American Chemical Society

Division of Medicinal Chemistry
ABSTRACTS

226th ACS National Meeting

New York, NY
September 07-11, 2003 **D. L. Flynn, Program Chair**

SUNDAY MORNING

- **Androgen Receptor Directed Therapies**

L. G. Hamann, Presiding Papers 1-3

SUNDAY AFTERNOON

- **Peripheral Nociceptive Mechanisms**

C. M. Flores, Organizer Papers 4-10

- **Second Generation ErbB Inhibitors**

J. Morris, Organizer, Presiding Papers 11-14

MONDAY MORNING

- **Graduate Student Fellowship Symposium**

W. J. Brouillette, Organizer, Presiding Papers 15-19

- **General Oral Papers**

D. L. Flynn, Organizer; K. A. Jacobson, Presiding Papers 20-29

MONDAY AFTERNOON

- **New Developments in Antithrombotic Therapy**

S. Chackalamannil, Organizer, Presiding Papers 30-35

- **The Role of Organic Synthesis in Early Clinical Drug Development**

S. Caron, Organizer, Presiding Papers 36-41

MONDAY EVENING

- **Sci-Mix**

D. L. Flynn, Presiding Papers 63, 73, 78, 81, 85, 93, 95-96, 108, 117-118, 123, 129, 147, 149, 153, 160, 163, 168, 173, 185, 194, 226, 230, 232-233, 236, 240, 251, 254-255, 257-259, 262, 264, 274, 288, 294, 302-303, 311, 320, 338, 353

TUESDAY MORNING

- **Smissman Bristol-Myers Squibb Award Symposium**

G. L. Grunewald, Organizer, Presiding; D. L. Flynn, Organizer Papers 42-45

TUESDAY AFTERNOON

- **Aspartyl Peptidase Drug Discovery**

D. G. Brown, Organizer, Presiding Papers 46-50

- **Histamine H3 Receptor Ligands**

R. Aslanian, Organizer, Presiding Papers 51-55

TUESDAY EVENING

- **Poster Session**

D. L. Flynn, Organizer Papers 56-200

WEDNESDAY MORNING

- **Inflammation: New Results and Novel Targets**

D. Rotella, Organizer, Presiding — Papers 201-205

- **Protein Families as Targets**

W. Cornell, Organizer, Presiding; L. McQuire, Organizer — Papers 206-210

WEDNESDAY AFTERNOON

- **Emerging Therapies for Treatment of Asthma**

S. Ananthan, Organizer, Presiding — Papers 211-214

- **Targeting Protein-Protein Interactions**

C. R. Wagner, Organizer, Presiding — Papers 215-220

WEDNESDAY EVENING

- **Poster Session**

D. L. Flynn, Organizer — Papers 221-355

THURSDAY MORNING

- **General Oral Papers**

D. L. Flynn, Organizer; C. R. Wagner, Presiding — Papers 356-365

THURSDAY AFTERNOON

- **General Oral Papers**

D. L. Flynn, Organizer, Presiding — Papers 366-368, 370-375

DIVISION OF MEDICINAL CHEMISTRY

1.

NOVEL SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS). ***Duane D. Miller***[1], *Yali He*[1], *Craig A. Marhefka*[1], *Igor M. Rakov*[1], *Seoung Soo Hong*[2], *Dong Jin Hwang*[1], *Michael L. Mohler*[1], *Svetlana N. Kirichenko*[1], *Suni M. Mustafa*[1], *Vipin A. Nair*[1], *Renukadevi Patil*[1], *Kiwon Chung*[2], *Karen A. Veverka*[2], *Mitch S. Steiner*[2], *K. Gary Barnette*[2], *Donghua Yin*[1], *Weiqing Gao*[3], *Jeffrey D. Kearbey*[3], *Huiping Xu*[3], *Juhyun Kim*[3], *Jiyun Chen*[3], *Casey Bohl*[3], *and James T. Dalton*[3]. *(1) Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, 847 Monroe Ave Suite # 327, Memphis, TN 38163, (2) GTx, Inc, Memphis, TN 38163, (3) Division of Pharmaceutics and Pharmaceutical Chemistry, The Ohio State University, College of Pharmacy*

Since the discovery of the therapeutic benefits of testosterone in the 1930s, a variety of androgen preparations have been introduced and tested clinically. Following our initial discovery of nonsteroidal androgens (SARMs) reported in 1998, our laboratories have designed and synthesized series of nonsteroidal compounds in collaboration with the ARTA (Androgen Receptor Targeting Agents) program of GTx Inc., and explored the structure-activity relationships for androgenic and anabolic activities, both in vitro and in vivo. Nonsteroidal SARMs were identified from this very promising new class of drug candidates for further clinical development. Androgenic and anabolic activity was evaluated in vivo. The clinical indications of androgens are as replacement therapy for hypogonadal men, anemias, primary osteoporosis, muscular diseases, replacement therapy for aging men and for regulation of male fertility. The present study aimed to identify SARMs with in vivo pharmacological activity and clinical utility in man.

2.

DESIGN AND STRUCTURAL ANALYSIS OF A NOVEL SERIES OF BICYCLIC AR ANTAGONIST. ***Mark E. Salvati***[1], *Ricardo Attar*[2], *Arron Balog*[2], *Stanley Krystek*[3], *Rogelio Martinez*[4], *Dacia Pickering*[1], *John Tokarski*[3], *Jack Sack*[5], *Weifeng Shan*[1], *Donna Wei*[1], *and Hong Zhu*[1]. *(1) Oncology Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-7410, mark.salvati@bms.com, (2) Oncology Biology, Bristol-Myers Squibb Pharmeceutical Research Institute, (3) CAD Group, Bristol-Myers Squibb Pharmaceutical Research Institute, (4) Lead Synthesis Group, Bristol-Myers Squibb Pharmaceutical Research Institute, (5) Macro-Molecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute*

Prostate cancer (CaP) is the 2nd leading cause of cancer related deaths in men, claiming 37,000 lives in 1999. Androgen ablation is the gold standard treatment for advanced CaP, with non-steroidal antagonist of the androgen receptor (AR) playing an increasing role in this treatment regiment. Currently all androgen ablation therapy is palliative with 50% of all patients advancing to androgen refractory CaP in 18 months. In an effort to find novel antagonist of the AR, we applied structural based search techniques to identify a novel series of [2.2.1]-bicyclic imide based AR antagonist. These initial leads were characterized by co crystallization with the AR wild type and T877A LBD. From this structural information, computer mediated drug design was applied to better understand the underlying mechanism of antagonism of AR. Application of these efforts lead to the development of a novel series of [2.2.1]-bicyclic hydantoin based AR antagonists with superior potency.

3.

ROLE OF COREGULATORS IN ANDROGEN RECEPTOR FUNCTION. ***Myles Brown***, *Division of Molecular and Cellular Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, 44 Binney Street, Boston, MA 02115, Fax: 617-632-5417, myles_brown@dfci.harvard.edu*

Androgen receptor (AR) is required for sexual differentiation and is implicated in the maintenance of bone and muscle mass and in the development and growth of prostate cancer. We have found distinct functions for cofactor proteins and gene regulatory elements in the assembly of AR-mediated transcription complexes. The formation of an activation complex involves AR, co-activators, and RNA polymerase II recruitment to both the enhancer and promoter of a target gene. In contrast, the formation of a repression complex in response to AR antagonists involves recruitment of co-repressors that bind only at the promoter and not the enhancer. These findings support the concept that gene and cell type specific differences in coregulator recruitment can be exploited in the development of novel selective androgen receptor modulators or SARMs.

4.

ANALGESIC PROFILE OF A-317491, A P2X3 RECEPTOR ANTAGONIST. ***Michael F. Jarvis***, *Global Neuroscience Discovery, Abbott Laboratories, Abbott Park, IL 60064-6123, michael.jarvis@abbott.com*

The activation of P2X3 and P2X2/3 receptors on peripheral and central sensory afferents contributes to the pro-nociceptive effects of ATP. A-317491 is a novel non-nucleotide antagonist that blocked recombinant human and rat P2X3 and P2X2/3 receptor-mediated calcium flux (Ki=22-92 nM) and native P2X3 and P2X2/3 rat DRG receptors being selective (IC50 > 10 mM) over other P2 receptors and other drug recognition sites. The effects of A-317491 were stereospecific, the R-enantiomer being less active. A-317491 dose-dependently (ED50=30 mmol/kg, s.c.) reduced CFA-induced thermal hyperalgesia in rat and was most potent (ED50=10-15 mmol/kg, s.c.) in attenuating thermal hyeralgesia and mechanical allodynia following chronic nerve constriction injury. A-317491 was ineffective (ED50 > 100 mmol/kg, s.c.) in reducing nociception in animal models of acute, post-operative and visceral pain.

5.

MUSCARINIC AND NICOTINIC ACETYLCHOLINE RECEPTORS: THE YIN AND YANG OF PERIPHERAL CHOLINERGIC PAIN MODULATION. ***Christopher M. Flores***, *Analgesics, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215 628 3297*

The remarkable diversity in subtype heterogeneity, signaling mechanisms and expression patterns of muscarinic (mAChR) and nicotinic (nAChR) acetylcholine receptors gives rise to an impressive repertoire of functions with commensurate opportunities for therapeutic intervention. Using a multi-methodological approach, we have demonstrated that while both mAChR and nAChR agonists are antihyperalgesic in the formalin model of orofacial pain, with the effects of the former being mediated by peripheral M2 receptors, they exhibit opposite effects on the capsaicin-evoked neurosecretion of CGRP from peripheral nociceptors, mediating inhibition and potentiation, respectively. Moreover, we have used triple labeling histochemistry to colocalize the M2 mAChR and multiple nAChR subunit mRNAs to VR1- and/or CGRP expressing sensory neurons in the trigeminal ganglion. Collectively, these studies indicate that, similar to their role in modulating peripheral motor neuron function at the NMJ, mAChR and nAChR receptors mediate, respectively, inhibitory and excitatory actions on peripheral sensory neurons, including nociceptors, and thus may be targets for novel analgesic drugs.

6.

NOVEL N-TYPE CALCIUM CHANNEL BLOCKERS EFFICACIOUS IN ANIMAL MODELS OF CHRONIC PAIN. ***Terry Snutch***[1], *Z.P. Feng*[1], *F. Belardetti*[1], *T. Vanderah*[2], *G.W. Zamponi*[3], *and F. Porreca*[2]. *(1) NeuroMed Technologies Inc, 301-2389 Health Sciences Mall, University of British Columbia, Vancouver, BC V6T 1Z4, Canada, Fax: 604 822 9978, (2) Department of Pharmacology, University of Arizona, (3) Department of Physiology and Biophysics, University Of Calgary*

N-type calcium channels play a crucial role in mediating spinal neurotransmission and are strong candidates for pain intervention. While the N-type channel blocking peptide Ziconotide® is highly efficacious for the treatment of a variety

of neuropathic and inflammatory pain conditions it must be delivered by intrathecal administration and there remains a significant opportunity to develop small organic molecule blockers of the N-type channel. Utilizing a combined rationale drug design and direct electrophysiological screening approach, several novel classes of small organic molecules selective for the N-type channel were identifiedt. The lead compounds show IC50 values ~ 30 to 60 nM and exhibit ~ 30 to greater than 1000 fold selectivity over L-type calcium channels. NMED-126 and NMED-160 are orally efficacious in the Chung, Bennett and inflammatory pain models. Preclinical analyses show no significant adverse affects related to heart rate, blood pressure or changes in balance and gait.

7.

PERIPHERAL PAIN TARGETS. ***Michael Williams**, Cephalon Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: 847-615-8547*

Over the past decade, considerable advances have been made in understanding the complexity of the systems involved in pain signaling. Many new targets have been identified with the search for drug like compounds for these at various stages. The latter include the marketed COX-2 inhibitors (celecoxib, rofecoxib, etc), neuronal nicotinic receptor agonists (ABT 594) that are are advancing in clinical trials, neurokinin-1 antagonists (MK 869. etc.) that failed to show efficacy in humans despite activity in animal models, and sodium (NW 1029) and P2X3 (A-317491) channel antagonists that been evaluated in animals. Other potential pain targets include NGF, prostanoid, bradykinin, CCK, melanocortin, prokineticin, CGRP, galanin, muscarinic cholinergic, cannabinoid, SNSRs (sensory neuron specific receptors) receptors, ASIC, N-type calcium, vanilloid/TPRV and non voltage gated potassium (TREK, TRAAK, TWIK etc.) channels.

8.

SENSORY NEURON SPECIFIC GPCRS. ***Andy Dray**, Department Of Pharmacology, AstraZeneca Research & Development Montreal, 7171 Frederick-Banting, St Laurent, QC H4S 1Z9, Canada, Fax: 514-832-3229*

GPCRs are an abundant class of membrane bound receptors involved in regulation of nervous system excitability. Many GPCRs are involved in pain transmission and are the targets for present (e.g; opioids) and future analgesics. The identity of approximately 200 orphan receptors is being sought. Criteria for their involvement in pain include localization in pain pathways as well as functional involvement determined by molecular and chemical interventions. We have recently identified a family of GPCRs, sensory neuron specific receptors (SNSRs), localized exclusively in small, nociceptive sensory neurons (somatic & trigeminal) in a number of species. Several neuropeptides derived from the opioid precursor families POMC (g2-MSH) and proenkephalin A (BAM8-22), potently activated SNSR through a naloxone-insensitive mechanism. In vivo studies (flexor-reflex and tail-immersion) indicted that these ligands were pronociceptive supporting a role for SNSRs in nociception.

9.

TRPV CHANNELS IN PAIN. ***Michael Caterina**, Department of Biological Chemistry, Johns Hopkins University, School of Medicine, 408 Biophysics Building, 725 North Wolfe Street, Baltimore, MD 21205, Fax: 410-955-5759, caterina@jhmi.edu*

The TRPV ion channel subfamily is of considerable interest in the context of its involvement in nociception and other sensory processes. The founding member, TRPV1 (VR1) is highly expressed in a subset of small-to-medium diameter sensory neurons and is activated by capsaicin and pungent vanilloids, protons, noxious heat (> 42°C) or a variety of lipid compounds. Mice lacking TRPV1 are insensitive to vanilloids and defective in the detection of noxious heat (e.g. inflammatory thermal hyperalgesia). TRPV2 (VRL-1) is expressed in a subset of medium-to-large diameter neurons and is activated by very high temperatures (> 52°C) or growth factors. TRPV3 and TRPV4 are warmth-gated ion channels with a slightly lower activation threshold (~33°C). TRPV4 can alternatively be activated by the phorbol derivative, 4a phorbol 12,13-didecanoate or by hypoosmolarity and may participate in mechanosensation.

