rohman³, Bharshar S Vijay³, Diptendu Gaswami³, **Jinshan Chen**¹, michael.j.chen@pfizer.com. (1) Pfizer Worldwide Research & Development, United States (2) WuXi AppTec, China (3) TCG Lifesciences, India

HTS identified oxazoles as inhibitors of GSK-3beta. Medicinal chemistry efforts to optimize the series resulted in analogs with exquisite kinase selectivity, good CNS

exposure and a dose dependent reduction of brain p-Tau in rat. The most advanced analog in the series, compound 6, further demonstrated a 10-fold safety window when evaluated against several proliferation biomarkers. This presentation outlines the GSK-3beta hit to lead optimization process.

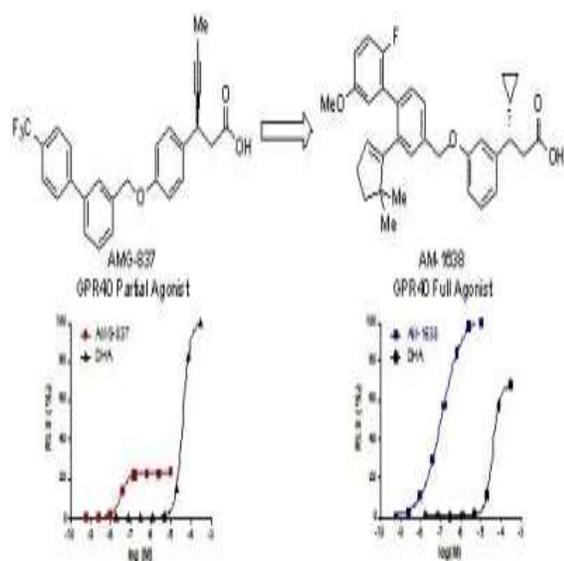


MEDI 223

Discovery of AM-1638: A potent and orally bioavailable GPR40 full agonist

Sean P Brown, *sebrown@amgen.com*, Paul J Dransfield, Jonathan B Houze, Marc Vimolratana, Vatee Pattaropong, Liusheng Zhu, Julio C Medina, Simon Wong, Gayathri Swaminath, Dan Lin, Jane Zhang, Run Zhuang, Qi Guo. Medicinal Chemistry, Amgen, South San Francisco, Ca 94080, United States

GPR40 (FFA1) is a G-protein-coupled receptor, primarily expressed in pancreatic islets. When activated, GPR40 elicits increased insulin secretion only in the presence of elevated glucose levels. A potent, orally bioavailable small molecule GPR40 agonist is hypothesized to be an effective antidiabetic posing little or no risk of hypoglycemia. We recently reported the discovery of AMG 837, a potent partial agonist of GPR40. Here, we present the structural optimization leading from the GPR40 partial agonist AMG 837 to the structurally and pharmacologically distinct GPR40 full agonist AM-1638. Moreover, we demonstrate the improved in vivo efficacy that GPR40 full agonist AM-1638 exhibits compared to partial agonist AMG 837.



MEDI 224

C—H oxidations and organic synthesis

M. Christina White, white@scs.uiuc.edu. Department of Chemistry, University of Illinois at Urbana-Champaign, United States

Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing control of chemical reactivity and synthesizing stereochemically and functionally complex molecules with higher levels of efficiency. Although it has been well demonstrated that given ample time and resources, highly complex molecules can be synthesized in the laboratory, too often current reaction manifolds do not allow chemists to match the efficiency achieved in Nature. Traditional organic methods for installing oxidized functionality rely heavily on acid-base reactions that require extensive functional group manipulations (FGMs) including wasteful protection-deprotection sequences. Due to their ubiquity in complex molecules and inertness to most organic transformations, C—H bonds have typically been ignored in the context of methods development for total synthesis. Discovery and development of highly selective oxidation methods for the direct installation of oxygen, nitrogen and carbon into allylic and aliphatic C—H bonds of complex molecules and their intermediates are discussed. Unlike Nature which uses elaborate enzyme active sites, this chemistry harnesses the subtle electronic, steric, and stereoelectronic interactions between C—H bonds and small molecule transition metal complexes to achieve high regio-, chemo-, and stereoselectivities. Our current understanding of these interactions gained through empirical and mechanistic studies will be discussed. Novel strategies for streamlining the process of complex molecule synthesis enabled by these methods will be presented. Collectively, our program aims to change the way that complex molecules

are constructed by defining the principles that govern reactivity of C—H bonds in complex molecule settings.

MEDI 225

Medicinal chemistry and beyond: Seizing opportunities along the way

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The focus of this talk will be on seizing and creating opportunities in Pharma/Biotech. With a strong foundation in Medicinal Chemistry, creativity, hard work and a little luck, doors can be opened and the potential prospects are nearly limitless. I will speak to my career path from medicinal chemistry to division president of a synthetic biology company (while going to business school along the way) and the lessons learned over the past 15 year journey.

MEDI 226

Design and synthesis of orally bioavailable TF-Factor VIIa inhibitors

Peter W. Glunz¹, *peter.glunz@bms.com*, **Xiaojun Zhang**¹, **Yan Zou**¹, **Wen Jiang**¹, **Swanee Jacutin-Porte**¹, **Alexandra H. Nirschl**¹, **Xuhong Cheng**¹, **Carolyn A Weigelt**², **Daniel L Cheney**², **Anzhi Wei**³, **Alan R Rendina**⁴, **Joseph M Luetttgen**⁴, **Robert M Knabb**⁴, **Gang Luo**⁵, **Timothy Harper**⁵, **Pancras C Wong**⁴, **Ruth R Wexler**¹, **E Scott Priestley**¹. (1) Discovery Chemistry, Bristol-Myers Squibb, Princeton, NJ 08543, United States (2) CADD, Bristol-Myers Squibb, Princeton, NJ 08543, United States (3) Protein Science and Structure, Bristol-Myers Squibb, Princeton, NJ 08543, United States (4) Discovery Biology, Bristol-Myers Squibb, Princeton, NJ 08543, United States (5) PCO MAP, Bristol-Myers Squibb, Princeton, NJ 08543, United States

Inhibitors of the tissue factor-Factor VIIa complex (TF-FVIIa) have shown strong antithrombotic efficacy in animal models with minimal bleeding liability, suggesting the TF-FVIIa complex is an important therapeutic target for the treatment of thrombotic disorders. Starting from a zwitterionic benzamidine-containing phenylglycine acyl sulfonamide lead, strategies were explored to replace the benzamidine and acyl sulfonamide moieties to improve permeability and oral bioavailability. The charged acylsulfonamide moiety was successfully replaced with both neutral heteroaryl groups and conformationally constrained-benzylamides. Combining a constrained pyrrolidine derivative with weakly basic benzamidine replacements led to highly potent, selective and orally bioavailable TF-FVIIa inhibitors.

MEDI 227

De novo purine biosynthesis: Then and now

Steven M. Firestine, *sfirestine@wayne.edu*. *Pharmaceutical Sciences, Wayne State University, Detroit, MI 48201, United States*

De novo purine biosynthesis is one of two pathways for the synthesis of purines. Although purine biosynthesis is a primary metabolic pathway, research has shown that the pathway is different for microorganisms versus humans. The difference is centered on the synthesis of the intermediate, 4-carboxy-5-aminoimidazole ribonucleotide (CAIR). In microbes, CAIR is prepared from 5-aminoimidazole (AIR) by the action of two enzymes. The first, N5-carboxyaminoimidazole ribonucleotide (N5-CAIR) synthetase, synthesizes N5-CAIR from AIR. The second enzyme, N5-CAIR mutase prepares CAIR from N5-CAIR. Humans do not possess either enzyme and instead directly convert AIR into CAIR using the enzyme AIR carboxylase. This divergence provides a biochemical rationale for targeting purine biosynthesis in the development of new antimicrobial agents. In this seminar, I will present our research on understanding the function of N5-CAIR synthetase and mutase as well as our efforts at developing selective inhibitors of these enzymes.

MEDI 228

Long and winding road: Retaining focus on science in a world of business and politics

Amy Ripka, *ripkaa@yahoo.com*. *SAR Consulting, Reading, MA 01867, United States*

The journey from graduate student to practicing medicinal chemist has become increasingly convoluted and torturous over the last 10-15 years as the industry has endured numerous layoffs, mergers and a drastic increase in outsourcing of chemistry jobs. The demand on experienced chemists to balance cost with innovation has reached a breaking point while simultaneously the opportunities and mentoring available for younger chemists is at a crossroads. This talk will detail through scientific and non-scientific stories one chemist's attempt to navigate the murky waters of scientific innovation within the confines of the business and political structures we have set up to accomplish these goals as well as comment on possible positive paths forward towards a more fruitful future.

MEDI 229

Mycobacterial sulfur metabolism

Carolyn Bertozzi, *crb@berkeley.edu*. *Departments of Chemistry & Molecular & Cell Biology, University of California, Berkeley, United States*

Mycobacterium tuberculosis (Mtb) infections are difficult to treat owing to the requirement of multiple drugs administered over many months, the emergence of drug-resistant strains, and a complex lifecycle that can include a drug-refractory latent stage. Mtb adapts to diverse environments during disease progression by influencing host cells

and altering its own metabolic state. Glycolipids of the outermost capsular layer are thought to contribute to host-pathogen interactions; their underlying biosynthetic machineries might offer new targets for Mtb therapy. Metabolic pathways essential for survival during latency are also attractive drug targets. This presentation will focus on our exploration of sulfur metabolism as a new niche for anti-tuberculosis drug discovery and on the sulfated glycolipid SL-1 as a possible modulator of Mtb virulence.

MEDI 230

Thermodynamic rules to achieve high affinity and selectivity

Ernesto Freire, ef@jhu.edu. Biology and Biophysics, Johns Hopkins University, Baltimore, MARYLAND 21218, United States

High affinity and selectivity are two essential properties of drug molecules. Since the binding affinity is determined by the sum of enthalpic and entropic contributions, extremely high affinity necessitates optimization of both contributions to binding. An efficient approach requires accurate prediction of the contributions of specific interactions and chemical functionalities to the enthalpy and entropy of binding. Selectivity has been difficult to achieve, especially for targets that belong to large families of structurally and functionally related proteins. There are essentially two ways of improving selectivity during lead optimization: 1) introducing chemical modifications that improve affinity towards the target to a higher extent than to off target molecules; and, 2) introducing chemical modifications that actually lower affinity towards off target molecules. Maximal selectivity is achieved when both conditions apply simultaneously. Accurate thermodynamic rules derived from the affinity and selectivity optimization of protease inhibitors will be discussed.

MEDI 231

Impact of lipophilic efficiency on compound quality

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Lipophilic efficiency indices such as LLE and LELP were introduced supporting balanced optimization of potency and ADME profile. Analyzing the impact of these metrics on ADME and safety properties and binding thermodynamics we found that both LLE and LELP help identifying better quality compounds. LLE is sensible for the development stages but does not prefer fragment-type hits, while LELP has advantage on this class of compounds and discriminates preferred starting points effectively. Both LLE and LELP have significant impact on ADME and safety profiles, however LELP outperforms LLE in risk assessment. Our results suggest that monitoring lipophilic efficiency metrics could contribute significantly to compound quality and might improve the output of medicinal chemistry programs.

MEDI 232

Tactical applications of lipophilic efficiency in drug design

Kevin D. Freeman-Cook, *kevin.freeman-cook@pfizer.com*. Department of Medicinal Chemistry, Pfizer, San Diego, CA 92121, United States

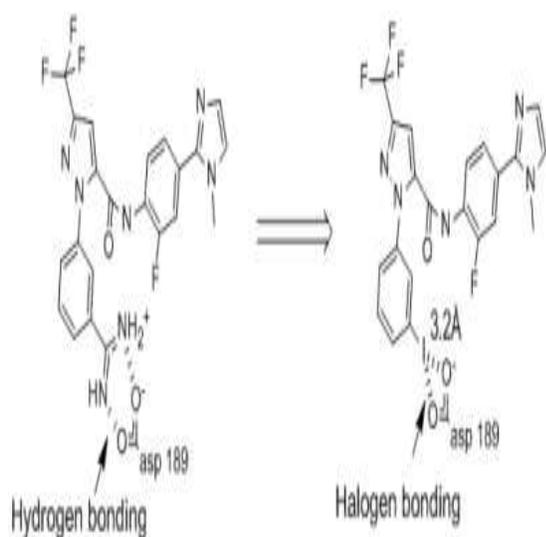
Over the past two decades, the importance of the role of physicochemical properties in compound survival has been extensively documented. While Lipinski's "rule of 5" remains a helpful mnemonic, it is widely accepted that success is more likely by operating well within those property space parameters. Of all properties that are easily understood (and computed) at design, lipophilicity is the most critical to the ultimate success or failure of a given compound. Thus, lipophilic efficiency (LipE) is arguably the single most important efficiency parameter in drug design. This talk will demonstrate how the simultaneous use of LipE and property-space analysis has played a critical role in the success of a number of Pfizer drug discovery programs.

MEDI 233

Molecular recognition in drug design

Patrick Y. S. Lam, *patrick.ys.lam@gmail.com*. Lam Drug Discovery Consulting, LLC; formerly at BMS, Chadds Ford, PA 19317, United States

Molecular recognition is the study of nonbonded interactions between molecules. This field has flourished in the past decades, generating numerous rules and restrictions which govern intermolecular interactions through supramolecular host/guest chemistry and macromolecular structural biology. Besides the three commonly-used classical interactions (hydrogen bonding, Coulombic interaction and hydrophobic interaction), there are numerous other interactions that have not been utilized in drug design. This review will highlight these novel interactions useful for innovative drug design. The author will also highlight the **first successful utilization of halogen bonding in rational drug design**. In 1996, inspired by Lommerse's observation, we successfully utilized the electro-positive tip of halogen to replace amidine to interact with the conserved electro-negative asp 189 of Factor Xa (238th ACS National Meeting. Org Div abs. 58, 2009; C&E News, Sep 21, 2009, p39-42).



MEDI 234

Assessing atropisomer axial chirality in drug discovery and development

Steven R. LaPlante, steven.laplante@boehringer-ingelheim.com. Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Laval, Quebec H7S 2G5, Canada

The presentation addresses the pharmaceutical implications of a largely overlooked alternative source of drug chirality – atropisomerism, which has the distinct feature of creating molecular chirality as a result of hindered rotation about a bond axis. Due to this time-dependent feature, drug discovery campaigns have notoriously become more complex or even abandoned. A variety of chemotypes will be presented as an aid for flagging atropisomeric compounds, along with computational and experiment tools for predicting and revealing their existence. Once identified, medicinal chemists have multiple options that range from avoiding atropisomerism to designing compounds that rotate faster or slower, with the goal of preparing for development requirements. A categorization scheme is proposed as a guide to help bridge the efforts of chemists at the early drug discovery stages with later efforts of development scientists. Overall, this presentation emphasizes the view that atropisomeric compounds can be successfully developed with caution and proper management.

MEDI 235

Neoclerodane diterpenes as atypical opioid receptor ligands

Thomas Edward Prisinzano, prisinza@ku.edu. Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045, United States

The neoclerodane diterpene salvinorin A is the major active component of the hallucinogenic mint plant *Salvia divinorum* Epling & Játiva (Lamiaceae). Since the finding that salvinorin A exerts its potent psychotropic actions through the activation of opioid receptors, the site of action of morphine and related analogues, there has been much interest in elucidating the underlying mechanisms behind its effects. These effects are particularly remarkable, because (1) salvinorin A is the first reported non-nitrogenous opioid receptor agonist, and (2) its effects are not mediated by 5-HT_{2A} receptors, the classical target of hallucinogens such as LSD and mescaline. This talk will outline our research program, illustrating a new direction to the development of tools to further elucidate the biological mechanisms of drug tolerance and dependence. The information gained from our efforts is expected to facilitate the design of novel agents to treat pain, drug abuse, and other CNS disorders.

MEDI 236

Design, synthesis, and biological significance of potent, isoform selective inhibitors of phospholipase D2

Matthew C O'Reilly¹, matthew.c.oreilly@vanderbilt.edu, Sarah A Scott², H. Alex Brown^{1,2}, Craig W Lindsley^{1,2}, Rob Lavier². (1) Department of Chemistry, Vanderbilt University, Nashville, TN 37232, United States (2) Department of Pharmacology, Vanderbilt University, Nashville, TN 37232, United States

Phospholipase D (PLD) modulates the lipid second messenger phosphatidic acid (PA) by catalyzing the hydrolysis of phosphatidyl choline to PA. The two mammalian PLD isoforms share 53% sequence homology and are controlled by different regulatory mechanisms. Their distinct cellular roles have been difficult to deconstruct due to the lack of tools to affectively modulate PLD activity. Progress to define each isoenzyme's roles would be greatly enhanced if selective small-molecule inhibitors were available. This talk will detail our efforts to synthesize potent and selective PLD2 inhibitors using iterative library synthesis coupled with pharmacological characterization and DMPK data. Considerable progress has been made in developing 50-75 fold selective PLD2 inhibitors. Novel SAR has been found to greatly bias scaffolds toward PLD1 or PLD2 inhibition. These findings led to the development of potent, dual PLD1/2 inhibitors with central penetrance. This presentation will focus on the synthesis, SAR, and biological significance of PLD2 inhibitors.

MEDI 237

Parallel discovery and co-crystallization of multiple small molecule scaffolds to inhibit P53/MDM2/MDM4 using ANCHOR.QUERY

Kareem Khoury¹, kak70@pitt.edu, Yijun Huang¹, David Koes², Sigland Wolf³, Grzegorz Popowicz³, Tad Holak^{3,5}, Carlos Camacho², Alexander Dömling^{1,4}. (1) Department of Pharmaceutical Science, University of Pittsburgh, Pittsburgh, Pennsylvania 15232, United States (2) Department of Computational Biology, University of Pittsburgh,

Pittsburgh, Pennsylvania 15232, United States (3) Max Plank Institute für Biochemie, München, Germany (4) Department of Pharmacy, University of Groningen, Groningen, Netherlands Antilles (5) Department of Chemistry, Jagiellonian University, Cracow, Poland

In the majority of cancers, the p53 pathway is non-functional because either p53 is mutated or the negative regulators of p53, MDM2 and MDM4, are over-expressed, preventing p53 from suppressing cancer cell growth. Using innovative computational approaches our lab set forth to predicted and validated novel classes of MDM2 and MDM4 inhibitors based on multicomponent reaction (MCR) chemistry.

Computational screening of a very large chemical space of billions of potential small molecules inhibitors of p53/MDM2/MDM4 derived from MCRs containing tryptophan mimics were achieved using our web-based design **ANCHOR.QUERY** (<http://anchorquery.ccbb.pitt.edu/>). Complex drug like compounds were synthesized in one-pot MCR fashion. Compounds were tested via various in vitro and in vivo assays. Lead compounds based on different scaffolds were co-crystallized with MDM2 or MDM4.

Herein we describe our ANCHOR-based approach for the discovery of two scaffolds, and give insight into the p53/MDM2/MDM4 chemotype requirements based on our multiple co-crystal structures.

MEDI 238

Structural effects of fluoroquinolone class antibiotics on lethality

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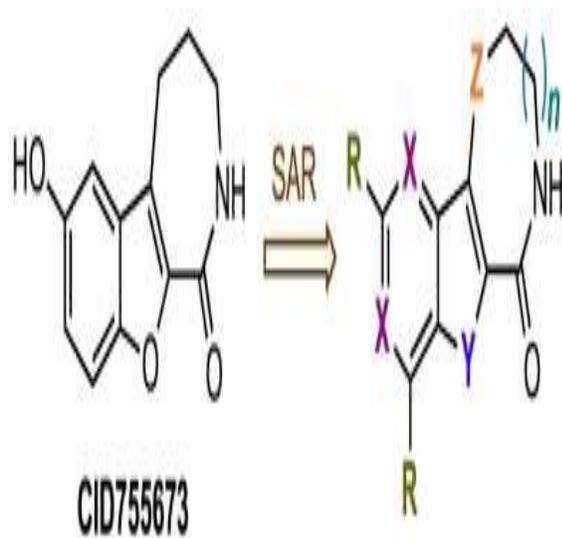
Different fluoroquinolone antibiotics display different lethality profiles. Studies presented here examine the effect that fluoroquinolone structure has on the ability of these antibiotics to kill bacteria under different conditions. Novel fluoroquinolones were synthesized and subsequently tested for their relative ability to kill bacteria in the presence or absence of ongoing protein biosynthesis. A systematic approach was taken, where a single position on the fluoroquinolone core was changed while keeping the other positions constant. A novel semi-synthetic approach was used to synthesize C-8-methoxy fluoroquinolones with structural variations at the N-1 position. The effect that these and other structural variations at other positions on the fluoroquinolone core have on lethality will be addressed. Data from *in vitro* assays and molecular modeling are beginning to provide an understanding of what structural features of quinolone-class agents are important for observed differences in lethality profiles with bacteria.

MEDI 239

Synthesis and structure-activity relationship of inhibitors of protein kinase D

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Protein kinase D (PKD) comprises a novel family of serine/threonine kinases and diacylglycerol (DAG) receptors responsible for the regulation of multiple cancer-promoting pathways. Recently, our group reported the first potent and selective PKD inhibitor, **CID755673**, which inhibits all PKD isoforms and shows specificity toward PKD over several related kinases. In order to further enhance the selectivity and potency of these compounds for an *in vivo* application, several analogs were prepared and their *in vitro* inhibitory potency was evaluated.



MEDI 240

Development of therapeutic antibody conjugates via unnatural amino acid chemistry

Stephanie A. Kazane¹, skazane@scripps.edu, **Benjamin M. Hutchins**¹, **Erik D. Wold**¹, **Jun Y. Axup**¹, **Chan Hyuk Kim**¹, **Tsoetne D. Javahishvil**², **Shailaja Srinagesh**², **Mark K. Shimazu**², **Semsi Ensar**², **Vaughn V. Smider**¹, **Peter G. Schulz**¹. (1) The Scripps Research Institute, United States (2) Ambrx, Inc, United States

Immunoconjugates and bispecific antibodies are of considerable interest in oncology because of their ability to target tumor cells with high specificity while leaving healthy

tissue unharmed. Recombinant antibodies and antibody conjugates are now a major class of therapeutics. The FDA has approved over twenty therapeutic antibodies; however, there are still significant discovery and manufacturing issues due to conjugation methods. The primary goal of my research hopes to overcome these obstacles by incorporating site-specific unnatural amino acids (UAAs) into the constant region of antibodies. These UAAs have reactivity orthogonal to the twenty canonical amino acids and can be conjugated effectively to different moieties (e.g. hydroxylamines) to create geometrically controlled bispecific antibodies and immunoconjugates. We have site-specifically labeled various antibodies (anti-Her2, anti-CD20, anti-CD3, etc.) with single-stranded DNA and PNA (peptide nucleic acids). This technique allows for control over both the valency and orientation of multivalent proteins by exploiting the sequence specific base pairing of oligonucleotides. Libraries of “binder” (e.g. antibodies) and “effector” (e.g. toxins) molecules can be easily generated, creating a combinatorial library of all possible multivalent conjugates that can then be rapidly screened for therapeutic agents.

MEDI 241

Structure-based discovery of novel ligands of GPCRs: Adenosine receptors and P2Y receptors

Kenneth A. Jacobson, *kajacobs@helix.nih.gov*. Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, United States

We explore structure activity relationships at both adenosine receptors (ARs) and P2Y receptors for nucleotides, to provide selective agents as pharmacological probes and potential therapeutic agents. *In silico* structure-based approaches are useful for both AR antagonists and agonists. The crystal structure of the A_{2A}AR bound to a highly substituted agonist detects conformational changes leading to activation. The 3D knowledge of receptor binding and activation promises to be useful in new drug discovery. Structural insights, enabled by molecular modeling, have guided to introduction of novel adenosine derivatives as A₁AR agonists and highly selective A₃AR agonists containing constrained bicyclic substitution of ribose that maintains a North (N) conformation. A₃AR agonists, which protect normal tissue and reduce viability of pathological cells, are in advanced trials for inflammatory diseases and liver cancer; A₃AR ligands are being explored for glaucoma. Novel fluorescent and radiolabeled probes and strategically designed dendrimer conjugates of GPCR ligands are based on functionalized congeners. Future directions include the study of A₃AR agonists to prevent chronic neuropathic pain and P2Y₆ receptor agonists for treatment of diabetes.

MEDI 242

Survey of drug delivery strategies in discovery space

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Over the past decade, scientific as well as business needs have pushed the pharmaceutical industry to more closely align drug discovery and drug development, in order to more rapidly advance optimal preclinical drug candidates (PDCs). Towards this end, pharmaceutical scientists now routinely provide enabled formulations for key *in vivo* studies in discovery and work together with medicinal chemists to help identify and progress promising PDCs.

This presentation gives an overview of some effective drug delivery tools Pharm R&D can bring to bear in Discovery space. We also describe some examples where various partner groups from Merck Discovery and Development worked together to increase the speed of drug lead identification, optimization and the PDC approval process.

MEDI 243

Improving drug absorption through supersaturation

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Modern drug discovery frequently leads to drug candidates that are highly potent but poorly soluble. The extent of absorption for such molecules is often limited by the solubility and/or dissolution rate of their most stable crystalline form in aqueous media at physiological pH. Their bioavailability can increase if supersaturated in the gastrointestinal fluid relative to the stable form. Supersaturation of poorly soluble drugs may be achieved by dosing the molecule as a salt, cocrystal, amorphous dispersion, solution in an organic vehicle, or metastable polymorph. Ritonavir, a protease inhibitor, precipitates as an oil when dosed from organic solutions and crystallizes slowly, leading to increased absorption and oral bioavailability. In contrast, salts of the COX-2 inhibitor, celecoxib, recrystallize in seconds, offering no increase in bioavailability unless formulated with excipients that inhibit crystallization. This presentation will focus on supersaturation strategies, with emphasis on characterization and monitoring of solid form during dissolution.

MEDI 244

Application of scalable amorphous drug delivery systems in discovery and clinical development

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Up to 70% of compounds in modern Discovery portfolios are insoluble in water. More than ever before, many of these compounds are being advanced into the clinic. As such, the pharmaceutical industry is increasingly embracing new technologies that can enable high absorption of these compounds. Amorphous solid dispersions are being utilized extensively and have demonstrated recent commercial success. Preferred processes are spray drying and twin-screw melt extrusion, which are well established.

However, the need for rigorous science-based methods for rapid and early selection of amorphous solid dispersion formulations remains, especially for application in Discovery. Such methods would ideally address 1) selection of excipient and API loading, 2) assessment of in vivo relevant performance, 3) solid-state characterization, and 4) solid dosage form considerations. This presentation will provide an overview of these critical scientific issues that must be addressed in order to develop commercially viable, robust, and stable formulations.

MEDI 245

Material sparing methods for amorphous solid dispersion screening

Joe Lubach, *lubach.joseph@gene.com. Small Molecule Pharmaceutical Sciences, Genentech, Inc., South San Francisco, CA 94080, United States*

Selection and development of an amorphous formulation is often viewed as time, cost, and material intensive. Screening and preparation of amorphous formulations often must wait until tens or hundreds of grams of material are synthesized. A number of small-scale experimental methods based on solvent evaporation have been developed for creating a wide array of solid dispersions using only milligrams of material. Such experiments can aid in polymer and excipient selection, drug:polymer ratio, and whether or not the desired oral exposures can be achieved with an amorphous formulation. Critical factors such as drug:polymer miscibility and apparent solubility gains can be evaluated to help select the optimal formulation to move into *in vivo* studies. Case studies using model drugs indomethacin, itraconazole, and a development candidate illustrate the utility of the method. Earlier screening, selection, and characterization can significantly help to reduce the risk, time, and cost of developing an amorphous formulation.

MEDI 246

Hot-melt extrusion for drug delivery

James C. DiNunzio, *james.dinunzio@roche.com. Roche Pharmaceutical and Analytical R&D, United States*

Melt extrusion is a well characterized industrial manufacturing technology that has been in use for over a century for a range of applications. First applied to commercial pharmaceutical products in the early 1980's, this technology has emerged as a first line choice for the production of amorphous solid dispersions, controlled release products, melt granulations and shaped delivery systems. Consisting of six major steps (feeding, conveying, melt compounding, devolatilization, pumping and shaping) extrusion provides unique flexibility to match process specification to desired product attributes. The continuous, solvent free nature of the process and ability to implement in-line monitoring make extrusion one of the preferred platforms for the production of high volume amorphous solid dispersions. This presentation describes the fundamental

aspects of melt extrusion for pharmaceutical applications, with a focus on the production of amorphous solid dispersions for oral bioavailability enhancement.

MEDI 247

Role of lipids to improve the bioavailability and absorption of BCS class IV drug compounds

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With the increasing number of poorly water soluble drug compounds under development, the pharmaceutical industry is being challenged to find appropriate formulation strategies and technologies for achieving pharmacologically relevant absorption and/or bioavailability of such compounds. One such strategy is the use of lipid-based drug delivery systems to overcome the barriers that inhibit drug absorption. This oral presentation will discuss the mechanisms by which lipids overcome these biological barriers and thus enhance the absorption and bioavailability of such drug compounds.

MEDI 248

Nanotechnology and pharmaceuticals: Harnessing drug nanoparticles for systemic drug delivery

Dennis Leung, dennis_leung@merck.com. Merck & Co., Inc., United States

Nanotechnology has emerged as a powerful new platform for the pharmaceutical industry and has had a significant impact on drug development from preclinical studies to commercial marketed products. For example, increasing drug exposures in preclinical species has been a formulation challenge in addressing safety issues of drug candidates and nanosuspensions provide a potential technology to achieve this while providing line of sight into development.

Drug nanoparticles have unique properties that can provide advantages for drug delivery. Due to their small size, nanoparticles can increase the bioavailability of poorly soluble drugs through increased dissolution rate. Nanoparticles with high drug loadings can be achieved. In addition, nanoparticles can be dosed through a range of administration routes, ranging from oral, intraperitoneal, intravenous, inhalation, and topical delivery. An overview of current nanotechnology approaches, optimization of formulation parameters, and case studies will be presented.