10.

TTX-SENSITIVE AND TTX-RESISTANT SODIUM CHANNELS. ***Patricia Salvati**, L. Faravelli, and O. Veneroni, Newron Pharmaceuticals SpA, Via L. Ariosto, 21, Bresso (MI), Italy, Fax: 39 02 966 81 333*

Voltage gated sodium channels (VGSC) play an important role in the generation of ectopic discharges after nerve injury. Adult rat DRG neurons express six VGSC _-subunits (Navl.l, Navl.6, Navl.7, Navl.8, Navl.9 and Nax) which underlie distinct sodium currents: fast TTXs, slow TTXr and persistent TTXr, based on kinetic properties and sensitivity to tetrodotoxin (TTX). The expression of Navl.3 (TTXs), Navl.8 (TTXr) and Navl.9 (TTXr) channels is developmentally regulated and is altered in models of inflammatory and neuropathic pain. NW-1029 is a novel VGSC blocker with preferential inhibitory effects on TTXr currents in depolarized in vitro conditions, with long lasting anti-hyperalgesic and anti-allodynic oral activity in animal models of neuropathic and inflammatory pain. This activity is not accompanied by CNS-related side effects.

11.

DISCOVERY AND PROFILE OF GW572016, A DUAL REVERSIBLE EGFR / ERBB-2 TYROSINE KINASE INHIBITOR. ***Robert J. Mullin**, Deptartment of Oncology Biology, GlaxoSmithKline R&D, 79 T.W. Alexander Drive, Rm 205, Bldg #4301, Reseach Triangle Park, NC 27709, Fax: 919-315-3749, robert.j.mullin@gsk.com*

The erb family members, EGFR and ErbB-2, are transmembrane tyrosine kinases receptors which play a role in cellular proliferation and anti-apoptotic biology in a variety of malignancies and are currently the focus of a number of biological and small molecule therapies. Employing a biologically driven medicinal chemistry driven strategy, GW572016, N-{3-Chloro-4-[(3-fluorobenzyl)oxy]-phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, a potent reversible dual EGFR/ErbB-2 inhibitor was identified. Evaluation of GW572016 indicated that it demonstrated a high degree of selectivity vs a panel of kinases and was a selective inhibitor of both EGFR and ErbB-2 driven cellular proliferation. Biochemical profiling revealed potent inhibition of EGFR and ErbB-2 phosphorylation and modulation of downstream signal transduction pathways. In vivo testing determined that GW572016 had pharmacokinetic, drug stability and xenograft antitumor properties appropriate for progression to clinical evaluation. Currently GW572016 is in clinical trials.

12.

SELECTIVE INHIBITORS OF ERBB2. ***John C. Kath**[1], James Atherton[1], Gabriella Barbacci-Tobin[1], Samit K. Bhattacharya[1], Charles A. Boos[1], Brian P. Boscoe[1], Mary Campbell[1], Kevin G. Coleman[1], Eric D Cox[1], Nicolas V. Currier[1], Erling O. Emerson[1], Kathleen Gerdin[1], Peter Goodwin[1], Shawn Harriman[1], Jitesh P. Jani[1], Tricia A. Kwan[1], Zhengyu Liu[1], Erin N. Mairs[1], Alan M. Mathiowetz[1], Penelope E. Miller[1], Joel Morris[1], James D. Moyer[1], Leslie R Pustilnik[1], Kristina Rafidi[1], Daniel T. Richter[1], Amber Rouch[1], Erik A. Soderstrom[1], Carl B. Thompson[1], Norma J. Tom[1], Matthew D. Wessel[1], Steven M. Winter[1], Jun Xiao[1], Xumiao Zhao[1], and Ken K. Iwata[2]. (1) Department of Cancer Research, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, john_c_kath@groton.pfizer.com, (2) OSI Pharmaceuticals*

The erbB family of receptor tyrosine kinases has been shown to play an important role in a variety of cancers. The activation and subsequent homo- or heterodimerization of erbB family members initiates a signal transduction cascade leading to cell growth and overexpression, mutation or overstimulation of these kinases can lead to a transformed phenotype. Within the erbB family, erbB2 is particularly important because it is thought to be the preferred heterodimerization partner for all the other erbB family members. While efforts to discover small molecule inhibitors selective for EGFR (erbB1) relative to erbB2 have been successful, inhibitors selective for erbB2 have not been reported. Using matching erbB2 and EGFR kinase and cellular assays as a primary means to guide medicinal chemistry, CP-724714, a potent and selective erbB2 inhibitor has been advanced into clinical development.

13.

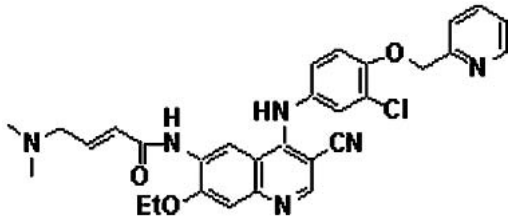
NEW DUAL INHIBITORS OF HER1 AND HER2 PROTEIN TYROSINE KINASES. ***Gregory D. Vite***[1], *Harold Mastalerz*[1], *Brian E. Fink*[1], *Ashvinikumar V. Gavai*[1], *John T. Hunt*[2], *John S. Tokarski*[3], *Dolatrai M. Vyas*[1], *and Tai W. Wong*[2]. *(1) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6601, gregory.vite@bms.com, (2) Oncology Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, (3) Department of Structural Biology and Modeling, Bristol-Myers Squibb Pharmaceutical Research Institute*

The clinical and commercial success of Herceptin, a monoclonal antibody used in the treatment of breast cancer, has provided target validation for the erbB2 or HER2 receptor tyrosine kinase. Additionally, recent clinical studies with the monoclonal antibody Erbitux and quinazoline-based ATP mimics suggest that targeting the EGFR or HER1 receptor tyrosine kinase is a viable strategy for treatment of solid tumors of epithelial origin. The extensive homology of the catalytic sequences of the two receptors suggests that it should be feasible to design inhibitors that occupy the ATP binding pockets of both receptor kinases. We and others have been exploring the potential of small molecule kinase inhibitors targeted to both the HER2 and HER1 receptors with the goal of achieving added clinical benefit from dual-acting agents. This presentation reveals Bristol-Myers Squibb's evaluation of several chemical classes as potential HER2/HER1 dual inhibitors and summarizes the efforts on a promising series of pyrrolotriazine-based inhibitors.

14.

NOVEL SUBSTITUTED 4-ANILINOQUINOLINE-3-CARBONITRILES AS ORALLY ACTIVE, IRREVERSIBLE BINDING INHIBITORS OF HER-2 KINASE. ***Hwei-Ru Tsou****, Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, Fax: 845-602-5561, Tsouh@wyeth.com*

Previously, we described a series of 4-anilinoquinoline-3-carbonitriles that are orally-active, irreversible-binding inhibitors of the EGFR kinase. One of them, EKB-569, is currently in clinical trials as anti-tumor agent in EGFR overexpressing tumors. EKB-569 is thought to function by forming a covalent bond with the thiol of cysteine-773 within the ATP binding site of EGFR. In Her-2, a closely related receptor kinase, this residue is conserved as cysteine-805. We synthesized a series of new substituted 4-anilinoquinoline-3-carbonitriles with enhanced activity against the Her-2 kinase resulting in a lead compound HKI-272. [^{14}C]-labeled HKI-272 binds selectively and irreversibly to Her-2 in BT474 cells. Furthermore, this new series demonstrates excellent oral activity in Her-2 dependent human tumor xenograft models.



HKI-272

15.

DESIGNING PROTEIN DIMERIZERS. ***Jonathan Carlson***[1], *A. Kanter*[1], *P. E. Pineda*[1], *V. Cody*[2], *and C. R. Wagner*[1]. *(1) Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455, carls200@tc.umn.edu, (2) Hauptman-Woodward Medical Research Institute, Inc*

In an effort to explore the mechanism and application of induced protein dimerization, we synthesized a flexible methotrexate (MTX) dimer, demonstrated its ability to selectively dimerize E. coli dihydrofolate reductase (ecDHFR), and evaluated the factors regulating its ability to induce cooperative dimerization. Significant findings included the apparent conformational stability of bis-MTX in aqueous solution, the strength of favorable protein-protein interactions in bis-MTX–ecDHFR dimers, and the selectivity of dimerization for ecDHFR relative to mouse DHFR (>107). Ongoing chemical investigations have included further analysis of the conformational behavior of bis-MTX, construction of MTX-based dimerizers with a range of linker lengths and flexibility, and synthesis of DHFR dimerizers based on alternate ligands. Further research has probed the role of specific amino acid residues in stabilizing the protein dimer interface. Finally, we have applied the tools of DHFR dimerization to explore chemically induced protein polymerization, with implications for both novel materials and nanotechnology.

16.

FLUORESCENT INTERCALATOR DISPLACEMENT (FID) ASSAY FOR ESTABLISHING SEQUENCE SELECTIVITY AND BINDING AFFINITY OF DNA BINDING MOLECULES. ***Winston C. Tse***[1], *Brian E. Fink*[2], *Young-Wan Ham*[1], *and Dale L. Boger*[1]. *(1) Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Rd., La Jolla, CA 92037, Fax: 858-784-7550, (2) Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute*

The regulation of gene expression is based on the sequence selective recognition of nucleic acids by repressor, activator, and enhancer proteins. It is widely recognized that selective control of such processes holds significant promise in therapeutic medicine. In efforts toward selecting candidate ligands that display selectivity for an ensemble of related sequences characteristic of regulatory proteins, we recently reported the development of a fluorescent intercalator displacement (FID) assay for establishing binding affinity and sequence selectivity of DNA binding molecules. The method is technically non-demanding and amenable to high-throughput technologies. Its ability to screen a single compound against a library of DNA binding sites generating a complete DNA binding profile and to screen a library of compounds against a predetermined sequence demonstrating selection is described. Combined with quantitative FID titrations to establish absolute binding constants, the assay provides a high resolution technique to reveal DNA binding properties of small molecules.

17.

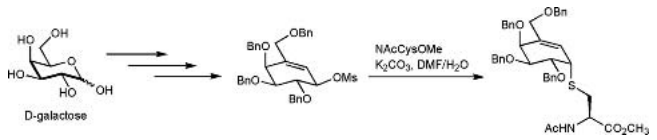
SYNTHESIS, STRUCTURE, AND FUNCTION OF THE DIAZONAMIDES. ***Anthony W. G. Burgett****, Michael G. Roth, and Patrick G. Harran, Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9038, Fax: 214-648-6455, anthony.burgett@email.swmed.edu*

The diazonamides are structurally novel marine natural products exhibiting potent anti-mitotic, cytotoxic activity against cultured human cancer cell lines. After more than a decade since being discovered, the mode of action and potential of this class of compounds as lead pharmaceuticals remains unknown. The success of our synthetic efforts has allowed for a comprehensive investigation into the diazonamide pharmacology. Structure-activity relationships have been explored, and probe analogs necessary to elucidate the mode of action and identify the diazonamide cellular target have been synthesized. The employment of these synthetic tools has allowed for extensive advancements in understanding the diazonamide biological activity, and these discoveries suggest a possible mode of action for this unique class of compounds.

18.

STRATEGIES FOR THE SYNTHESIS OF GLYCOPEPTIDE ISOSTERES. ***Lisa J. Whalen****, and Randall L. Halcomb, Department of Chemistry and Biochemistry, University of Colorado, Campus Box 215, Boulder, CO 80309-0215, Fax: 303-492-5894, whalenl@colorado.edu*

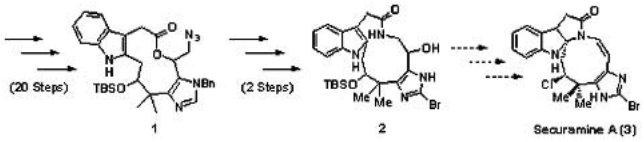
Due to their biological relevance, there is a need for glycoproteins with a defined sequence. However, they are difficult to isolate as homogeneous substances from natural sources. As a result, the development of efficient methods for synthesizing homogeneous glycoproteins has fallen to organic chemists. One strategy uses carbohydrate isosteres to facilitate the preparation of glycopeptides that are structurally similar but not identical to wild type. Using this approach, we have shown that an electrophilic galactose equivalent will react chemoselectively with cysteine nucleophiles to generate glycosyl amino acid isosteres. Progress toward extending this technology to the synthesis of glycopeptide isosteres will be reported.



19.

PROGRESS TOWARD THE TOTAL SYNTHESIS OF SECURAMINE A. *John L. Wood,* ***J. Brad Shotwell****, Stuart C. Chaffee, and Peter Korakas, Department of Chemistry, Yale University, Sterling Chemistry Laboratory, PO Box 208107, New Haven, CT 06520-8107, Fax: 203-432-6144, john.wood@yale.edu, john.shotwell@yale.edu*

Securamine A (3) is a structurally intriguing alkaloid possessing a pyrroloindole core joined via a modified isoprene subunit to a functionalized imidazole ring. Recent work in our laboratory has involved preparation of key lactone 1 and its tandem azide reduction/ring expansion to macrolactam 2. Ongoing efforts to introduce the key neopentyl chloride and enamide functionalities will be described.



20.

DESIGNING AN ENRICHED SCREENING LIBRARY FOR THE DISCOVERY OF NON-NUCLEOSIDE INHIBITORS OF THE HCV NS5B RNA POLYMERASE. ***Uli Schmitz****, Martin Kirk, Kevin Fung, Samantha Koo McCoy, Derek Latour, Emil Michelotti, Jeff Pouliot, Christopher roberts, Lillian Lou, and Ron Griffith, Genelabs Technologies Inc, 505 Penobscot Drive, Redwood City, CA 94063, ulis@genelabs.com*

Hepatitis C is considered a major public health threat and current therapies still call for major improvements. The virus causing Hepatitis C (HCV) is a single-stranded RNA virus, whose replication in liver cells relies on several virally-encoded nonstructural proteins, including the NS5b RNA-dependent RNA polymerase. To date, only a few non-nucleoside inhibitors have been published and the wide range of inhibitors for HIV reverse transcriptase, a functionally and structurally closely related polymerase, have been reported to be inactive against HCV NS5b. Recognizing that kinases and RNA polymerases have a common substrate, ATP, one would expect that a compound collection targeted against a variety of kinases should have a higher hit-rate against the NS5b polymerase compared to a diverse random library of the same size. Based on chemotypes found in ~50 diverse kinase and ATPase inhibitors found in the literature, we selected over 30,000 compounds from one particular commercial source and subjected them to a rigorous diversity pruning step. Our final HTS library indeed produced a hit rate of ~1% in our primary NS5b polymerase assay. Details of the selection process and the screening results will be discussed.

21.

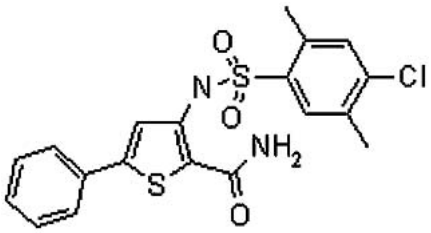
INHIBITORS OF THE HEPATITIS C VIRUS NS5B RNA-DEPENDENT RNA POLYMERASE. ***Pierre L. Beaulieu***[1]*, Volkard Austel*[2]*, Michael Bös*[1]*, Yves Bousquet*[1]*, Gulrez Fazal*[1]*, Jean Gauthier*[1]*, James Gillard*[1]*, Sylvie Goulet*[1]*, Steven LaPlante*[1]*, Marc-André Poupart*[1]*, Daniel Lamarre*[1]*, Sylvain Lefebvre*[1]*, Ginette McKercher*[1]*, Martin Marquis*[1]*, Arnim Pause*[1]*, Charles Pellerin*[1]*, and George Kukolj*[1]*. (1) Research Division, Boehringer Ingelheim Canada Ltd, 2100 Cunard street, Laval, QC H7S2G5, Canada, Fax: 450-682-8434, pbeaulieu@lav.boehringer-ingelheim.com, (2) Boehringer Ingelheim Pharma KG, Germany*

An estimated 3% of the world population is currently infected with the hepatitis C virus (HCV), a major cause of chronic liver disease that can progress to liver cirrhosis and hepatocellular carcinomas. There is currently an unmet medical need for HCV treatments with improved efficacy and side effect profile. The NS5B RNA dependent RNA polymerase is a virally-encoded enzyme that is essential for HCV replication and offers new opportunities for the development of novel antiviral therapies. Screening of our sample collection with an HCV polymerase assay using recombinant NS5B protein from the 1b genotype identified a series of benzimidazole 5-carboxamide derivatives with specific low-micromolar inhibitory activity. Optimization of this class of inhibitors to low nanomolar potencies and insight into their possible mechanism of action will be presented. In addition ex vivo proof of concept was demonstrated with inhibitors having low-micromolar potency in a cell-based assay quantifying replication of HCV sub-genomic replicons.

22.

DISCOVERY AND SAR STUDIES OF 2,3,5-TRISUBSTITUTED THIOPHENE DERIVATIVES: A NOVEL CLASS OF HCV NS5B RNA DEPENDENT RNA POLYMERASE INHIBITORS. ***T. Jagadeeswar Reddy***[1]*, Laval Chan*[1]*, Melanie Proulx*[1]*, Sanjoy Kumar Das*[1]*, Oswy Zeno Pereira*[1]*, Carl Poisson*[1]*, Nghe P Nguyen-Ba*[1]*, Constantin Yannopoulos*[1]*, Liliane Halab*[1]*, Marc Courchesne*[1]*, Caroline Roy*[1]*, Richard Bethell*[2]*, Ming-Qiang Zhang*[1]*, Arshad Siddiqui*[1]*, Maud David*[2]*, Lucille L'Heureux*[2]*, Jean Bédard*[2]*, Olivier Nicolas*[2]*, Bettina Hamelin*[3]*, Kelly Dong*[3]*, Nathalie Rioux*[3]*, Martine Hamel*[2]*, Nicolas Morin*[2]*, Philippe Asselin*[2]*, Carole Chagnon Labelle*[3]*, Gilles Roberge*[3]*, Michael N. G. James*[4]*, Meitian Wang*[4]*, Kenneth K.-S. Ng*[4]*, and Maia M. Cherney*[4]*. (1) Department of Medicinal Chemistry, Shire BioChem Inc, 275 Armand-Frappier Blvd., Laval, QC H7V 4A7, Canada, Fax: 450-978-7777, treddy@ca.shire.com, (2) Department of Virology, Shire BioChem Inc, (3) Department of Pharmacology, Shire BioChem Inc, (4) Department of BioChemistry, Canadian Institutes for Health Research Group in Protein Structure and Function / University of Alberta*

NS3 chymotrypsin-like protease and NS5B RNA dependent RNA polymerase (RdRp) are probably the most studied targets for anti-Hepatitis C (HCV) therapy as they have been shown to be crucial for viral replication. In continuation of our ongoing research on Hepatitis C, we have identified a new class of NS5B polymerase inhibitor **1** from our screening efforts. Structure Activity Relationship (SAR) studies of compound **1** have delineated the optimal substitution pattern for replicon activity, e.g. a carboxylic acid group at the 2-position of thiophene ring. The ability to inhibit replication of viral subgenomic RNA (replicon) in Huh-7 cells was determined using the system developed by Bartenschlager *et. al*. The structure of several polymerase-inhibitor complexes have also been elucidated by soaking experiments and this led to the identification of an allosteric binding site within the thumb region about 30 Å from the active site. In summary, SAR studies of **1** resulted in potent inhibitors of HCV NS5B mediated subgenomic viral replication and the profile of these compounds warranted further evaluation as preclinical candidates.



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23.

BACTERIAL RNASE P INHIBITORS: A NOVEL APPROACH TO NEW ANTIBIOTICS. ***Michael A. Sturgess****, Paul S. Eder, Susan Erickson-Viitanen, Alicia Green, Oscar W. Huang, Gordon D. Powers, and Samala J. Rao, Message Pharmaceuticals, 30 Spring Mill Dr, Malvern, PA 19355, Fax: 610-695-0957, sturgess@messagepharm.com*

RNase P is a ribozyme involved in the processing of pre-tRNA within all cells. Recent evaluation of the bacterial RNase P riboenzyme has demonstrated that this system has the potential to be a useful target for the development of novel classes of antibiotics. A recently completed *N. gonorrhoeae* RNase P HTS program has identified a number of distinct classes of compounds capable of inhibiting this ribozyme. In addition, these compounds have been shown to demonstrate varying degrees of differential activity against a partially purified human RNase P preparation. Here we document some of our early findings on one series of guanylhydrazone derived RNase P inhibitors.

24.

SYNTHESIS AND ANTI-HEPATITIS VIRUS ACTIVITY OF |Á, |Â-GALACTOSYL CERAMIDES. ***Kuanqiang Gao****, and R.M. Moriarty, Department of Chemistry, University of Illinois, 845 W Taylor St, Chicago, IL 60607, Fax: 312-996-0431, kgao2@uic.edu*

A representative |Á-Galceramide (|Á-Galcer) KRN7000, can activate NKT cells through CD1d molecules, which play essential role in the generation of strong anti-Hepatitis B and C activity of KRN7000. Further investigation of the mechanism and structure-activity relationship prompted the synthese of 4 galceramide

derivatives, O-(D-galactopyranosyl)-2-hexacosylamino-D-threo-1,3-octadecandiol (1) and O-(D-galacto pyranosyl)-2-hexacosylamino-L-threo-1,3-octadecandiol (2)and their isomers (3) and (4). The key intermediates D-threo and L-threo dihydrosphingosines have been synthesized starting from D-serine and L-serine respectively in 5 steps and the total synthesis required only 12 steps, thus yielding final compounds in good yields. These compounds will be tested for anti-Hepatitis B and C activities.

25.

5-AMIDO- AND 5-SULFONAMIDO-INDOLYL QUINOLINONES: NOVEL SERIES OF POTENT KDR (VEGFR-2) KINASE INHIBITORS THAT EXHIBIT ENHANCED PHARMACOKINETICS. ***Mark E. Fraley***[1], *Kenneth L. Arrington*[1], *Patrice A. Ciecko*[2], *Kathleen E. Coll*[3], *George D. Hartman*[1], *David C. Heimbrook*[3], *William F. Hoffman*[1], *Yuntae Kim*[1], *Rosemary C. McFall*[3], *Georgia McGaughey*[1], *Keith Rickert*[3], *Laura Sepp-Lorenzino*[3], *Jennifer M. Shipman*[3], *Kenneth A. Thomas*[3], *and Bradley K. Wong*[2]. *(1) Department of Medicinal Chemistry, Merck & Co., Inc, West Point, PA 19486, Fax: 215-652-6345, mark_fraley@merck.com, (2) Department of Drug Metabolism, Merck & Co., Inc, (3) Department of Cancer Research, Merck & Co., Inc*

Angiogenesis is a critical process for the growth and metastasis of solid tumors that relies on the expression of vascular endothelial growth factor (VEGF), a selective endothelial cell mitogen whose mitogenic signaling is mediated through the receptor tyrosine kinase KDR (VEGFR-2). Previously, we described the design, synthesis, initial SAR and *in vitro/in vivo* characterization of a novel indolyl quinolinone class of ATP-competitive KDR kinase inhibitors. Herein we detail further design modifications toward the optimization of this lead series including the incorporation of 5-amido and 5-sulfonamido groups in the indolyl ring system that resulted in enhanced physical and pharmacokinetic properties with retained levels of inhibitory activity. For example, compound **2** bearing a 5-sulfonamido indolyl substituent exhibited good potency (KDR IC50=10 nM, Cell KDR autophos IC50=27 nM) and a favorable pharmacokinetic profile in dog (Cl=0.5 mL/min/kg, t1/2=6.4 h, %F=63%).

26.

1,5-DIARYLBENZIMIDAZOLES AND 3,7-DIARYLIMIDAZOPYRIDINES AS INHIBITORS OF THE VEGF-RECEPTOR KDR. ***Zhicai Wu***[1], *Mark T. Bilodeau*[2], *Mark E. Fraley*[3], *John C. Hartnett*[2], *April M. Cunningham*[4], *Adrienne E. Balitza*[2], *Timothy J. Koester*[2], *Mildred L. Kaufman*[2], *Edward S. Tasber*[2], *Patrice A. Ciecko*[5], *Kathleen E. Coll*[6], *William F. Huckle*[7], *Randall W. Hungate*[4], *Richard Kendall*[2], *Rosemary C. McFall*[6], *Xianzhi Mao*[8], *Ruth Rutledge*[2], *George D. Hartman*[2], *and Kenneth A. Thomas Jr.*[6]. *(1) Medicinal Chemistry, Merck & Co., Inc, WP14-2, P.O. Box 4, Sumneytown Pike, West Point, PA 19486, Fax: 215-652-7310, zhicai_wu@merck.com, (2) Department of Medicinal Chemistry, Merck Research Laboratories, (3) Department of Medicinal Chemistry, Merck & Co., Inc, (4) Department of Medicinal Chemistry, Merck, (5) Department of Drug Metabolism, Merck Research Laboratories, (6) Department of Cancer Research, Merck, (7) Department of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, (8) Department of Cancer Research, Merck Research Laboratories*

1,5-Diarylbenzimidazoles and 3,7-Diarylimidazopyridines have been identified as potent inhibitors of KDR kinase activity. These series were developed with a goal of finding compounds with optimal drug-like properties. This presentation will describe detailed structural modifications that enhance solubility, lower protein binding, and provide compounds with excellent potency and pharmacokinetic profiles. A detailed comparison between these series will also be provided.

27.

DESIGN AND SYNTHESIS OF THE FIRST GENERATION OF NOVEL, POTENT, SELECTIVE AND IN VIVO ACTIVE (BENZOTHIAZOL-2-YL) ACETONITRILE INHIBITORS OF THE C-JUN-N-TERMINAL-KINASE (JNK). ***Pascale Gaillard***[1], *Isabelle Jeanclaude-Etter*[1], *Steve Arkinstall*[2], *Yves Cambet*[3], *Montserrat Camps*[4], *Christian Chabert*[4], *Dennis Church*[1], *Denise Gretener*[3], *Serge Halazy*[1], *Antony Nichols*[3], *and Jean-Pierre Gotteland*[1]. *(1) Department of Chemistry, Serono Pharmaceutical Research Institute, 14, Chemin des Aulx, 1228 Geneva, Switzerland, pascale.gaillard@serono.com, (2) Department of Biology, Serono Reproductive Biology Institute, (3) Department of Biotechnology, Serono Pharmaceutical Research Institute, (4) Department of Biology, Serono Pharmaceutical Research Institute*

Several lines of evidence support the hypothesis that c-Jun-N-terminal Kinase (JNK) plays a critical role in a wide range of diseases including apoptosis-related disorders and severe inflammatory conditions. Screening of our internal compound collection for inhibitors of JNK3 led to the identification of (benzothiazol-2-yl)acetonitrile derivatives as potent and selective JNKs inhibitors. Chemistry and initial SAR on this unique kinase inhibitor template was explored starting from hit AS007149. Investigation of the SAR rapidly revealed that the (benzothiazol-2yl)acetonitrile pyrimidine core was crucial to keep good level of potency and selectivity on JNK3. Further optimization led to the identification of an optimal distal chain significantly improving the biological and biopharmaceutical profile of the compounds leading to the discovery of compound AS601245. The in vitro and in vivo anti-apoptotic as well as anti-inflammatory properties of this new class of JNK inhibitors was then further investigated. We will describe the initial SAR efforts leading to the identification of AS601245 and its biological properties associated.

28.