MEDI 249

Cocrystal solubility and thermodynamic stability: Pharmaceutical implications

Nair Rodriguez-Hornedo, *nrh@umich.edu*. Department of Pharmaceutical Sciences, University of Michigan, United States

The ability to engineer the aqueous solubility of inherently insoluble pharmaceutical compounds by cocrystal formation has important implications for the development of drug delivery systems. Cocrystals owe their large solubility range to the numerous structures, diverse molecular characteristics and solution phase behavior of cocrystal components. Most research in this field has focused on the application of supramolecular chemistry concepts to the design of cocrystals while cocrystal formation and structure-property relationships are not well understood. One of the fundamental consequences related to the nature of cocrystal components and their solution phase behavior is the ability to tailor the solubility of cocrystals by the careful selection of coformers and control of solution conditions.

This talk will present the underlying mechanisms for cocrystal formation and a theoretical foundation for controlling cocrystal solubility and stability by considering the contributions of ionization and micellar solubilization of cocrystal components. The findings from this work demonstrate that cocrystal stability and solubility can be tailored by the selection of coformer and solubilizing additives such as surfactants, thus providing an unprecedented level of control over cocrystal solution behavior.

MEDI 250

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

Agustin Casimiro-Garcia, *agustin.casimiro-garcia@pfizer.com*, Robert P Schaum, Declan Flynn, Christopher F Bigge, Gary Bolton, Jing Chen, Lucinda Cohen, Jo Ann Davis, Danette A Dudley, Jeremy J Edmunds, Teresa Ellis, Noe Erasga, Nadia Esmaeil, Ronald J Heemstra, Mehran Jalaie, Chitase Lee, Jeffrey F Ohren, Robert Ostroski, Hud L Risley, Meera Tugnait. Pfizer Worldwide Research and Development, Groton, CT 06340, United States

Patients at high risk of cardiovascular events often present with multiple risk factors such as hypertension, obesity, hypertriglyceridemia and insulin resistance. This clustering of cardiovascular morbidities is often referred as the metabolic syndrome. Currently, there are no therapies whereby both hypertension and insulin resistance can be simultaneously treated with the same pharmaceutical agent. Our group recently reported on a series of imidazo[4,5-*b*]pyridines with dual pharmacology as selective angiotensin II type 1 receptor (AT1) antagonists and partial agonists of PPAR γ . The combined beneficial effect of targeting these receptors was demonstrated in animal models of hypertension (SHR) and diabetes (ZDF) in which efficacious lowering of blood pressure and robust lowering of glucose and triglycerides, respectively, were observed. A number of areas for improvement were identified with the initial lead of this series, including efficacy, physicochemical and pharmacokinetic properties, and DDI

issues. In this presentation our strategy to improve this series, the synthesis and in vitro evaluation of new imidazo[4,5-*b*]pyridines, as well as, the in vivo pharmacology profile and preclinical pharmacokinetic parameters of the compounds selected as candidates for development will be provided.

MEDI 251

Discovery of pyrrolo[2,1-*f*][1,2,4]triazine C5-ketones as potent, orally active inhibitors of tropomyosin-related kinases

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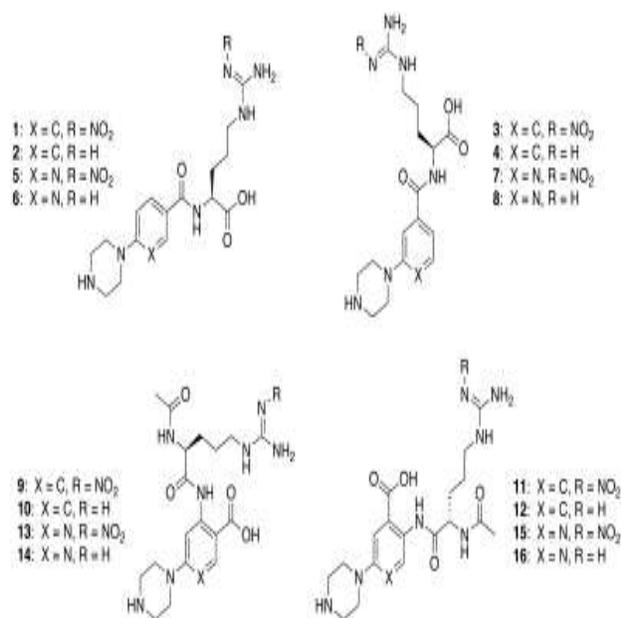
The tropomyosin-related kinases (Trks) are a family of receptor tyrosine kinases composed of three members: TrkA, TrkB and TrkC. Activation of the Trks through binding specific neurotrophins is thought to play an important role in the differentiation, survival, and proliferation of certain neuronal populations. More recently, several lines of evidence suggest that activating point mutations, over-expression, or activating chromosomal rearrangements involving the Trks may play critical roles in the development of certain malignancies, including neuroblastoma, ovarian and pancreatic cancer. As a result, small molecule inhibitors of the Trks may provide therapeutic benefits against several cancer types. Herein, we report our efforts toward the development of potent, selective, and orally efficacious Trk inhibitors based on the pyrrolo[2,1-*f*][1,2,4]triazine scaffold. The structure-activity relationships, pharmacokinetic properties, activity in a pharmacodynamic model, and *in vivo* efficacy in a model of human colon cancer will be presented.

MEDI 252

Design, synthesis, and testing of group-1 specific neuraminidase inhibitors

Christine R Cuthbertson¹, Christopher E Duymich¹, Carrie L Gaudard¹, Joseph M Hanisko¹, Joye B Kallgren¹, Alexander J Kravat¹, Catalina C Martinez¹, Andrew L Monroe¹, Bradley J Somers¹, Joe D Beckmann², **Jeffrey A Turk**¹, *turk@alma.edu*. (1) Chemistry, Alma College, Alma, Michigan 48801, United States (2) Biochemistry, Alma College, Alma, Michigan 48801, United States

Neuraminidase (NA) is best known for its role in proliferation of the influenza virus. Newly reported crystal structures of N1, N4 and N8 indicate the active sites of group-1 NAs are very different from group-2 NA enzymes. We believe the larger active site of group-1 NAs should be accessible to more specific and tighter-binding inhibitors. Accordingly, this presentation will detail the design, synthesis and testing of small inhibitory molecules of group-1 neuraminidase.



MEDI 253

Utilization of PubChem's BioAssay Database for drug discovery: Identification of Mcl-1 inhibitors with novel chemical scaffolds

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The PubChem's BioAssay Database currently contains bioactivity screens from 1644 HTS programs with descriptions of each bioassay, covering thousands of targets, and providing millions of bioactivity outcomes. However, utilizing these resources towards identifying lead compounds for further development is still challenging. Through the NIH MLSCN Program, we have optimized ultra-HTS time-resolved fluorescence resonance energy transfer based assay to discover small-molecule inhibitors which block the interaction of Mcl-1 with either of two binding partners, Noxa and Bid. This assay was used to screen 102,255 compounds and 1384 hits were identified after secondary dose dependent screening. In order to identify the most promising hits, we integrated a computational structure-based searching strategy by applying induced-fit docking. Compounds for further evaluation were selected after analyzing the obtained docking poses and identifying which compounds mimic at least two conserved interactions that BH3 peptides have with the Mcl-1 protein. 56 compounds were purchased and characterized by using several different biochemical (fluorescence polarization and surface plasmon resonance based binding assays) and biophysical methods (N¹⁵

HSQC NMR spectroscopy) for their binding to the Mcl-1 protein and their selectivity against the other four members of the Bcl-2 family. Among the most potent identified compounds, 9 new chemical scaffolds were confirmed as binders to Mcl-1 with different selectivity profiles against five members of the Bcl-2 family. These results indicate that integrating the structure-based searching strategy for analyzing the published results in the PubChem's BioAssay Database represents useful tools towards identifying the most promising leads for the purpose of drug discovery.

MEDI 254

Synthesis and evaluation of dasatinib amino acid derivatives for their anticancer and protein tyrosine kinase activity

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Dasatinib is an orally active non-selective tyrosine kinase inhibitor that is used for treatment of adult chronic myeloid leukemia and Philadelphia positive acute lymphoblastic leukemia. Herein, dasatinib-amino acid conjugates were synthesized and evaluated for comparative tyrosine kinase inhibition and anticancer activities. Dasatinib was reacted with Boc-protected *N*-terminal amino acids, followed by Boc deprotection to afford 15 dasatinib-amino acid conjugates. Compounds were screened against Abl, Csk, and Src. IC₅₀ values of selected derivatives illustrated the capacity to modulate dasatinib by at least ten-fold. Src IC₅₀ values ranged from 0.25–6.6 nM. Dasatinib-arginine derivatives showed higher selectivity towards Abl compared to Csk and Src, and exhibited slightly higher inhibition activity than dasatinib. On the other hand, introducing glutamic acid and cysteine residues reduced the inhibition activity significantly for all three kinases. All compounds inhibited the cell proliferation of SK-OV-3 and CCRF-CEM cells similar to dasatinib at a concentration of 1 μM.

MEDI 255

Hsp90 inhibitors derived from the natural product, novobiocin

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The 90 kDa heat shock protein (Hsp90) is an attractive therapeutic target for the treatment of various diseases, including cancer and neurodegeneration. Hsp90 inhibitors currently in clinical trials for the treatment of cancer, target the N-terminus of the molecular chaperone and exhibit a detrimental heat shock response. In contrast, agents that block the Hsp90 C-terminus do not induce the heat shock response, which provides an advantage for Hsp90 C-terminal inhibitors in the treatment of cancer. Extensive structure-activity relationship studies on novobiocin, the first Hsp90 C-

terminal inhibitor, have produced a new set of potent analogues. A library of novobiocin analogues that exhibit potent anti-cancer activities will be discussed.

MEDI 256

Arylbicycloheptylamines as novel uncompetitive NMDA receptor antagonists

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Uncompetitive N-Methyl-D-aspartic acid receptor (NMDAR) antagonism is an important pharmacological strategy in the therapy for various neurodegenerative diseases including Alzheimer's disease and other dementias. Using a phencyclidine pharmacophore, a series of novel conformationally restricted arylbicycloheptylamines have been designed and synthesized as novel uncompetitive NMDAR antagonists. Several of the compounds exhibited moderate to significant binding affinity (K_i) for the PCP site of the NMDAR channel as measured by *in vitro* competition studies using ^3H -MK-801 in rat forebrain. Several compounds have shown selectivity for NMDAR over other CNS sites as compared to their non-constrained analogs. Binding values at additional CNS receptor sites, measured by *in vitro* studies are presented. *In vitro* neuroprotection studies using NMDA induced toxicity in rat Hippocampal slices are presented. Finally, several compounds displayed promising *in vivo* neuroprotection in the maximal electroshock test in rat and mice.

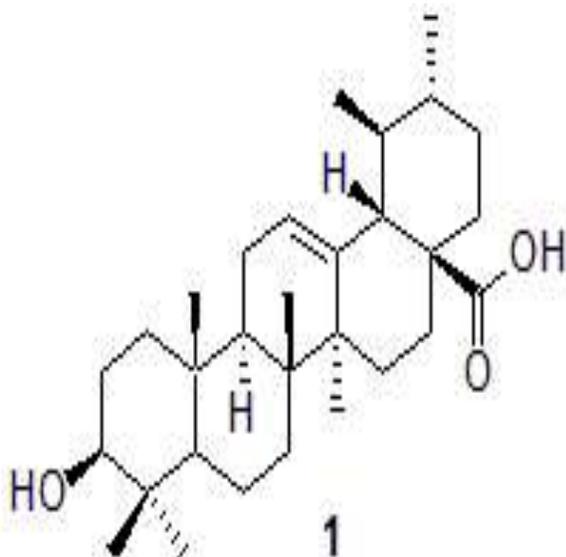
MEDI 257

New fluoro-derivatives of ursolic acid with improved antitumor activity

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Ursolic acid **1** is a pentacyclic triterpenoid present in fruits and vegetables, and has been found to have some antitumor and chemopreventive activities *in vitro* and *in vivo* models of cancer. Fluor is a highly desirable atom, and added in to key positions of active molecules can improve metabolic and chemical stability, membrane permeability and binding affinity. We introduced a fluor into the ring C of ursolic acid **1** and synthesized a series of ursane fluorolactone derivatives with esters, carbamates or a carbonyl group at position C₃, and a cyano group at position C₂. Imidazole, methylimidazole and triazole rings in conjugation with an unsaturated α,β ketone in ring A of the ursane fluorolactone backbone were also synthesized. The antiproliferative effects of these new compounds were tested in a pancreatic cancer cell line Aspc-1,

and the structure-activity relationship (SAR) was analyzed. The best compound was found to have improved antiproliferative activity 19-fold over ursolic acid **1**. Mechanistic studies revealed that this compound arrested cell cycle at the G1 phase with 1 μ M through increase of p21^{waf1}, and induced apoptosis at 8 mM with the upregulation of NOXA and the downregulation of c-FLIP. These data suggest that fluorolactone derivatives of ursolic acid **1** inhibit cancer cell growth through novel pathways.



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MEDI 258

Synthesis and biological evaluation of nonhydrolyzable nucleotide analogs based on squaric acid

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Nucleotide analogues with modifications on 5'-triphosphate fragment have been extensively used as probes for examination of functions and structures of enzymes that are overexpressed in cancer cells. However, the ionic character of phosphate functionality leads to the lack in membrane permeability; therefore phosphate containing molecules usually are not perfect biologic probes. Thus discovery of the appropriate phosphate mimics are very important for finding enzyme inhibitors. Towards this endeavor the synthesis of new nonhydrolysable nucleotide analogues in which phosphate is replaced by squaric acid moiety has been attempted. Moreover

substitution of the bridging oxygen atom in α , β or β , γ positions of triphosphoric acid with the CH_2 and CF_2 group provides increasing stability toward enzymatic hydrolysis. Additionally introduction of squaric acid into triphosphate analogue could potentially reveal new interaction with the active sites not present in the case of natural nucleotide triphosphates.

MEDI 259

Development of targeted imaging and therapeutic agents for Cholecystokinin 2 receptor expressing cancers

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The use of conventional chemotherapeutics is limited by their indiscriminate accumulation in both cancer and healthy cells. However, ligand-targeted therapies can deliver cytotoxic agents selectively to malignant cells. The Cholecystokinin 2 Receptor (Gastrin / CCK2R) is overexpressed in a variety of cancers, including medullary thyroid and hepatocellular carcinomas, gastric, colorectal, pancreatic and small cell lung cancers. We can image and treat these cancers using a small molecule CCK2R antagonist as a targeting ligand. The radio imaging conjugate binds CCK2R expressing cells with nanomolar affinity ($K_D = 30$ nM) and localizes primarily to CCK2R+ subcutaneous tumors. Similar specificity was observed with a targeted near infrared dye conjugated to this antagonist. Blockade of tumor targeting upon administration of excess unlabelled conjugate and the absence of targeting to CCK2R-negative tumors confirmed the specificity of these targeted conjugates. Treatment with a chemotherapeutic conjugate was also shown to have curative effects on subcutaneous tumors in mice.

MEDI 260

SAR development and target identification studies on a class of novel bacterial virulence inhibitors

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Bacterial resistance is an ever-present and increasing threat in the field of medicine that necessitates the development of antibiotics with novel mechanisms of action. Virulence factors have recently been recognized as an attractive target for antibiotic development. Inhibitors of virulence that do not affect bacterial growth could result in a weakened bacterial population that is more easily cleared by the host's immune system, while

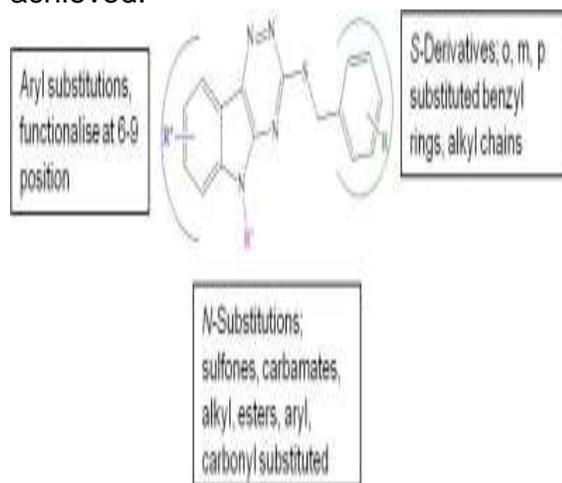
potentially avoiding the induction of evolved resistance. A high-throughput screen (HTS) for compounds able to attenuate the expression of the virulence factor streptokinase (SK) in Group A Streptococcus identified a promising lead compound that served as a starting point for SAR development. Gene expression microarray studies suggested several of the developed compounds were also competent inhibitors of biofilm formation in *Staphylococcus aureus* and *Staphylococcus epidermidis*. A concurrent effort to identify the macromolecular target(s) of these compounds using chemical probes is underway.

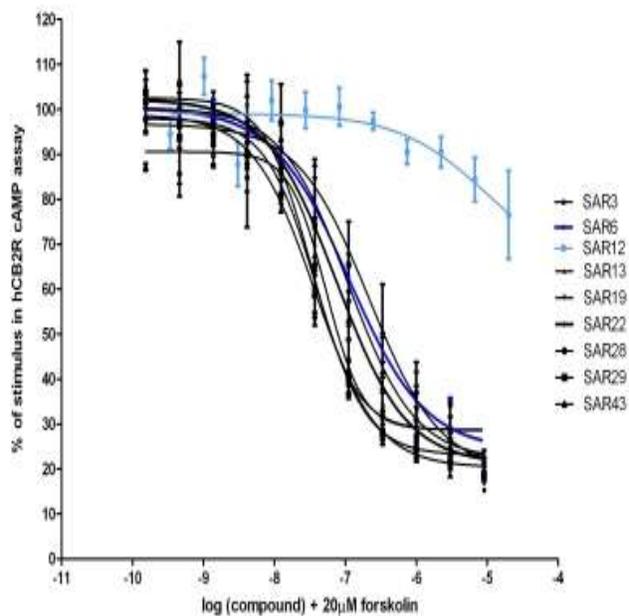
MEDI 261

Identification and optimisation of selective cannabinoid receptor 2 agonists

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The endocannabinoid system (ECS) is possibly the most important physiological system in the development, maintenance and repair of the human body. Our principal aim is to identify a novel molecule, with appropriate physical, absorption, distribution, metabolic stability and excretion (ADME) properties that acts as a selective CB2R. An *in silico* screen was carried out mining our in-house library using a known CB2R agonist (HU-308) as a template. We aim to develop structure activity relationship to gain an understanding of the active site as no crystal structure of the CB2R exists. With over 100 synthesised compounds, good SAR has been established at various positions on our lead hit, high CB2R selectivity (>1000 fold) and activity (low nanomolar) has been achieved.





An *in vivo* assay has also been developed and provided evidence that our compounds are anti-inflammatory, we now aim to optimise parameters to a proof of principle compound for preferential administration methods.

MEDI 262

Some recent tactical application of bioisosteres in drug design

Nicholas A. Meanwell, Nicholas.Meanwell@bms.com. Department of Medicinal Chemistry, Bristol-Myers Squibb, Wallingford, CT 06492, United States

Bioisosterism is a powerful concept in drug design that has found widespread application and continues to be an important tactical element in contemporary drug discovery campaigns. A bioisostere offers potential value by providing an opportunity to probe the effect of steric size and shape, dipole and electronic properties, lipophilicity and polarity, or acidity and basicity and relate these to biological effect, which may be functional mimicry or antagonism of a biological regulator. In addition to modulating potency and function, isosteres have demonstrated utility in addressing problems associated with pharmacokinetic and pharmaceutical properties, specificity, toxicity and metabolic activation pathways *in vivo* in addition to being a source of novel intellectual property. This presentation will capture examples of some of the more interesting tactical applications of bioisosteres in drug design with both a focus and organization based on solving some of the problems commonly encountered by medicinal chemists.

MEDI 263

Identifying novel bioisosteres

Tim Cheeseright, *tim@cresset-group.com*, Mark Mackey, James Melville, Martin Slater, Robert Scoffin. Cresset BMD, Welwyn Garden City, Herts AL7 3AX, United Kingdom

Bioisosterism has played a central role in the development of drug molecules almost from the outset of the pharmaceutical industry. The promise of bioisosterism is that the properties of a compound can be fine-tuned without affecting its underlying biological activity. This promise is not however without its challenges. Successfully applying bioisosterism to achieve the desired molecular outcome is difficult because of the fundamental problem that chemical structure is an unreliable indicator of biological activity. Small changes in a molecule can have profound impact on a compound's activity, specificity and toxicity, whilst completely different chemotypes may have near identical biological activity profiles. More rigorous and reproducible methods for suggesting relevant, non-obvious and yet synthetically intuitive bioisosteres would have wide applicability.

We will present a method for identifying novel bioisosteres that uses the key attributes of an active compound to find alternative scaffolds and R groups. Basing our method on the physical characteristics of a molecule – its shape and distribution of charge at the surface – enables us to identify molecules that carry little structural similarity as having high probability of behaving in the same way in a biological setting. At all times we consider bioisosteres in the context of a whole molecule, enabling us to maintain whole molecule properties that are important for binding. For example, when considering bioisosteric replacements for a scaffold, we want the electronic and steric properties of the pendant groups to be considered. This approach ensures that only the best bioisosteres are suggested for synthesis.

We will exemplify our approach with practical examples and applications with respect to recent experience as well as considering some classic case histories. We will outline the benefits but also the limitations of the approach as well as considering the challenges that remain in the identification of bioisosteres.

MEDI 264

Bioisosteres in the design of integrase strand transfer inhibitors

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HIV Integrase strand transfer inhibitors have become the focus of significant research efforts recently in a quest to find new antiretroviral agents. Mechanistically, this class of active site inhibitors block a phosphodiester transesterification step during the viral DNA nicking of host chromatin (strand transfer). This presentation will discuss the design of drug molecules that bind to a pair of Mg²⁺ cofactors and act as bioisosteres of the strand transfer transition state. The focus will be on surveying the various chemotypes

used by our group and others that take advantage of a conserved two-metal binding pharmacophore while creatively optimizing potency, resistance profiles and preclinical pharmacokinetic properties through subtle structural modifications.

MEDI 265

Shape and structural diversity of bioisosteres and scaffolds in exemplified medicinal chemistry space

Nathan Brown, *nathan.brown@icr.ac.uk*. Division of Cancer Therapeutics, The Institute of Cancer Research, United Kingdom

Methods for bioisosteric replacement, and the sub-field of scaffold hopping, are of key importance in the rational design of new chemical entities. Their appropriate application to identify the most relevant replacements whilst covering the diversity of replacements has been demonstrated to reduce the time taken to the synthesis of clinical candidates [1].

Many computational methods exist for the identification of bioisosteric and scaffold replacements. Two new methods are here presented that are design to assist in these challenges: identifying molecular scaffolds that are more relevant in medicinal chemistry analysis [2] and the calculation of the three-dimensionality of groups and scaffolds [3]. These methods are applied to develop a greater understanding of the properties of the derived substructures of functional groups and scaffolds from exemplified medicinal chemistry space. Their application has highlighted key learning that is anticipated to enhance medicinal chemistry design in the future.

Our new scaffold identification method has now been applied to scaffold hopping. We report its application in a scaffold hopping campaign that has produced novel and diverse hit matter over a control experiment. This hit matter has since been validated successfully in biochemical testing and x-ray crystallography.

References

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MEDI 266

Designing small molecules that mimic protein-protein-interface regions: Should we be searching for a big fish or Moby Dick?

Kevin Burgess, *burgess@tamu.edu*. Department of Chemistry, Texas A&M University, United States

The human genome, and those of many organisms that relate to human disease, are sequenced. This data can be related directly to proteins; for instance, the primary sequence of all the proteins in the human body is known, and knowledge of this kind is fueling a revolution in cell biology largely focused on protein-protein interactions in cell signaling processes. Synthetic chemistry can support this effort by providing compounds that mimic or disrupt protein-protein interactions.

Earlier work from our group has featured macrocyclic dipeptide mimics as mimics of b-turns at hot spots for protein-protein interactions. Those studies led to smaller, less peptidic, and more synthetically accessible compounds: these are examples of *minimalist mimics* of secondary structure. This talk proposes some key criteria for minimalist mimics, and describe how the idea of *universal mimics* I grows out of this. Pivotaly, the key criteria for designing small molecules that mimic hot spots, or combinations of hot spots at protein-protein interactions are described.

MEDI 267

You've found a fragment, now what?

Daniel Erlanson, *derlanson@carmot.us*. Carmot Therapeutics, Inc., San Francisco, CA 94158, United States

Fragment-based lead discovery (FBLD) is a powerful method to identify drug leads. Rather than requiring large libraries of drug-sized molecules, fragment-based approaches rely on smaller libraries of small molecular fragments. Historically, the primary practical challenges were finding fragments and advancing low-affinity fragments to more potent molecules. The first challenge has recently become much more tractable with the development and increasing automation of powerful biophysical screening methods. Advancing fragments to leads, however, remains a significant hurdle. "Growing" fragments by appending moieties to an initial hit is usually the default choice. Linking two fragments can boost potency, but this strategy is often undermined by imperfections in the linker. Both approaches are particularly difficult without structural information. This presentation will review the state of the art in FBLD and briefly introduce Chemotype Evolution, a fragment-driven lead-finding technology in which one fragment serves as an anchor from which to "fish" for a second fragment.

MEDI 268

Fragment fat wobbles too: Implications of promiscuous Pim-1 kinase fragment inhibitor hydrophobic interactions for FBDD

Andrew C Good, *andrewcgood1@gmail.com*, Jinyu Liu, Bradford Hirth. Genzyme, Waltham, MA 02451, United States

We have studied the subtleties of fragment docking and binding using data generated in a Pim-1 kinase inhibitor program. Crystallographic and docking data analyses have

been undertaken using inhibitor complexes derived from an SPR fragment screen, a virtual needle screen, an inhibitor optimization program and a de novo designed fragment inhibitor hybrid. The data highlight that fragments which do not fill their binding pocket can exhibit promiscuous hydrophobic interactions due to the lack of steric constraints imposed on them by the boundaries of said pocket. As a result docking modes that disagree with an observed crystal structure but maintain key crystallographically observed hydrogen bonds still have potential value in ligand design and optimization. This observation runs counter to the lore in FBDD that all fragment elaboration must be based on the parent crystal structure alone.

MEDI 269

Computational tools for facilitating the fragment to lead process

Ian D Wall, ian.d.wall@gsk.com, Stephen D Pickett, Martin R Saunders, Ceara Rea. Computational and Structural Chemistry, GlaxoSmithKline, Stevenage, Hertfordshire SG1 2NY, United Kingdom

The fragment to lead process is one of the most challenging steps in FBDD. Examples from real FBDD projects will illustrate what computational approaches can contribute, covering areas such as, data management and analysis, binding site characterisation, the design of extensions to fragment hits and the impact that ligand-based methods can have in FBDD. The deficiencies of current approaches, and prototype methods we have in development to address them will also be discussed.

MEDI 270

Fragment-based approaches to difficult and less difficult targets

Chris Abell, ca26@cam.ac.uk. Department of Chemistry, University of Cambridge, Cambridge, Cambridgeshire CB2 1EW, United Kingdom

The talk will focus on fragment-based approaches to targets involved in tuberculosis and cancer. The tuberculosis targets will include early stage and more developed projects against enzymes on the coenzyme A pathway, and also studies on cytochrome P450s. Examples of targets that have proved less tractable will be discussed. The cancer targets all involve protein-protein interactions. The special challenges these targets pose will be highlighted.

MEDI 271

Design of HCV NS5B Palm I allosteric site binders using a structure-based lead generation approach

Francisco X. Talamas, francisco.talamas@roche.com. Discovery Chemistry, Hoffmann-La Roche, Inc., Nutley, NJ 07110, United States

The HCV polymerase enzyme (NS5B) plays an important role in the viral cycle and it has been targeted for the development of compounds with antiviral activity. In our efforts to find hits as starting points for our drug discovery program, we utilized a HTS approach and fragment screening. In this talk, it will be described the approach we took to generate leads. This approach consisted of the design of new leads based on a model built with the primary interactions of a fragment and other known binders in the allosteric site Palm I.

MEDI 272

Discovery of potent neutral factor VIIa inhibitors

Nicholas R Wurtz, nicholas.wurtz@bms.com, Brandon L Parkhurst, Wen Jiang, Indawati DeLucca, Xiaojun Zhang, Daniel Cheney, Alan Rendina, William Metzler, Anzhi Wei, Joseph Luetzgen, Pancras Wong, Dietmar Seiffert, Ruth R Wexler, E. Scott Priestley. Department of Research and Development, Bristol-Myers Squibb, Princeton, NJ 08543, United States

Inhibitors of the clotting cascade serine protease Factor VIIa (FVIIa) have shown strong antithrombotic efficacy in preclinical thrombosis models with minimal bleeding liabilities. However, discovery of orally active FVIIa inhibitors has been largely unsuccessful because high affinity binding has required a basic group to bind Asp189 in the S1 pocket, limiting permeability. In an attempt to discover permeable, neutral P1 groups, we undertook a multidisciplinary fragment screening effort, involving virtual screening, high concentration enzyme assays, NMR binding studies and crystallography. A dihydroisoquinolinone P1 fragment discovered in this effort was spliced into a phenylglycine FVIIa inhibitor chemotype to produce a neutral, selective, and permeable FVIIa inhibitor. Subsequent optimization of the P1 region guided by fragment screening results led to a novel series of FVIIa inhibitors with low nanomolar potency.

MEDI 273

Vemurafenib: Discovery to market

Prabha N. Ibrahim, pibrahim@plexxikon.com. Non-Clinical Development, Plexxikon Inc, Berkeley, California 94710, United States

The BRAF oncogene is found in over 50% patients with metastatic melanoma and is prevalent in other cancer types as well. Pharmaceutical industry efforts to develop small molecule inhibitors of BRAF kinase began in earnest only after mutations in BRAF were discovered in 2002. Plexxikon discovered vemurafenib (PLX4032) as part of a series of orally available, mutant-selective, BRAF inhibitors using our 'Scaffold-based Drug Discovery' platform, which employs early co-crystallography to enhance the screening and chemistry optimization paradigm. Vemurafenib was approved in the U.S. following a rapid clinical development path for the treatment of BRAF mutated metastatic melanoma.

MEDI 274

Redox-directed drug mining: Small molecule stress modulators for anticancer intervention

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Pharmacological induction of oxidative and proteotoxic stress has recently emerged as a promising strategy for chemotherapeutic intervention targeting cancer cells. Small molecule prooxidant intervention may cause cytotoxic deviations from redox homeostasis that induce apoptosis in malignant cells, already exposed to high constitutive levels of reactive oxygen species, without compromising viability of non-transformed cells. Similarly, pharmacological induction of cytotoxic overload with dysfunctional proteins may trigger preferential apoptosis in cancer cells without compromising viability of normal cells that display lower constitutive levels of endogenous proteotoxic stress. Guided by a differential phenotypic screen for the identification of compounds that selectively induce melanoma cell oxidative stress and apoptosis without compromising viability of primary human melanocytes, we have interrogated a focused library of FDA-approved non-oncological drugs containing redox-active pharmacophores. Our data demonstrate feasibility of a focused 'drug-mining' approach that identifies redox-directed drugs amenable to oncological repurposing for therapeutic induction of cytotoxic oxidative and proteotoxic stress.

MEDI 275

Structure-activity and bioavailability studies drive development of cationic Mn porphyrins as cancer and central nervous system therapeutics

Ines Batinic-Haberle¹, *ibatinic@duke.edu*, **Ivan Spasojevic**². (1) Department of Radiation Oncology, Duke University Medical School, Durham, NC 27710, United States (2) Department of Medicine, Duke University Medical School, Durham, NC 27710, United States

Electron-deficient *ortho* Mn(III) *N*-substituted pyridylporphyrins (MnPs) are promising therapeutics for diseases where cellular redox status (ratio of endogenous reactive species and antioxidants) is perturbed. These compounds were developed based on: (1) redox property of Mn site; (2) ability to eliminate superoxide as efficiently as superoxide dismutase (SOD) enzymes; and (3) efficacy in protecting SOD-deficient *E. coli* and *S. cerevisiae*. Their SOD-like potency parallels their efficacy in reducing peroxynitrite and several other reactive species, as well as reactivity towards signaling protein cysteines. Such actions, dominated by electron-deficiency of Mn site, translate into redox modulation of cellular transcriptional activity, and in turn leads to suppression of inflammatory and immune disorders. The core *N*-pyridylporphyrin structure was further modified to increase MnP mitochondrial accumulation and transport across

blood-brain barrier. Remarkable efficacy of MnPs in cancer, radiation injury, diabetes and central nervous system disorders, along with most recent optimization efforts, drives MnPs aggressive clinical development.

MEDI 276

Targeting the Keap1/Nrf2/ARE pathway and the heat shock response for chemoprotection

Albena T Dinkova-Kostova¹, *a.dinkovakostova@dundee.ac.uk*, **Tadashi Honda**². (1) *Medical Research Institute, University of Dundee, Dundee, United Kingdom* (2) *Department of Chemistry, Institute of Chemical Biology and Drug Discovery,, State University of New York at Stony Broo, Stony Brook, NY 11794,, United States*

The cytoprotective Keap1/Nrf2/ARE pathway and the heat shock response are targets for cancer prevention and treatment of chronic inflammation, cardiovascular and neurodegenerative diseases. Anti-inflammatory acetylenic tricyclic bis(cyano enones) bearing two highly electrophilic Michael acceptor moieties are potent inducers of these pathways and powerful protectors against the toxicity of electrophiles and oxidants in cells and in vivo. Furthermore, these inducers have excellent systemic bioavailability in animals when applied either topically or incorporated in the diet. Monocyclic cyano enones, representing fragments of rings A and C of the tricyclic compounds, reveal that exceptionally high (low nanomolar) inducer potency is the result of the simultaneous presence of two cyano enone functions within a rigid three–ring system, which is further enhanced by spatial proximity of an acetylenic function. Detailed understanding of the structural elements that determine high potency is essential for the development of specific and selective lead compounds as clinically-relevant chemoprotective agents.

MEDI 277

Inhibitors of heat shock proteins

Gabriela Chiosis, *chiosisg@mskcc.org*. *Molecular Pharmacology and Chemistry/Medicine, Memorial Sloan-Kettering Cancer Center, New York, United States*

In many diseases, among which cancer and neurodegeneration, the development of a pathologic phenotype is associated with dysregulation of multiple pathways and molecules. To adapt, cells co-opt heat shock proteins (HSPs) to help maintain a functional cellular state under the transforming pressure. Among the major HSPs are Hsp90 and Hsp70, proteins that act in an interconnected but also distinct fashion to regulate the disease phenotype. Consequently, approaches that target these HSPs are especially promising in treating several diseases. This talk will present some of our efforts in the design, development and clinical translation of HSP inhibitors.

MEDI 278

Discovery of small molecule inhibitors of E1 activating enzymes

Paul Fleming, *paul.fleming@mpi.com*. Medicinal Chemistry, Millennium Pharmaceuticals, Cambridge, MA 02139, United States

The clinical success of bortezomib has demonstrated that targeting the Ubiquitin Proteasome System (UPS) can be a viable strategy to treat cancer. A second class of targets within the UPS are the E1 activating enzymes including UBA3 (NEDD8 Activating Enzyme) and UBA1 (Ubiquitin Activating Enzyme.) Millennium has pioneered the discovery of mechanism based small molecule E1 inhibitors that form covalent adducts with the Ubl substrates of E1s. MLN4924, a UBA3 inhibitor, is the first example of this class of inhibitors to enter clinical trials. We have extended our efforts to UBA1, which regulates activation of ubiquitin. We have identified potent inhibitors of UBA1 that, in cultured cells and mouse xenograft models, result in a significant reduction of ubiquitin conjugates and in the accumulation of UPS substrates. The inhibitors display strong antitumor activity in several xenograft models, suggesting that inhibition of UBA1 is a promising strategy to treat cancer.

MEDI 279

Enzymatic preparation of non-natural amino acids

James Gage, *jgage@asymchem.com*. Asymchem Inc., Morrisville, North Carolina 27560, United States

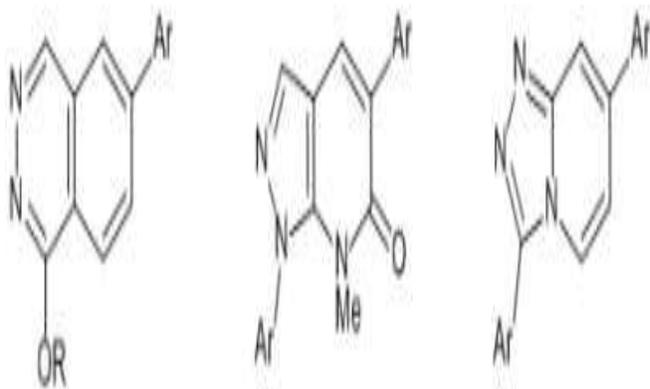
Non-natural amino acids are increasingly prevalent as building blocks in drug candidates and recently approved drugs. This talk will focus on development of efficient enzymatic manufacturing processes for the large scale preparation of different classes of both L- and D- non-natural amino acids. Special attention will be given to the scope of substrates accepted by useful amino acid dehydrogenases and amino transferases and scale up considerations for implementation in production.

MEDI 280

Practical synthesis of heterocyclic p38 MAP kinase inhibitors

Oliver R Thiel, *othiel@amgen.com*. Chemical Process Research & Development, Amgen, Thousand Oaks, CA 91320, United States

Development of practical synthetic approaches for biologically active compounds can trigger the discovery of new synthetic methodology. In this presentation we summarize the chemistry discovered and developed to support advancement of p38 MAP kinase inhibitors into toxicology and clinical studies. Three different heterocyclic cores will be discussed. Green Chemistry principles were applied to arrive at safe and practical reaction conditions to enable large scale supplies of these clinical candidates.



MEDI 281

Process development: Case studies in API synthesis

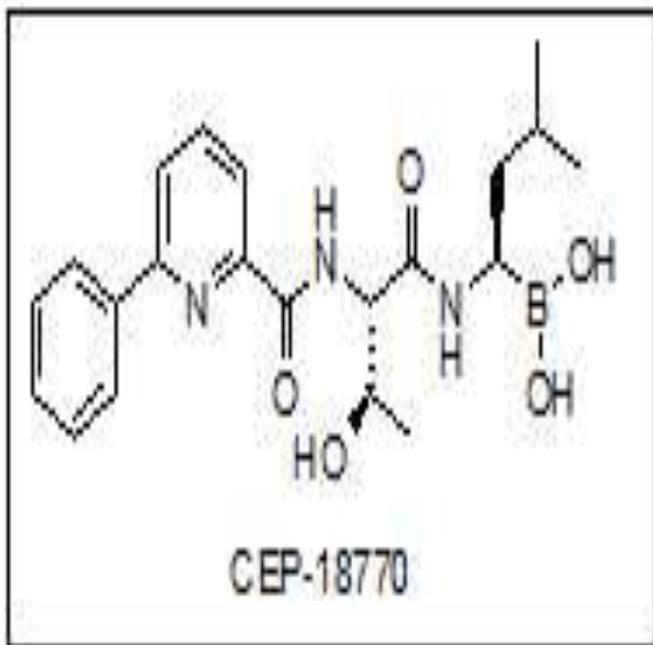
Huan Wang, *Huan.2.wang@gsk.com*. API Chemistry and Analysis, GlaxoSmithKline, King of Prussia, PA 19406, United States

Case studies are given in API synthesis at GSK, highlighted by efficient, selective and cost effective approaches to drug candidates.

MEDI 282

Route selection and optimization of the process for the highly potent proteasome inhibitor CEP-18770

Michael A Christie, *michael.christie@tevapharm.com*, **Renee C Roemmele**. Chemical Process Research and Development, Teva Branded Pharmaceutical R&D Inc., Malvern, PA 19355, United States



CEP-18770 is a boronopeptide proteasome inhibitor currently in clinical trials. The evolution of the synthetic process from preclinical testing through Phase 3 supplies will be discussed. An efficient four step process is described, the key to which is use of a crystalline diethanolamine adduct for purification of the product. In addition, details of how the handling of this highly potent compound evolved from a make-shift laboratory through a purpose-built highly potent compound handling facility will be detailed.

MEDI 283

Development of novel catalytic technologies for the preparation of HCV polymerase inhibitors

David M. Barnes, david.barnes@abbott.com. Process Research and Development, Abbott Laboratories, North Chicago, IL 60064, United States

Synthesis of a novel drug candidate often requires the development of new chemistry and reaction conditions. This can be driven by the need for higher efficiency, or increasingly by the need to avoid certain reagents or byproducts, such as genotoxic impurities (GTIs).

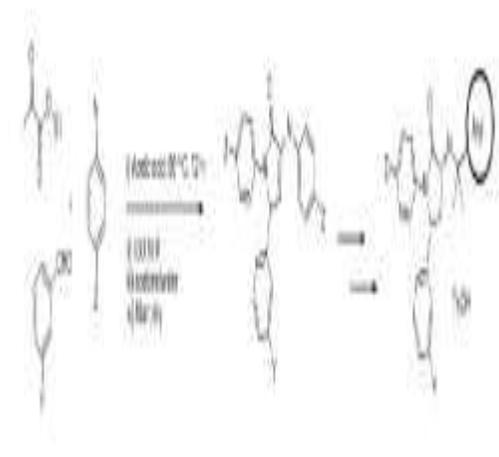
This presentation details the discovery of catalytic technologies to enable the efficient preparation of an HCV polymerase inhibitor and the development of a new route to mitigate GTI concerns. Included are catalysts to effect C-N, as well as C-C, bond formation.

MEDI 284

Development of enabling chemistry into the 2-pyrrolidinone scaffold common to the Lilly CB1 inverse-agonists

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This talk will discuss the development efforts conducted to enable the delivery of Lilly's 2-Pyrrolidinone CB1 Inverse agonists from the discovery phase into the early development phase. During the span of this work, multiple routes were explored, but ultimately, a three-component coupling reaction was developed for scale-up. This talk will highlight the evolution of the synthesis that was ultimately utilized to deliver API-1.



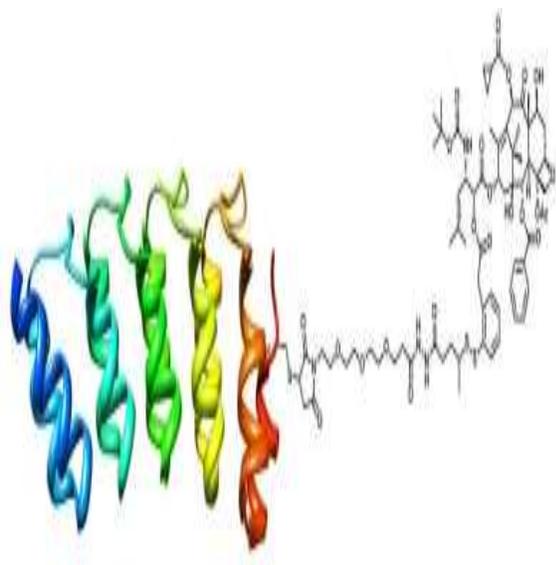
MEDI 285

Synthesis and biological evaluation of novel DARPin-PEG₃-SB-T-1214 bioconjugates targeting CD-326 (EpCAM)

William T. Berger¹, chembill631@yahoo.com, Manuel Simon³, Bela Ruzsicska², Eduard H. Melief², Andreas Pluckthun³, Iwao Ojima^{1,2}. (1) Department of Chemistry, State University of New York, United States (2) Institute of Chemical Biology, State

University of New York, United States (3) Department of Biochemistry, University of Zurich, Switzerland

One of the most common issues associated with the development of effective chemotherapeutics, is their inherent lack of specificity. Traditional chemotherapy relies solely on the assumption that cytotoxic agents will be more readily taken in by rapidly dividing cancer cells. In actuality, many other types of rapidly dividing healthy tissues (e.g., bone marrow, hair follicles) can also be affected, leading to off-target systemic toxicity. Thus we have synthesized and evaluated several tumor-targeting drug conjugates bearing self-immolative disulfide linkers as well as vitamins and mAb's as tumor-targeting modules with substantial success. Building upon these successes, two novel SB-T-1214 bioconjugates were covalently linked, via a cleavable linkage (self-immolative disulfide and ester PEG based linkers), to a Designed Ankyrin Repeat Protein (DARPin, Ec1), and evaluated *in-vitro* for both cytotoxicity and specificity. The synthesis of these novel tumor-targeting drug conjugates and the results of their biological evaluations are discussed.



MEDI 286

Macrocyclic inhibitors of ALK

Padmaja K Polam¹, ppolam@incyte.com, Richard B Sparks¹, Boshan Liao², Maryanne Covington², Karen Gallagher², Peggy A Scherle², Andrew P Combs¹. (1) Discovery Chemistry, Incyte Corporation, Wilmington, Delaware 19880, United States (2) Discovery Biology, Incyte Corporation, Wilmington, Delaware 19880, United States

A novel class of macrocyclic diaminopyrimidines was discovered as potent inhibitors of a variety of kinases, including Anaplastic Lymphoma Kinase (ALK). Structure-based design was used to design linkers between the two aryl substituents to constrain the conformation of the diaminopyrimidine core to that known to bind in the kinase ATP binding site. Further structure-activity relationships were established that afforded selective ALK inhibitors. The details of the design, synthesis and SAR of these macrocyclic inhibitors will be described.

MEDI 287

8-Quinolyl-N-arylcarbamates as re-activators of mutant p53 and potential antitumor agents

*Arlene Melendez, Joseph Lee, Gregory Nalesnik, Randa Barsoom, David King, Emily Tine, Megan MvAleavy, Bimalendu DasMahapatra, **Ronald J Doll**, rdoll@drew.edu, Tharani Theivakumar, Charles A. Dana Research Institute (RISE), Drew University, Madison, New Jersey 07940, United States*

p53 is activated when a cell is stressed by such things as oncogenic activation, metabolic changes, etc. This results in DNA repair, cell growth arrest, apoptosis and angiogenesis inhibition. The p53 signaling pathway is dysfunctional in essentially all human cancers, and about 50% have mutated p53. Anti-tumor therapies targeting p53 has been an active field of research, including approaches to re-activate mutant p53 by small molecules. A recent publication describing compounds in the 8-quinolyl-N-arylcarbamate class as inhibitors of angiogenesis, by inhibiting the MetAB2 protease and possibly activating wild type p53. We show that some compounds in this class also re-activate mutant p53 in human tumor cells, as determined by the production of p21, and may contribute to the anti-tumor effects of this class of compounds. This has led us to identify new compounds in this class that re-activate mutant p53.

MEDI 288

Development of amidine-based sphingosine kinase 1 inhibitors

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Sphingosine 1-phosphate (S1P) is a bioactive lipid that has been identified as an accelerant of cancer progression. The sphingosine kinases (SphKs) are the sole producers of S1P and thus SphK inhibitors may prove effective in cancer mitigation and chemosensitization. Herein we present the design and synthesis of amidine-based nanomolar SphK1 subtype-selective inhibitors. A homology model of SphK1, trained with this library of amidine inhibitors, was then used to predict the activity of additional, more potent, inhibitors. Lastly, select amidine inhibitors were validated in human

leukemia cells, where they significantly reduced endogenous S1P levels at nanomolar concentrations.

MEDI 289

Improving the pharmacokinetics of amidine-based sphingosine kinase inhibitors

Joseph D Houck¹, *jdh4y@virginia.edu*, **Andrew J Kennedy**¹, **Yugesh Khare**², **Kevin R Lynch**², **Timothy L Macdonald**^{1,2}. (1) Department of Chemistry, University of Virginia, Charlottesville, VA 22904, United States (2) Department of Pharmacology, University of Virginia, Charlottesville, VA 22904, United States

Over the past decade, the sphingosine kinases (SphKs) have been identified as potential therapeutic targets of interest in proliferative diseases, as they are known to play a role in cell cycle regulation. The two isoforms, SphK1 and SphK2, control the production of the potent growth signaling molecule sphingosine 1-phosphate (S1P), shown to be elevated in a variety of cancers. A series of potent, amidine-based SphK inhibitors have been prepared and have been shown to reduce cellular S1P concentrations across a variety of cell lines and in whole animals. However, one drawback of these inhibitors is their short half-life *in vivo*. One strategy to circumvent this problem is to use isosteres to increase the longevity of this class of inhibitors. The design, synthesis, and evaluation of SphK inhibitors containing amide isosteres are described.

MEDI 290

Polyisoprenylated cysteinyl amide inhibitors of polyisoprenylated methylated protein methyl esterase

Byron J Aguilar, *byron_j_aguilar@yahoo.com*, **Randolph Duverna**, **Nazarius S Lamango**. College of Pharmacy & Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, United States

Subclasses of patients who do not express current cancer drug targets and are resistant to modern therapies are being uncovered. Identification of cancer biomarkers and novel targets is important for developing more effective therapies. Polyisoprenylated cysteinyl amide inhibitors (PCAls) are being designed to target polyisoprenylated methylated protein methyl esterase (PMPMEase), a key enzyme of the polyisoprenylation pathway. Effective inhibition of this enzyme results in cancer cell death possibly through interference with polyisoprenylated protein metabolism and function. Such inhibitors may serve as lead compounds for the development of drugs to address an area of unmet need. This includes cancer patients with mutated hyperactive Ras whose tumors are resistant to MAb and kinase inhibitors targeting EGFR. Rational drug design, *in silico* analysis, and enzymatic assay have identified high affinity, specific PMPMEase inhibitors with micromolar K_i values. Herein, we present the design and synthesis of novel PCAls and their chemical and pharmacological properties.

MEDI 291

Design, synthesis, and evaluation of polyisoprenylated phosphoramidate inhibitors

Randolph Duverna, *randolph1.duverna@famu.edu*, Byron J Augilar, Nazarius Lamango. College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida 32307, United States

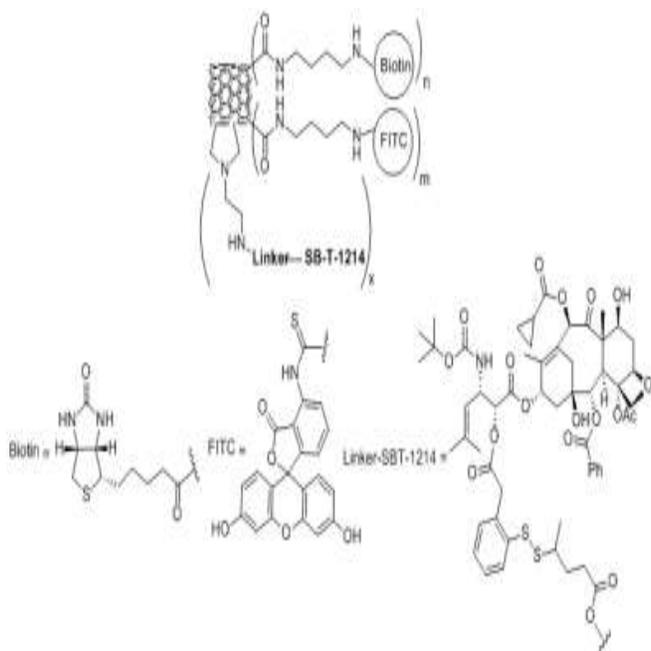
Ras mutations and hyperactivity has been the subject of many anticancer drug development efforts aimed at curbing the excessive growth-stimulatory activity. While most of the polyisoprenylation pathway enzymes have been the targets of these efforts, polyisoprenylated methylated protein methyl esterase (PMPMEase) has only recently been identified as a novel target for the synthesis of putative anticancer agents. Here, the rational design and synthesis of polyisoprenylated phosphoramidate inhibitors (PPAIs) are reported. The PPAIs incorporate a phosphoramidate moiety onto scaffold of a highly selective high affinity substrate to afford high affinity selective inhibitors of PMPMEase with submicromolar K_i values.

MEDI 292

Functionalized-SWNT as a versatile platform for tumor-targeted drug delivery and dual therapy

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A novel functionalized single-walled carbon nanotube-based (*f*-SWNT) drug delivery vehicle (DDV) platform has been developed. The salient features of this nano-DDV are: a) biocompatible *f*-SWNT for targeted and specific delivery with a TTM such as biotin and a fluorescent probe, covalently linked to SWCNTs *via* appropriate spacers b) potent, cytotoxic drug covalently bound to the *f*-SWNT *via* a mechanism-based cleavable 'smart linker' that is activated upon internalization, and c) dual therapy using the synergistic effect of a potent anticancer agent and thermal ablation. These DDVs have been synthesized and characterized using various analytical techniques. The specificity of this conjugate and the synergistic effect of thermal ablation and cytotoxicity has been assessed using biotin receptor positive cancer cell line.

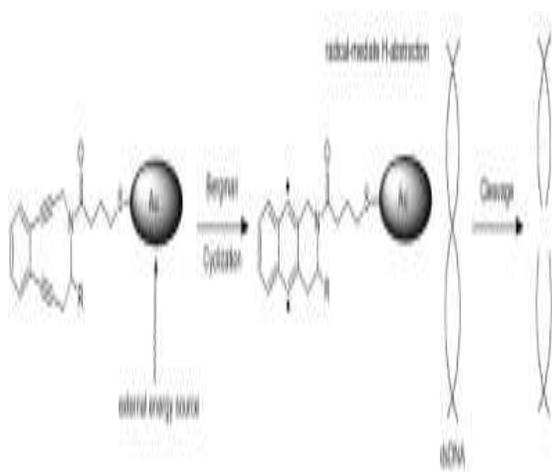


MEDI 293

New synthetic routes to thiolated derivatives of enediyne conjugates for subsequent nanoparticle conjugation

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Tunable and synthetically accessible thiolated enediyne conjugates capable of undergoing a thermally induced Bergman cyclization have been explored. Enediyne-conjugated gold nanoparticles are non-toxic and magnetic B waves induce the enediyne to Bergman cyclization for potent DNA cleavage.



MEDI 294

Discovery of MK-2206: The first oral allosteric Akt kinase inhibitor for the treatment of cancer

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Activation and deregulation of the PI3K/Akt pathway are common to many cancers. The three isoforms of the serine/threonine kinase Akt (PKB) play an important role in the regulation of cell survival, proliferation and growth. Enhanced Akt activity has been correlated to cancer drug resistance and survival in a number of human cancers. Our goal was to identify oral allosteric Akt inhibitors with potent activity in xenograft models of human cancers. Truncation of early leads and optimization of benzylic substitution resulted in the identification of MK-2206, the first oral allosteric Akt kinase inhibitor that is currently in Phase II clinical trials. MK-2206 shows dose proportional pharmacokinetics with significant Akt inhibition at the maximum tolerated dose in humans, as well as evidence of single agent activity in patients. The medicinal chemistry effort leading to the first oral allosteric Akt inhibitors, and ultimately to the discovery of MK-2206, will be presented.

MEDI 295

Design and construction of supramolecular nanobeacons for tumor site detection and imaging

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Molecular beacons that could convert specific chemical reactions or binding events into measurable signals are essential tools to help understand cellular and subcellular activities at the molecular level. Current *in vivo* use of molecular beacons is limited by their poor stability and easy degradation due to exposure of the linker between the reporter and the quencher to the physiological environment. In this context, we show a proof-of concept design and synthesis of a new type of supramolecular nano-beacon that is resistant to non-specific enzymatic degradation in the self-assembled state but can be effectively cleaved by the target enzyme in the monomeric form. Our results showed that the nano-beacon molecule with a cleavable peptide linker self-assembles into spherical nanostructures of approximately 11 nm under physiological conditions. Enzyme digestion experiments showed that these nano-beacons could serve as an indicator for both the presence and quantity of cathepsin-B, a lysosomal enzyme that is over-expressed in many cancerous cell lines. *In vitro* study further supports our concept as 5-FAM fluorescence was observed after incubated in MCF-7 cells for 30 minutes and fluorescence intensity was quantified by flow-cytometry.

MEDI 296

Lead optimization of lactam based HDAC inhibitors

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Histone deacetylases (HDACs) are important enzymes in chromatin remodeling and epigenetic regulation of genes. Many recent studies have shown that recruitment of abnormal HDACs are associated with carcinogenesis and the control of HDACs have been considered for anti-cancer chemotherapy. Currently a small molecule inhibitor of HDACs, SAHA has been approved for the treatment of advanced cutaneous T-cell lymphoma (CTCL).

Designed lactam based HDAC inhibitors are composed of cap group, lactam core and zinc binder. Cap groups have substituents in aromatic rings. Lactam cores are consisting of δ - or γ -lactam and linked to cap group by 1~4 carbon chain length. Zinc binder is hydroxamic acid, which is chelated to zinc ion in active site of HDAC. The series of lactam core HDAC inhibitors showed a good *in vitro* inhibitory activities. The results of docking study showed lactam core HDAC inhibitors are similar to binding mode of SAHA. KBH-A118, the initial candidate among δ -lactam analogues, however, was appeared severe problems in pharmacokinetics study; poor oral exposure and oral bioavailability. KBH-A118 showed a good caco-2 cell permeability but it showed poor metabolic stability. This result reflected that the poor oral bioavailability is caused by microsomal instability. Thus, for improving the microsomal stability, various approaches were performed changing δ -lactam to γ -lactam, reducing carbon chain length, and introducing substituents on cap group for blocking NIH shift. Consequently, KBH-A248,

metabolically stable of γ -lactam based HDAC inhibitor, showed good pharmacokinetics properties.

MEDI 297

Effects of T-antigen specific peanut agglutinin (PNA) on LS180 colon cancer cell growth: Potential interaction with MLS128 monoclonal antibody against Tn-antigen

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Since PNA was shown to be mitogenic for HT29 colon cancer cells by binding to T-antigen (Gal β 1-3GalNAc α -Ser/Thr) highly expressed in colon cancer cells, namely to CD44v6, and stimulating c-Met phosphorylation followed by subsequent mitogen-activated protein kinase activation (Singh *et al. Glycobiology* 2001 & 2006), we studied effects of PNA on LS180 colon cancer cell growth. Addition of PNA, at 2.5 and 25 μ g/ml, in serum-free medium containing 0.1% BSA significantly stimulated the growth of LS180 cells to levels of 118.0 ± 0.05 % and 123.3 ± 0.02 % (n=8), respectively, of that without PNA on day 3. HGF, the ligand for c-Met, did not stimulate LS180 cell growth. Growth stimulatory effects of PNA were inhibited by anti-Tn-antigen (GalNAc α -Ser/Thr) MLS128, which suppressed LS180 cell growth in the medium containing 1% FBS (Morita *et al. Biosci. Trends* 2009). The results suggested possible interactions between PNA and MLS128 signaling pathways.

MEDI 298

Novel inhibitors of IDO

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The discovery and SAR of novel inhibitors of indoleamine 2,3-dioxygenase-1 (IDO-1) are described. The compounds are characterized by a unique scaffold that includes a hydroxyamidine moiety attached to a fruazan ring. Enzymatic and cellular assays revealed these hydroxyamidine compounds are very potent inhibitors of IDO-1. The initial lead compounds were identified from a high-throughput screen and efficiently synthesized in only three steps.

MEDI 299

Synthesis and evaluation of vitamin D3 analogs as Hedgehog pathway inhibitors

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Hedgehog (Hh) Signaling is an embryonic developmental pathway responsible for tissue proliferation, patterning and differentiation. Generally, in adults its role is limited to maintaining tissue homeostasis; however, several forms of cancer, specifically Basal Cell Carcinoma and Medulloblastoma are driven by dysregulation in this signaling cascade. Therefore, selective inhibition of the hyperactive pathway is a validated strategy to treat Hh-dependent tumors. Vitamin D3 (VD3), the physiologically inactive precursor of calcitriol, was recently identified as an Hh inhibitor. Unfortunately, off-target effects due to metabolic conversion of VD3 to calcitriol and consequent activation of the Vitamin D Receptor have been observed. Modifications of the VD3 scaffold have revealed optimal regions for substitutions to afford first generation VD3 analogues with enhanced potency, target selectivity and improved metabolic stability. The synthesis and biological evaluation of second generation VD3-based analogues as selective Hh inhibitors will be presented.

MEDI 300

Design, synthesis, and biological evaluation of vitamin D3 analogs as selective Hedgehog signaling pathway inhibitors

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During the last ten years, cellular signaling pathways that control cellular growth and proliferation have been evaluated as potential cancer targets. The Hedgehog (Hh) signaling pathway is one such molecular network. Dysregulation of the Hh pathway results in constitutive activation of Hh signaling leading to uncontrolled cellular growth and progression, which has been identified in an array of human cancers. In particular, basal cell carcinoma (BCC) and medulloblastoma have been shown to develop from specific mutations within the Hh signaling pathway. Recently, studies demonstrated that vitamin D3 (VD3) down-regulated Hh signaling in Hh-dependent cell culture and murine models of BCC. The evaluation of first generation VD3 analogues as Hh pathway inhibitors has identified several regions of the sterol scaffold that are amenable to modification. Results from these studies have guided the rational design and synthesis of several second generation classes of VD3-based analogues as potent, selective Hh pathway inhibitors.