DESIGN, SYNTHESIS AND BIOLOGICAL PROPERTIES OF THE FIRST GENERATION OF NOVEL, POTENT AND SELECTIVE (BENZOYLAMINOMETHYL)-THIOPHENE SULFONAMIDE INHIBITORS OF THE C-JUN-N-TERMINAL-KINASE (JNK). ***Thomas Rueckle***[1], *Marco Biamonte*[1], *Tania Grippi-Vallotton*[1], *Steve Arkinstall*[2], *Yves Cambet*[3], *Montserrat Camps*[4], *Christian Chabert*[4], *Dennis Church*[1], *Serge Halazy*[1], *Xuliang Jiang*[5], *Isabelle Martinou*[3], *Antony Nichols*[3], *Wolfgang Sauer*[1], *and Jean-Pierre Gotteland*[1]. *(1) Department of Chemistry, Serono Pharmaceutical Research Institute, 14, Chemin des Aulx, 1228 Plan-les-Ouates, Geneva, Switzerland, thomas.ruckle@serono.com, (2) Department of Biology, Serono Reproductive Biology Institute, (3) Department of Biotechnology, Serono Pharmaceutical Research Institute, (4) Department of Biology, Serono Pharmaceutical Research Institute, (5) Department of Chemistry, Serono Reproductive Biology Institute*

Several lines of evidence support the hypothesis that c-Jun N-terminal Kinase (JNK) plays a critical role in a wide range of diseases including apoptosis-related disorders and severe inflammatory conditions. Screening of our internal compound collection for inhibitors of JNK3 led to the identification of 2-(Benzoylaminomethyl)-thiophene sulfonamides as novel, potent and selective JNKs inhibitors. Chemistry and initial SAR on this novel and unique kinase inhibitor template was explored starting from hit AS004509. Whereas the left- and central hand parts of the molecule were rapidly revealed as instrumental to maintain the potency on the enzyme, many right hand part variants were investigated and this led to the identification of 2-(Benzoylaminomethyl)-thiophene sulfonamides benzotriazole AS600292 as the first potent and selective JNK inhibitor of this class which demonstrated a protective action against neuronal cell death induced by growth factor- and serum deprivation. We will describe the initial SAR effort leading to the identification of AS600292 and its biological properties associated.

29.

COMPREHENSIVE EMPIRICAL DATASET FOR CORRELATING SMALL-MOLECULE STRUCTURE WITH KINASE INHIBITION. ***C. Nicholas Hodge***, *and William P. Janzen, Amphora Discovery Corp, 419 S. San Antonio Rd, Los Altos, CA 94022, Fax: 650-941-2129, nick.hodge@amphoracorp.com*

Rapidly optimizing drug lead potency and selectivity requires accurate information on its interactions with desired and undesired targets. Traditional approaches generate reproducible data on hundreds of compounds within narrow series, and if the selected series fails, time is lost without having gained much information. An alternative to this serial approach is to create a full dataset of relevant ligand-target interactions that guides the optimization of a wide choice of scaffolds with desired properties. This approach requires control of the purity, identity and concentration of small molecules, and screening methods that are very accurate as well as fast. Here we report results of 90,000 purified, drug-like molecules tested against 22 kinases, including clinically interesting enzymes and counterscreens, with standard deviations of about 3%. We describe patterns of activity for known and novel inhibitors, and show that, using this approach, remarkably selective series of compounds can be identified in a diverse, low molecular weight library.

30.

SYNTHETIC TAILOR-MADE OLIGOSACCHARIDES AS NEW ANTITHROMBOTIC AGENTS. ***Maurice Petitou**, Cardiovascular Thrombosis Department, Sanofi-Synthelabo Recherche, 195, route d'Espagne, 31036 Toulouse cedex, France, Fax: 33-561 162 286, maurice.petitou@sanofi-synthelabo.com*

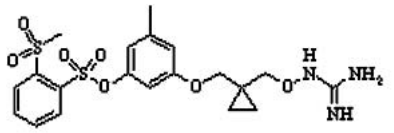
We will discuss our research on synthetic oligosaccharides whcih selectively activate the inhibitory activity of antithrombin towards various serine proteinases. We first synthesized pentasaccharides closely related to the antithrombin binding domain of heparin (the active site), as well as analogues displaying different pharmacokinetic profiles. Selective inhibitors of coagulation factor Xa were thus obtained that represent a new class of antithrombotic drugs currently being evaluated or launched worldwide. We then designed larger oligosaccharides that inhibit both factor Xa and thrombin in the presence of antithrombin. They are devoid of undesired non-specific interactions with blood proteins, particularly with platelet factor 4. Clinical trials are ongoing to prove the therapeutic benefits of this new type of coagulation inhibitors.

This work was carried out in collaboration with Organon as part of reserch on antithrombotic oligosaccharides.

31.

DISCOVERY OF POTENT, SELECTIVE, ORALLY BIOAVAILABLE SMALL MOLECULE THROMBIN INHIBITORS USING OXYGUANIDINES AS GUANIDINE MIMETICS. ***Tianbao Lu**, 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Drive, Exton, PA 19348, Fax: 610-458-8249, tianbao.lu@3dp.com*

Thrombin (Factor IIa), a serine protease, plays a pivotal role in both fibrin generation penultimate to clot formation and platelet activation. Recent efforts in the field of thrombin inhibitor research have focused on the identification of compounds with good oral bioavailability and pharmacokinetic characteristics. In this presentation, we report two novel series of non-peptidic phenyl-based, highly potent, highly selective and orally active thrombin inhibitors exemplified by I and II using oxyguanidines as guanidine mimetics. The structure activity relationship, x-ray crystal structures, pharmacokinetic data and efficacy results will be discussed.



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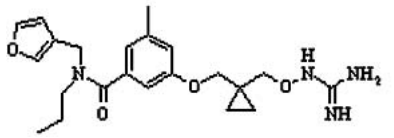

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32.

DESIGN, SYNTHESES AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A NOVEL SERIES OF FACTOR XA INHIBITORS CONTAINING THE NAPHTHALENE-PYRAZOLE RING SYSTEM-PART II. ***Bing-Yan Zhu**[1], Zhaozhong Jia[1], Wenrong Huang[1], Yanhong Wu[1], John Woolfrey[1], Susan Edwards[2], Ann Arfsten[2], Sherin Halfon[2], Uma Sinha[2], Stan Hollenbach[2], Athiwat Hutchaleelaha[3], Joe Lambing[3], Gary Park[3], and Robert M. Scarborough[1]. (1) Department of Medicinal Chemistry, Millennium Pharmaceuticals, Inc, 256 East Grand Ave., South San Francisco, CA 94080, Fax: 650-244-9287, bingyan.zhu@mpi.com, (2) Department of Biology, Millennium Pharmaceuticals, Inc, (3) Department of DMPK, Millennium Pharmaceuticals, Inc*

Factor Xa plays a pivotal role in the blood coagulation cascade. Inhibition of factor Xa represents an attractive therapeutic approach for the treatment and prevention of thrombotic diseases. In our previous communication, we have reported a novel series of naphthalene-pyrazole molecules as highly potent and specific factor Xa inhibitors. However, many of potent inhibitors judged by Ki only displayed moderate anticoagulant activity as assessed by plasma based thrombin generation (TG) and/or blood clotting prothrombin time (PT) assays. In this oral presentation, we will report the further SAR development of various P4 motifs designed to increase aqueous solubility. The resulting new inhibitors display excellent plasma based anticoagulant activity and good PK profiles.

$FXa\ K_i = 1\ nM$
$TG\ IC_{50} = 0.53\ \mu M$

33.

HETEROCYCLIC COAGULATION INHIBITORS: DESIGN, SYNTHESES AND BIOLOGICAL PROPERTIES OF ORALLY ACTIVE, DUAL DIRECT THROMBIN AND FACTOR XA INHIBITORS. ***Uwe J. Ries**, Department of Chemical Development, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach/Riss D-88397, Germany, Fax: +49-7351-547169, uwe.ries@bc.boehringer-ingelheim.com*

Excessive uncontrolled activation of the hemostatic system results in thromboembolic diseases, a major cause of morbidity and mortality in western societies. The central role of the serine proteases factor Xa and thrombin in the hemostasis make them attractive targets for antithrombotic therapy. Dual inhibitors of both factor Xa and thrombin are suitable anticoagulants, which block the generation as well as the activity of already existing thrombin. The combination of both effects in one single molecule may thus result in therapeutically useful antithrombotic agents at lower plasma concentrations compared to selective inhibitors. Supported by protein crystallography we designed quinoxalinone and benzimidazole derivatives, which directly inhibited thrombin and factor Xa at nanomolar levels. Potent in vitro antithrombotic activities and promising in vivo pharmacokinetic profiles were observed. As most interesting example BIBT 1011 BS was selected for clinical development as oral anticoagulant.

34.

IMIDAZOLE ACETIC ACID INHIBITORS OF THROMBIN- ACTIVATABLE FIBRINOLYSIS INHIBITOR (TAFI). ***Harold G. Selnick**, Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 4, West Point, PA 19486, Fax: 215-652-3971, hal_selnick@merck.com*

Thrombin-activatable Fibrinolysis Inhibitor (TAFI), a circulatory zinc-metallocarboxypeptidase, is an important regulator of fibrinolysis. Thrombin converts TAFI to TAFIa, which then removes C-terminal arginine and lysine residues on partially degraded fibrin clots. These basic residues normally serve as binding sites for tissue plasminogen activator (tPA) and its substrate plasminogen, thereby accelerating the production of plasmin and subsequently clot lysis. TAFIa therefore functions to stabilize fibrin clots by removing these binding sites, and preventing additional plasmin generation. Potent TAFIa inhibitors that are selective versus the related carboxypeptidases CPA, CPN, and CPM but not CPB have been identified. In addition, several compounds were shown to accelerate clot lysis in vitro in a dose dependent manner. The syntheses, structure activity relationships surrounding S1, S1′, and putative Zn-ligands of several potent imidazole acetate series will be discussed. In addition pharmacokinetic properties and in vivo efficacy will be presented.

35.

THROMBIN RECEPTOR (PAR-1) ANTAGONISTS AS ANTITHROMBOTIC AGENTS. ***Han-Cheng Zhang**[1], Bruce E. Maryanoff[1], Claudia K. Derian[1], Patricia Andrade-Gordon[1], David F. McComsey[1], William J. Hoekstra[1], Kimberly B. White[1], Brenda L. Poulter[1], Bruce P. Damiano[1], Michael F. Addo[1], Wai-Man Cheung[1], Andrew L. Darrow[1], Michael R. D'Andrea[1], Donna Oksenberg[2], Elwood E. Reynolds[2], Anjali Pandey[2], and Robert M. Scarborough[2]. (1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, Spring House, PA 19477, Fax: 215-628-4985, hzhang@prdus.jnj.com, (2) COR Therapeutics, Inc. (now part of Millennium Pharmaceuticals)*

Thrombin plays a key role in arterial thrombus formation by activating platelets through protease-activated receptors (PARs). There is keen interest in the antithrombotic potential of thrombin receptor (PAR-1) antagonism, particularly since the blockade of PAR-1 would not interfere with thrombin's role in the coagulation cascade. Progress has been made in identification of agents to block the function of PAR-1 in vitro and in vivo. Guided by PAR-1 agonist peptide structure-function data, in conjunction with computer modeling, we

discovered a novel class of indole- and indazole-based peptide-mimetics as antagonists of PAR-1. The series was optimized through the power of efficient solid-phase parallel synthesis to arrive at potent, PAR-1 selective lead antagonists to conduct in vivo proof-of-principle studies in several animal models. The blockade of PAR-1 in non-human primates protected against thrombus formation and vessel occlusion following arterial injury, providing direct evidence that PAR-1 is the primary receptor that mediates thrombin's prothrombotic actions in primates. Our results suggest that a PAR-1 antagonist may have potential for the treatment of thrombotic disorders in humans.

36.

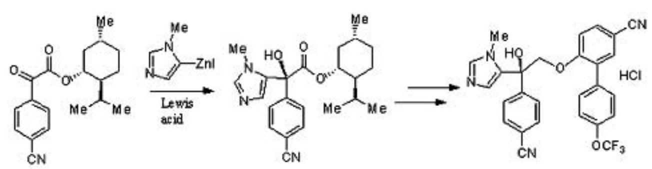
INTRODUCTORY REMARKS: RECENT CHANGES IN EARLY DEVELOPMENT ENVIRONMENT. ***Stephane Caron***, *Pfizer Global Research and Development, Groton, CT 06340, stephane_caron@groton.pfizer.com*

The impact of changes in drug development, especially in our regulatory environment, and how the process chemists adapt will briefly be discussed.

37.

DEVELOPMENT AND OPTIMIZATION OF THE ASYMMETRIC SYNTHESIS OF ABT-100. ***Albert W. Kruger***, *Michael J. Rozema, Bridget D. Rohde, James Jien-Heh Tien, Weijiang Zhang, Lakshmi Bhagavatula, and Bhadra Shelat, GPRD Process Research, Abbott Laboratories, 1401 Sheridan Rd, North Chicago, IL 60064-6285, Fax: 847-938-2258, albert.kruger@abbott.com*

ABT-100 is the second generation farnesyltransferase inhibitor (FTI) clinical candidate from Abbott for the treatment of cancer. Initial preclinical investigations showed much promise but only racemic material was available. Small amounts of enantiomerically pure ABT-100 were available by resolution on a chiral phase (HPLC), but due to limited solubility, scale-up was impractical. For further preclinical, clinical and toxicologic evaluation, an asymmetric synthesis was required. The enantioselective synthesis begins with transesterification of a commercially available keto-ester to the L-menthyl ester. Diastereoselective addition of an imidazoylzinc iodide reagent catalyzed by a Lewis acid generates the hydroxy ester. After chemoselective reduction of the ester function, the resulting diol was coupled with a suitably substituted biaryl fluoride through a base mediated SNAr reaction which afforded ABT-100 in 37% overall yield and excellent purity.



38.

PRACTICAL SYNTHESIS OF CELL ADHESION INHIBITORS VIA CRYSTALLIZATION-DRIVEN DYNAMIC TRANSFORMATIONS. ***Nathan K. Yee***, *Magnus Eriksson, Vittorio Farina, Rogelio P. Frutos, Suresh Kapadia, and Elio Napolitano, Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc, P.O. Box 368, 900 Ridgebury Rd., Ridgefield, CT 06877-0368, nyee@rdg.boehringer-ingelheim.com*

The Self-Regeneration of Stereocenters principle is successfully applied to the stereospecific synthesis of a class of cell adhesion inhibitors. The overall selectivity in the formation of cis-imidazolidinones and trans-oxazolidinones was boosted in both cases by a novel and unusual crystallization-driven transformation, which is a significant advancement to Seebach's original protocol. The utilization of this new protocol for the development of a practical and efficient synthesis of a cell adhesion inhibitor BIRT377 will be discussed.