MEDI 301

Improved synthesis of the C-linked glucoside and glucuronide of 4-hydroxybenzylretinone (4-HBR)

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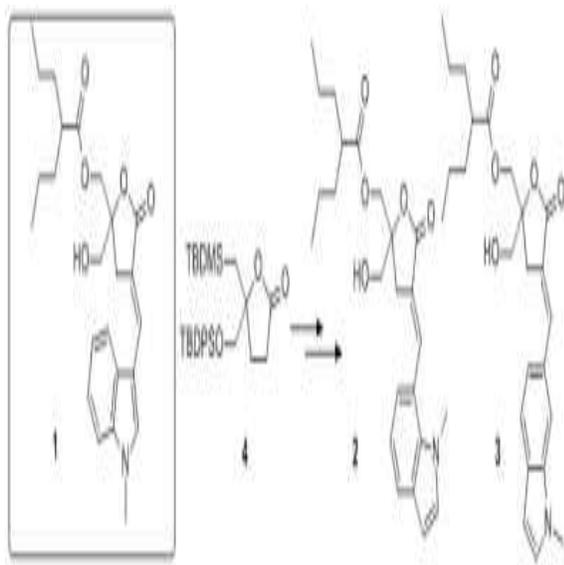
All-trans retinoic acid analogues are effective as both cancer chemopreventive and chemotherapeutic agents, but their dose-limiting toxicity has limited their usage. The O-glucuronide (4-HPROG) of N-(4-hydroxyphenyl)retinamide (4-HPR) has been found to be a more effective agent, and also has not displayed classical retinoid toxicities in previous studies. Its carbon-linked analog (4-HPRCG) shows even more promise, as does its carbon-linked glucose derivative. Subsequent conversion of the amide linkage in 4-HPRCG to the carbon-linked ketone (4-HBRCG) further improves activity. However, the syntheses of these compounds are lengthy, costly, and require many chromatographic purifications. To this end we have redesigned and streamlined their syntheses for ease of scale up. These new synthetic routes to the fully carbon-linked 4-HBRCG and 4-HBRCglucose derivatives of 4-HBR using classical carbohydrate chemistry and Suzuki coupling as its key methodologies, will be presented.

MEDI 302

Synthesis of N-methylsubstituted indololactones as selective activators of Ras guanyl nucleotide-release proteins (RasGRP)

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N-methyl substituted dicaylglycerol-indololactones are effectors of PKC isoforms and exhibit substantial selectivity between RasGRP3 and α PKC, been **1** the most selective known compound for RasGRP. In an effort to explore the influence of structural variations of these analogues on the activation selectivity, we have synthesized isomers **2** and **3** where the indole moiety is connected to the lactone through positions 6 and 7 of its phenyl ring. Conveniently protected lactone **4** was prepared starting from commercial 1,3-dihydroxyacetone **5** in four steps. The synthesis and selectivity between RasGRP and α PKC activation will be described.

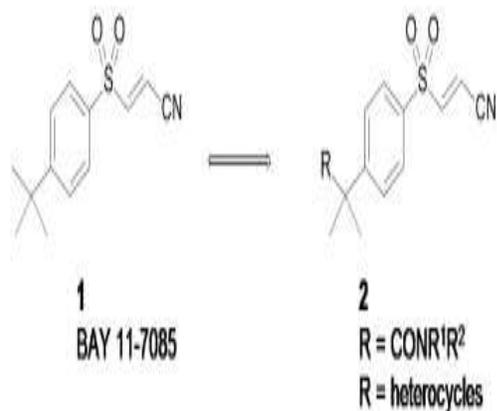


MEDI 303

Sulfonylacrylonitriles as inhibitors to peritoneal carcinomatosis

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Surgical resection of intra-abdominal cancers can lead to peritoneal carcinomatosis, a fatal form of metastasis where cancer cells implant on the lining of the peritoneal cavity. Prior in vivo murine studies have shown that BAY 11-7085 (**1**) induces apoptosis of colon and pancreatic cancer cells during cell adhesion. Analogs bearing the same sulfonyl acrylonitrile fragment found in **1** were prepared featuring amide and heterocyclic substitutions (**2**) and were assessed in vitro and in vivo in a murine peritoneal carcinomatosis model as potential post-operative treatments following pancreatic resection.



MEDI 304

Efficient synthesis of an activated tubulysin B derivative for ligand targeting

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Tubulysins are natural products isolated from myxobacterial species. As cytoskeleton interacting agents, tubulysins are mitotic poisons and are extremely potent cytotoxins, thus exceeding the cell growth inhibition of any clinically relevant traditional chemotherapeutic. Structurally, tubulysins are closely related linear tetrapeptides comprised of unusual and/or hydrophobic amino acid segments. The isolation of a single natural tubulysin from culture extracts requires multistep chromatography and provides only limited quantities. Several total syntheses of natural tubulysins and some structurally simplified analogues have been reported, but their application is limited to small lab scale. Among the multiple challenging synthetic and stereochemical issues, most striking is the generation of the labile *N,O*-diacyl *N,O*-acetal.

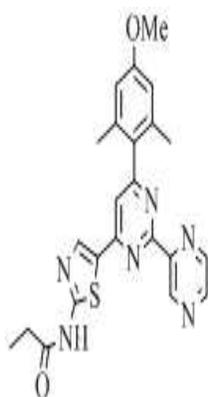
Herein, we present a streamlined total synthesis of a tubulysin B derivative modified for conjugation with targeting ligands. This convergent protocol produces gram quantities of the desired derivative utilizing only simple medium pressure reverse phase and normal phase column chromatography. In addition, isolation of highly toxic tubulysin B as a synthetic intermediate is avoided.

MEDI 305

Modulation of cofilin phosphorylation by inhibition of the Lim family kinases

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The design, synthesis, and SAR for a series of aminothiazole pyrimidines as potent LIMK1 and LIMK2 inhibitors are described. Appropriate choice of substituents led to molecules with good selectivity for either enzyme. An advanced member (compound **31**) of the series was shown to effectively interfere with the phosphorylation of the LIM kinases substrate cofilin. Consistent with the important role of the LIM kinases in regulating cytoskeletal structure, treated cells displayed dramatically reduced F-actin content.



31: LIMK1 IC₅₀ = 58 nM
LIMK2 IC₅₀ = 38 nM
TESK1 IC₅₀ = 455 nM
TESK2 IC₅₀ = 252 nM

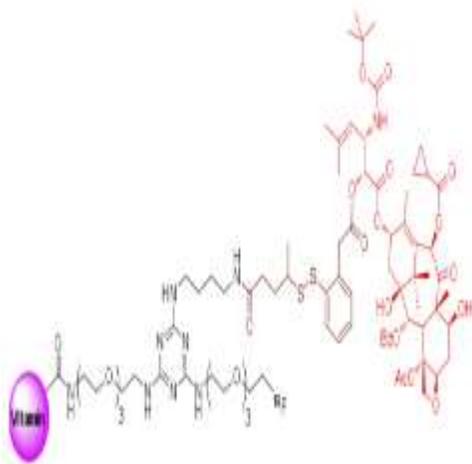
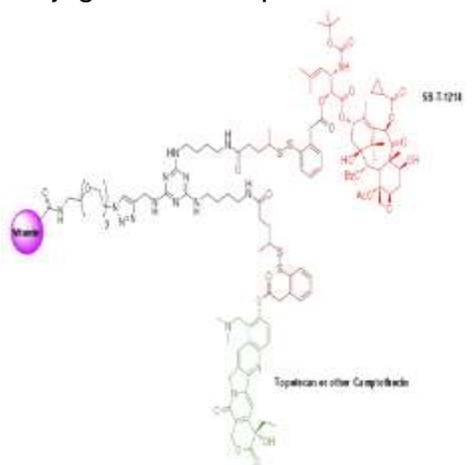
MEDI 306

Synthesis and biological evaluation of novel dual-warhead tumor-targeting drug conjugates bearing a taxoid and a camptothecin

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Vitamins, such as biotin and folic acid, have demonstrated significant uptake in a variety of cancer cells. Thus, vitamins have been incorporated as tumor-targeting modules

(TTM) for drug conjugates. Previously in our lab, we have developed vitamin-linker-taxoid conjugates that have exhibited enhanced selectivity towards cancer cells. Along those lines, we have designed novel tumor-targeting drug conjugates bearing dual-warheads with a 1,3,5-triazine splitter. We have selected newer-generation taxoids, which have demonstrated synergy with camptothecins in select cancer patients. Accordingly, we designed novel dual-warhead tumor-targeting drug conjugates with SB-T-1214 and derivatives of camptothecin as our warheads. Biotin and folic acid were chosen as TTM to increase the tumor-specificity of the drug conjugate. To assess biodistribution of the drug conjugate, we designed and synthesized a novel taxoid-based tumor-targeting fluorine probe with a 1,3,5-triazine core and a single imaging agent. The synthesis and biological evaluation of these novel tumor-targeting drug conjugates will be presented.

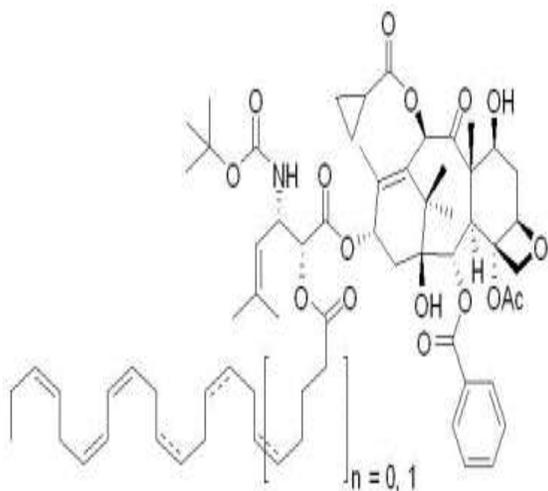


MEDI 307

Preclinical evaluation of PUFA conjugates of next generation taxoid SB-T-1214

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Conjugation of drugs to polyunsaturated fatty acids (PUFAs) has been shown to greatly alter their pharmacokinetic profile, resulting in higher plasma protein binding and slower clearance. In addition, PUFAs are rapidly taken up by growing tumors and PUFA-drug conjugates exhibit tumor specific accumulation *in vitro* and *in vivo*. Next generation taxoids possess a marked increase in activity against multi-drug resistant tumors, and conjugation of these compounds to the PUFAs docosahexaenoic acid (DHA) and α -linolenic acid (LNA) have provided novel anti-cancer agents with greatly improved efficacy. During the course of our preclinical studies on these compounds, their pharmacokinetic profile has been investigated, as well as their cancer cell specificity *in vitro*. These results, combined with our *in vivo* efficacy studies and pathological examinations will be presented.



MEDI 308

New chemosensitizing strychnos alkaloids to improve clinical drug efficacy

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Multidrug resistance (MDR) is a major impediment in the successful treatment of cancer. It is characterized by increased drug efflux mediated by ATP-binding cassette transporter P-glycoprotein (Pgp). Pgp inhibitors (e.g., verapamil) were found to abolish the drug transport across cellular membranes, and to reverse MDR in vincristine-resistant cancer cell lines. In the cancer cell lines overexpressing Pgp, these inhibitors modulate Pgp activity and re-sensitize the cancer cells to chemotherapeutic agents.

Novel methods for chemical synthesis of derivatives of natural products as validated drug sources. The asymmetric synthesis of *Strychnos* alkaloids akuammicine, dihydroakuammicine, norfluorocurarine, dehydroleuconicine B, leuconicine A and leuconicine B was accomplished using methodology recently published by the Andrade group. Enabled by *N*-sulfinylamine chemistry, our novel sequential one-pot spirocyclization/*aza*-Baylis-Hillman method and Heck cyclization, we were able to make sufficient quantities of pure, synthetic natural products to begin biological evaluation.

Alkaloids prepared as above were evaluated by an *in vitro* Pgp-Glo assay (Promega) to characterize inhibitory activity of test compounds on Pgp. Assessment of ATPase activity of human recombinant Pgp discriminated if a test compound was a substrate, had inhibitory, or had no effect on Pgp activity. These experiments showed that dihydroakuammicine was the most potent inhibitor followed by leuconicine B and norfluorocurarine. Akuammicine and dehydroleuconicine B had little effect, whereas leuconicine A stimulated ATPase activity suggesting it is a Pgp-substrate. . Our results indicate that the synthesized compounds could be effective reversal agents useful to improve anticancer activity of Pgp substrate.

MEDI 309

Fragment-based design, synthesis, and biological evaluation of a series of novel PDK1 inhibitors

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The 3-Phosphoinositide-Dependent Kinase-1 (PDK1) is a monomeric serine/threonine kinase and is one of the promising oncology target of significant current interest for the drug development due to its central role in the PI3K/AKT/mTOR pathway. It phosphorylates highly conserved Ser or Thr residues in the activation loop of several AGC super family kinases including PKC, SGK, PKB/Akt, p70S6K, and PDK-1 itself. A significant proportion of about 40–50% of all tumors involve mutations in PIP3-3-phosphatase (PTEN), which results in elevated levels of PIP3 and enhanced activation of PKB/AKT, p70S6K, SGK and the inhibitors of PDK-1 could provide a valuable

therapeutic agents for the treatment of cancer. With the application of fragment-based design strategies, a template screening with a collection 1100 small <250 low molecular weight fragments to small molecule hit generation lead to the identification of multiple PDK1 inhibitor scaffolds and they are within the RO3 chemical space suitable for further optimization. The sequential combination of *in silico* low molecular weight template selection based on hydrogen bonding to S160/A162 hinge residues, a high concentration (100 mM) biochemical assay and hit validation computationally through protein-ligand X-ray crystal structure provided 9 fragment hits of which 5-Br,4-I-1*H*-indazol-3-amines which exhibited 82.46 and 44.48 mM PDK1 activity. Concurrently, we carried out scaffold-hopping searches at 2-site points for hydrophobic and solvent pocket fragments. With the addition of one fused heterocyclic ring, the potency increased to 8.79 and 10.89 μ M. Our systematic fragment based workflow lead to the preparation of target molecules in 4 steps beginning with the condensation, cyclization, and reduction and finally installing the hydrophobic binding site fragments under normal amide coupling. Subsequent SAR and follow-up screening led to the discovery of HCI-1680 as potent PDK1 activity with an IC₅₀ of 97 nM. Additional productive interactions sites with PDK1 were introduced to further improve both biochemical and cellular activities in panel of cancer cells. In particular in PTEN deficit cell lines the HCI-1680 exhibited 5 nM potency. Moreover the lead compound had high ligand efficiency with promising solubility and permeability parameters. The details of fragment-based strategy, SAR and synthesis aspects will be presented.

MEDI 310

Design and synthesis of hydroxylamine derivatives as indoleamine 2,3-dioxygenase inhibitors

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Current research describing the role of indoleamine 2,3-dioxygenase (IDO) and its mechanism of action suggests that the inhibition of IDO with small molecule inhibitors, especially in conjunction with chemotherapy, can provide an effective and novel cancer treatment strategy. The search for potent and biocompatible inhibitors has become an attractive area of research. The Malachowski group, in collaboration with biologists at the Lankenau Institute for Medical Research (LIMR), are currently exploring O-alkyl hydroxylamine derivatives as inhibitors of IDO and the results of our studies will be described.

MEDI 311

Electron-transfer based combination therapy of cisplatin with a molecular promoter for cancer treatment

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Cisplatin is the first and most widely used platinum-based chemotherapy drug and is now the cornerstone agent in treating a variety of cancer, including ovarian cancer, testicular cancer, cervical cancer, bladder cancer, lung cancer, head and neck cancer, lymphomas cancer and brain tumors. However, its application is often limited by severe toxic side effects and resistance possessed by various cancers. Recently, we have discovered a new dissociative electron transfer (DET) mechanism of action of cisplatin. Here, we show that the combination of cisplatin with a molecular promoter (PM) can overcome the drawbacks of cisplatin. We found that this combination significantly enhances the killing of human cervical cancer (HeLa) and lung cancer (A549) cells but not normal cells. Furthermore, this combination significantly increases DNA double-strand breaks and apoptosis in cancer cells. These results demonstrate that this novel combination treatment results in a strong synergetic effect in cytotoxicity of cisplatin.

MEDI 312

Synthesis, characterization, and antitumor activity of imidazolium cation derivatives

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We report the antitumor activity of a panel of compounds largely based on 4,5-dichloroimidazole and its derivatives against various cancer cell lines, including non-small cell lung cancer lines (NCI-H460). The addition of substituents at the N-1 and N-3 positions of the imidazole precursor, especially those with planar, aromatic rings, greatly increases the antitumor activity of the complexes. This activity has been demonstrated for a variety of substituents, and for both the asymmetric and symmetric corresponding imidazolium cations. The synthesis, characterization, and MTT studies of these complexes will be discussed.

MEDI 313

Synthesis and biological activity of Largazole analogs targeting histone deacetylases

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Targeting epigenetic regulation of gene expression is a promising approach to develop treatments for a variety of human disorders. HDAC inhibitors are one of the most extensively studied classes of compounds that target epigenetic gene regulation. Two HDAC inhibitors are currently in clinical use as anticancer drugs. A major challenge in HDAC inhibitor research is the development of isoform and class-selective HDAC inhibitors to reduce undesirable side effects resulting from their off-target activity. Largazole is a potent and selective HDAC inhibitor isolated from a marine cyanobacterium of the genus *Symploca*. We have synthesized several largazole analogues in which the surface recognition head group and the metal binding motif have been altered. The synthesis and the biological activity of these largazole analogues will be presented.

MEDI 314

Developing small molecule inhibitors of the CREBBP bromodomain-histone interaction

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Bromodomains are acetyl-lysine (KAc)-binding motifs that serve to recognise the post-translational modification of numerous protein classes. The coactivator CREB-binding protein (CREBBP) contains a bromodomain that binds specific KAc marks, and misregulation of CREBBP activity has been linked to neurodegeneration, oncogenesis and inflammation.[1]

Small molecule chemical probes have recently been developed for the BET family of bromodomains and have been used to validate the therapeutic potential of disrupting KAc binding.[2] Herein, we report on progress towards a potent and selective inhibitor of the CREBBP bromodomain KAc interaction. Co-crystal structures of early lead compounds have revealed that the potency and selectivity of the lead compound results from binding in an induced fit pocket. A combination of *in silico* screening, parallel chemistry and biophysical assays have driven the structure-based design of novel CREBBP bromodomain-binding compounds.

[1]: *Expert reviews in molecular medicine* **2011** , 13:e29.

[2]: *Nature* **2010**, 468, 1067. *Cell* **2011** , 146, 604.

MEDI 315

Design and development of cucurbitacin analogs inhibiting MAPK pathway cascade for the treatment of melanoma

Mahmoud S Ahmed, *mahmoud.salama@sdstate.edu*, **Fathi T. Halaweish**, *Department of Chemistry and Biochemistry, South Dakota State University, Brookings, SD 57007, United States*

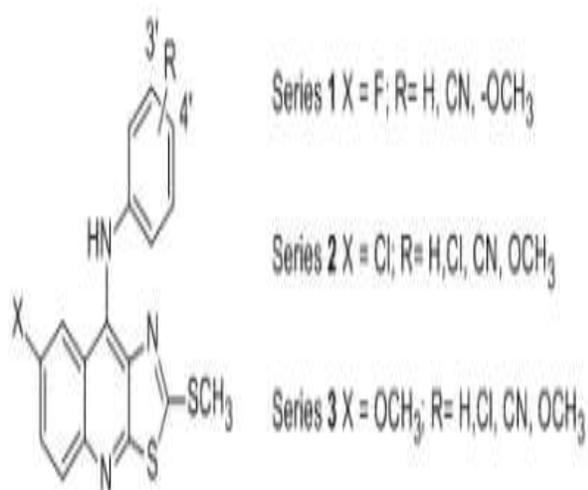
Melanoma is the most lethal among skin cancer types, causing about 75 % of all skin cancer deaths. B-Raf mutations show high incidence in melanoma. Inhibition of MEK can lead to induce apoptosis. Therefore, Inhibition of the MAPK signaling at any level can assist for treatment of melanoma. Molecular docking study was conducted using a library of 960 compounds containing native, semi-synthesized cucurbitacins, and cucurbitane structures over B-Raf and MEK crystal structures using in-silico modeling OpenEye[®] and SYBYL[®] software packages. In-vitro biological evaluation was conducted using MTT assay. The results show 300 ligands of the native and the semi-synthesized cucurbitacins have higher binding affinity to the hydrophobic pocket of the crystal structures compared to standard MEK inhibitors such as PD-0325901. They show a better IC₅₀ in-vitro at A-375 and SK-MEL28 cell lines ranging from 0.54-3.75 μ M. Binding to B-RAF using ELISA and QSAR models will be presented showing the possibility for synthesis of potential candidates.

MEDI 316

Synthesis, cytotoxic activity, and SAR analysis of novel derivatives of 9-anilino-7-substituted-2-(methylthio)thiazolo[5,4-*b*]quinoline

Ricardo Anguiano-Moreno, *ricardoanguiano@live.com.mx*, **Jose Solano-Becerra**, **Jose Esquivel-Hernandez**, **Alfonso Lira-Rocha**, *Farmacia, Facultad de Química, UNAM, Mexico, D.F. 04510, Mexico*

Previously, we reported the synthesis and cytotoxic evaluation of several 9-anilino-2-(methylthio)thiazolo[5,4-*b*]quinoline derivatives with a fluorine atom at 7-position. This modification did not improve the activity. Novel derivatives of 9-anilino-7-substituted-thiazolo[5,4-*b*]quinoline were synthesized and tested in vitro against several human tumor cell lines. In general, 7-chloro and 7-methoxy derivatives were more active than 7-fluoro analogues. SAR analysis indicated that the activity is regulated by the substitution pattern at the aniline ring. Additional studies about electronic properties of all compounds indicated that LUMO energy values and dipole moment orientation are related to the cytotoxic activity.

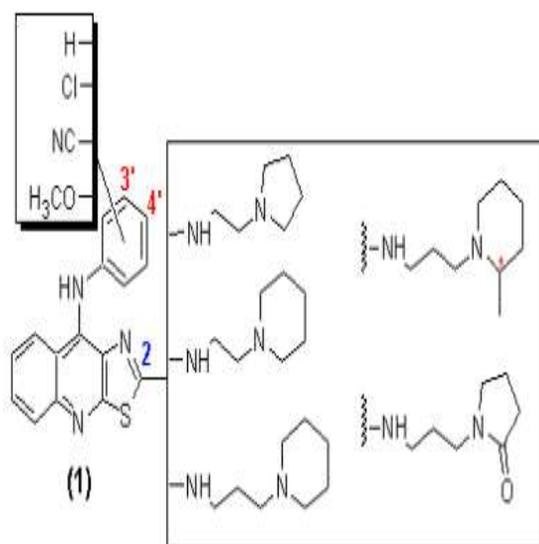


MEDI 317

Synthesis and QSAR studies of 9-anilinothiazolo[5,4-*b*]quinoline derivatives with *in vitro* antitumor activity

Adrián Kémish López-Rodríguez, kemishlopez@hotmail.com, José Solano-Becerra, Alfonso Lira-Rocha. Farmacia, Facultad de Química, UNAM, Mexico, D.F. 04510, Mexico

A novel series of thiazolo[5,4-*b*]quinoline derivatives has been synthesized, showing good cytotoxic activity against human tumor cell lines (HeLa, SW-480, SW-620 and K-562). In order to analyze the structural requirement for the activity through 2D-QSAR, molecular models for these compounds were obtained at the MM and DFT B3LYP/6-31G* level of theory. The results pointed at the orientation of the dipole moment vector as a fundamental factor and, according to the correlation equations, the most relevant descriptors for the activity were related to their cell internalization properties (log P and PSA). The ability to create non-bonding interactions through charge-transfer complexes (E LUMO) was also relevant.

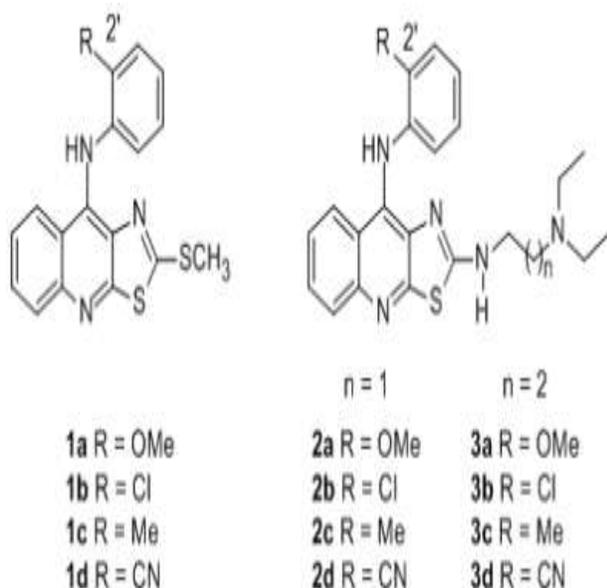


MEDI 318

Synthesis, cytotoxic activity, and molecular modeling of novel derivatives of 9-anilino-2'-substituted- thiazolo[5,4-*b*]quinoline as potential antitumor agents

Alfonso Lira-Rocha, lira@unam.mx, Ana S. Teloxa-Cuahutle, Jose Solano-Becerra. Farmacia, Facultad de Química, UNAM, Mexico, D.F. 04510, Mexico

As indicated by previous results, the substitution pattern in the aniline ring plays a key role in the cytotoxic activity of 9-anilino-2-(methylthio)thiazolo[5,4-*b*]quinoline derivatives. To explore in more detail the structural determinants of the compound's cytotoxicity, a new series of thiazoloquinoline analogues with different substituents at 2'-position of aniline ring was synthesized and its cytotoxic activity on Hela and K-562 cell lines was tested *in vitro*. The biological activities recorded have been analyzed along with supporting data from molecular modeling studies of the new compounds.

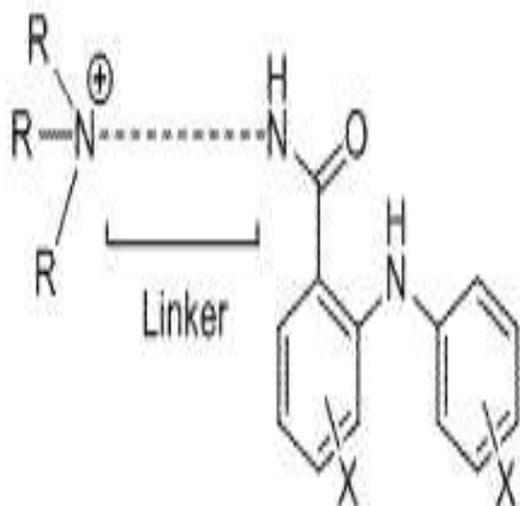


MEDI 319

Synthesis and biological evaluation of selective MEK-5 inhibitors

Suravi Chakrabarty¹, *chakrabartys@duq.edu*, **Si Qin**¹, **Patrick T Flaherty**¹, **Darlene Monlish**², **Jane Cavanaugh**², **Sankar Manepalli**³, **Jeffry D Madura**³. (1) Division of Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania 15282, United States (2) Division of Pharmacology, Duquesne University, Pittsburgh, Pennsylvania 15282, United States (3) Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282, United States

The mitogen activated protein kinase (MAPK) pathway is a family of interrelated signal transduction kinases involved in complex signaling events mediating cell differentiation, proliferation, and death. Extracellular mitogen or ligand binding begins a signaling cascade that activates MEK resulting in phosphorylation of its corresponding and specific ERK substrate (extracellular signal-regulated kinase). ERK-5 is the only known substrate of MEK-5. The MEK-5/ERK-5 pathway is involved in cell survival, anti-apoptotic signaling, angiogenesis, and cell motility. MEK-5 is significantly up regulated in specific cancers including breast and prostate cancers. We synthesized a series of diphenylamines based on a revised homology model of MEK5 based on the X-ray crystal structure of MEK-1 (PDB ID: 3EQC). Synthesis and biological evaluation of novel amide and aryl variations will be presented.



MEDI 320

Design, synthesis, and biological evaluation of substituted furo[2,3-*d*]pyrimidines as potent antimetabolic agents that circumvent Pgp and β III-tubulin mediated resistance

Aleem Gangjee¹, **Ravi Kumar Vyas Devambatla**¹, drk_vyas@yahoo.co.in, Shruti Choudhary¹, Ruoli Bai², Ernest Hamel². (1) Division of Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania 15282, United States (2) Division of Cancer Treatment and Diagnosis, Frederick National Laboratory for Cancer Research, Frederick, Maryland 21702, United States

Agents that interfere with microtubules, including the vinca alkaloids and the taxanes, are important antitumor agents. Despite the unprecedented success of these agents in cancer chemotherapy, multidrug resistance is a major limitation. We recently reported *N*-(4-methoxyphenyl)-*N*,5-dimethylfuro[2,3-*d*]pyrimidin-4-amine (**1**) as a potent antimetabolic tubulin-binding agent. Compound **1** inhibited tubulin polymerization, the binding of [³H]colchicine to tubulin, and circumvented P-glycoprotein (Pgp) and β III-tubulin mediated resistance. Based on the anti-tubulin activity of **1**, we designed eight compounds with variations in the alkyl and aryl substituents at the *N*4-position. These analogs were synthesized by treating the 4-amino analog with appropriate aryl iodides followed by *N*⁴-alkylation. The 4-amino analog was synthesized by treating 1-hydroxypropan-2-one with malononitrile followed by cyclization with formamidine hydrochloride. The synthesis and preliminary biological activity of these analogs will be presented.

MEDI 321

Design, synthesis, and preclinical evaluation of 7-benzyl -N-substituted phenyl-5H-pyrrolo[3,2-d]pyrimidin-4-amines as single agents with antitubulin and antiangiogenic activity as antitumor agents

Aleem Gangjee¹, Roheeth Kumar Pavana¹, kp.roheeth@gmail.com, Michael A Ihnat², Ernest Hamel³. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, United States (2) Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73117, United States (3) Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, Frederick National Laboratory for Cancer Research, National Cancer Institute, Frederick, MD 21702, United States

Agents that interfere with microtubule functions are important antitumor agents. Antiangiogenic agents target tumor angiogenic mechanisms that are vital for tumor growth and metastasis. Antiangiogenic agents are usually not tumoricidal but are mainly cytostatic. Combination chemotherapy with antiangiogenic and cytotoxic agents have shown significant promise and several studies with such combinations are in progress in the clinic. Single agents with both antiangiogenic activities as well as cytotoxicity would afford single agents that would circumvent pharmacokinetic problems of multiple agents, would avoid drug-drug interactions, could be used at lower doses to alleviate toxicity, could be devoid of overlapping toxicities, and could delay or prevent tumor cell resistance. We have designed, synthesized and evaluated novel pyrrolo[3,2-d]pyrimidines that inhibit both vascular endothelial growth factor receptor-2 (VEGFR-2) for antiangiogenic effects and tubulin for cytotoxic effects in single agents. These agents afford combination chemotherapeutic potential in single agents. We have identified a compound with potent anticancer activity in aggressive basal like breast cancer (BLBC) and triple negative breast cancer (TNBC) lines. It also showed sensitivity in taxol resistant cells indicating that they are unlikely to be Pgp or MRP substrates [unlike taxol] and possesses relative selectivity of kill on tumor versus normal cell types. It reduces tumor size in vivo and vascularity in two flank xenograft models in mice and rats, superior to docetaxel and sunitinib, without overt toxicity to the animals. The design, synthesis and biological activities of these analogs will be presented.

MEDI 322

Design, synthesis, and biological evaluation of 6-substituted pyrrolo[2,3-d]pyrimidines as potent inhibitors of tumors expressing folate receptors via GARFTase inhibition

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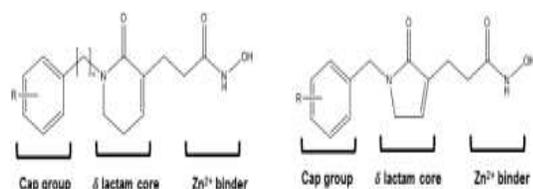
One of the major hurdles in cancer therapy is the inability of chemotherapy agents to selectively target tumor cells over normal tissues. The multi-enzyme-targeted anticancer drug pemetrexed (PMX) suffers from dose-limiting toxicity due to its membrane transport by the reduced folate carrier (RFC) which is ubiquitously expressed in normal and tumor cells. We recently reported a series of 6-substituted pyrrolo[2,3-*d*]pyrimidine thienoyl antifolates. The most active of this series (**AG71**) included a 4 carbon bridge and a thienoyl ring and was selectively transported into cells by folate receptors (FRs) and the proton-coupled folate transporter (PCFT) (but not RFC) whereupon it inhibited *de novo* purine biosynthesis at the level of glycinamide ribonucleotide formyltransferase (GARFTase). **AG71** was highly active toward both KB and IGROV1 tumors; in SCID mice with KB tumors, **AG71** was also highly active against both early and advanced stage tumors. Based on our results with **AG71**, a series of 6-substituted pyrrolo[2,3-*d*]pyrimidines with side chain variations in the bridge were designed and synthesized as analogs of **AG71**. These analogs are part of the SAR study of FR α and/or PCFT transport and GARFTase inhibition. The analogs were tested for anti-proliferative effects on KB human tumor cells and on Chinese hamster ovary (CHO) sublines engineered to individually express RFC (PC43-10), PCFT (R2/PCFT4), and FR α (RT-16). Analogs synthesized in this study showed subnanomolar IC₅₀ values against KB tumor cells in culture. Drug effects were completely abolished by excess folic acid establishing FR-mediated uptake. Similar to **AG71**, no RFC activity is observed for these compounds. Whereas PMX is a multi-targeted agent with inhibitory effects on both *de novo* thymidylate and purine nucleotide biosynthetic pathways, the anti-proliferative effects of these compounds were abolished by adenosine but not thymidine, establishing exclusive inhibition of purine biosynthesis. The design, synthesis and biological activities of these analogs will be discussed.

MEDI 323

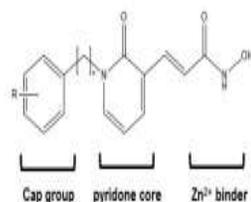
Discovery of pyridone based HDAC inhibitors for metabolic stability

Misun Cho, cielo8512@naver.com, Eunhyun Choi, Chulho Lee, Jee Sun Yang, Gyoonee Han. Department of Biotechnology, Yonsei University, Seoul, Seoul 120-149, Republic of Korea

Histone deacetylases (HDACs) are known to be a significant enzyme of epigenetic regulations and they are a well-known therapeutic target for cancer. Human HDAC enzymes have 11 isoforms and most of them are zinc-dependent enzymes which play the roles of proliferation, de-differentiation and anti-apoptosis in cancer cells. We reported on δ -lactam and γ -lactam based HDAC inhibitors. They showed high activity in *in vitro* HDAC inhibitory assays and cancer cell growth inhibitory assays. Most of them, however displayed low metabolic stability in mouse liver microsomes mainly due to the NIH shift or hydrolysis of hydroxamic acid moiety. So, we introduced a conjugation system by replacing lactam with pyridone of core group, which places conjugated double bonds between the pyridone core and hydroxamic acid



Lactam core HDAC inhibitors



Pyridone core HDAC inhibitors

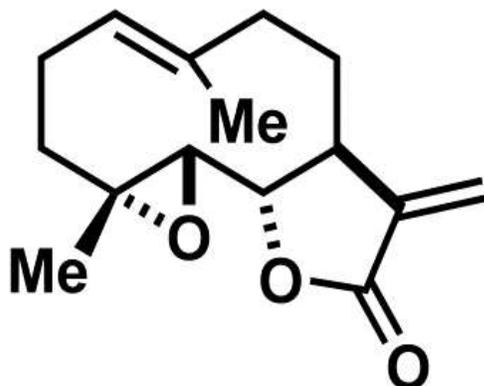
. Consequently, Most of pyridone based HDAC inhibitors showed similar or better HDAC enzyme inhibitory activity, and metabolic stability. A1399 proved to be especially powerful as HDAC inhibitors, because of the highest rate of activity in *in vitro* HDAC enzyme inhibitory, cancer cell growth inhibitory assays and having potent selectivity to HDAC1 and HDAC6.

MEDI 324

Synthesis and anticancer evaluation of sesquiterpene lactone analogs

Daniel A Harki, daharki@umn.edu, Timothy Andrews, John Widen, Dan Wang, Joseph Hexum. Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55414, United States

Parthenolide (PTL) is a plant-derived natural product from feverfew and a well-established active component of many natural medicines. Recent discoveries that PTL targets cancer stem cell populations in multiple cancers have sparked significant interest in developing PTL for applications in cancer chemotherapy. To elucidate the mechanism of cancer stem cell toxicity by PTL, which is not currently established, we have developed a number of PTL-based chemical probes for applications in protein pull-down and analysis studies. We have also synthesized a number of PTL-inspired natural product analogues in order to optimize potency, specificity, and pharmacokinetics. Our progress in both areas will be presented.



parthenolide (PTL)

MEDI 325

Inhibition of cancer cell proliferation via a combination of glutaminase C and tissue transglutaminase inhibition

William P. Katt¹, wpk8@cornell.edu, **Marc A. Antonyak**¹, **Richard A. Cerione**^{1,2}. (1) Department of Molecular Medicine, Cornell University, Ithaca, NY 14853, United States (2) Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853, United States

One key difference between cancer cells and normal cells is the Warburg effect, a system of metabolic changes that cause cancer cells to depend upon glutamine metabolism rather than glycolysis. A key player allowing glutamine metabolism to fuel cell functions is glutaminase C. 968, an inhibitor of glutaminase C, retards the aberrant growth exhibited by numerous cancer systems, and limits tumor formation in mice, while having little effect upon normal cells. Another key cancer phenotype, oncosome formation, has recently been shown to require the action of tissue transglutaminase (tTg). Since oncosomes presumably form from metabolic byproducts, we had hypothesized that glutaminase C might be linked to tTg function. Indeed, a synergy arises when numerous human cancer cell lines are treated with 968 and with the tTg inhibitor monodansylcadaverine. This represents the possibility of an inhibitory mechanism targeting two cancer-specific processes, which may allow for less toxic cancer therapies.

MEDI 326

Dasatinib-fatty acid conjugates: Synthesis and evaluation of tyrosine kinase inhibitory and anticancer activities

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Dasatinib is a multi-kinase inhibitor that is used clinically for treatment of patients with chronic myeloid leukemia (CML). Dasatinib was reacted with fatty acids in the presence of EDC.HCl/HOBt and NMM as coupling and activating reagents, respectively, to afford 10 dasatinib-fatty acid conjugates in 70-95% yield. The compounds were screened against Abl, Csk, and Src at concentrations of 250 pM, 800 pM, and 8 nM, respectively, for comparison with dasatinib. Among all derivatives, acetyl derivative exhibited slightly higher inhibitory activity against Abl, Csk, and Src than dasatinib, and showed modest selectivity against Abl. Introduction of longer chain fatty acids with 8-12 methylene groups was detrimental and significantly reduced inhibitory activities against all three kinases. Among all derivatives, dodecanoyl dasatinib was found to be 5-10% more efficient than dasatinib in the inhibition of SK-OV-3 and CCRF-CEM proliferation at the concentration of 1 μ M after 72 h incubation.

MEDI 327

Discovery and SAR of novel 2-substituted benzylidene-3-oxo-2,3-dihydrobenzofuran-7-carboxamide derivatives as poly(ADP-ribose)polymerase-1 inhibitors

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A novel series of 2-substituted benzylidene 3-oxo-2,3-dihydrobenzofuran-7-carboxamide derivatives, with built-in intramolecular hydrogen bonding mediated pseudotricyclic ring system, were designed, synthesized and evaluated as inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1). The docked conformation of the 3-oxo-2,3-dihydrobenzofuran-7-carboxamide in the PARP-1 active site revealed a more favorable interaction with the amino acids for this scaffold. Successful synthesis of the target compound **7** (3-oxo-2,3-dihydrobenzofuran-7-carboxamide) was carried out using different synthetic approaches which was found to be active with an IC₅₀ value of 16.0 μ M. Further condensation of compound **7** at the 2-position with the benzaldehyde provided compound **8** with an IC₅₀ value of 12.0 μ M. This novel core, amenable for 2-position substitution, opened a new avenue for the search of the more potent PARP-1 inhibitors.

MEDI 328

Discovery and SAR of novel 2,3-dihydrobenzofuran-7-carboxamide derivatives as poly(ADP-ribose)polymerase-1 inhibitors

Maulik R Patel¹, malkpatel@yahoo.com, Aaditya Bhatt¹, Frank R Fronczek², Tanaji T Talele¹. (1) Department of Pharmaceutical Sciences, College of Pharmacy, St. John's University, Queens, New York 11439, United States (2) Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

A novel series of substituted 2,3-dihydrobenzofuran-7-carboxamide derivatives, with a built-in intramolecular hydrogen bonding mediated pseudotricyclic ring system, were designed, synthesized and evaluated as inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1). A structure-based design strategy resulted in lead compound **3** [2,3-dihydrobenzofuran-7-carboxamide, IC₅₀ = 9.45 μM]. Substitution on the 2-position of compound **3** with the methyl group, led to formation of racemate **13a**, with an IC₅₀ of 10.44 μM. Classical chiral resolution of the carboxylic acid precursor for *rac*-**13a** by formation of crystalline salts with (-)-brucine dihydrate and (-)-α-methylbenzyl amine followed by conversion to target carboxamides produced (+)-**13a** and (-)-**13a** enantiomers with IC₅₀ values of 8.44 μM and 6.34 μM, respectively. Substituting the fluoro group at 5-position of the lead compound **3** led to the formation of compound **20** (IC₅₀ = 2.12 μM) with >4-fold improvement in activity. Binding mode of the potent compounds within the active site of PARP-1 will direct future structure optimization efforts.

MEDI 329

Imidazopyridazine derivatives as pan-JAK inhibitors for rheumatoid arthritis

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The four members of the Janus (JAK) family of kinases (JAK1, JAK2, JAK3 and TYK2) are involved in signal transduction of inflammatory mediators implicated in the pathogenesis of several autoimmune diseases. Small molecule inhibitors of JAK kinases have demonstrated therapeutic efficacy in clinical trials in rheumatoid arthritis (RA).

This poster will focus on the design, synthesis and biological activity of a series of imidazopyridazines as potent pan-JAK inhibitors. Systematic SAR efforts addressed to improve potency and permeability of starting molecules led to the identification of an

advanced lead with balanced activities against JAK1-3, good pharmacokinetics and proven efficacy in the rat adjuvant-induced arthritis (AIA) model.

MEDI 330

Kv1.3: A promising target for the treatment of autoimmune diseases

Stefan Tasler, *stefan.tasler@4sc.com*, **Sylvia Pruetting**, **Svetlana Hamm**, **Tobias Dreker**. 4SC Discovery GmbH, Planegg-Martinsried, Germany

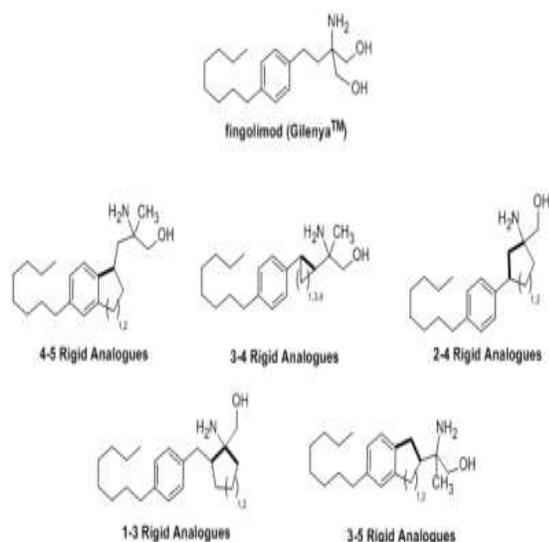
The voltage-gated potassium channel Kv1.3 is a crucial player in maintaining the activation signal within T-cells and is evaluated as a promising target for the treatment of autoimmune diseases like multiple sclerosis, rheumatoid arthritis, diabetes and psoriasis. Our Lead Optimization program resulted in a set of potent Kv1.3 inhibitors with tunable selectivity, solubility and stability. Selected representatives displayed highly encouraging ameliorative effects in several different animal models relevant in the context of autoimmune diseases, like pristane-induced arthritis and allergic contact dermatitis, comparable or even slightly favourable over positive controls methotrexate, betamethasone or tacrolimus.

MEDI 331

Synthesis and biological evaluation of conformationally constrained fingolimod analogs

Michael J Ferracane¹, *mjf4ze@virginia.edu*, **Andrew J Kennedy**¹, **Ran Zhu**¹, **Perry C Kennedy**², **Kevin R Lynch**², **Timothy L Macdonald**¹. (1) Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904, United States (2) Department of Pharmacology, University of Virginia, Charlottesville, Virginia 22908, United States

The immunosuppressant fingolimod was recently approved for the treatment of MS. Its therapeutic effects and side effects are mediated via the sphingosine-1-phosphate receptors S1P₁ and S1P₃ respectively. S1P₅ is poorly understood but holds potential therapeutic value due to its expression in oligodendrocytes. We have synthesized fingolimod rigid analogs in an attempt to increase potency and S1P₁-S1P₅ selectivity. We hope to determine the ligand binding mode for each receptor using our library's SAR, the S1P₁ crystal structure, and molecular modeling.



MEDI 332

Macrocyclic inhibitors of JAK

Brian R Wayland, bwayland@incyte.com, Brent Douty, Eddy Yue, Andrew Combs, Boshan Liao, Yanlong Li, Alexander Margulis, Karen Gallagher, Maryanne Covington, Rich Wynn. Incyte Corporation, Wilmington, DE 19880, United States

A novel set of macrocyclic compounds were designed and synthesized and were found to be very potent inhibitors of a number of kinases including janus kinases (JAKs). The macrocycles are based on a diaminopyrimidine scaffold that was constrained to maximize binding affinity. The goal of maintaining or increasing biological activity in a locked conformation was achieved by varying the type of linker and the length of the linker. The discovery and SAR of these macrocycles will be described.

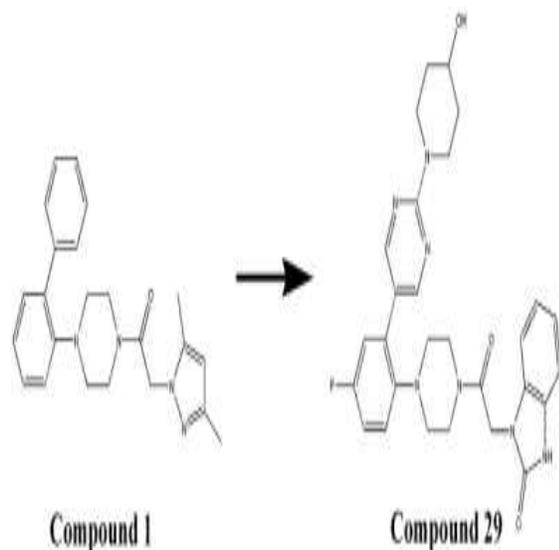
MEDI 333

Optimization of a biaryl series of CXCR₃ antagonists

Anthony Prokopowicz, anthony.prokopowicz@boehringer-ingenelheim.com, Frank Wu, Di Wu, Alan Swinamer, Jennifer Kowalski, Sabine Ruppel, Erick Young, Donna Skow, Raj Nagaraja, Sandy Schreyer. Department of Research, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT 06877, United States

The CXCR₃ signaling axis has been implicated in a variety of autoimmune, pulmonary, cardiometabolic, and oncology disease indications. This has prompted exploration of this pathway for potential therapeutic intervention strategies. A screen of our own compound collection for CXCR₃ antagonists identified the biaryl compound **1** as an

interesting hit amenable to further modification. This poster will summarize efforts to balance optimization of potency, metabolic stability, hERG inhibition, and solubility which culminated in the discovery of **29** with an attractive in vitro profile.



MEDI 334

Discovery and in vivo evaluation of novel dual PI3K β/δ inhibitors

Felix Gonzalez-Lopez de Turiso¹, felgonza@amgen.com, Youngsook Shin¹, Matthew Brown¹, Mario Cardozo¹, Yi Chen¹, David Fong³, Xiaolin Hao¹, Xiao He¹, Kirk Henne², Yi-Ling Hu³, Michael G. Johnson¹, Todd Kohn¹, Julia Lohman¹, Helen J. McBride³, Lawrence R. McGee¹, Julio C. Medina¹, Daniela Metz³, Kent Miner³, Deanna Mohn³, Vatee Pattaropong¹, Jennifer Seganish¹, Jillian L. Simard¹, Sharon Wannberg³, Douglas A. Whittington⁴, Gang Yu³, Timoty D. Cushing¹. (1) Department of Therapeutic Discovery, Amgen Inc., South San Francisco, CA 94080, United States (2) Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., South San Francisco, CA 94080, United States (3) Department of Inflammation Research, Amgen Inc., Thousand Oaks, CA 91320, United States (4) Department of Therapeutic Discovery, Amgen Inc., Cambridge, MA 02142, United States

Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that play a key role in the control of a wide number of cellular functions including metabolism, cell growth and motility. Class IA PI3Ks are comprised of PI3K α , β and δ and the sole representative of class IB PI3K is PI3K γ . In terms of tissue distribution, PI3K α and β are ubiquitously expressed whereas PI3K γ and δ are mainly expressed in leukocytes. This expression pattern, in conjunction with mouse genetic studies has established these enzymes as promising targets for the treatment of a number of inflammatory and oncologic diseases. To evaluate the in vivo impact of inhibiting both PI3K β and δ isoforms a series of novel

small molecule inhibitors of these two enzymes was identified. The optimized pyrrolo pyridine analog **17** was a potent and selective PI3K β / δ dual inhibitor that displayed suitable physicochemical properties and pharmacokinetic profile for animal studies. Analog **17** was found to be efficacious in animal models of inflammation such as a keyhole limpet hemocyanin (KLH) study and in a collagen-induced arthritis (CIA) disease model in rats. These studies highlight the potential therapeutic value of inhibiting both the PI3K β and δ isoforms in the treatment of a number of inflammatory diseases.

MEDI 335

Structure-activity relationships (SARs) and mechanism of action of a potent class of N-acylethanolamine acid amidase (NAAA) inhibitors

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N-Acylethanolamine acid amidase (NAAA) is a cysteine hydrolase involved in the regulation of the levels of the endogenous lipid signaling molecules oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) by hydrolyzing these compounds to ethanolamine and the corresponding fatty acid. Several studies have shown that PEA exerts anti-inflammatory and antinociceptive effects in animals by engaging the peroxisome proliferator-activated receptor- α (PPAR- α). Sustaining PEA signaling at PPAR- α by protecting this lipid amide from degradation is therefore envisaged as a novel approach for the treatment of pain and inflammatory states. In this communication, we will discuss the SARs of threonine-derived β -lactones as NAAA inhibitors which led to the discovery of the first single-digit nanomolar inhibitor of NAAA. Furthermore, we will present high resolution LC-MS/MS data demonstrating that β -lactones inhibit human NAAA activity by S-acylation of the catalytically active N-terminal cysteine residue (Cys126) of this enzyme.

MEDI 336

Hydrophobicity of nanoparticles dictates immune response in vitro and in vivo

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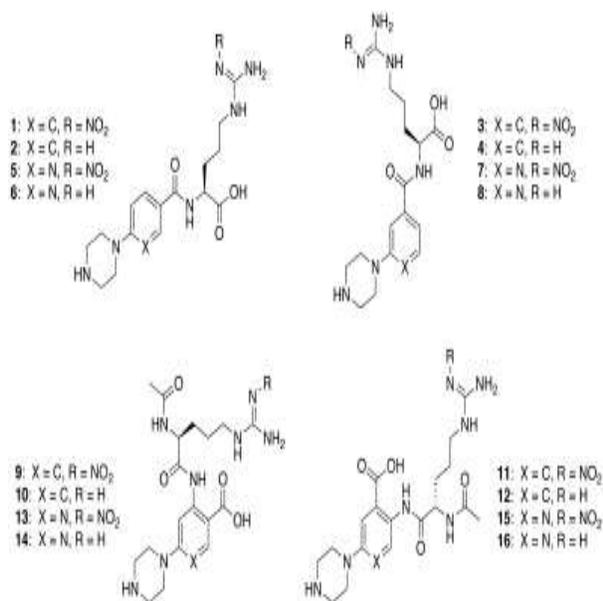
Tuning the immune system response is an important factor in the development of new nanomaterials for applications *in vivo*. However, most macromolecular systems do not allow a systematic study of immune activation, given that the change of one chemical parameter usually causes important structural variations, complicating the relationship. To address this problem, we designed a series of structurally uniform nanoparticles that allow the study of specific chemical factors involved in different biological processes. Employing this family of nanoparticles with splenocytes as the experimental model, we determined the effect of hydrophobicity on the immune response, a parameter theorized to be involved in immune activation. For that purpose, cytokine expression profiles were contrasted against the calculated partition coefficient (LogP, a hydrophobicity index) of the nanoparticle headgroups. A linear increase in immune response was observed when hydrophobicity increased *in vitro*. Using mice as the experimental model a similar response was observed *in vivo*, with variations only at large hydrophobic values, caused principally by nanoparticle biodistribution. These results evidence the importance of hydrophobicity in immune activation, an issue of relevance for both harnessing and understanding the evolution of the innate immune system.

MEDI 337

Group-1 specific neuraminidase inhibitors containing an aromatic scaffold

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Neuraminidase (NA) is best known for its role in proliferation of the influenza virus. Newly reported crystal structures of N1, N4 and N8 indicate the active sites of group-1 NAs are very different from group-2 NA enzymes. We believe the larger active site of group-1 NAs should be accessible to more specific and tighter-binding inhibitors. Accordingly, this presentation will detail the design, synthesis and testing of small inhibitory molecules that are specific toward group-1 neuraminidase.

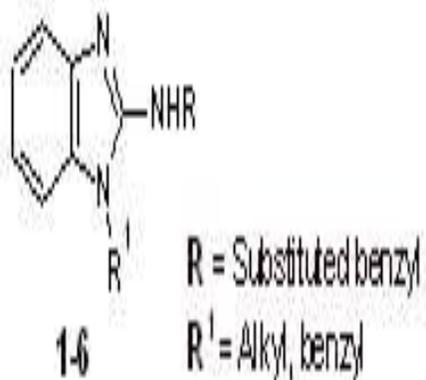


MEDI 338

Synthesis and in vitro antiprotozoal activity of novel 1,2-disubstituted-1H-benzimidazole derivatives

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A series of six novel 1,2-disubstituted-1H-benzimidazole derivatives (**1-6**)



were synthesized and evaluated in vitro against the protozoa *Entamoeba histolytica*, *Giardia intestinalis* and *Trichomonas vaginalis*. Results show that compounds **1-6** were

up to 40, 30, and 2.5 times more active than metronidazole against these parasites, respectively. The synthesis, methodology and results of the in vitro assay will be presented.

MEDI 339

Structural and physicochemical properties of anti-Chagas agents reported in the ChEMBL database and identification of benzoylisoquinolines as potential trypanocidal agents

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Parasitic infections continue to be societal and health burdens, affecting millions of people, mainly in developing countries. The high toxicity, lack of efficacy, resistance, and high cost, highlight the need for the development of new antiparasitic drugs. Here, we present the analysis of the structural and physicochemical properties of compounds tested against *T. cruzi* reported in the ChEMBL database. 3-benzoylisoquinolones were synthesized via Gabriel-Colman rearrangement, and subsequent electrophilic aromatic substitution at position 3 of the benzoyl ring. Two of the samples evaluated exhibited greater trypanocidal activity than the reference drug benznidazole at the assayed concentrations. Chemical space projection of the synthesized compounds along with 3067 structures with known activities against *T. cruzi* shows that the isoquinolones occupy a sparsely-populated region of chemical space. In addition, 2D and 3D structural similarity analyses revealed micromolar and submicromolar inhibitors of *T. cruzi* in ChEMBL with high similarity to the synthesized molecules.

MEDI 340

Potent inhibition of Norwalk virus 3C protease by peptidyl α -ketoamides and α -keto heterocycles

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Noroviruses belong to the Norovirus genus of the Caliviridae family. They are the most common cause of acute gastroenteritis in US and worldwide, accounting for ~23 million

cases in US. Norwalk virus (NV), a prototype of noroviruses, is a small, enveloped virus with a single-stranded, positive sense 7.7-kb RNA genome, which encodes a polyprotein precursor which is co- and post-translationally processed by a virus-encoded cysteine protease to generate mature non-structural proteins. Processing of the polyprotein by Norwalk virus 3C protease is essential for virus replication. NV 3C protease has emerged as an attractive target for the discovery of therapeutics for norovirus infection. Toward that end, the structure-based design, synthesis, and biochemical evaluation of peptidyl α -ketoamides and α -keto heterocycle (figure 1) inhibitors of Norwalk virus 3C protease, will be presented.

MEDI 341

Inhibition studies of triosephosphate isomerase by novel substituted benzimidazole carboxamides

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Triosephosphate isomerase (TIM) has been identified as an important enzyme that plays a crucial role in the energy production for protozoa. It has been found that some benzimidazole derivatives can bind to the enzyme and act as inhibitors. These types of compounds are scaffolds for the design of potential selective strong inhibitors of TIM. As part of our research focused on the structural requirements for the development of benzimidazole derivatives with antiparasitic activity, six novel substituted *N*-(1*H*-benzimidazol-2-yl)-1*H*-benzimidazole-5(6)-carboxamides (**B1-B6**) were designed by docking with the TIMs from *Trypanosoma cruzi*, *Trypanosoma brucei* and *Entamoeba histolytica*. These compounds were synthesized and evaluated in vitro against the recombinant enzymes to validate the model. The results of the docking study and enzyme inactivation are will presented

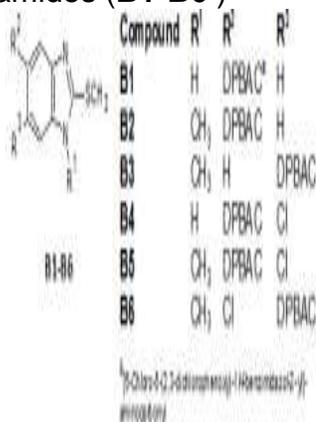
MEDI 342

Synthesis and in vitro antiprotozoal activity of novel substituted benzimidazole carboxamides

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A series of six novel substituted *N*-(1*H*-benzimidazol-2-yl)-1*H*-benzimidazole-5(6)-carboxamides (**B1-B6**)



were synthesized and evaluated in vitro against the protozoa *Entamoeba histolytica*, *Giardia intestinalis* and *Trichomonas vaginalis*. Compounds **B1-B6** showed more activity than metronidazole, the drug of choice against these parasites, mainly against *E. histolytica*. The synthesis, methodology and results of the in vitro assay will be presented

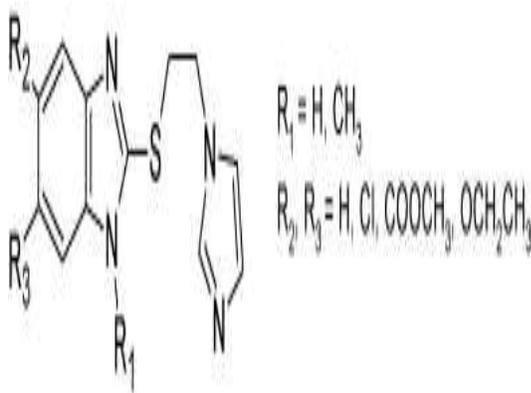
MEDI 343

Synthesis and antiprotozoal activity of some 2-[[2-(1*H*-imidazol-1-yl)ethyl]sulfanyl]-1*H*-benzimidazole derivatives

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Parasitic diseases are still a major health problem in developing countries. Mucosal infections by protozoa affect more than a billion people every year. The most important protozoan infections include giardiasis, amoebiasis and trichomonosis, whose causal agents are *Giardia intestinalis*, *Entamoeba histolytica* and *Trichomonas vaginalis*, respectively. During the last decade benzimidazole nucleus emerged as a promising

scaffold to develop new antiprotozoal agents. As part of our effort to find new antiparasitic agents, in this work we report the synthesis of 19 new 2-{[2-(1*H*-imidazol-1-yl)ethyl]sulfanyl}-1*H*-benzimidazole derivatives and their in vitro antiprotozoal activity.



All compounds synthesized were tested against the protozoa *T. vaginalis*, *G. intestinalis* and *E. histolytica*. Experimental evaluations revealed a strong activity for all compounds tested having IC₅₀ values in the nanomolar range, which were even better than the drug of choice for these parasites (metronidazole).