39.

LARGE SCALE SYNTHESIS OF CRYPTOPHYCIN 52 (LY355703). ***James A. Aikins***, *Tony Zhang, and Takia Oglesby, Chemical Process Research and Development Division, Lilly Research Laboratories, Indianapolis, IN 46285-4813, JAA@lilly.com*

In an effort directed towards the synthesis of a key structural component of the oncolytic agent Cryptophycin 52 (LY355703) fragment A, we needed to develop an enabling technology for a large scale synthesis of the trans geometric isomer of compound 2. Conventional methods involving in-situ generated lactol from six-membered lactone intermediate to trans-styrenoid derivative with triphenylphosphonium ylide afforded a 1:1 ratio of E to Z geometric isomers. Similarly, reaction with Horner-Emmons reagent yielded at best a ratio of 7:1 in favor of the trans isomer. Benzyldiphenylphosphine oxide (BDPPO), a Horner-Wittig variant, is reported in literature to react with aromatic aldehydes to form trans geometrical product4 exclusively. We report here reaction of in-situ generated lactol with anion stabilized BDPPO which resulted in excellent overall yield of styrene product and a 29:1 ratio of E: Z isomer. The scale up to generate multi-kilogram quantities of 2, limitation of the ring size of lactones to styrenoid derivatives as well as mechanistic rational for favorable results of the reaction will be covered.

40.

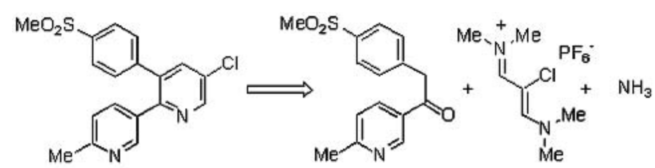
ASYMMETRIC HYDROGENATION: A NEW PROCESS TO PREGABALIN. ***William S. Kissel***, *Pfizer Global R&D, Pfizer Inc, 188 Howard Avenue, Holland, MI 49424, Fax: 616-392-8916*

Pregabalin is a drug candidate currently under development by Pfizer for epilepsy, generalized anxiety disorder, and neuropathic pain. Though the current manufacturing route is efficient and robust, it suffers from the intrinsic inefficiency of being a racemic synthesis with a late-stage resolution. We have developed an asymmetric synthesis that sets that asymmetric center by an asymmetric hydrogenation using Rh-MeDuPHOS catalyst. Setting the asymmetric center in the proper conformation is projected to improve the throughput and cost significantly. The development of an effective route to our asymmetric hydrogenation substrate was essential for an efficient process. This was accomplished by use of a Baylis-Hillman condensation, acylation of the allylic alcohol, and a pi-allyl palladium carbonylation to form the desired allylic nitrile precursor. By improving the throughput the new synthesis will also significantly reduce waste thus making a greener process.

41.

DEVELOPMENT OF CARBO- AND HETEROCYCLIZATIONS: APPLICATION TO A PRACTICAL SYNTHESIS OF THE COX-II SPECIFIC INHIBITOR ETORICOXIB. ***Jean-Francois Marcoux***, *Department of Process Research, Merck & Co, Inc, 126 E Lincoln Avenue, Rahway, NJ 07076, Fax: 732-594-1499, jeff_marcoux@merck.com*

A practical preparation of substituted vinamidinium hexafluorophosphate salts and their use in the synthesis of functionalized pyridines, pyridones and pyridine N-oxides via a novel annulation reaction will be described. The methodology has been extended to the large scale preparation of the COX-2 specific inhibitor Etoricoxib (5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl) pyridine), as well as a series of analogs. The unprecedented electrocyclization reaction of vinamidinium salts to form substituted anilines and phenols will also be discussed.



42.

APPLICATIONS OF CELL CULTURE MODELS OF THE INTESTINAL MUCOSA IN DRUG DISCOVERY. ***Ronald T. Borchardt***, *Department of Pharmaceutical Chemistry, The University of Kansas, 2095 Constant Avenue, Lawrence, KS 66047, Fax: 785-864-5736, rborchardt@ku.edu*

Pharmaceutical companies have become increasingly interested in assessing the "developability" of compounds early in drug discovery by determining their "drug-like" properties (e.g., solubility, chemical stability, metabolism, cell permeation) in addition to their "pharmacological" properties (e.g. receptor binding). Most pharmaceutical companies have taken a "reductionist" approach to the problem and have established high throughput screens to rapidly assess those physicochemical and biological characteristics that most significantly influence the "developability" of a drug candidate. For example, the intestinal mucosal cell permeation characteristics of structural hits, leads and drug

candidates are now estimated routinely using in vitro cell culture models (Caco-2 cell, MDCK cells, MDCK-MDR1 cells, and/or MDCK-MRP2 cells). Professor Borchardt's presentation will focus on the advantages and disadvantages of these in vitro cell culture models and how these models can be used to predict a compound's permeation characteristics across the intestinal mucosa in animals and humans.

43.
ROLE OF DRUG METABOLISM STUDIES IN LEAD OPTIMIZATION. ***Dhiren R. Thakker**, Division of Drug Delivery and Disposition, School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, dhiren_thakker@unc.edu*

Metabolic transformations represents an important mechanism by which drugs and other xenobiotics are cleared from the body. Oxidation, reduction, hydrolysis, and conjugation reactions are among the most important metabolic reactions involved in the clearance of drug molecules. Hepatic, and in some cases extrahepatic, metabolism is often a key clearance mechanism, that determines the duration of pharmacodynamic response of a drug. Metabolic enzymes in intestine and liver pose a formidable barrier for optimum delivery of orally administered drugs. Often, modulation of the enzyme activity (inhibition or induction) by a drug or its metabolites could lead to drug interactions and adverse drug effects. The use of in vitro and in vivo approaches to (i) evaluate the metabolic clearance of drug molecules, (ii) screen for drug candidates with acceptable metabolic stability and design metabolically stable drug candidates, and (iii) screen for modulation of enzyme activity (inhibition of induction) will be discussed.

44.
PLACE FOR PRODRUGS IN LEAD OPTIMIZATION. ***Valentino J. Stella**, Pharmaceutical Chemistry, The University of Kansas, 2095 Constant Avenue, Lawrence, KS 66047, Fax: 785-864-5736, stella@ku.edu*

A significant number of marketed molecules are prodrugs yet the use of prodrugs to address solutions to the formulation and delivery of problematic drugs is often disdained in both big pharma as well as in emerging companies. Newer drug candidates appear to be growing in size and complexity of structure often resulting in limited aqueous solubility, metabolic stability, permeability etc. With the advent of HTS receptor based assays, we often fall in the "high affinity trap" where flexibility to then build in desirable pharmaceutical properties is lost. Simultaneous HTS of pharmaceutical properties can identify better lead candidates with a higher probability of becoming clinically useful pharmaceuticals. A case can be made that many of the undesirable properties of drug candidates can be addressed via prodrug intervention but it is increasingly obvious that this intervention must occur during the drug design and discovery process. This talk will try to build the case for early prodrug intervention in the design of new drugs.

45.
IMPORTANCE OF DRUG DELIVERY AND PREFORMULATION IN LEAD OPTIMIZATION. ***Michael J. Hageman**, Pharmaceutical Sciences, Pfizer, 301 Henrietta Street, 0216-209-650, Kalamazoo, MI 49007*

Obtaining drug delivery to the intended target is critical during lead optimization, ranging from in vitro receptor or cell-based assays and continuing into the in vivo pharmacokinetic, pharmacology and toxicology screens. The physicochemical properties of a molecule can often play a critical role in assay results and the resultant ambiguity often coupled to an already variable biological readout. Assessment of physicochemical properties such as solubility, lipophilicity, pKa, protein binding, aggregation potential, precipitation potential, surface activity, and chemical stability, can all be used to assist in interpretation of screening data and in the selection of formulation strategies for desired exposure at these early stages. The application of drug delivery technologies and their place in a lead optimization funnel should be pursued based on the deconvolution and identification of delivery limiting factors. Delivery and formulation technologies applied within the Discovery funnels include solubilization by 1) cosolvents, surfactants, cyclodextrins and pH or combinations thereof and 2) approaches to enhance dissolution of solids through nanoparticulates, high-energy solids, and salt selection. Understanding the relevant drug like properties relative to formulation feasibility and drug exposure during lead optimization is critical to the potential success of a compound moving into development.

46.
SUBSTRATE SPECIFICITY PROFILES AND THE DESIGN OF ASPARTYL PEPTIDASE INHIBITORS. ***Ben M. Dunn**[1], Bret B. Beyer[1], Jamie Rubin[1], Nathan E. Goldfarb[1], and John B. Dame[2]. (1) Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, P.O. Box 100245, Gainesville, FL 32610-0245, Fax: 352-846-0412, bdunn@college.med.ufl.edu, (2) Department of Pathobiology, University of Florida College of Veterinary Medicine*

Three combinatorial libraries were prepared to explore the subsite specificity of human, malarial, and fungal enzymes. Library 1 scanned the P1 position in the sequence, Lys-Pro-Xaa-Glu-P1/Nph-Xaa-Leu, where Nph=*p*NO_2Phe, Xaa=mixture of 19 amino acids (the 20 proteinogenic ones plus Nle, minus Cys and Met), and the slash (/) indicates the point of cleavage. Library 2, specific for plasmepsins, scanned the P1′ position in the sequence, Lys-Pro-Ile-Xaa-Nph/P1′-Gln-Xaa, where the Nph residue was moved to the P1 position. A second P1′ library, specific for *Candida albicans* SAPs, had sequence Lys-Pro-Ile-Xaa-Nph/P1′-Arg-Xaa. Aliquots of all three libraries were tested with 11 enzymes in a spectrophotometric assay. Pools with the highest initial velocities of cleavage were analyzed by LC-MS (ESI) to separate and quantify the products of cleavage. With the collected information from these analyses, we designed peptidomimetics (methyleneamino) that were found to be potent and selective inhibitors of selected enzymes.

47.
KINETIC STUDIES ON BACE: CONFIRMATION OF AN ISO-MECHANISM. ***Jovita Marcinkeviciene**, Chemical Enzymology, Bristol Myers-Squibb Co, 311 Pennington-Rocky Hill Rd., Pennington, NJ 08534, Fax: 609-818-6935, jovita.marcinkeviciene@bms.com*

The steady-state kinetic mechanism of BACE catalyzed proteolytic cleavage was evaluated using product and statine- (Stat(V)) or hydroxyethylene-containing (OM99-2) peptide inhibition data, solvent kinetic isotope effects and proton NMR spectroscopy. The noncompetitive inhibition pattern observed for both cleavage products, together with the independence of Stat(V) inhibition on substrate concentration, suggests a uni-bi-iso kinetic mechanism. According to this mechanism, the enzyme undergoes multiple conformation changes during the catalytic cycle. If any of these steps are rate limiting to turnover, an enzyme form preceding the rate limiting conformational change should accumulate. An insignificant solvent kinetic isotope effect on kcat/Km, a large inverse solvent kinetic isotope effect on kcat, and the absence of any SKIE on the inhibition onset by Stat(V) during catalysis together indicate that the rate limiting iso- step occurs after formation of a tetrahedral intermediate. A short and strong hydrogen bond (at d 13.0 ppm and f of 0.6) has been observed by NMR spectroscopy in the enzyme-hydroxyethylene peptide (OM99-2) complex which presumably mimics the tetrahedral intermediate of catalysis. Collapse of this intermediate, involving multiple steps and interconversion of enzyme forms, has been suggested to impose a rate limitation, which is manifested in a significant SKIE on kcat. We propose that a conformational change related to the reprotonation of aspartates during or after the bond-breaking event is the rate limiting segment in the catalytic reaction of BACE, and ligands binding to other than the ground-state forms of the enzyme might render pharmacologically more relevant inhibitors.

48.
STRUCTURE-BASED DESIGN OF INHIBITORS OF HUMAN BRAIN MEMAPSIN 2 (β-SECRETASE). ***Arun K Ghosh**[1], Geoffrey Bilcer[1], Thippeswamy Devasamudram[1], Lin Hong[2], Gerald Koelsch[2], and Jordan Tang[2]. (1) Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607, arunghos@uic.edu, (2) Protein Studies Program, Oklahoma Medical Research Foundation*

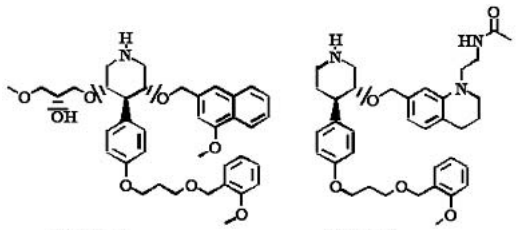
Memapsin 2 (β-secretase) is a membrane associated aspartyl protease which is one of two proteases that cleave the β-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-β peptide (Aβ) in the human brain. This is a key event in the pathogenesis of Alzheimer's disease (AD) and as a consequence, memapsin 2 has become an excellent target for drug-design for the treatment of AD. Based upon knowledge of kinetics and specificity, we initially designed a number of peptidomimetic inhibitor leads incorporating nonhydrolyzable dipeptide isosteres. Subsequently, we determined the crystal structures of a number of inhibitors complexed with memapsin 2. These structures now serve as important molecular templates for structure-based design of memapsin

inhibitors. Based upon protein-ligand crystal structures, we have reduced the molecular weight, reduced the peptidic features and designed selectivities in our lead inhibitors. Structure-based design, structure-activity studies and selectivity issues will be discussed.

49.

PIPERIDINE INHIBITORS OF RENIN. ***Hans Peter Maerki**, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd, Bldg. 092/1.10B, CH-4070 Basel, Switzerland, Fax: ++4161 6886459, hans_p.maerki@roche.com*

Inhibition of renin targets the potentially most attractive rate-limiting step of the RAS (renin-angiotensin system) and thus blocks the RAS at source. Non-peptidomimetic compounds of the piperidine type represent an entirely novel class of renin inhibitors potentially free of the draw-backs seen with peptidomimetic compounds so far. First nanomolar compounds, however, proved to be highly lipophilic. Further synthetic optimization in several series has led to the identification of candidate compounds with improved physicochemical properties. They display potent and long lasting blood pressure lowering effects in conscious sodium depleted marmoset monkeys and double transgenic rats harboring both the human angiotensinogen and renin genes. RO0661132 in addition prevents mortality and normalizes proteinurea and kidney tissue damage in these rats when given over a period of 4 weeks. These data suggest that treatment of chronic renal failure patients with a renin inhibitor might result in a significant improvement of the disease status.



RO0661132

IC_{50} (h. renin, buffer assay): 0.067 nM

RO0661168

IC_{50} (h. renin, buffer assay): 0.039 nM

50.

EVOLUTION OF NOVEL, ORALLY EFFICACIOUS RENIN INHIBITORS: A TOPOGRAPHICAL DESIGN APPROACH TOWARDS ALISKIREN. ***Juergen Maibaum**, Novartis Institute for Biomedical Research Basel, Novartis Pharma AG, Klybeckstrasse 220, WKL-136.683, 4002 Basel, Switzerland, Fax: 041-61-69-61163, juergen_klaus.maibaum@pharma.novartis.com*

Renin activity and hyperactivation of the renin-angiotensin-system (RAS) has been recognized as major contributing factor in the pathogenesis of cardiovascular diseases including hypertension. Targeting the first and rate-limiting step, and the physiological specificity of renin, allow renin inhibitors to selectively block this system entirely at source, providing additional potential benefits in blood pressure control over agents that interfere more downstream with the RAS. Despite this high attractiveness, renin has been a difficult target for developing therapeutically useful inhibitors due to limited oral bioavailability of many peptidic transition-state analogues designed over the last two decades. Our efforts following a topographical design concept resulted in a novel class of non-peptide peptidomimetics with promising physico-chemical and pharmacokinetic properties. Iterative crystallographic resolution of ligand-enzyme complexes demonstrated an unprecedented interaction to a non-substrate binding pocket as important for strong renin inhibition. The presentation will discuss the structure-based design leading to Aliskiren, a highly potent, orally effective new-generation renin inhibitor currently undergoing extensive clinical trials.

51.

NEW FINDINGS AND PHARMACOLOGY IN HISTAMINE H3 RECEPTOR BIOLOGY: THERAPEUTIC IMPLICATIONS AND CHALLENGES. ***Timothy W. Lovenberg**, Nicholas I. Carruthers, Ann J. Barbier, Sandy J. Wilson, P. Curt Mazur, Wei Xiao, and Richard Apodaca, Neuroscience, Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, Fax: 858-450-2090, tlovenbe@prdus.jnj.com*

The histamine H3 receptor has been heralded as a potential drug target in a number of disease areas, particularly in the central nervous system. The cloning of the human H3 receptor has provided the stimulus to search for chemical templates to explore H3 receptor pharmacology and biology. Recognizing the deficiencies of the existing imidazole-based ligands we specifically sought to identify novel non-imidazole based structures. The presentation will highlight, for the first time, the in vitro and in vivo pharmacology of one of these ligands, particularly in relation to models of arousal, cognition and food intake. In addition our presentation will highlight some of the more recent biological findings about the H3 receptor including the creation and characterization of H3-receptor deficient mice.

52.

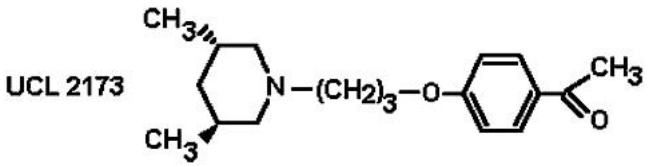
HISTAMINE H_3RECEPTORS IN THE PERIPHERY: ROLE IN THE REGULATION OF NASAL PATENCY AND ALLERGIC CONGESTION. ***John A. Hey**[1], Lori M. Varty[1], Eric Gustafson[2], Robert W. Egan[1], Robert Aslanian[3], Kevin McCormick[3], and Robbie L. McLeod[1]. (1) Allergy, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, john.hey@spcorp.com, (2) Functional Genomics, Schering-Plough Research Institute, (3) Department of Chemical Research, Schering-Plough Research Institute*

In the nose, mast cell derived histamine (HA) promotes allergic congestive disease. Histamine H_1 antagonists inhibit the rhinorhea but do not block the congestion. Sympathetic tone to nasal capacitance veins regulates mucosal swelling and nasal patency. Activation of histamine H_3 receptors on sympathetic nerve endings in nasal mucosa elicits vasodilation leading to congestion. In vitro and in vivo studies were conducted to define the role of H_3 receptors on vasomotor tone and nasal patency. These studies show that H_3 receptor activation inhibits sympathetic vasoconstriction in pig and human nasal mucosa. Pretreatment with H_3 antagonists blocks the inhibitory effect of histamine H_3 activation due to exogenous or endogenous HA by inhibiting NE release. In vivo studies in an experimental congestion model using acoustic rhinometry shows that combined histamine H_3 and H_1 receptor blockade produces a decongestant effect equivalent to sympathomimetic agents without hypertension. It is proposed that combined blockade of histamine H_3 and H_1 receptors confers decongestant activity upon the H_1 activity without the hypertensive liabilities.

53.

DESIGN OF POTENT NON-IMIDAZOLE HISTAMINE H3-RECEPTOR ANTAGONISTS. ***C. Robin Ganellin**[1], Fabien Leurquin[1], Titi T Akinleminu[1], Sangita Halai[1], Yuan Hui Zhao[1], Holger Stark[2], Walter Schunack[3], Xavier Ligneau[4], Jean-Michel Arrang[5], and Jean-Charles Schwartz[5]. (1) Department of Chemistry, University College London, London WC1H OAJ, United Kingdom, Fax: + 44 0 7679 7463, c.r.ganellin@ucl.ac.uk, (2) Institut für Pharmazeutische Chemie, Johann Wolfgang Goethe Universität, (3) Institut für Pharmazie, Freie Universität Berlin, (4) Bioprojet Biotech, (5) Unité de Neurobiologie et Pharmacologie Moléculaire (U109), INSERM*

Initially, the most potent histamine H3-receptor antagonists resembled histamine in being imidazole derivatives. The imidazole moiety, however, impedes entry into the central nervous system and may cause interaction with the P450 series of metabolizing enzymes. We therefore sought non-imidazole antagonists. Starting from histamine derivatives containing additional binding groups which confer antagonist activity, the imidazole ring was then removed. This approach provided N-ethyl-N-(4-phenylbutyl)amine as a lead (Ki=1.3 ìM). Several series of homologous O and S isosteric tertiary amines with substituents in the phenyl ring were synthesized. Structure-activity studies furnished potent compounds, e.g. UCL 2173 N-[3-(p-acetophenoxy)propyl]-3,5-trans-dimethylpiperidine which has a Ki=1.8 ± 0.3 nM for increasing [3H]histamine release from rat cerebral cortex synaptosomes and ED50=0.12 ± 0.05 mg/kg per os in mice on brain tele-methylhistamine levels. Unlike the corresponding imidazole compound (acetoproxifan hKi=87 ± 7 nM), UCL 2173 is also potent at the human H3 receptor (hKi=1.0 ± 0.1 nM).



54.

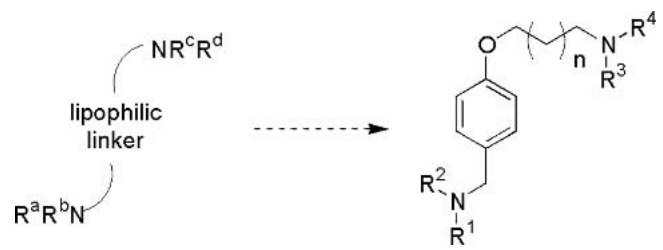
HISTAMINE H_3 RECEPTOR ANTAGONISTS: FROM HIGH THROUGHPUT SCREENING (HTS) TO DRUG-LIKE MOLECULES. ***Ramin Faghih***[1], *Youssef L. Bennani*[1], *Lawrence A. Black*[1], *Marlon Cowart*[1], *Wesley Dwight*[1], *Timothy A. Esbenshade*[1], *Gerard B. Fox*[2], *Sujata M. Gopalakrishnan*[3], *Kathleen M. Krueger*[1], *Huaqing Liu*[1], *Jia-Bao Pan*[2], *Glenn A. Reinhart*[4], *Jeffrey F. Waring*[5], *Betty B. Yao*[1], *Henry Zhang*[6], *and Arthur A. Hancock*[1]. *(1) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6123, Fax: 847-937-4143, ramin.faghih@abbott.com, (2) CNS Diseases Research, Global Pharmaceutical Research and Development, Abbott Laboratories, (3) Biological Screening, Global Pharmaceutical Research and Development, Abbott Laboratories, (4) Integrative Pharmacology, Global Pharmaceutical Research and Development, Abbott Laboratories, (5) Cellular and Molecular Toxicology, Global Pharmaceutical Research and Development, Abbott Laboratories, (6) Medicinal Chemistry Technologies, Global Pharmaceutical Research and Development, Abbott Laboratories*

Histamine H_3 receptor (H_3R) antagonists are promising candidates for the treatment of many CNS disorders. Historically, H_3 ligands have been imidazole derivatives, although such compounds are likely to have undesirable interactions with CYP isoenzymes. We were interested in finding non-imidazole based compounds for the treatment of human disease, prompting us to screen the Abbott compound-library for potential H_3 antagonists. A-923 was identified from HTS as a non-imidazole compound with 2 nM affinity at rat H_3Rs. However A-923 suffered from poor receptor selectivity and ADME properties. A systematic modification of A-923 led to the identification of A-304121, a potent, H_3R-selective and orally bioavailable compound. Nevertheless, its cationic amphiphilic characteristics induced phospholipidosis in both in vitro and in vivo assays. While this shortcoming could be addressed by a simple derivative, A-317920, both compounds demonstrated suboptimal affinities for human H_3Rs (hH_3Rs). Extensive SAR studies to improve hH_3R affinity led to two new compounds, A-320436 and A-349413. Unfortunately, further characterization of these substances revealed poor oral bioavailability. Further SAR redirection led to a new series of potent and selective H_3 antagonists typified by A-349821, which have high affinity for both rat and human H_3Rs. This compound displayed in vivo efficacy in animal models of learning and showed other desirable drug-like properties. The synthesis, SAR, in-vitro/vivo pharmacological data of prototypical compounds exemplifying these diverse series will be discussed.

55.

DIAMINE-BASED HUMAN HISTAMINE H_3 RECEPTOR ANTAGONISTS. ***Richard Apodaca***, *Curt A. Dvorak, Wei Xiao, Ann J. Barbier, Jamin D. Boggs, Sandy J. Wilson, Timothy W. Lovenberg, and Nicholas I. Carruthers, Neuroscience, Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, Fax: 858-450-2049, rapodaca@prdus.jnj.com*

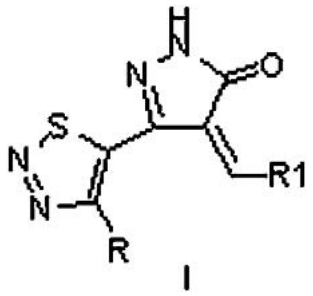
The histamine H3 receptor mediates the release of histamine and other neurotransmitters in the CNS, in addition to other functions. Structure-activity relationships available to us through high throughput screening of our corporate compound collection against the human H3 receptor, and some published work available at the time, suggested a remarkably simple pharmacophore consisting of two basic nitrogen atoms flanking a lipophilic core. We reasoned that a readily-accessed chemical series that incorporated this structural motif could furnish a viable platform for the development of H3 receptor ligands with drug-like properties. To test this idea, a series of 4-(aminoalkoxy)benzylamines was selected. The synthesis and in vitro biological properties of these and related compounds will be discussed.



56.

1,2,3-THIADIAZOLE SUBSTITUTED PYRAZOLONES: POTENT VEGFR-2/KDR KINASE INHIBITORS, SHOWING ORAL ANTI-TUMOR PROPERTIES IN NUDE MICE. ***Rabindranath Tripathy***, *Jasbir Singh, Edward R. Bacon, Thelma S. Angeles, Shi X. Yang, Mark S. Albom, Lisa Aimone, Joe Herman, Candy Robinson, Hong Chang, Bruce A. Ruggeri, Craig Dionne, and John P. Mallamo, Cephalon Inc, 145 Brandywine Parkway, West Chester, PA 19380, Fax: 610-738-6558, rtripath@cephalon.com*

Vascular endothelial growth factor (VEGF) and its cell surface receptor VEGFR-2/KDR are considered to play important role in angiogenesis, which is vital for survival and proliferation of tumor cells. In recent years several classes of small molecule based VEGFR-2 kinase inhibitors have been reported in the literature as anti-angiogenic agents for possible treatment against a wide variety of cancer. Recently we disclosed a structure-based kinase inhibitor design strategy which led us to identify a new class of VEGFR-2/KDR kinase inhibitors bearing heterocyclic substituted pyrazolones as the core template. Fine tuning the heterocyclic segment lead to identification of the thiadiazole series of pyrazolones (I) as potent & selective VEGFR-2/KDR kinase inhibitors. SAR, PK data and anti-tumor properties of these pyrazolone-based inhibitors will be presented.



I

57.

DEVELOPMENT OF 3-METHYLPYRIDIN-2-YL-AMINOTHIAZOLE INHIBITORS OF THE VEGF RECEPTOR (KDR). ***Adrienne E. Balitza***[1], *Mark T. Bilodeau*[1], *Leonard D. Rodman*[1], *Peter J. Manley*[1], *George D. Hartman*[1], *Kathleen E. Coll*[2], *Rosemary C. McFall*[2], *Keith W. Rickert*[2], *Jennifer M. Shipman*[2], *Bin Shi*[2], *Laura Sepp-Lorenzino*[2], *Carolyn Buser-Doepner*[2], *Xianzhi Mao*[2], *Kenneth A. Thomas*[2], *Cynthia Miller-Stein*[3], *and Bradley K. Wong*[3]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P. O. Box 4, WP 14-2, West Point, PA 19486, adrienne_balitza@merck.com, (2) Department of Cancer Research, Merck Research Laboratories, (3) Department of Drug Metabolism, Merck Research Laboratories*

Angiogenesis, the growth of new blood vessels from the established vasculature, has been implicated in the progression of such diseases as diabetic retinopathy, rheumatoid arthritis, and cancer. The growth and metathesis of solid tumors relies on the up-regulation of vascular endothelial growth factor (VEGF). The VEGF receptor tyrosine kinase VEGFR-2 (KDR) is a mitogenic receptor selectively expressed on endothelial cells. We have designed and synthesized a series of 3-methylpyridin-2-yl-aminothiazoles, a new class of potent KDR inhibitors with excellent pharmacokinetic properties. A particular compound will be highlighted which is potent in both enzyme and cell based assays and also has an exceptional pharmacokinetic profile in three species. Additionally, the 3-methyl pyridine substituent has been shown to provide enhanced levels of kinase selectivity. A rationale for this selectivity enhancement, based on molecular modeling, will be provided.