MEDI 344

Biosynthesis of bicyclo[2.2.2]diazaoctane fungal alkaloids: Malbrancheamide, paraherquamide, and (+)/(-)-notoamide

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Nature has provided a variety of stereoselective tools, which are encoded for within gene clusters of various organisms from all over the world, that catalyze specific chemical reactions to generate complex natural products. One particular class of natural products, the bicyclo[2.2.2]diazaoctane fungal alkaloids, has recently garnered much interest due to their unique synthetic chemistry and clinical applications. Affordable and efficient high throughput sequencing techniques, combined with bioinformatic analyses of genomes for identification of biosynthetic gene clusters, have facilitated a sequence-based discovery approach to the biosyntheses of structurally similar fungal alkaloids. *Despite advancements in technology, a strong biochemical understanding of the chemical transformations that produce a variety of similar products and the*

development of a methodical chemical biology approach are necessary to broaden the pool of chemical diversity. Here, we summarize the progress in genome mining and identification of four fungal alkaloid gene clusters (+)/(-)-notoamide, paraherquamide, and malbrancheamide. By comparative analysis, we are able to construct a putative biosynthetic pathway for each product based on biochemical and bioinformatic data. These data have allowed us to progress toward a better understanding of the biosynthetic pathways that construct these molecules and include the pursuit of an elusive Diels-Alderase candidate that is expected to form the bicyclo[2.2.2]diazaoctane core.

MEDI 345

Study of asymmetric quinoline methanols as antimalarial compounds

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Malaria is caused by *Plasmodium* and is responsible for about 780.000 deaths every year. Research of a new antimalarial chemotherapy has become urgent because of parasite resistance to classical drugs. Mefloquine (Lariam®) is a commercial antimalarial drug whose use may induce adverse side effects, such as insomnia, depression, and suicide. All these effects might be related to the accumulation of (-)-erythro-mefloquine into the brain.

To this purpose, we have realized an efficient asymmetric synthesis route of each enantiomeric mefloquine analogs. The obtained compounds were analyzed by biological tests (*in vitro* activities, cytotoxicity, research of mechanism of action) and showed encouraging results on different *Plasmodium falciparum* strains (3D7 and W2). Consequently, other tests like *in vivo* activities and crossing blood-brain barrier are in progress.

MEDI 346

Discovery of orally available serine palmitoyltransferase inhibitors for chronic hepatitis C patients

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Although direct-acting antiviral agents (DAA) for chronic hepatitis C (CHC) have been approved by the U.S. FDA, several patients treated with DAA in combination with ribavirin relapsed in clinical, making it necessary to develop novel antivirals which avoid emerging viral resistance required. We are interested in identifying a novel HCV replication inhibitor that manipulates host cell factors to solve the resistance issues. At the previous ACS meeting, we presented a novel host factor-targeting anti-HCV agent, NA808, which showed strong inhibition of sphingolipid biosynthesis with potent anti-HCV replicon activity ($IC_{50}=2nM$) and significant viral reduction in humanized-liver chimeric mice. Although the oral absorption of NA808 was poor in rat ($BA<1\%$), pro-drug approach and chemical modifications improved the AUC, bringing improved bioavailability. We have identified an orally available serine palmitoyltransferase inhibitor, CH8755, which not only showed remarkably improved oral bioavailability, but also converted well to an active substance without severe toxicity in rat. In this study, the profiles of an anti-HCV clinical candidate will be discussed.

MEDI 347

Binding mode prediction of HCV NS3A protease inhibitors

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Computer-aided drug design methodologies are valuable tools that can be used for prediction of the binding mode of small molecules in the three-dimensional structure of a protein. This task becomes more challenging if the ligand is flexible, the case of many known potent inhibitors of HCV NS3A protease. The flexibility of the inhibitors and the fact that the active site of the NS3A protease is flat and featureless makes it difficult to model the designed inhibitors.

A docking protocol for the prediction of NS3A protease inhibitors has been developed that includes a Monte Carlo simulation step, a molecular dynamic step and a minimization step. Re-docking experiments using crystallized ligand-protein structures have been used to optimize the parameters. The docking protocol has been applied to a diverse set of synthesized NS3A protease inhibitors in our lab.

MEDI 348

Small molecule inhibitors of malate synthase against *M. tuberculosis*

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A broad consensus exists in the TB research community that the key to shortening the duration of drug therapy, and to decreasing relapse rates, lies in the specific targeting of the pathways essential to the non-replicating persistence (NRP) state of *Mtb*. One such target is malate synthase (MS or GlcB), an enzyme in glyoxylate shunt. It has been shown that disruption of the glyoxylate shunt attenuates bacterial persistent and virulence in immunocompetent mice. Recent success in the structure elucidation of the MS protein and the availability of functional assays for MS opens a way to apply computer-aided drug design methods in concert with medicinal chemistry efforts to discover new therapeutic agents for NRP TB. The structure-based and ligand-based drug design methods were used to generate leads with chemical diversity. 95 compounds were tested in vivo and in vitro against malate synthase. At 60 uM concentration, one compound inhibited more than 90% of MS activity, and two compounds inhibited around 60%. At 300 uM concentration, one compound inhibited more than 70% of MS activity, one compound inhibited around 40%, eight compounds more than 20%, and four compounds more than 10% of activity of MS. In MABA assay, 8 compounds having % Inhibition > 70% at 128 uM and 12 compounds having % Inhibition > 70% at Conc. 100 ug/ml. 9 compounds have a MIC value less than 100 ug/ml in LORA. 10 compounds that were active in both MABA and LORA were tested against Vero cell toxicity with 5 compounds having an IC50's ranging from ca 5-70 uM. In this study the design, SAR, computational analysis, and future plans will be discussed.

MEDI 349

Synthesis of heterocyclic aryl sulfones and the investigation of their potential therapeutic uses

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Sulfones are compounds that have shown activity against many diseases such as; malaria, tuberculosis, leprosy, HIV; and consequently are highly desirable lead molecules for research. In this laboratory, a two-step approach has identified novel therapeutic targets for prospective sulfone products. The first step utilized high throughput screening of small molecule databases through a program called Shape Signature. This program yielded sulfone products of interest which have antitumor, antibacterial or analgesic properties. The second step would include the synthesis and assay screening of derivatives from active lead molecules to confirm activity.

These aryl sulfone products are typically accessed through acid catalyzed rearrangements from the sulfonanilide to a sulfone product. This method provided a quick means to obtain sulfone products from the sulfonanilide intermediates. This presentation will focus on the synthesis of carbazole, iminostilbene, and imidodibenzyl sulfone due to previously synthesized analogs that have shown to have therapeutic activities.

MEDI 350

Allosteric HIV-1 protease inhibition: Design, synthesis, and biological evaluation of novel 1,4-benzodiazepines as β -hairpin flap mimetics

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Traditional HIV-1 protease (HIV-1 PR) inhibitors target the enzyme active site in a competitive fashion; however, owing to mutations there, many drugs are losing their efficacy. New anti-HIV drugs with novel modes of inhibition are urgently needed. HIV-1 PR is a C_2 -symmetric homodimer where the enzyme's active site is "gated" by two glycine-rich, anti-parallel β -hairpin flaps (residues 43-58) that recognize each other predominantly through hydrophobic interactions. Targeting the flaps with small-molecules that can control flap conformation represents a novel and allosteric mode of HIV-1 PR inhibition, which may afford inhibitors that are refractory to mutations. Herein, we present the synthesis of novel therapeutic agents constructed around a 1,4-benzodiazepine scaffold, a well-known functional β -turn mimetic, which have been designed to mimic one of the β -hairpin flaps and probe into the "eye" site, thereby preventing flap closure. Preliminary biological studies suggest our novel compounds demonstrate promising inhibition of HIV-1 PR.

MEDI 351

7-(2-phenoxyethoxy)-4(1H)-quinolones as antimalarials

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Malaria is one of the most destructive diseases in the world annually affecting over 200 million people and killing almost one million people per year. Although several antimalarial agents are currently used successfully, the emergence of multidrug resistance signals the importance to developing new antimalarials. Previously, compound ICI56,780 was reported to display causal prophylactic and blood schizonticidal activity in rodent malaria models. Unfortunately, ICI56,780 generated rapid parasitological resistance in *P. berghei* infected mice. Herein the synthesis of analogues of ICI56,780 with low EC50 values against *P. falciparum* will be presented. By introducing ortho-substituted aryl groups at the 3-position of the 7-(2-phenoxyethoxy)-4(1H)-quinolone core, good activities with low cross resistance indexes to atovaquone were obtained.

MEDI 352

Bioguided phytochemical studies on *Phyllanthus amarus*

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Phyllanthus amarus of the Euphorbiaceae family is the most widespread of the genus *Phyllanthus* and is a common annual weed which has been used extensively in Ghana and Chinese traditional medicine for the past centuries for gonorrhoea, Hepatitis B and other sicknesses. The anti-typhoid activity of *P. amarus* however is yet to be studied. Typhoid fever is a leading cause of death in developing countries because of few antibiotic options and increasing multi-drug resistance. Preliminary studies have shown that *P. amarus* has activity against *Salmonella typhi*. This poster discusses the bioguided phytochemical steps towards identifying the compound(s) in *P. amarus* that have anti-typhoid activity. Authenticated *P. amarus* samples were thoroughly washed with water, sun-dried, milled and extracted with 95% ethanol by soxhlet extraction. The crude ethanolic extract was evaporated, filtered through silica gel collected into fractions and purified by HPLC. Results of spectroscopic characterization and bioassay will be presented.

MEDI 353

Synthesis and SAR studies on rhodanine analogs as allosteric inhibitors of HCV NS5B polymerase

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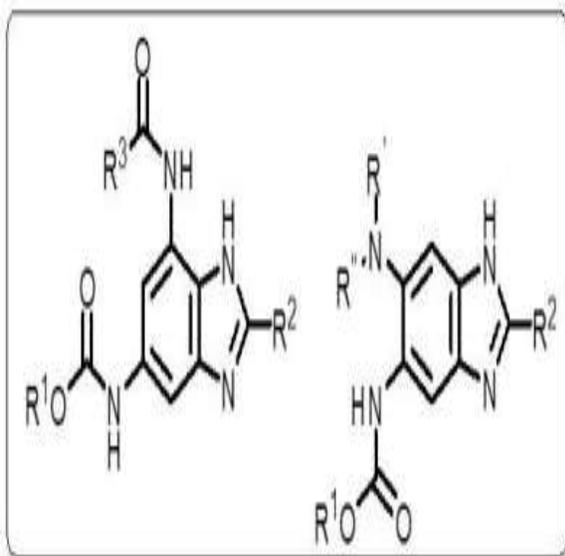
Hepatitis C virus (HCV) NS5B polymerase is pivotal for replicating the viral RNA genome and is therefore an important target for therapeutic intervention of HCV infection. Starting from our lead compound (2-(5-(2,4-dichlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid, IC₅₀ = 10.6 μM), we have carried out extensive SAR around the C-5-benzylidene substituent leading to the identification of (2-(5-(3-phenoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid) with an IC₅₀ value of 7.7 μM. Further SAR optimization will be based on identification of optimal substituents at the phenoxy ring. The synthesis, biological evaluation and SAR of these derivatives will be discussed.

MEDI 354

Design, synthesis, optimization, and biological evaluation of novel trisubstituted-benzimidazoles as efficacious antitubercular and antimicrobial agents, targeting FtsZ

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FtsZ is a ubiquitous protein that plays an essential role in bacterial cytokinesis. Inhibition of FtsZ (de)assembly leads to absence of septum formation, eventually causing cell lethality. Therefore, we hypothesized that FtsZ-inhibitors can be developed into broad-spectrum antibacterial agents possessing novel mechanism of action. Based on rational drug design, a library of novel trisubstituted-benzimidazoles was synthesized and number of which exhibited MIC₉₉ values of ≤ 0.5 μg/mL against drug sensitive and drug resistant *Mtb* cells. Several lead compounds inhibited *Mtb*-FtsZ assembly while enhancing the GTPase activity which was supported by SEM images of *Mtb* cells and TEM images of *Mtb*-FtsZ nucleation/polymerization. Furthermore, lead compounds were found to be active *in vivo* in the rapid animal model. As FtsZ is highly conserved, a large number of benzimidazoles exhibited excellent MIC values against various other pathogens. Synthesis, optimization and *in vitro* and *in vivo* biological evaluation of novel benzimidazoles against *Mtb* and other pathogens will be presented.



MEDI 355

Antimicrobial activity of 4,5,6,7-tetrachlorobenzimidazolium based silver carbene complexes

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Bacterial resistance to current treatments is beginning to appear all across the world. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are on the rise in hospitals and in communities across the United States. Silver N-heterocyclic carbene complexes have shown promising results as antimicrobial agents, displaying activity against both Gram-positive and Gram-negative bacteria. Three silver carbene complexes (**SCCs**) based on 4,5,6,7-tetrachlorobenzimidazole has been synthesized, characterized, and tested against a panel of clinical strains of bacteria. These complexes proved highly efficacious with minimum inhibitory concentrations ranging from 0.25-6 µg/mL. Overall, the complexes were effective against highly resistant bacteria strains, such as MRSA, weaponizable bacteria, such as *Yersinia pestis*, and pathogens found within the lungs of cystic fibrosis patients, such as *Pseudomonas aeruginosa*, *Alcaligenes xylosoxidans*, and *Burkholderia gladioli*. Two **SCCs** also showed clinically relevant activity against a silver-resistant strain of *Escherichia coli* J53+pMG101 based on MIC testing.

MEDI 356

Acylated cyclic polyarginine cell-penetrating peptides as molecular transporters and antibacterial agents

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Most of the reported arginine-rich cell-penetrating peptides (CPPs) for enhancing the drug delivery are linear peptides, and have more than seven arginines to retain the cell penetration properties. Herein, we synthesized a number of polyarginine peptides (R₅ and R₆) as template CPPs, and explored the effect of acylation and cyclization. The molecular transporter property of acylated cyclic R₅ (e.g., dodecanoyl-[R₅]) was compared with those of acylated linear R₅ (e.g., dodecanoyl-(R₅)) and unmodified cyclic R₅ ([R₅]) (10 μM) using flow cytometry. The combination of acylation and cyclization enhanced the cellular uptake of a fluorescence-labeled phosphopeptide (F-GpYEEI) (5 μM) in human SK-OV-3 cancer cell lines by three-fold, showing higher uptake than heptaarginine (R₇) and TAT peptides. The hydrophobic dedecanoyl moiety improved the uptake, possibly through interaction with the phospholipids in the cell membrane. Both dodecanoyl-[R₅] and dodecanoyl-[R₆] showed potent antibacterial activities against *Staphylococcus aureus* ATCC 29213 with MIC values of 4.3-4.9 ng/mL.

MEDI 357

Two-metal pharmacophore design strategy utilized discovery of carbamoyl pyridone integrase inhibitors

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HIV-1 integrase is a virally encoded enzyme essential for replication. Since diketo acid inhibitors were identified many efforts have been directed toward the discovery of integrase strand transfer inhibitors (INSTi). These efforts have culminated in the discovery of raltegravir, the first marketed HIV-1 INSTi. However, there is significant opportunity for improvement including overall dose burden, dosing interval and potency against resistant viruses. By using a two-metal pharmacophore based design strategy, a core carbamoyl pyridone motif was constructed to effectively coordinate two magnesium cofactors while templating an aromatic group into a hydrophobic pharmacophore space. The series exhibited potent antiviral activity with promising DMPK properties. Optimization of this series led to the discovery of dolutegravir which demonstrated the sought after differentiation and improvements over existing drugs.

MEDI 358

Synthesis and optimization of selective *N*-phenylethyl piperazine analogs as sigma-2 receptor antagonists

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Drugs that have the capability to suppress the psychostimulant activities of methamphetamine are highly sought after technologies, yet little success has been achieved due to the number of receptors with which the substance interacts. It has been shown that selective sigma receptor antagonists attenuate many of the stimulant (σ) and neurotoxic (σ_2) effects of methamphetamine, indicating that drug development aimed specifically at sigma receptors has the potential to yield an effective treatment for the stimulant and neurotoxic effects of methamphetamine. A previously synthesized compound, UMB24 has shown selectivity for σ_2 . Radioligand binding assays were performed to determine receptor subtype selectivity and molecular modeling was performed using the conformationally sampled pharmacophore approach. The aim of this project is to synthesize analogues of UMB24 to determine the optimal conformation of ring constrained analogues to enhance the selectivity for σ_2 .

MEDI 359

Towards the synthesis of C5-C14 bridged analogs of thebaine

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Morphine and related opioid analgesics are an important class of therapeutics agents, yet their use is limited by the rapid development of tolerance. Increased doses build constipation, leading to severe complications. Our approach to designing an opioid analgesic with reduced tolerance is to design a drug with a mixed profile of mu opioid agonism and delta opioid antagonism, a profile demonstrated to lead to lower degrees of tolerance. The design necessitates the introduction of a bridge across the morphinan skeleton from C5 to C14, a new scaffold. Our synthesis starts from thebaine, which was alkylated at C5 position with ethylchloroformate, followed by reduction to the corresponding alcohol. This was oxidized using $H_2O_2/HCOOH$ followed by hydrogenation to obtain the key intermediate. This was the focus of C5-C14 ring closure reactions, new analogs were synthesized, assessed their opioid receptor binding activities in vitro and selected candidates were planned to test in vivo.

MEDI 360

Binding ensemble profiling with (f)photoaffinity labeling (BEProFL): Development of clickable GBR-12909 photoprobes for dopamine transporter (DAT) structure-function studies

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Currently there are no FDA approved medications clinically indicated for cocaine addiction. GBR-12909 is a well-known dopamine transporter (DAT) inhibitor that showed tremendous promise in treating cocaine abuse. However, its development was halted after phase II clinical studies due to observations of long QT syndrome. Despite its clinical significance, the specific drug-protein contacts responsible for GBR-12909's anti-addiction properties remain unknown. Based on established structure-activity relationships for GBR-12909, we have rationally designed and synthesized several clickable photoprobes for application of a BEProFL approach, which couples photoaffinity labeling with molecular modeling in order to map the binding sites and poses of ligands within target proteins. After pharmacological evaluation, the probes will be used in DAT photoaffinity labeling experiments, wherein the results will be coupled with 3-D DAT molecular modeling in order to identify amino acids involved in the therapeutic action of GBR-12909.

MEDI 361

Binding ensemble profiling with (f)photoaffinity labeling (BEProFL): Mapping the binding sites and poses of selective serotonin reuptake inhibitors (SSRIs) within the serotonin transporter (SERT)

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SSRIs represent first-line agents for the treatment of anxiety and depression. Despite the well-documented success of SSRIs, the specific drug-protein interactions that lead to clinical efficacy remain unknown. In order to understand how SSRIs interact with SERT at the molecular level, we are developing clickable photoaffinity ligands based on fluoxetine and citalopram. Using established structure-activity relationships, we have rationally designed, synthesized, and pharmacologically evaluated several SSRI probes containing a photoreactive group and a click chemistry handle, thus enabling application of a "Binding Ensemble Profiling with Photoaffinity Labeling" (BEProFL) approach. In turn, covalently-modified SERT samples were generated via photoaffinity labeling and mass spectrometry studies of enriched photolabeled SERT are currently in progress to determine specific drug-protein contacts. The results will be coupled with 3-D SERT

molecular modeling in order to map the binding sites and poses of citalopram and fluoxetine as SSRIs within SERT

MEDI 362

Binding ensemble profiling with (f)photoaffinity labeling (BEProFL): Mapping the binding sites and poses of Bupropion within the dopamine transporter (DAT) and nicotinic acetylcholine receptors (nAChRs)

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Despite the well-documented success of bupropion as a smoking cessation agent (Zyban) and antidepressant (Wellbutrin), the specific drug-protein interactions that lead to its clinical efficacy remain unknown. Via application of a BEProFL approach, which couples photoaffinity labeling with molecular modeling, we aim to map the binding sites and poses of bupropion within the DAT and selected nAChRs. In order to meet this objective, a photoreactive bupropion analog was rationally designed, synthesized, and pharmacologically evaluated at the DAT and selected nAChRs. A subsequent ¹²⁵I analog was shown to bind covalently to hDAT expressed in cultured cells and mapped to the channel lining M2 segment of the *Torpedo* nAChR via photoaffinity labeling. This probe is currently being mapped in selected neuronal nAChRs. Additionally, a probe based on bupropion's known active metabolite is being pursued. These bupropion photoprobes are expected to serve as useful tools for DAT and nAChR structure-function studies.

MEDI 363

Novel routes to a structurally diverse library of substituted-γ-butyrolactones: Synthesis and preliminary evaluation as muscarinic ligands

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Muscarinic acetylcholine receptors have five subtypes i.e. M1-M5 with physiological roles range from controlling smooth muscle tone to neurotransmitter release in the central nervous system. Hence these receptor subtypes have been investigated as potential therapeutic targets for agents capable of treating Alzheimer's disease, Parkinson's disease, COPD, urinary incontinence and muscle spasms. Previous work

identified lactones and nitrogen-containing heterocycles as useful scaffolds for the design of muscarinic ligands. Our interest in preparing libraries of functionally diverse compounds for screening in drug discovery projects led to the development of efficient routes to substituted γ -butyrolactones and nitrogen containing heterocyclic rings. Combinations of the two scaffolds via various linker systems provided a novel compound library that was screened in muscarinic receptor binding assays. The development of novel synthetic methods, the results of preliminary binding data and the structure activity relationship for the series are discussed.

MEDI 364

C-linked replacements of the methyl-imidazole subunit of γ -secretase modulators

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The cleavage of amyloid precursor protein via β - and then γ -secretases leads to the production of amyloid- β peptides (A β) of various chain lengths. This production of A β is thought to be a leading factor in the development of Alzheimer's disease. Of the various A β fragments generated, A β -42 is prone to forming amyloid plaques in the brain. The development of γ -secretase modulators (GSM's) provides a means to alter the production from A β -42 to shorter, more soluble A β fragments. In addition, GSM's provide an attractive alternative to γ -secretase inhibitors since they do not block other γ -secretase functions such as Notch processing. We report on a series of oxadiazoline and oxadiazine GSM's with novel heterocycle replacements of the terminal methyl-imidazole moiety of our earlier leads. In addition to possessing a modulator profile, these molecules reduced A β -42 in rat CSF, and in some cases the reduction was equal to the methyl-imidazole control.

MEDI 365

SAR study, synthesis, and biological activity of lurasidone hydrochloride (LATUDA): New treatment drug for schizophrenia

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Lurasidone hydrochloride (LATUDA[®]) received approval by FDA on 2010 for the treatment of schizophrenia. Lurasidone is a full antagonist at dopamine D₂, serotonin 5-HT_{2A} and 5-HT₇ receptors. And also a partial agonist at 5-HT_{1A} receptors; it is believed to be potentially related to effects on cognition and mood. Of particular note is that lurasidone has minimal affinities for receptors that might induce adverse events. The low affinity for alpha 1 noradrenergic receptor suggests lower risk for orthostatic

hypotension. Moreover the minimal affinity for 5-HT_{2C} and histamine H₁ receptors suggests lower liability for weight gain as well. The lack of affinity for cholinergic M₁ receptors enables to avoid anticholinergic side effects. We could proudly say that these fine profiles were achieved by exquisite design of molecule structure. Here, we report the structure and activity relationships, synthesis and pharmacological profiles of lurasidone.

MEDI 366

Quantitative insights into pharmacological profiles for lurasidone and other antipsychotics by the thermodynamics integration method

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Lurasidone hydrochloride (LATUDA[®]), a novel antipsychotic, has potent binding affinity for D₂ and 5-HT_{2A} receptors, and negligible affinity for H₁ and M₁ receptors. Our previous docking study and structural analysis suggested that lurasidone acquired the high selectivity for the “desired” GPCRs by the combination of the cyclohexyl-linker and the norbornane-2,3-dicarboximide moiety. In order to validate the previous binding models of lurasidone and gain quantitative insights into the different pharmacological profiles of other antipsychotics, we carried out the calculation of the binding free energy based on the thermodynamics integration method for lurasidone, ziprasidone, and olanzapine to the four GPCRs. As a result, we obtained good correlation between the calculation and experiment binding free energy for all drug–receptor pairs. This correlation enables to discuss the difference in the pharmacological profiles of three antipsychotics quantitatively based on the thermodynamics of the drug–receptor interactions with the structural water and the protein flexibility.

MEDI 367

Beta-Secretase (BACE1) inhibitors for Alzheimer's disease

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According to the amyloid cascade hypothesis, Alzheimer's disease pathogenesis is characterized by the buildup and deposition of amyloid beta (A β) plaques in the brain. β -Secretase (BACE-1) initiates this process by cleaving β -amyloid precursor protein (APP) at what will ultimately be the N-terminus of A β . Thus, targeting the inhibition of BACE has been of significant interest for more than a decade. We will report the

discovery of a series of morpholine-derived amidines for the BACE-1 inhibitor program. These inhibitors offer improved selectivity and ligand efficiency profiles as compared to alternative series in the literature. The development of a library-enabled synthetic route allowed for the rapid optimization of potency. Subsequent examination of ADME characteristics quickly highlighted a challenge of limited brain penetration. Strategies executed to mitigate this liability will be presented.

MEDI 368

Tetrahydropyridopyrimidine inhibitors of phosphodiesterase 10A for treatment of the positive and cognitive symptoms of schizophrenia

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We present the discovery of a novel series of tetrahydropyridopyrimidine phosphodiesterase 10A inhibitors originating from a proprietary Merck HTS lead. Systematic compound optimization afforded molecules with low nanomolar potencies, excellent pharmacokinetic properties, and clean ancillary profiles. Following oral dosing, leading inhibitors displayed *in vivo* target engagement measured by elevated rat striatal cGMP levels. They also display robust dose-dependent efficacy in key pharmacodynamic assays including the psychostimulant-induced rat hyperlocomotion assay and the conditioned avoidance response assay for anti-psychotic activity, as well as the novel object recognition assay, a measure of episodic-like memory. Leading inhibitors also showed negligible activity in the adverse event assays measuring circulating prolactin levels, rodent catalepsy, and body weight gain compared to positive controls.

MEDI 369

Development of novel positive allosteric modulators for metabotropic glutamate receptor subtype 5

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Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS), acting through both metabotropic and ionotropic glutamate receptors. Metabotropic glutamate receptors (mGluRs) are members of the G-protein-coupled receptor (GPCR), characterized by a large extracellular N-terminal ligand-binding domain and 7-helical transmembrane domain. The mGluR5 belongs to the subgroup I of mGluRs. Experimental evidence from animal models has shown that, activation of mGluR5 by positive allosteric modulators (PAMs), is highly neuroprotective after traumatic brain injury (TBI). In our on-going project to develop PAMs for mGluR5, novel compounds with good potency, selectivity and efficacy have been synthesized. The design, structural-activity relationship (SAR), and biological evaluations of the new PAMs are detailed

MEDI 370

Substitued 5-(alkylthio)-4-(arylamino)pyrimidine derivatives as corticotropin releasing factor receptor 1 (CRFR1) antagonists

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Hyperactivation of corticotropin releasing factor (CRF) in stress response system pathways is linked to stress-related psychopathology. The CRF receptor antagonists, particularly CRF receptor 1, have been proposed as novel therapeutic agents for depression, anxiety and addiction disorders. CRF is a 41 amino acid containing peptide released from the Para ventricular nucleus (PVN) of the hypothalamus. It is a critical to the integrity of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress. CRF mediates its actions through two G protein-coupled receptors: CRF receptor 1 (CRFR1) and CRF receptor 2 (CRFR2). While CRFR1-mutant mice display a depleted stress response and display anxiolytic-like behavior, CRFR2-mutant mice are hypersensitive to stress and display anxiogenic-like behavior. Thus CRFR1 antagonists may provide novel therapeutic agents for treating anxiety, depression and addictive disorders.

Numerous peptide and non-peptide molecules have been shown to inhibit CRF mediated stress disorders through CRFR1. In our studies, we have synthesized several new 5-(alkylthio)-4-(arylamino)pyrimidine derivatives as potential CRFR1 antagonists. These derivatives were analyzed for their effect on mRNA expression of several markers of psychopathology including; CRF1, serotonin transporter (SERT), the cAMP

response element-binding (CREB), monoamine oxidase-A (MAO-A), dopamine transporter (DAT), dopamine β -hydroxylase (DBH) and cAMP levels in α T3-1 pituitary mouse cell line and compared with Antalarmin. Some of the derivatives showed comparable results with Antalarmin. These compounds will be also evaluated for their binding affinities to CRF1 receptors and those showing comparable parameters of interaction with CRFR1 as Antalarmin will be further evaluated in animal studies.

MEDI 371

In silico study approach for the synthesis of cytosine analogs targeting the $\alpha_4\beta_2$ nAChR

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Cytosine is a natural alkaloid used in European countries as a smoking cessation drug due to its affinity towards the $\alpha_4\beta_2$ nAChR. However, cytosine shows low bioavailability with serious side effects. Designing cytosine analogs with a higher affinity towards the receptor would reduce the dose needed to suppress the dopaminergic response and the toxic side effects of cytosine. Our approach involves the use of molecular docking and QSAR studies to develop cytosine analogs that express a higher affinity for nAChR $\alpha_4\beta_2$ than commercially available drugs. OpenEye® was used to create a virtual library of cytosine analogs and predict their interaction with the $\alpha_4\beta_2$ nAChR. Several cytosine analogs with higher affinity than varenicline were synthesized. Binding affinity (K_i) values were used to prepare a QSAR analysis and predict the K_i values for the already synthesized compounds which ranged between 44-3236 nM. Synthesis of cytosine analogs and the *in silico* studies will be presented.

MEDI 372

Investigation of piperazine derivatives as sigma receptor ligands with methamphetamine antagonist activity

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Sigma receptors are associated with various central nervous system disorders schizophrenia, regulation of motor behavior, convulsions, anxiety, and the psychostimulant effects of drugs of abuse. At least two different types of sigma (sigma-1

and sigma-2) receptors have been identified. It has been demonstrated that antagonism of the sigma-1 receptor can attenuate the toxic and stimulant effects of methamphetamine. We have designed and synthesized several piperazine derivatives that possess high affinity and selectivity for sigma receptors. These compounds have been tested *in vivo* and demonstrated blockade of the behavioral and toxic effects of methamphetamine.

MEDI 373

Selective sigma-2 receptor ligands derived from tetrahydroisoquinolone

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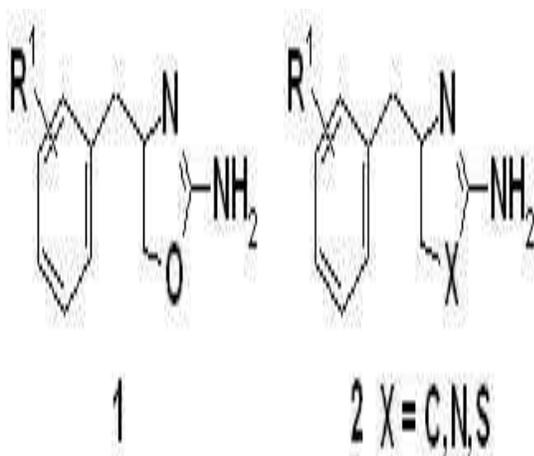
Sigma receptors are known to be involved in several areas of central nervous system disorders including the actions of drugs of abuse. In our ongoing effort to obtain highly selective sigma receptor ligands, we have synthesized a series of tetrahydroisoquinolone derivatives that demonstrate selectivity for sigma-2 receptors. This is important because there are no truly selective sigma-2 ligands available to probe the pharmacology associated with this subtype. These compounds should help to serve as tools for the scientific community and aid in this regard. The role of sigma-2 receptors in the actions of psychostimulants is not entirely clear but our results demonstrate that these compounds can block the behavioral effects of cocaine.

MEDI 374

Structure genotoxicity relationships of selective alpha_{2C}-AR agonists

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The α_{2C} adrenergic receptor (AR) subtype is involved in many central nervous system processes and contributes to spinal analgesic actions.^[1] In this context, new agonists discriminating α_{2C} -AR from α_{2A} -AR open up the perspective of drug discovery for robust analgesia without cardiovascular and sedative side-effects.^[2] Chemical modulation around 2-amino-oxazoline **1** led to the identification of selective α_{2C} -AR agonists^[3] but hampered by *in vitro* and *in vivo* genotoxicity.



The general approach of capturing structure-genotoxicity relationships to get rid of this liability will be depicted. In particular, identification of key structural features responsible for genotoxicity was realized. From these efforts, a new back up chemical series **2** was identified overcoming genotoxicity issues related to scaffold **1** .

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Acknowledgements

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MEDI 375

Virtual screening and computational optimization for the discovery of covalent prolyl oligopeptidase inhibitors with activity in human cells

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Prolyl oligopeptidase (POP) is a serine endoprotease linked to neurodegenerative (e.g. Alzheimer's disease) and psychiatric (e.g. bipolar disorder) disorders. By using computational tools along with evaluation of synthetic feasibility, a first series of constrained covalent inhibitors exhibiting activity and selectivity for POP was developed. We present here the discovery of a new chemical scaffold discovered by a fully automated **virtual screening**.

A virtual hit molecule together with analogues were selected for synthesis and made in one to five chemical steps. Biological evaluation and metabolic stability have also been investigated. This new scaffold shows not only activity in the high nanomolar range in intact cells but also acceptable metabolic stability.

In conclusion, we described herein a scaffold with an improved profile compare to our first developed inhibitor. Investigation on the pharmacokinetic and thermodynamic profile of this scaffold is currently performed.

MEDI 376

Structure activity relationships and molecular modeling of the N-(3-pivaloyloxy-2-benzylpropyl)-N'-[4-(methylsulfonylamino)benzyl] thiourea template for TRPV1 antagonism

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The structure activity relationships of *N*-(3-acyloxy-2-benzylpropyl)-*N'*-4-[(methylsulfonylamino)benzyl] thioureas, which represent simplified RTX-based vanilloids, were investigated by varying the distances between the four principal pharmacophores and assessing binding and antagonistic activity on rTRPV1. The analysis indicated that a 3-pivaloyloxy-2-benzylpropyl C-region conferred the best potency in binding affinity and antagonism. The molecular modeling of this best template with the tetrameric homology model of rTRPV1 was performed to identify its binding interactions with the receptor.

MEDI 377

Norcamphor based NMDA receptor antagonists

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Our group has been investigating design and syntheses of N-methyl-D-aspartate receptor (NMDAR) antagonists as possible neuroprotective agents. Such compounds can be useful in the treatment of various disorders including epilepsy, Alzheimer's disease and neuropathic pain. Previous efforts by our group have confirmed 2-arylbornan-2-amines to be significant micromolar antagonists in vitro. These compounds have also displayed anticonvulsant activities in vivo. However, the compounds are racemic. Four diastereomers are possible for each compound. Stereoselective synthetic as well as resolution schemes have been devised to yield each enantiomer of target compounds starting with commercially available norcamphor. Grignard reaction gave racemic alcohol which was converted into diastereomers and separated. Target compounds resulting from such intermediates can help shed light on the pharmacophore for binding on NMDAR.

MEDI 378

Antioxidant properties of novel NMDA receptor antagonists and radiosensitizers

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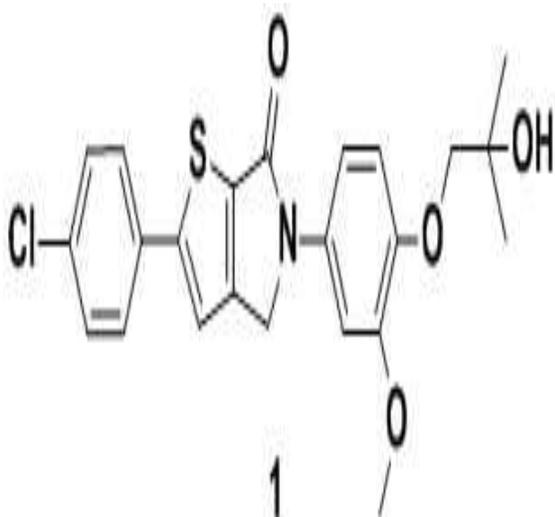
Our studies examined the antioxidant properties of two classes of compounds, N-methyl-D-Aspartate receptor (NMDAR) antagonists and radiosensitizers. Antioxidant properties can augment or attenuate desired functions of these compounds, which are their abilities to treat neurodegenerative diseases and cancers, respectively. We evaluated the capability of each compound to scavenge reactive oxygen species (ROS) using nitric oxide (NO) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical activity assays. The results showed insignificant decrease of free radical production in both assays. Hence, we conclude that the antioxidant properties seem not to have a negative effect on desired biological activity of the radiosensitizer compounds. For the NMDAR antagonists, the observations suggest that they do not have a secondary antioxidant mechanism of reducing ROS. We are now examining the abilities of these compounds to inhibit ROS production in a human neuroblastoma cell line (SK-N-SH). Correlation of results of chemical and biological assays will be examined.

MEDI 379

Thienopyrrolones as potent melanin-concentrating hormone receptor 1 (MCHR1) antagonists for the treatment of obesity

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Abstract: Melanin concentrating hormone (MCH) is a cyclic 19 amino acid peptide synthesized primarily in the lateral hypothalamus and zona incerta. ICV injection of MCH in rats stimulates food intake while fasting results in an increase in MCH expression. Mice lacking the MCH gene are lean, hypophagic and have increased metabolic rates while mice overexpressing MCH are hyperphagic and overweight. A lean, hypophagic phenotype is also observed in mice in which the MCH receptor (MCHR1) has been deleted. Therefore, it is generally believed that MCHR1 antagonists could be used as a potential treatment for obesity. In this poster, we present the synthesis and SAR of a series of novel thienopyrrolone MCHR1 antagonists, exemplified by 2-(4-chlorophenyl)-5-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-4H-thieno[2,3-c]pyrrol-6(5H)-one (**1**).



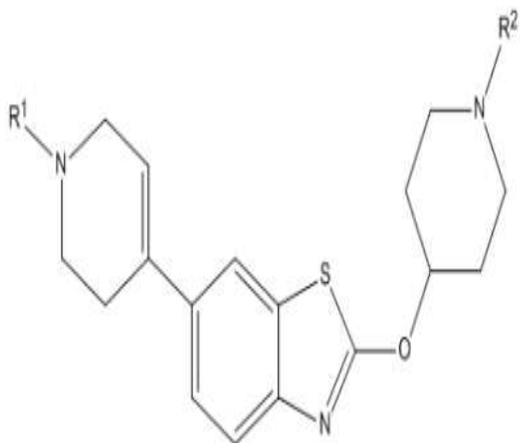
MEDI 380

Discovery of novel benzothiazole derivatives as potent GPR119 agonists for the treatment of type II diabetes

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GPR119 is a G-protein-coupled receptor mainly expressed in pancreatic islets and gastrointestinal tract. Activation of the GPR119 receptor stimulates glucose-dependent insulin secretion from β -cells and GLP1 secretion from the L-cells. Thus, agonists of

GPR119 are promising oral glucose lowering agents for type II diabetes. Here we report the discovery of a novel class of benzothiazole analogs as potent GPR119 agonists. The synthesis, structure-activity relationship (SAR) studies and the in vivo preclinical pharmacology will be discussed.

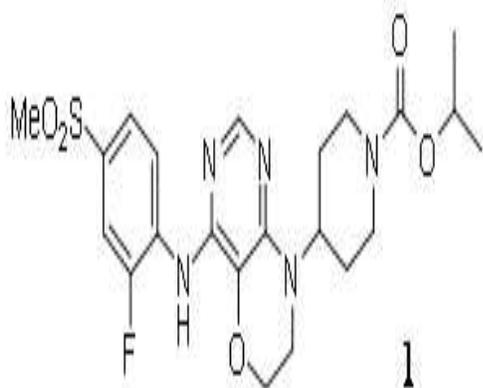


MEDI 381

Synthesis and SAR of bicyclic pyrimidines as GPR119 receptor agonists

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GPR119 is a G protein-coupled receptor expressed predominantly in pancreatic b-cells and in enteroendocrine cells in the gastrointestinal tract. GPR119 agonists have been shown to stimulate glucose-dependent insulin release by direct action in the pancreas and to promote secretion of the incretin GLP-1 by action in the GI tract. GLP-1 has well-established anti-diabetic effects. This dual mechanism of action has generated significant interest in the discovery of small molecule GPR119 agonists as a potential new treatment for type 2 diabetes. We have identified a novel class of GPR119 agonists based on a bicyclic pyrimidine core, exemplified by isopropyl 4-(4-((2-fluoro-4-(methylsulfonyl)phenyl)amino)-6H-pyrimido[5,4-b][1,4]oxazin-8(7H)-yl)piperidine-1-carboxylate (**1**). Herein, we describe the discovery, structure-activity relationships (SAR) and in vivo studies of this and related chemotypes.



MEDI 382

Discovery of orally active, potent, and selective CB1 antagonists

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Obesity is linked to an increased risk of hypertension, coronary heart disease, stroke, certain cancers, and type 2 diabetes among other health issues. Based upon a recent study, greater than one-third of the US population was considered obese. It has been shown that increased stimulation of cannabinoid receptor type 1 (CB1) via endocannabinoids such as anandamide (AEA) and 2-archidonoylglycerol (2-AG) can lead to weight gain in animals and humans. Research regarding CB1 antagonists/inverse agonists has been popular. CNS penetrating compounds such as rimonabant and taranabant that have a high affinity for the CB1 receptor are effective in reducing body weight and the motivation for excess food intake. Unfortunately, these compounds possess on-target mechanism based adverse effects due largely to their CNS penetrating nature. Additional research has suggested that CB1 antagonists that are close analogs of rimonabant but are restricted to the periphery may reduce excessive appetitive behavior while avoiding neuropsychiatric side effects. One of our strategies was to explore the effect of replacing the central aromatic ring found in most CB1 antagonists/inverse agonists with a non-aromatic group. Here we report the SAR of an amide library based on a central cyclohexene ring. CB1 binding affinity, selectivity over CB2, and the oral efficacy in a diet-induced obese mouse model will be discussed.

MEDI 383

HA-binding peptide functionalized dendron: Synthesis and application as a BMP-2 peptide carrier

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Hydroxyapatite (HA) is now widely used as the coating surface of bone grafts. Materials that have strong binding affinity with HA draw a tremendous amount of interest due to their application in drug-targeting for bone healing applications. To enhance the binding affinity of HA-binding peptide, a multivalent binding strategy is pursued in this work. A series of dendrons was designed and synthesized to elucidate how the binding valency and the length of flexible linkage would influence the binding affinity. Moreover, the focal point of the HA-binding peptide functionalized dendron will be derivatized with BMP-2 peptide that shows osteoinductivity. It is anticipated that this design can sequester the bioactive BMP-2 peptide on the surface of an HA-coated bone graft and induce bone formation locally, which may provide a potentially effective and safe method to introduce BMP-2 peptide into bone grafts.

MEDI 384

Identification of phenylcyclohexylamine derivatives as novel I_{Kur} blockers

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Atrial Fibrillation (AF) is the most common form of cardiac arrhythmia and leads to an estimated 80,000 strokes each year. Cardiac rhythm is controlled by the electrical behavior of cardiac myocytes, with multiple ionic currents contributing to the overall cardiac action potential duration. A shortened action potential duration is characteristic of AF. The ultra-rapid delayed rectifier potassium current (I_{Kur}) is involved in the early and plateau phase components of the cardiac repolarization process and compounds which inhibit I_{Kur} lead to an increase in action potential duration and a potential treatment for AF. The I_{Kur} channel is functionally expressed in the atria but not ventricle and therefore selective blockers of this channel have the potential to treat AF without the ventricular liabilities associated with inhibition of multiple channels or channels expressed in both the atria and ventricles. A series of phenylcyclohexylamine derivatives have been prepared as novel blockers of I_{Kur} for the potential treatment of AF. The structure-activity relationship of these compounds was explored for I_{Kur} activity and target potency was increased concomitant with improving the CYP inhibition profile.

MEDI 385

Design and synthesis of phenylpyrrolidine phenylglycineamides as highly potent and selective TF-FVIIa inhibitors

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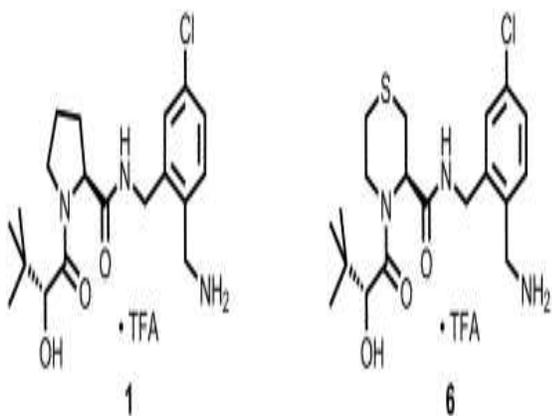
Inhibitors of the Tissue Factor/Factor VIIa (TF-FVIIa) complex are promising novel anticoagulants which show excellent efficacy and minimal bleeding in preclinical models. Based on a zwitterionic phenylglycine acyl sulfonamide, a series of phenylglycine benzamide TF-FVIIa inhibitors was designed to improve permeability and oral bioavailability. Optimization of the benzamide and conformational constraint with a pyrrolidine ring lead to potent TF-FVIIa inhibitors with promising oral bioavailability, but promiscuous activity in an *in vitro* safety panel of receptors and enzymes. Introducing an acid on the pyrrolidine ring resulted in a series of highly potent, selective and efficacious TF-FVIIa inhibitors. The pyrrolidine acid TF-FVIIa inhibitors showed high clearance and short $t_{1/2}$ in dog PK studies.

MEDI 386

SAR of heterocyclic core analogs of a direct thrombin inhibitor

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Thrombin is a serine protease that plays a key role in blood clotting. Pyrrolidine **1** is a potent thrombin inhibitor discovered at Merck several years ago. Seven analogs of **1** in which the pyrrolidine core was replaced with various heterocycles were prepared and evaluated for activity against thrombin, clotting factors VIIa, IXa, Xa, and XIIa, and trypsin. The thiomorpholine analog **6** was the most active, essentially matching the thrombin inhibitory activity of **1** but with improved selectivity over trypsin.

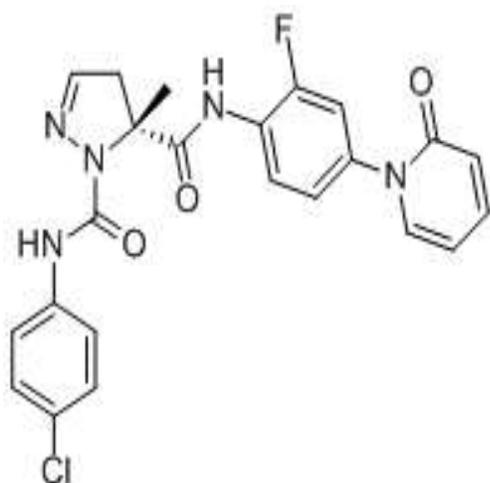


MEDI 387

PF-00190434: A novel, orally bioavailable Factor Xa inhibitor with a synthetically challenging, chiral 5,5-disubstituted pyrazoline core

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In an effort to discover back-up analogs for Pfizer's phase II clinical candidate eribaxaban, we identified PF-00190434 as a novel, orally bioavailable FXa inhibitor. While initial studies on PF-00190434 suggested an improved pharmacokinetic profile to eribaxaban, its synthetically challenging 5,5-disubstituted pyrazoline core hindered its preparation for advanced biological studies. Here-in, we report on PF-00190434 and the synthetic efforts that helped enable its large scale preparation.



MEDI 388

Large-scale synthesis of potent chymase inhibitor: A drug candidate for the treatment of cardiac insufficiency

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Chymase is one of the neutral proteinases present in mast cell granules and it is considered that a chymase inhibitor is useful as a preventive or a remedy for various diseases. In terms of the delivery for clinical study, a concise and practical synthesis of a drug candidate chymase inhibitor has been developed via a robust process route and efficient polymorph studies. Over 100 kg of Active Pharmaceutical Ingredient (API) has been prepared successfully. Through the appropriate studies which fit the Quality by Design framework for pharmaceutical development activities, a potential API crystal form has been controlled and selected from among several types of polymorph. Our poster discusses the large-scale synthetic route and the selection process of the potential API crystal form in more detail.

MEDI 389

Allosteric modulation of thrombin: Design, synthesis, and inhibition properties of sulfated benzofuran trimers

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Thrombin, the ultimate serine proteinase of the blood coagulation, is a prime target for regulating clot formation. Its dual opposing roles – pro-coagulant as well as anti-coagulant – places significant emphasis on regulating, rather than completely inhibiting its generation. We hypothesized earlier that small allosteric modulators of thrombin may offer this advantage and designed sulfated benzofuran dimers (Sidhu et al. *J. Med. Chem.* **2011**, *54*, 5522-5531). We report the design and study of advanced molecules based on this initial success. A library of sulfated benzofuran trimers was designed taking cue from potent dimeric structures. The library included trimeric units containing one or two negatively charged groups either in form of a sulfate or carboxylate moiety. The library was synthesized using a multi-step scheme in which microwave-based sulfation formed the final step to result in water soluble, but hydrophobic, small molecule. Chromogenic substrate hydrolysis assay showed thrombin inhibition potency from high microM to nanoM IC_{50} and efficacy of 50 - 80 %. Michaelis-Menten studies showed that the inhibition arises only from a reduction in the V_{MAX} with minimal effect on the K_M of the chromogenic substrate. Human plasma clotting assays with selected potent trimers showed very good anticoagulant activity. These results indicate that sulfated benzofuran trimers are highly promising lead anticoagulants and the first small molecule, allosteric modulators of thrombin designed to date.

MEDI 390

Nonsaccharide, small molecule mimetics of heparin as allosteric activators of antithrombin

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The physiologic mechanism of heparin pentasaccharide is antithrombin activation for accelerated inhibition of factor Xa. Tetrahydroisoquinoline (THIQ) was earlier designed as a nonsaccharide scaffold for antithrombin activation. We hypothesized that tetrasulfated *N*-arylacyl THIQ molecules with an extended linker should facilitate targeting the pentasaccharide binding site of antithrombin. A focused library was synthesized utilizing a strategy of less than 5 steps. A THIQ derivative containing a 4-atom linker and 2,5-disulfate phenyl substitution exhibited antithrombin activation only 3.8-fold less than that achieved with heparin pentasaccharide. Yet, the affinity of the promising activator was moderate because of conformational isomerism across the amide bond. Mechanistically, the activator appears to utilize the pre-equilibrium pathway of activation. Advanced *N*-arylalkyl, *N*-arylalkenyl, and *N*-bis THIQ derivatives were designed based on these results. Overall, this work suggests a strong possibility of rationally designing sulfated aromatic molecules as clinically relevant antithrombin activators.

MEDI 391

O²-Functionalized methylamine diazeniumdiolates as potential nitroxyl prodrugs

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Primary amine diazeniumdiolates have emerged as new pH-dependent donors of nitroxyl,¹ a potential therapeutic agent for treating congestive heart failure. Preparing primary amine diazeniumdiolate salts generally pose significant challenge on account of low thermodynamic stabilities. We report a novel dehydrohalogenation-based synthesis for preparation of caged methylamine diazeniumdiolates (MA/NO) starting with O²-derivatized RR'N–N(O)=N–OR" as a synthon. Caged MA/NO analogs exist as dynamic equilibrium mixture of Z- and E-isomeric forms in solution, first ever reported in an acyclic system. Crystallographic identification of Z-conformer, determination of pK_a, and pH-dependent fluxional behaviour of isomeric mixtures has been studied. Cytochrome P450-mediated metabolism of O²-benzyl analog and HNO/NO release profile of several MA/NO analogs have been reported augmenting their development as potentially new HNO/NO prodrugs of diazeniumdiolate origin.

Reference:

Andrei et al *J. Am. Chem. Soc.* **2010** , 132, 16526-16532.

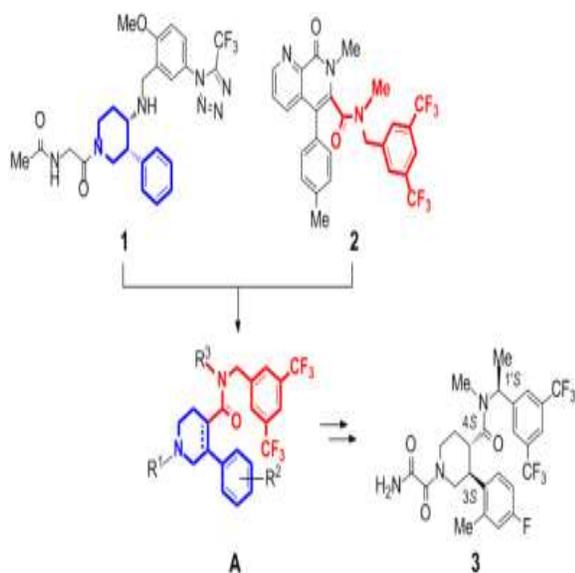
MEDI 392

Novel 3-phenylpiperidine-4-carboxamides as highly potent and long-acting oral neurokinin-1 (NK₁) receptor antagonists that show anti-OAB effects

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In studies directed toward the development of an orally available anti-OAB (overactive bladder) drug, we explored 3-phenylpiperidine-4-carboxamide derivatives **A** as tachykinin NK₁ receptor antagonists. This series was generated by the hybridization of substructures from two types of tachykinin NK₁ receptor antagonists **1** and **2** that we previously discovered. Compound **3** showed a good PK profile across four animal species and high CNS efficacy in a guinea pig GR-73637-induced locomotive activity assay at 1 and 24 h after oral administration. This presentation will also include synthetic details and SAR information for this series. In addition, we will present a

comparative PK/PD analysis between compound **3** and some representative known compounds.



MEDI 393

Discovery of selective AXL kinase inhibitor CH5451098 and its biological activity

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Growth arrest-specific protein 6 (Gas6) and the tyrosine kinase receptor AXL (Gas6/AXL) signal is one of the major biological paths to mesangial proliferation in kidney. The inhibition of mesangial proliferation via the Gas6/AXL signal is a potential therapeutic target for treating kidney diseases. Seeking to obtain small molecule AXL kinase inhibitors, we conducted screening. Our screening hit, CH5246453, showed sub-micromolar inhibitory activity to AXL; however, the kinase selectivity was moderate with several drawbacks. Our derivatization of CH5246453 using the structure-activity approach clarified the inhibitory activity and selectivity and erased the drawbacks. As a result, we have obtained our optimized compound, CH5451098, with nano-molar inhibitory activity and high selectivity to AXL. The X-ray co-crystal structure clearly explains the strong AXL inhibitory activity and high selectivity. The compound also displayed a significant efficacy *in vivo*. We report our efforts which led to CH5451098 and describe its biological activity.

MEDI 394

Membrane configuration optimization for in vitro blood-brain barrier models

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The creation of an *in vitro* blood-brain barrier (BBB) model is crucial to study the cellular biology of the BBB and its role in drug transport studies. A typical *in vitro* BBB model consists of a porous membrane submerged in culture medium that supports monolayer cell growth. The range of system variable set points (membrane configuration, media composition) and cell culture variable set points (species, generation, co-culture setup) used to create an *in vitro* BBB model is large, and we present an extensive screen of membrane configuration effects to select an optimized model. Primary mouse brain cell cultures are used to screen several model parameters, and selection of the optimal configuration is based on the ability of endothelial cells to form a tight barrier across the different configurations as measured with three characterization techniques: transendothelial electrical resistance, diffusive permeability of a fluorescently labeled solute, and immunocytochemistry microscopic visualization.

MEDI 395

Design of zeolite microneedles for regulated transdermal drug delivery

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Microneedle is a promising and effective way for transdermal drug delivery. Conventional materials for microneedles include silicon, metals and polymers. However they pose some problems on production cost, mechanical properties and biocompatibility with humans.

This work presents zeolite as a competitive and biocompatible material for microneedles. A low-cost, scalable fabrication process was developed that produces zeolite microneedles of good mechanical strength. The biocompatibility of zeolite microneedles was examined on rat and no acute allergic response was observed. An active infusion transdermal patch using the new zeolite microneedles was assembled and tested both in-vitro and in-vivo. A smart polymer was used to provide linear delivery of analgesic and insulin. In-vitro diffusion study has been carried out using the patch

across pig skin, while in-vivo study was done on diabetic rat. The results show that constant delivery rate of pharmaceuticals can be maintained in both tests.

MEDI 396

Direct measurements of mechanical properties of condensed DNA for gene delivery using optical tweezers

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Many nonviral carriers have been developed to deliver nucleic acids by forming nanoscale complexes. However, there has been limited success in increasing their transfection efficiency due to lack of mechanistic understanding at the molecular level. Our hypothesis is that gene delivery efficiency is largely determined by the mechanical properties of the condensed complex. To test this hypothesis, we directly measured the mechanical properties of DNA: carrier complex using optical tweezers. Histidine-lysine polymer, polyethyleneimine and poly-L-lysine were used to form nanoscale complexes with a single DNA molecule. As carriers were introduced, a sudden decrease in DNA extension occurred at a specific force level which was defined as critical force. These critical forces were dependent on specific carriers and their concentration. Significant reduction in DNA extension length was observed in the force ranges tested. The characteristics of force profiles and the implications for optimizing molecular structures of cationic carriers will be discussed.

MEDI 397

Complete analysis on the two base pair sequence recognition by Hx (p-anisylbenzimidazole)•pyrrole and Hx•imidazole pairings

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Pyrrole (Py) and Imidazole (Im) polyamide analogs of distamycin are small molecules that bind in the minor groove at specific sequences of DNA and regulate gene function. Despite their potential in drug discovery or as tools in molecular and cell biology, their usefulness is limited by their ability to enter cells and concentrate in the nucleus. There

is thus an effort to develop polyamides that are trackable in cells. Thus there is an immediate need for the design of novel heterocyclic DNA sequence cognitive units that exhibit all the positive qualities as Py and Im, and be inherently fluorescent. Our group has recently published a novel class of hybrid Hx-amides, which contain a fluorescent p-anisylbenzimidazole or Hx group. Pairing of Hx with PI, PP and IP provided evidence that it mimics “PyPy” in recognizing two contiguous base pairs in a similar way as polyamides. To complete our examination of the Hx functionality, the remaining molecule in this series, HxII, was successfully synthesized. The DNA binding properties of HxII will be reported along with a discussion on sequence recognition by Hx/polyamide pairings and gene control.

MEDI 398

Quantitative investigation of a vaginal ring formulation using Raman imaging

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An intravaginal ring is a drug delivery device that provides targeted and extended release of an active pharmaceutical ingredient (API). Intravaginal rings are composed of a physiologically inert polymer into which an API or multiple API's have been incorporated. The ring is typically developed using design of experiments in which device is designed and manufactured, then tested to determine the drug release profile. The results are then analyzed and the data used to select lead candidates. Raman imaging, which allows high precision, spatially resolved determination of the local API concentration (C_{API}) throughout the ring, is used to characterize the device. By measuring C_{API} at preselected times during elution testing (analogous to dissolution testing of solid dosage forms), the API dissolution and transport behavior in the polymer matrix can be very accurately deduced. This allows more effective design of the rings and fewer design iterations for faster and less expensive development.

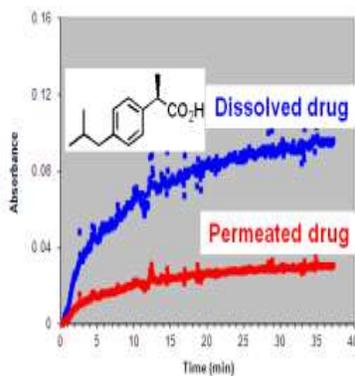
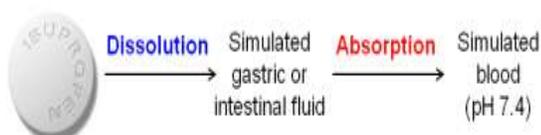
MEDI 399

Combined dissolution–permeability experiment for simulating absorption of pharmaceutical drugs using a diffusion cell and a PC-controlled UV spectrophotometer

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Many initially promising pharmaceutical drug candidates fail because of poor absorption in the body, and the earlier such failures can be identified the better. Standard tests

involve performing separate dissolution and permeability assays, the most popular being PAMPA. In this poster, we describe a low-cost combined dissolution-permeability experiment which simultaneously follows both the dissolution of a formulated pharmaceutical drug and its subsequent permeation through a lipid-coated membrane. For these studies, we have used a simple diffusion cell, guard column, peristaltic pump and UV spectrophotometer; equipment that is available in most research labs or affordable on a limited budget. The process has been automated with a macro program. Various over the counter drugs have been examined (ibuprofen, naproxen, ranitidine, phenylephrine) to date using this method. The absorption of different formulations has been compared and the results used to predict blood plasma profiles.