58.

7-ALKENYL AND 7-ALKYNYL-4-PHENYLAMINO-3-QUINOLINECARBONITRILES AS SRC KINASE INHIBITORS. ***Ana C. Barrios Sosa***[1], *Fei Ye*[1], *Diane H. Boschelli*[1], *Dennis W. Powell*[1], *Jennifer M. Golas*[2], *and Frank Boschelli*[2]. *(1) Chemical Sciences, Wyeth Research, 401 N Middletown Rd., Pearl River, NY 10965, (2) Oncology, Wyeth Research*

The nonreceptor tyrosine kinase Src is involved in signaling pathways responsible for controlling cell proliferation, migration and angiogenesis. Elevated Src activity/expression has been associated with several disease states, including cancer and osteoporosis. Therefore, inhibitors of this kinase could prove useful in various therapeutic areas. We previously identified 7-alkoxy-4-anilino-3-quinolinecarbonitriles as potent Src kinase inhibitors. Herein we report the

synthesis and SAR of a series of C-7 alkenyl and C-7 alkynyl substituted 3-quinolinecarbonitrile derivatives. For the introduction of the alkenyl substituent a Stille or Heck Pd catalyzed reaction was employed. Similarly, the incorporation of the C-7 alkynyl substituent was achieved via a Sonogashira coupling reaction.

59.

COMPUTATIONAL STRUCTURE-BASED DATABASE SEARCHING FOR THE DISCOVERY OF SMALL MOLECULE LIGANDS OF PTEN PROTEIN. ***Zengjian Hu***[1]*, Zhendong Zhu*[1]*, Zhong-Yin Zhang*[2]*, Alan I. Faden*[3]*, Vilen Movsesyan*[3]*, and Shaomeng Wang*[1]*. (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, huzj@umich.edu, (2) Department of Molecular Pharmacology, Albert Einstein College of Medicine, (3) Department of Neuroscience, Georgetown University Medical Center*

PTEN, also known as MMAC1 or TEP1, plays an important role to modulate the cellular functions. It controls the phosphoinositide 3-kinasae signaling pathway for regulation of cell proliferation and cell survival, and suppresses cell migration, spreading, and the formation of focal adhesions. PTEN inhibitor can reduce or eliminate PTEN's growth suppression activity. Using the crystal structures of PTEN in complex with L(+)-tartrate molecule, we have carried out the computational structure-based 3D-database screening over large chemical databases containing more than 225,000 of structurally diverse, synthetic compounds or natural products to. Sixteen small molecule candidates were confirmed to effectively inhibit the activity of PTEN in biochemical assays. Several compounds were found to be able to promote the activity of AKT/PKB in whole cells. These small molecule PTEN inhibitors could serve as useful tools for investigating the physiological roles of PTEN and as initial lead compounds for further optimization.

60.

NOVEL INHIBITORS OF TNFα SYNTHESIS. ***Yun Feng Xie***[1]*, Ila Sircar*[1]*, Kirk Lake*[1]*, Sunil Kher*[1]*, Norma Wilson*[1]*, Shao Hui Zhang*[2]*, Alexei Bakhirev*[2]*, and Frank Gorcsan*[2]*. (1) Department of Chemistry, Tanabe Research Laboratories U.S.A., Inc, 4540 Towne Centre Ct, San Diego, CA 92121, Fax: 858-558-0650, (2) Department of Biology, Tanabe Research Laboratories U.S.A., Inc*

Tumor necrosis factor (TNFα) has been found to play a crucial role in the activation of immune response and inflammation. The elevated level of TNFα has often been discovered in various inflammatory diseases. The inhibition of TNFα signaling has proven therapeutically effective. For example, perturbation of TNFα function using anti-TNFα antibodies (infliximab) and soluble TNF receptor (Enbrel) have recently been approved for the treatment of rheumatoid arthritis, psoriatic arthritis and Crohns diseases. We have engaged in developing small molecule inhibitors of TNFα synthesis. Based on a screening hit, we have identified a new series of phthalazine derivatives as novel TNFα synthesis inhibitors. The syntheses and biological activities of these compounds will be presented.

61.

NOVEL PYRAZOLO(1,3-A)-1,3,5-TRIAZINE DERIVATIVES AS CYCLIN-DEPENDENT KINASE INHIBITORS. ***S Kim****, G Prevost, M. Lonchampt, L. Meijer, C. Thurieau, and J. Dong, Beaufour-IPSEN Group, Biomeasure Inc, 27 Maple Street, Milford, MA 01757-3650, sun.kim@biomeasure.com*

Cyclin-dependent kinases (CDKs) are key regulators in the process of cell cycle procession. Misregulation of CDK functions occurs with high frequency in major solid tumor types (e.g., breast, colon, ovarian, prostate and NSCLC carcinomas). Controlling the cell cycle by the means of small molecule CDK inhibitors has been a strategy for developing novel anticancer therapeutics with fewer side effects than the existing therapies. High throughput screening on our proprietary compound libraries has led to identify a novel class of pyrazolo(1,3-a)-1,3,5-triazine as inhibitors of CDKs. Systematically structural modifications on the initially discovered compounds yielded highly potent CDK inhibitors (e.g., CDK1, CDK2 and CDK5 inhibitors), which have IC50s in nanomolar range in the in vitro cell proliferation assays. The chemistry and biology of this class of compounds will be discussed.

62.

NOVEL PYRAZOL(1,3-A)-1,3,5-TRIAZINE DERIVATIVES AS CYCLIN - DEPENDENT KINASE INHIBITORS. ***Sun Kim****, G Prevost, M Lonchampt, L Meijer, C Thurieau, and J Dong, Department of Medicinal Chemistry, Biomeasure Inc./Beaufour-IPSEN Group, 27 Maple Street, Milford, MA 01757, Fax: 508-473-3531, sun.kim@biomeasure.com*

Cyclin-dependent kinases (CDKs) are key regulators in the process of cell cycle progression. Misregulation of CDK functions occurs with high frequency in major solid tumor types (e.g., breast, colon, ovarian, prostate and NSCL carcinomas). Controlling the cell cycle by means of small molecule CDK inhibitors has been a strategy for developing novel anticancer therapeutics with fewer side effects than the existing therapies. High throughput screening of our proprietary compound libraries has led to identify a novel class of pyrazolo(1,3-a)-1,3,5-triazine as inhibitors of CDKs. Systematic structural modifications on the initially discovered compounds yielded highly potent CDK inhibitors (e.g., CDK1, CDK2 and CDK5 inhibitors), that have IC_{50}s in the nanomolar range in cell proliferation assays *in vitro*. The chemistry and biology of this class of compounds will be discussed.

63.

SELECTIVE ITK INHIBITORS. 2. SAR OF 2-AMINO-5-(THIOARYL)THIAZOLES. ***Jagabandhu Das***[1]*, John Wityak*[1]*, Chunjian Liu*[1]*, Robert V. Moquin*[1]*, Joseph A. Furch*[1]*, James Lin*[1]*, Steven H. Spergel*[1]*, Arthur M. Doweyko*[2]*, Amrita Kamath*[3]*, Hongjian Zhang*[3]*, Kathleen D. O'Day*[4]*, Becky Penhallow*[4]*, Chen-Yi Hung*[4]*, Steven Kanner*[4]*, Tai-An Lin*[4]*, John H. Dodd*[1]*, and Joel C Barrish*[1]*. (1) Lawrenceville Discovery Chemistry, Bristol-Myers Squibb PRI, Provinceline Rd and Route 206, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-6804, jagabandhu.das@bms.com, (2) Pharmaceutical Research Institute, CADD, Bristol-Myers Squibb PRI, (3) PCO, Bristol-Myers Squibb PRI, (4) Lawrenceville Discovery Biology, Bristol-Myers Squibb PRI*

Itk(Emt, Tsk) is a member of the Tec family of non-receptor tyrosine kinases expressed mainly on CD4 positive T-cells. Mice deficient in Itk exhibit defects in T-cell signaling and development leading to reduced IL-2 production. Selective Itk inhibitors may therefore have utilities as an immunosuppressive agent in the treatment of rheumatoid arthritis, graft rejection, and other T-cell mediated immunological disorders. We report here synthesis and SAR studies with 2-amino-5-thioaryl-thiazoles that led to the identification of BMS-503519 as a potent and selective Itk inhibitor.

64.

SYNTHESIS AND BIOLOGICAL EVALUATION OF SELECTIVE INHIBITORS OF PDGF RECEPTOR AUTO PHOSPHORYLATION. ***Takayuki Furuta****, Teruyuki Sakai, Terufumi Senga, Midori Arai, Tatsushi Osawa, Tsuyoshi Nishitoba, Kazuo Kubo, Shinichi Ohyama, Kaname Kimura, Toshiyuki Shimizu, Akihiro Ueno, Rika Suzuki, Yasunari Fujiwara, Hideko Murooka, Yoshiko Kihara, Akemi Iwai, Kayoko Fukushima, Tetsuya Yoshino, Megumi Endo, Noriko Tawara, and Atsushi Miwa, Department of Medicinal Chemistry, Pharmaceutical Research Laboratories, Kirin Brewery Co., Ltd, 3 Miyahara, Takasaki, Gunma 370-1295, Japan, Fax: 027-346-8418, t-furuta@kirin.co.jp*

Platelet-Derived Growth Factor (PDGF) is known as a mitogen and chemotactic factor. Abnormal PDGF induced cell proliferation has been proposed to lead to proliferative disorders such as restenosis, liver cirrhosis, cancer and so on. Weüfve found N-substituted-Nüf-{4-(4-quinolyloxy)phenyl}urea derivatives are potent PDGF receptor auto phosphorylation inhibitor. Here, we present our effort to increase potency of the quinoline and the quinazoline derivatives. Our structure-activity studies in this series have improved their PDGF receptor auto phosphorylation inhibitory activities and subtype selectivity against other receptor tyrosine kinases (RTK) including c-Kit, KDR, Flt-3 and c-Fms. As the result of our design and synthesis, potent compound having good in vitro and in vivo activity has been obtained. Furthermore the compound (10mg/kg p.o. b.i.d.) has inhibited neointima hypertrophy after balloon catheter injury in porcine coronary artery.

65.

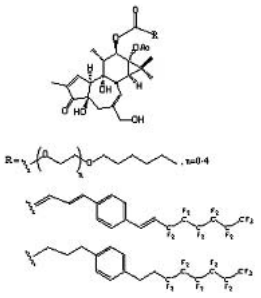
EXPLORATION OF AN AMINOTHIAZOLE DUAL HER2/HER1 KINASE INHIBITOR. ***Harold Mastalerz**, Ming Chang, Walter Johnson, John Kadow, David Langley, Gregory Vite, Dolatrai Vyas, Tai Wai Wong, and Guifen Zhang, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, harold.mastalerz@bms.com*

Members of the Epidermal Growth Factor Receptor family (HER1, HER2, HER3, and HER4) of receptor tyrosine kinases are overexpressed or constitutively activated in a variety of cancers for which there is often poor prognosis. Dual inhibition of the more important members of this family, the HER1 and HER2 kinases, is considered an particularly attractive strategy for drug development since it would target receptors that are activated both by ligand-induced dimerization and by heterodimerization. This work describes efforts to optimize an aminothiazole dual HER2/HER1 kinase inhibitor. The lead exhibited a broad spectrum of kinase inhibition and therefore the major focus was on achieving selective inhibition of the HER1 and HER2 kinases. This was guided by modeling studies of the aminothiazole in the ATP binding pocket of the HER1 kinase and the Src family tyrosine kinase, Lck.

66.

SYNTHESIS OF PHORBOL ESTERS WITH OLIGOETHYLENE GLYCOL SPACERS AND EVALUATION OF THEIR PKC ISOZYME SELECTIVITY – IDENTIFICATION OF A LIGAND OF HIGH SELECTIVITY FOR PKCε. ***Jayalakshmi Sridhar**[1], Alan P Kozikowski[1], Nancy Lewin[2], Jolene A Ayers[2], Larry V Pearce[2], and Peter M Blumberg[2]. (1) Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3970, Reservoir Rd., NW, Washington, DC 20007-2197, Fax: 202-6887-0738, js348@georgetown.edu, (2) Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute*

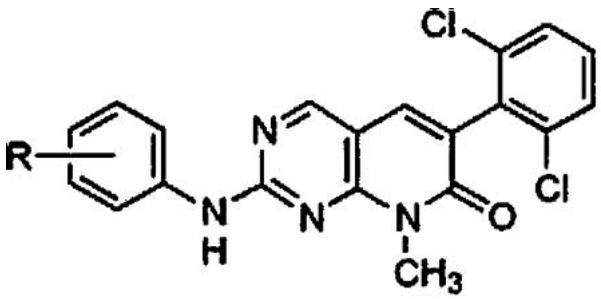
In our ongoing search for isozyme selective binding molecules for the PKC's, a series of n-hexyl esters of phorbol with variable lengths of oligoethyleneglycol spacers and polyfluorinated unsaturated/saturated esters of phorbol were synthesized. Their binding to the C1 domain of different PKC isozymes was assessed. Some of these esters showed very high specificity to PKCε. As PKCε plays a major role in neurite outgrowth, apoptosis, adhesion and motility, the controlled activation of PKCε could play a protective role in the treatment of cardiac ischemia and Alzheimer's disease, whereas its inactivation may suppress tumor promotion.



67.