Ibuprofen dissolution and permeation at pH 4.1

MEDI 400

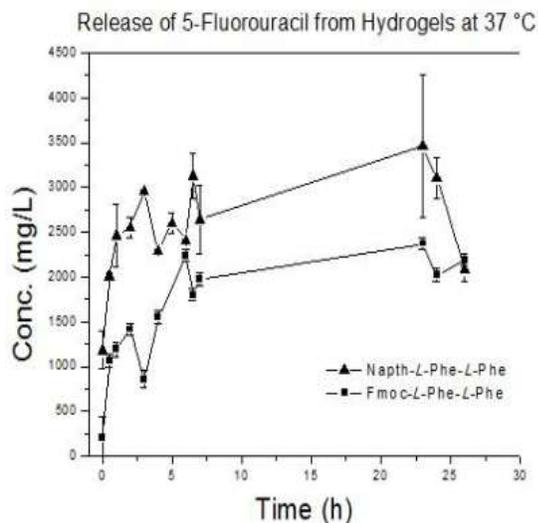
Therapeutic release from self-assembling hydrogels: Towards localised drug delivery

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Supramolecular hydrogels are attractive because of their potential applications in areas such as drug delivery, tissue engineering and 3-dimensional cell culture.

Because gels are porous, they can encapsulate drugs for localised delivery *in vivo*; this poses many unique advantages over current treatments.

Herein we present the release of 5-fluorouracil and paclitaxel from within Fmoc-*L*-Phe-*L*-Phe and naphthalene-*L*-Phe-*L*-Phe hydrogels at physiological conditions.



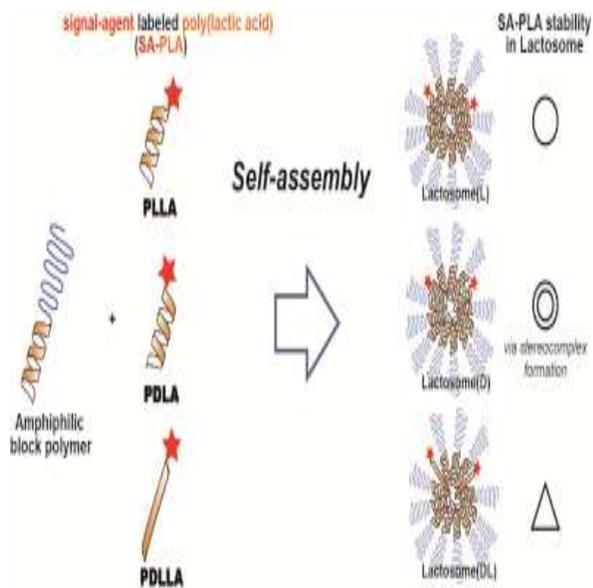
5-fluorouracil was released in therapeutically significant amounts, however, paclitaxel (not shown) showed barely any release, at physiologically relevant conditions.

MEDI 401

Controlled drug release from polymeric micelle, Lactosome, using stereochemistry of helical components

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Lactosome is a core-shell type polymeric micelle, which is prepared from poly(L-lactic acid)-*b*-poly(sarcosine) amphiphilic block polydepsipeptide. In the assembly, hydrophobic PLLA chain forms helical structure, therefore, the polymers regularly aligned and tightly packed. Similarly to other polymeric micelles, Lactosome can encapsulate hydrophobic compounds including anticancer drugs. Further, by attaching a PLLA chain to the drugs, Lactosome can more stably encapsulate them. This is because the PLLA chain attached to the drugs can be tightly packed with Lactosome constituent polymers. Poly(lactic acid) (PLA) has three types stereoisomers of poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), and poly(DL-lactic acid) (PDLLA). In this study, drug stability in Lactosome is examined by changing attached PLA stereochemistry. As a result, it was revealed that drug release from Lactosome can be controlled by PLA stereochemistry.



MEDI 402

Investigation of the interaction kinetics between small molecule inhibitors and the protein tyrosine phosphatase YopH from *Yersinia pestis*

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Catalytic activity assays are essential tools for evaluating the performance of inhibitors that target enzyme function. Although small molecule substrates such as *p*-nitrophenylphosphate (*p*NPP) are useful for screening inhibitors of protein-tyrosine phosphatases (PTPases), a detailed study of interactions with protein substrates is important for improving the potency of lead inhibitors. YopH is a highly active PTPase that exhibits weak peptide sequence specificity. We developed competitive and direct binding methods that can be adapted for high-throughput screening of small molecule inhibitors of relevant protein-protein interactions. Using results from measurements of surface plasmon resonance, we describe the kinetic interactions involving YopH, peptide substrates, and previously reported small molecule inhibitors of PTPase activity.

MEDI 403

T3P: Not just for amide bond formation anymore

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n-Propane Phosphonic Acid Cyclic Anhydride (T3P[®]) is an exceptional reagent for amide/peptide bond formation. T3P[®] has demonstrated its efficacy in the commercial scale manufacture of numerous APIs. Novel functional group transformations have recently been achieved with T3P[®], including – esterifications, the formation of nitriles, hydroxamic acids, Weinreb amides and isonitriles. Further, T3P[®] has demonstrated utility in facilitating both the Curtius and Lossen rearrangements. Oxidation of alcohols under mild conditions was also achieved with T3P[®]. T3P[®] is very easy to use and provides excellent selectivity, low epimerization and high yields. The desired product can be isolated by simple liquid/liquid extraction. Because of its superior performance in coupling reactions, hazardous additives such as explosive HOBt, are not required.

Numerous examples of these novel reactions will be presented, wherein the inherent advantages of T3P[®] will be highlighted.

MEDI 404

Identification and characterization of small molecules as potent and specific Epac2 antagonists

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Epac1 and Epac2, two isoforms of exchange proteins directly activated by cAMP (Epac), respond to the second messenger cAMP and regulate a wide variety of intracellular processes under physiological and pathophysiological circumstances. Accumulating studies support that Epac may represent new mechanism-based therapeutic targets for various human diseases. Novel Epac1- or Epac2-specific antagonists are desperately needed to discriminate their biological functions. Herein, we report the chemical design, synthesis, and pharmacological characterization of three different scaffolds as highly potent and selective antagonists of Epac2 with the aid of molecular docking. Several selective Epac2 inhibitors have been identified including **HJC0350**, which has an IC₅₀ value of 0.3 μM and is about 160-fold more potent than cAMP. **ESI-05**, **HJC0338** and **HJC0350**, selected from each series, have demonstrated no inhibition of Epac1-mediated Rap1-GDP exchange activity at 25 μM in the presence of equal concentration of cAMP, indicating that they are Epac2-specific antagonists.

MEDI 405

Structure-activity relationships in constrained benzylglycinamides: A molecular template for the design of state-dependent sodium channel blockers

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Voltage-gated sodium channel blocking activity is a characteristic of certain anaesthetic, antiarrhythmic, analgesic and antiepileptic drugs. However, many current therapies have mixed modalities, are associated with inconsistent efficacy and are poorly tolerated. Pathological conditions are often associated with rapid channel firing so compounds which slow channel cycling by preferential inactivated state-dependent binding, offer the opportunity to mediate disease states while interfering minimally with normal physiology.

Herein we describe the discovery and profile of state-dependent sodium channel blockers characterised by an embedded benzylglycinamide moiety. The imposition of specific stereoisomeric and conformational constraints enabled the identification of compounds with enhanced sodium channel selectivities, and modulation of their state-dependent properties. Structure activity relationships were identified for hERG blockade, and compound classes were discovered with desirable developability characteristics including metabolic stability, brain penetrancy and disease model efficacy.

MEDI 406

Temperature-dependent binding affinities between lumefantrine and hematin

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We have determined that the binding affinities for lumefantrine, and selected pro-drug fragments, used as a component of the ACT therapy Coartem (Novartis) to treat malaria, are highly dependent on temperature. Understanding such strong temperature binding dependence would have profound impact on resolving the mechanism of action of the parent drug. Using a Continuous Variation method of equilibrium analysis in a variety of solvent conditions, the temperature effects on the chemical equilibrium between lumefantrine/lumefantrine pro-drug fragments with Hematin was studied. Our results indicate that more than just a single interaction is responsible for the high binding affinity, and free energy of binding, of hematin for lumefantrine, and cannot be explained only by Lewis acid based adduct formation between the hydroxyl group on lumefantrine and the iron (III) in hematin.

MEDI 407

Development of fluorescent progesterone receptor ligand based on coumarin scaffold

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Progesterone receptor (PR) is a member of nuclear receptors, and it regulates specific gene transcription by binding to its endogenous ligand, progesterone. PR and progesterone are related to female reproductive function, and potential clinical utilities of PR ligands have also been reported. Compared with steroidal PR ligands, non-steroidal ligands could cause less side effects due to their cross-reactivity toward other steroid hormone receptors. So we have developed novel non-steroidal PR ligands based on coumarin scaffold. Considering the structures of reported non-steroidal PR ligands, 6-arylcoumarin moieties were set as PR ligand candidates, and their biological activities were evaluated by means of alkaline phosphatase assay in T47D human breast carcinoma cell line and competitive binding assay. Some compounds such as 7-diethylamino-6-phenylcoumarin showed potent PR antagonistic activity. In addition, its fluorescence was increased in the presence of PR, which suggested that it might be a candidate for fluorescent sensors for PR.

MEDI 408

Methyl analogs of quercetin for improved radical-scavenging activities

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The development of antioxidants with strong radical-scavenging activities has attracted considerable attention in recent years for preventing oxidative stress related diseases. Previously, we introduced methyl substituent ortho to the hydroxyl group of resveratrol, natural phenolic antioxidant in red wine, leading to very potent antioxidant with strong radical-scavenging activity. The enhanced radical scavenging activity may be attributed to the delocalization of phenoxyl radical generated in the reaction with radical species, due to hyperconjugation with the ortho methyl group. Here, we synthesized quercetin analogues where one or two ortho-positions of catechol hydroxyls are substituted with methyl groups. The antioxidative activities of mono and dimethyl analogues were examined using galvinoxyl radical as an oxyl radical species, showing 15-fold and 135-fold stronger radical scavenging activities than that of quercetin, respectively. These

results prove that introduction of methyl substituents ortho to the hydroxyl group is effective for improving radical scavenging activities of phenolic antioxidant.

MEDI 409

Simplified linker for regioselective oxidation of C-H bonds by an engineered P450 monooxygenase

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Regio- and stereoselective oxidation of unactivated C-H bonds remains a considerable hurdle in synthetic chemistry. Although there has been extensive work done to develop transition metal complexes and biological catalysts for this purpose, there has been limited success. Cytochrome P450 monooxygenases, a family of heme proteins that catalyze oxidative transformations with a high degree of regio- and stereoselectivity, may represent a source of promising biocatalysts. However, work remains in expanding the substrate scope and reducing the need for expensive heterologous redox partners. In this study, we employed a chimeric macrolide biosynthetic P450 PikC_{D50N}-RhFRED with remarkable substrate promiscuity, increased catalytic activity as compared to the wild-type enzyme, and exhibiting self-sufficiency. Using a "substrate engineering" strategy, we demonstrated the ability of PikC_{D50N}-RhFRED to regioselectively hydroxylate undecorated hydrocarbon rings and functionalized macrolactone rings by replacing the natural desosamine sugar. Furthermore, this simplified linker efficiently facilitated PikC_{D50N}-RhFRED oxidation and was easily cleaved.

MEDI 410

Simultaneous modifications of ligand in structure activity relationship studies: Should we consider the additivity or the cooperativity principle?

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Predicting the changes in ligand binding affinity in structure-activity relationship studies (SAR) is one of the biggest challenges in medicinal chemistry. This is particularly true when two or more structural modifications are carried out in the ligand simultaneously. In this study, we present data from a series of thermolysin inhibitors in which the changes in binding affinity caused by simultaneous structural modifications of the ligands are compared with the sum of the changes in binding affinity caused by the individual modifications. Double mutant cycles were used to accomplish these comparisons. Data show that the cooperativity principle (positive and negative cooperativity) is at work in some cases, while the additivity principle is at work in others.

The nature of the interaction between the modified ligand part and the host target, as well as the distance between the structural modifications could two of the factors determining which principle should be applied.

MEDI 411

Synthesis and SAR of 1-hydroxy-1H-benzo[d]imidazol-2(3H)-ones as inhibitors of D-amino acid oxidase

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D-Amino Acid Oxidase (DAAO) is a flavoenzyme that catalyzes the oxidation of D-amino acids to the corresponding imino acids and hydrogen peroxide and is predominantly responsible for clearance of orally administered D-serine in mice. Co-administration of D-serine and a small molecule DAAO inhibitor may mitigate the problem related to clinical use of D-serine for patients with schizophrenia by reducing DAAO-mediated metabolism of D-serine, thus enabling a dose reduction as well as prevention of nephrotoxicity. As a part of our continuous efforts to identify a new structural class of DAAO inhibitors, we designed and synthesized a series of 1-hydroxy-1H-benzo[d]imidazol-2(3H)-ones and evaluated their ability to inhibit a human form of DAAO. Structure-activity relationship of the new class of DAAO inhibitors will be presented in detail along with results from subsequent in vitro and in vivo ADME studies.

MEDI 412

Synthesis and evaluation of novel antioxidant prodrugs for the topical treatment of sulfur-mustard induced skin inflammation

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Sulfur mustard, [bis-(2-chloroethyl)sulfide] (SM), is a chemical warfare agent first synthesized in the early 19th century, however it remains a threat due to its possible use in a terrorist attack. SM is a powerful vesicant which triggers an up-regulation of a host of hydrolytic, collagenolytic, esteratic, cholinergic, and inflammatory processes within an oxidative stressed domain on lungs, skin, and eyes. No antidote or suitable therapeutic response for SM exposure exists. We have synthesized and screened 15 multi-functional therapeutics in which component pharmacophores target up-regulated

enzymes and are attached to a hydrolyzable core to provide “release” by skin enzymes. One agent, N-hydroxy-N-(4-hydroxy-3-methoxybenzyl)heptadecanamide, designed as an MMP-9, FAAH, and TRPV1 co-antagonist, showed 87% suppression of phorbol-ester induced inflammation in a mouse ear model. Other prodrugs which transported anti-oxidant and non-steroidal anti-inflammatory constructs joined by ester linkages showed promising, albeit lower, inflammation suppression. Syntheses, *in vitro*, and *in vivo* screening results are displayed.

MEDI 413

Synthesis of phosphatase resistant alpha-fluoro homoprenylphosphonate analogs of isoprenoid phosphate as inhibitors of the integral membrane phosphatase PDP1

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The isoprenoid diphosphates farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP) are products of the mevalonate pathway and are critical intermediates in the synthesis of cholesterol and for protein isoprenylation. The type 1 polyisoprenoid diphosphate phosphatase encoded by the PPAPDC2 gene (PDP1/PPAPDC2) is an integral membrane protein that preferentially hydrolyzes polyisoprenoid diphosphates including FPP and GGPP and is a regulator of isoprenoid phosphate metabolism. To provide chemical tools to study the cellular function of PDP1 we synthesized a small library of metabolically stabilized alpha-fluoro-homo phosphonate analogues of farnesyl monophosphate and geranylgeranyl monophosphate. Alpha-fluorophosphonate isoprenoid analogues were prepared in high yield from the anions of the corresponding phosphonate esters and N-fluorobenzenesulfonamide. The alpha-fluoro-homoisoprenoid phosphate analogues inhibited PDP1 hydrolysis of isoprenoid diphosphates *in vitro*.

MEDI 414

Development of bio-reducible polymer conjugate for siRNA delivery

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Efficient siRNA delivery is dependent not only on the ability of the delivery vehicle to target a specific organ but also its ability to enable siRNA entry into the cytoplasm of the target cells. Polymers with endosomolytic properties are increasingly being used as siRNA delivery vehicles due to their potential to facilitate endosomal escape and intracellular delivery. Addition of disulfide bonds in the backbone of these polymers was expected to provide degradability through reduction with glutathione in cytosol. This poster describes the synthesis of new endosomolytic bioreducible polymers that can be reversibly masked and can deliver the siRNA both *in vitro* and *in vivo*. These polymer conjugates gave good *in vitro* knockdown (KD) and did not demonstrate cytotoxicity in a MTS assay. Efficient mRNA KD for apolipoprotein B in mouse liver was observed with these polymer conjugates following IV dosing

MEDI 415

Expression, purification, and refolding of single chain antibodies (scFvs) from inclusion bodies

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Inclusion bodies accumulated in *Escherichia coli* are widely used for large-scale production of therapeutic proteins. Isolation and characterization of anti-Tn antigen 4E10 and anti-lacto-*N*-fucopentaose III 1F12 scFvs from a phage library were previously described [Yuasa *et al. J. Biol. Chem.* 285, 30587, 2010; Sakai *et al. J Biochem.* 147, 809, 2010]. Here, two scFv proteins purified from inclusion bodies were refolded using lauroyl-L-glutamate, a novel amino acid-based detergent [Kodou *et al. Protein Expr Purif.* 75, 46, 2011]. Inclusion bodies isolated from pET/4E10 or pET/1F12 transformed-bacterial cells were solubilized with 2.5% lauroyl-L-glutamate and subjected to reconstitution by multi-step dilution procedures into a buffer solution containing arginine and thiol/disulfide-exchange reagents. Approximately 70% were recovered as soluble proteins, which indicated that refolding in the presence of lauroyl-L-glutamate is superior to that done in the presence of guanidine hydrochloride. Determination of affinity/specificity of the refolded scFv proteins is in progress.

MEDI 416

Effects of anti-insulin-like growth factor-I receptor (IGF-IR) antibodies with or without the ER-retention signal KDEL on cancer cell growth

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Recombinant antibody consisting of the single-chain variable fragment (scFv) of 1H7 monoclonal antibody against IGF-IR and human IgG₁ Fc domain, scFv-Fc, has been found to exhibit inhibitory effects on breast cancer growth *in vitro* and *in vivo* [Li *et al. Cancer Immunol. Immunother.* 49, 243, 2000; Sachdev *et al. Cancer Res.* 63, 627, 2003]. In this study, we constructed an intrabody-type of 1H7 scFv-Fc which should have more potent growth inhibitory effects than 1H7 scFv-Fc. pCIneo expression vectors encoding 1H7 scFv-Fc-KDEL and 1H7 scFv-Fc as well as Fc-KDEL and Fc were constructed, and then introduced into MCF-7 breast cancer cells. Intracellular expression of 1H7 scFv-Fc KDEL and Fc-KDEL was confirmed by ELISA and immunofluorescent microscopy. MCF-7 cell growth was significantly inhibited by transfection of pCIneo-1H7 scFv-Fc-KDEL when compared to that of pCIneo-1H7 scFv-Fc-transfected cells. Whether or not the intrabody inhibits cell growth by retaining IGF-IR inside cells is under investigation.

MEDI 417

Purification of anti-insulin-like growth factor-I receptor (IGF-IR) single chain antibody (scFv) expressed in *Drosophila* S2 cells

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Recombinant antibodies, scFv-Fc and scFv, derived from anti-IGF-IR monoclonal antibody 1H7, were previously expressed in mammalian NSO and *E.coli* cells, respectively [Li *et al. Cancer Immunol. Immunother.* 49, 243, 2000; Kusada *et al. J. Biochem.* 143, 9, 2008]. Expression of 1H7 scFv proteins in *E. coli*, however, did not yield significant quantities. To achieve better yields, we used a *Drosophila* S2 cell expression system to express 1H7 scFv. The 1H7 scFv gene cloned into a pMT/BiP/V5-His expression vector was co-transfected with a pCoHygro selection vector into S2 cells. After 4-weeks culture in the presence of 0.3 mg/ml hygromycin B, stably-transfected cells were treated with 0.5 mM CuSO₄ to induce scFv protein expression. From culture supernatants, 1H7 scFv proteins were partially purified by Ni²⁺-Sepharose chromatography. IGF-IR binding activity measured using SPR and ELISA revealed production of active 1H7 scFv proteins. Alternative protocols are being tested to improve purification purity and yield.

MEDI 418

In vitro production of anticarbohydrate antibodies: Purification of anti-T antigen antibodies (scFvs) from *E. coli* inclusion bodies and *Drosophila* S2 cell culture media

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Phage display methods allow us to readily screen for protein genes of our interests. Functional characterization of gene products, however, is often troublesome due to the difficulty in expression of functionally active proteins. We have characterized T-antigen specific phage-displayed 1E6 and 1E8 scFv proteins (Matsumoto-Takasaki *et al. Biosci. Trends*, 2009). In this study, bacterial and insect expression systems were comparably employed for purification of 1E6 and 1E8 scFv proteins. Purification from *E. coli* inclusion bodies was performed as published (Matsumoto-Takasaki *et al. J. Biochem.* 2011). A pMT/BiP/V5-His vector with a 1E6 or 1E8 scFv gene was co-transfected with pCoHygro into S2 cells. After 4-weeks culture in the presence of 0.3 mg/ml hygromycin B, stably-transfected cells were treated with 0.5 mM CuSO₄ to induce scFv protein expression. scFv proteins were purified by Ni²⁺-Sepharose chromatography, then analyzed using SDS-PAGE, CD, ELISA, and SPR, which indicated the insect system appears to work better.

MEDI 419

Structural mechanism by which the GPCR CXCR4 transduces signaling events

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The human chemokine receptor CXCR4 is a member of the G-protein coupled receptor (GPCR) superfamily of proteins, which comprise approximately 30% of current drug targets. Activation of CXCR4 by its endogenous ligand CXCL12 (SDF-1 α), is critical for development and cell migration. The upregulation of CXCR4 in a variety of human cancers, and its role as an HIV co-receptor makes CXCR4 an increasingly important therapeutic target. Here we report a comprehensive functional analysis of CXCR4, identifying residues required for CXCL12-mediated signal transduction, complementing the recently published crystal structure of CXCR4. Using Shotgun Mutagenesis technology, we created a complete mutation library, individually targeting each of the 352 CXCR4 residues. Each CXCR4 variant was tested for protein expression, conformation, and function. Using this approach, we identified critical residues for CXCL12-mediated CXCR4 signal transduction, largely occupying the receptor transmembrane domains. The majority of critical residues do not appear to be involved in ligand binding or G-protein coupling, but rather cluster within specific alpha-helices that are known in GPCR family receptors to undergo significant conformational changes upon activation. Our results are consistent with a conserved structure-based hypothesis of GPCR signal transduction and suggest that the critical residues identified here are those that are required to mediate CXCR4 receptor signaling. These data may facilitate the elucidation of mechanisms underlying the transduction of GPCR signaling in general

and will also aid in drug design, providing insight for the specific targeting of residues that do not disrupt normal CXCL12-mediated CXCR4 signaling.

MEDI 420

Synthesis and evaluation of novel small molecules containing hydroxamic acid functionality with the zinc-dependent metalloenzymes such as histone deacetylase and anthrax metallo-beta-lactamase

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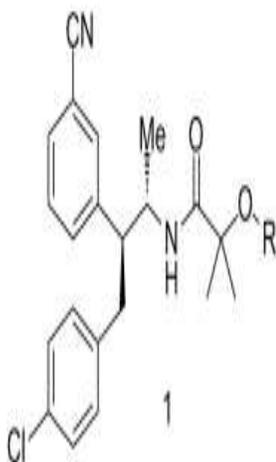
Hydroxamic acid functionality has been attracted for developing new small molecules against various zinc-dependent metalloenzymes due to the structural feature which is easy to coordinate with zinc metal ion in the active site of enzymes. We have synthesized N-hydroxy-6-(thieno[3,2-b]pyridin-7-yloxy)hexanamide and N-hydroxy-3-((6-(hydroxyamino)-6-oxohexyl)oxy)benzamide. The preliminary studies of these compounds have shown significant activities of both Anthrax metallo-*beta*-lactamase and histone deacetylase 8 (HDAC 8). We will describe the design and synthesis of these compounds which would be potentials of potent inhibitors for both targets

MEDI 421

Orally active polar analogs of taranabant, as CB1 inverse agonist

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A series of azine analogs (1) of the CB1 inverse agonist, taranabant[®], with lower LogD cf. to the lead, exhibited similar or improved food intake and weight loss effects, in rats, despite lower brain: plasma ratios. It was speculated that the decreased LogD of these compounds was the cause of their decreased propensity to cross the blood / brain barrier. We were interested in determining whether these polar analogs can achieve comparable food intake / weight loss effects with the lower brain : plasma ratios. This question constitutes a fundamental issue for CB1R as a target as it has been proposed that adequate in vivo efficacy is likely due to primarily engaging the CNS-expressed receptors. The synthesis, pharmacokinetic and pharmacodynamic properties of these potent azine CB1 inverse agonist of the clinical candidate taranabant[®], will be discussed.



R = Substituted Pyridines, Pyrazines, Pyridazines and Pyrimidines

MEDI 422

Discovery of novel androgen receptor coactivator binding inhibitors through high-throughput screen

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Current treatments for prostate cancer are centered on blocking androgen-signaling axis. While hormonal therapy is often initially successful, metastatic tumors inevitably become resistant with no further treatment recourse. Remarkably though, several mechanistic studies suggest that AR remains a viable target in these hormone refractory cancers despite AR mutations. Thus, novel therapeutics that target AR through secondary sites such as the co-activator binding pocket could provide unique druggable opportunities for AR inhibition. Based on an AR-gelsolin interaction screen of an in-house library of 170,000 compounds, and further follow-up of top hits with AR-driven gene expression, competitive vs. non-competitive activity, inhibition of VCaP cell proliferation, and downregulation studies, we have identified novel non-competitive AR leads. Further structure-activity relationship (SAR) revealed analogs with IC₅₀ in the range of 0.1-1 μM, and are equivalent or superior in inhibition to the best current anti-androgen, MDV3100. Studies are underway on select compounds for fine-tuned SAR as well as *in vivo* suitability.

MEDI 423

Reversible isomerization of spiroxindoles and identification of improved MDM2 inhibitors

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We have previously reported the design and synthesis of spiroxindoles as a new class of small-molecule inhibitors of the MDM2-p53 interaction. We report herein our detailed investigation on a novel reversible isomerization reaction for this class of spiroxindoles, which affords from a single diastereomer to four diastereomers. The binding affinities of these diastereomers to MDM2 differ by two orders of magnitude. Our study has yielded a set of highly potent MDM2 inhibitors with K_i values of 1-2 nM. In vivo evaluation showed that our best compounds are capable of achieving tumor regression in the SJS-1 osteosarcoma tumor xenograft model.

MEDI 424

Translating favorable ADME profile of a lead compound into virtual analogs in restricted physicochemical space

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The efforts of lead optimization projects are directed towards analogs that have favorable ADME profiles and are devoid of safety concerns whilst retaining target activity. In this work we present a novel computational platform to aid such projects by generating virtual analog libraries in physicochemical space regions compatible with the desired biological characteristics.

The main idea lying behind our approach is that many considered properties are governed by basic physicochemical parameters, such as ionization, lipophilicity, or molecular size. We have devised simple, yet accurate physicochemical models of intestinal absorption and passive permeation across the BBB, as well as general physicochemical rules that hold, even for protein-ligand interactions (P-gp, hERG inhibitor specificity). Changing parameter values may have distinct, even opposite effects on different ADME properties, and the impact of a particular parameter may depend on the allowed variation ranges of other parameters. Using the cumulative output of available predictive models enables us to account for the multitude of possible effects and identify the regions in physicochemical space that are most likely occupied by analogs with the needed combination of ADME properties. Advanced techniques are also applied to improve selection of substituents fitting within these regions, including custom Hammett equations for estimating the mutual effects of the core molecule and the modified substituent on the analog's pK_a .

The presented methods coupled with automatic analog generation in accordance with the imposed physicochemical restrictions make our software platform a valuable tool to guide drug discovery projects towards the most promising candidates.

MEDI 425

Optimization of a series of HCV NS5B thumb site II replication inhibitors results in improved potency and reduced resistance susceptibility

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Thiophene carboxylic acids, exemplified by VX-222, have shown excellent potency and good clinical efficacy as inhibitors of Thumb Site II of HCV polymerase NS5b. Herein we report further optimization of this chemotype which has resulted in improved potency against both wild-type virus and the known site II mutant M423T.

MEDI 426

Novel rapamycin analogs via metathesis

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We have developed a novel metathesis contraction reaction that allows for the single step transformation of rapamycin to a new scaffold. In the process of validating the synthetic methodology, several novel rapamycin analogs were generated and their FKBP12 binding and half-life profiled. The research goal of retaining biological activity of the parent rapamycin, while demonstrating a shorter half-life than the parent compound was accomplished. The structure of the new rapamycin analogs was confirmed by high field 2D NMR experiments.

MEDI 427

Discovery of bicyclic and tricyclic heterocycle derivatives as histamine H₃ antagonists for the treatment of obesity and type 2 diabetes

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The histamine H₃ receptor, which is predominantly expressed in the brain, regulates the synthesis and release of histamine directly. At the same time, it modulates other

neurotransmitters, such as dopamine, norepinephrine, acetylcholine, glutamate and serotonin indirectly. There are several in vivo studies that show a potentially beneficial effect of brain penetrating H₃ antagonists to treat obesity and type 2 diabetes. A series of bicyclic and tricyclic A-ring antagonists was synthesized and evaluated as a new lead of non-imidazole histamine H₃ receptor Antagonists. These compounds showed a single digit nanomolar potency in vitro, clean P450 and hERG profiles and a superior in vivo efficacy (in rodent models) due to a unusually high brain/plasma ratio.

MEDI 428

Synthetic mimics of free cholesterol that uniquely bind living mammalian cells

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Mammalian cells acquire exogenous cholesterol, a critical constituent of membranes, through multiple mechanisms involving structurally distinct cell surface receptors. Whereas cholesteryl esters are incorporated into lipoprotein particles that bind LDL and HDL receptors, mechanisms of cellular uptake of free (unesterified) cholesterol are not well understood. Our work has demonstrated that synthetic *N*-alkyl-3 β -cholesterylamines mimic trafficking properties of free cholesterol and avidly bind mammalian cell surfaces. This binding was predominantly receptor-mediated as evidenced by up to 80% inhibition upon co-addition of excess ezetimibe, free cholesterol, or cholesterol-3-sulfate as competitors. In an effort identify the receptor(s) responsible for these cellular interactions, we performed target identification studies using *N*-alkyl-3 β -cholesterylamines as photoaffinity labels. Because of the structural and functional similarities between *N*-alkyl-3 β -cholesterylamines and free cholesterol, the receptor(s) identified from this research may play a key role in the cellular uptake of cholesterol and/or charged cholesterol metabolites on the cell surface.