SYNTHESIS, IN VITRO AND IN VIVO CHARACTERIZATION OF PYRIDO[2,3-D]PYRIMIDINE TYROSINE KINASE INHIBITORS. ***Darren R. Veach**[1], Caryl Lambek[1], Chong-Yuan Liu[1], Justus Duyster[2], Tatiana Beresten[1], Wanqing Li[3], Nicholas C. Wolff[4], Robert L. Ilaria[4], Juri Gelovani[5], W. Todd Miller[3], Nikolas von Bubnoff[2], William G. Bornmann[1], and Bayard D. Clarkson[1]. (1) Sloan Kettering Institute, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021, veachd@mskcc.org, (2) Hämatologisches Forschungslabor - Klinikum rechts der Isar, Technische Universität München, (3) State University of New York at Stony Brook, (4) The University of Texas, Southwestern Medical Center, (5) Memorial Sloan Kettering Cancer Center*

Kinase inhibitors are an important class of anti-cancer drugs, Gleevec® being the frontrunner. Our goal was to develop inhibitors of BCR-Abl, an oncogenic kinase, with suitable pharmacological properties. Pyrido[2,3-*d*]pyrimidines are high pM to low nM, ATP-competitive inhibitors of BCR-Abl and c-Src. Known Abl / pyridopyrimidine cocrystal structures were used to direct our synthetic efforts. Significant antitumor activity was observed in different human cell lines, including MO7e/p210$^{bcr\text{-}abl}$ and K-562 cells (high BCR-Abl levels), and BT-474, PC-3, and A-172 cells (lower BCR-Abl levels). Pyridopyrimidines also inhibit Gleevec-resistant Ba/F3 cells expressing mutant BCR-Abl. Preclinical studies with PD166326 demonstrated a MTD of 60-65 mg/kg and moderate oral bioavailability ($t_{1/2}$ =~8 hrs) in mice. In conclusion, several newly developed pyridopyrimidines exhibited potent BCR-Abl inhibition *in vitro* and improved pharmacological properties. The pyrido[2,3-d]pyrimidines are significantly more potent than Gleevec, are active in Gleevec-resistant cells and therefore, represent a promising alternative to Gleevec therapy.



68.

SYNTHETIC STUDIES ON HETEROARYL CARBOXAMIDE DERIVATIVES AS NOVEL SYK INHIBITORS. ***Hiroyuki Hisamichi**[1], Souichirou Kawazoe[2], Ryo Naito[1], Akira Toyoshima[3], Atsushi Ichikawa[1], Akiko Orita[1], Masaya Orita[1], Ei-ichi Nakai[1], Makoto Takeuchi[1], Mitsuaki Ohta[1], and Shin-ichi Tsukamoto[1]. (1) Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd, 21, Miyukigaoka, Tsukuba, Ibaraki 3058585, Japan, Fax: +81-29-852-2971, hisamiti@yamanouchi.co.jp, (2) Institute for Technology Development, Yamanouchi Pharmaceutical Co., Ltd, (3) Drug Development Div, Yamanouchi Pharmaceutical Co., Ltd*

As a part of searching for spleen tyrosine kinase (Syk) inhibitors as potential therapeutic agents for allergy, heteroaryl carboxamide derivatives were synthesized and evaluated for inhibitory activities to Syk and to antigen-induced serotonin release from RBL-2H3 cells. Among these compounds, pyrimidine-5-carboxamide derivatives and pyrazine-2-carboxamide derivatives showed excellent Syk inhibitory activities with IC50 values below 10 nM and serotonin release inhibitory activities with IC50 values below 30 nM. Some of these compounds also exhibited inhibitory activities on passive cutaneous anaphylaxis model in mice (ID50=10-30 mg/kg, p.o.). These compounds, therefore, would be expected as a drug for the treatment of allerg. The synthesis and structure-activity relationships of these compounds will be presented.

69.

DESIGN AND SYNTHESIS OF 2-AMINO-N^4-(3-BROMO-PHENYL)-5-METHYL-6-SUBSTITUTED PYRROLO[2,3-*D*]PYRIMIDINES AS POTENTIAL RECEPTOR TYROSINE KINASE INHIBITORS. *Aleem Gangjee, Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu*

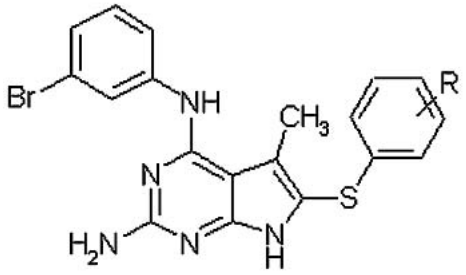
Abstract text not available.

70.

DESIGN AND SYNTHESIS OF 2-AMINO-N^4-(3-BROMO-PHENYL)-5-METHYL-6-SUBSTITUTED PYRROLO[2,3-*D*]PYRIMIDINES AS POTENTIAL RECEPTOR TYROSINE KINASE INHIBITORS. *Aleem Gangjee[1], **Xin Lin**[1], Michael Ihnat[2], and Shekhar Kamat[2]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Department of Cell Biology, The University of Oklahoma Health Science Center*

Mitogenic signaling and cellular events including cell proliferation, differentiation and growth can be triggered by activated receptor tyrosine kinases (RTKs) Tumor growth and metastasis in many instances involve the over-activation of RTKs. As a result, several small molecule inhibitors of RTKs are currently in clinical trials as potential antitumor agents. Recent studies indicate that inhibitor of several RTKs maybe beneficial in cancer treatment. On the basis of known RTK pharmacophores, compounds of general structure **1** were designed,

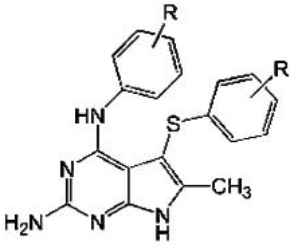
synthesized and evaluated as potential inhibitors of several RTKs. The synthesis and biological evaluation of these compounds will be presented.



71.

NOVEL 2-AMINO-4-ANILINO-6-METHYL-5-SUBSTITUTED PYRROLO[2,3-*D*]PYRIMIDINES AS POTENTIAL RECEPTOR TYROSINE KINASE INHIBITORS. *Aleem Gangjee[1], **Hiteshkumar Jain**[1], Michael Ihnat[2], and Shekhar Kamat[2]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Department of Cell Biology, The University of Oklahoma Health Science Center*

Activation of receptor tyrosine kinases (RTKs) results in autophosphorylation of specific tyrosine residues of proteins causing mitogenic signaling and cellular events including cell proliferation, differentiation and growth. A variety of tumors have dysfunctional RTKs, often overexpressed, and results in inappropriate signaling. Activation of dysfunctional RTKs has been implicated in tumor growth and metastasis. Several small molecule inhibitors of RTKs are currently in clinical trials alone or in combination with conventional chemotherapeutic agents. We have designed, synthesized and evaluated compounds of general structure **1** as potential inhibitors of RTKs. The synthesis and biological evaluation of these compounds will be presented.



1

72.

NOVEL PROTEIN KINASE INHIBITORS AS NEUROPROTECTIVE AND ANTI-PROLIFERATIVE AGENTS. ***James B. Jaquith**[1], Alain Laurent[1], John Gillard[1], Alex Fallis[2], Danielle Methot[3], Martine St-Jean[3], and Debbie Callaghan[4]. (1) Department of Chemistry, Aegera Therapeutics Inc, 810 chemin du Golf, Verdun (Montreal), QC H3E 1A8, Canada, Fax: 514-288-9280, james.jaquith@aegera.com, (2) Department of Chemistry, University of Ottawa, (3) Department of Molecular Biology, Aegera Therapeutics Inc, (4) Institute of Biological Sciences, Nation Research Council of Canada*

Uncontrolled cellular apoptosis is implicated in a number of disease states. The apoptosis of CNS and/or PNS neurons are related to neurodegenerative diseases such as Alzheimer's disease and neuropathic pain induced by diabetes and various chemotherapeutic agents. Tumor growth (cancer), psoriasis, inflammation, and MS (myelin degradation by aberrant T-cell populations) are diseases related to uncontrolled cellular proliferation. We have developed a novel series of bis-indole kinase inhibitors. Select compounds from this class displayed robust protection of CGNs to potassium withdrawal and cisplatin treatment, with IC(50)s ranging from 0.3 to 3 uM. Select compounds also induce or potentiate the Fas and chemotherapeutic induced apoptosis of various cancer cell lines. The therapeutic potential of these compounds is currently being investigated.

73.

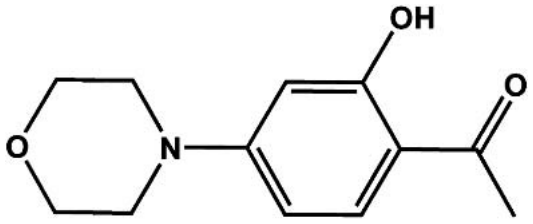
SYNTHESIS AND ACTIVITY OF NEW ARYL- AND HETEROARYL-SUBSTITUTED 5,6-DIHYDRO-4H-PYRROLO[1,2-B]PYRAZOLE INHIBITORS OF THE TRANSFORMING GROWTH FACTOR-β TYPE I RECEPTOR KINASE DOMAIN. ***J. Scott Sawyer**, Bryan D. Anderson, Douglas W. Beight, Robert M. Campbell, David K. Herron, Hong-Yu Li, William T. McMillen, Nicholas A. Mort, Stephen Parsons, Edward C. R. Smith, Karen S. Britt, Lei Yan, Faming Zhang, Theodore Goodson Jr., and Jonathan M. Yingling, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, jss@lilly.com*

The multi-functional cytokine transforming growth factor-β (TGF-β) is a member of a large family of growth factors involved in the regulation of a diverse array of biological processes including cell growth and differentiation, matrix modulation, and embryonic development. The TGF-β signaling pathway may play a role in a number of disease states involving inflammation, angiogenesis, and immune function, including fibrosis, wound healing, Alzheimer's disease, atherosclerosis, hypertension, restenosis, and cancer. We have expanded our previously reported series of pyrazole-based inhibitors of the TGF-β type I receptor kinase domain (TβR-I) to include new 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole analogues. Limited examination of the SAR of this new series in both enzyme- and cell-based in vitro assays resulted in the emergence of two sub-series featuring differing selectivity versus p38 MAP kinase. We have also achieved co-crystallization and X-ray analysis of potent examples of this new series with the TβR-I receptor kinase domain.

74.

DISCOVERY AND INITIAL SAR OF MORPHOLINE-BASED INHIBITORS OF DNA-DEPENDENT PROTEIN KINASE (DNA-PK) FOR USE AS RADIOSENSITIZERS IN CANCER TREATMENT. ***Edward A. Kesicki**[1], Robert J. Kaufman[2], James Halbrook[1], Adam Kashishian[1], and Kerry W. Fowler[1]. (1) ICOS Corporation, 22021 20th Avenue SE, Bothell, WA 98021, Fax: 425-489-9257, ekesicki@icos.com, (2) Gateway Chemical Technology, St. Louis, MO 63146*

DNA-dependent protein kinase (DNA-PK) is a trimeric protein complex consisting of a catalytic kinase subunit and a DNA-targeting heterodimer made up of Ku70 and Ku80 and is a key player in DNA double-strand break repair. Cell lines defective in DNA-PK function are sensitive to killing by double-strand break inducing treatments such as ionizing radiation. In addition, mice with the scid mutation have a defect in DNA-PK function that correlates with high radiation sensitivity. Therefore, we speculated that small-molecule inhibitors of DNA-PK could sensitize rapidly-dividing tumor cells to the effects of radiation treatment. Screening of the ICOS chemical library led to the discovery of two closely related hit compounds that were developed into our lead series. The synthesis and initial SAR of compounds in the series will be discussed, and positive tumor data from compound 1 in mouse models will be presented.



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75.

ELUCIDATION OF EXTENDED SUBSTRATE SPECIFICITY OF PROTEASE TARGETS. ***Jennifer A Williams**, Jennifer L. Harris, David C Tully, Bradley J. Backes, and H. Michael Petrassi, Department of Medicinal Chemistry, Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121, Fax: 858-812-1648, jwilliams@gnf.org*

Characterization of the substrate specificity can provide valuable pharmacophoric information about the protease. With a compendium of specificity data for an exhaustive collection of proteases, cleavage sequences that are truly selective for a single protease or subclass of proteases can be defined. A generalized strategy for defining the extended substrate specificity using combinatorial

peptide libraries will be presented, along with specific data for several proteases of therapeutic interest.

76.

INDOLE-3-AMIDINE BASED FACTOR XA INHIBITORS AS I.V. DELIVERED ANTITHROMBOTICS. *Ross Bentley[1], Mark Bobko[2], Christopher J. Burns[3], K.D. Brown[1], Daniel L. Cheney[4], Valeria Chu[1], Denis J. Colussi[1], William P. Dankulich[5], Timothy F. Gallagher[6], Robert D. Groneberg[7], Robert Leadley[1], G. Liang[8], **Daniel G. McGarry**[1], M. Mervic[2], Susan Morgan[1], Robert L. Morris[9], Kenneth Page[10], Sam S. Rebello[10], Joseph M. Salvino[11], Francis A. Volz[2], W. Wang[1], and Nicola Wilshire[10]. (1) Department of Cardiovascular Pharmacology, Aventis Pharmaceuticals Inc, US Rt-202/206, Bridgewater, NJ 08807-0800, Fax: 908-231-3577, daniel.mcgarry@aventis.com, (2) Department of Medicinal Chemistry, Aventis Pharmaceuticals Inc, (3) Department of Medicinal Chemistry, Viropharma, (4) Computer-Assisted Drug Design, Department of Macromolecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, (5) Department of Medicinal Chemistry, Merck Research Labs, (6) Department of Medicinal Chemistry, Glaxo Smith Kline, (7) Department of Medicinal Chemistry, Array Biopharma, (8) Department of Computer Aided Drug Design, Aventis Pharma, (9) Department of Medicinal Chemistry, Wyeth Pharmaceuticals, (10) Drug metabolism and pharmacokinetics, Aventis Pharmaceuticals Inc, (11) Combinatorial Chemistry, Adolor Corporation*

This presentation will describe the synthesis and pharmacology of a family of indole–3-amidines (I) that function as potent and selective inhibitors of the serine proteinase Factor Xa. Optimization of the physical properties of this series for use in an i.v. formulation will be discussed, as well as a strategy for the effective suppression of a hypotensive side effect in vivo.

77.

AMINOQUINAZOLINE, AMINOQUINOLINE AND AMINOISOQUINOLINE SUBSTITUTED 3(R)- AND 3(S)-AMINOPYRROLIDIN-2-ONE DERIVED FACTOR XA INHIBITORS. ***Julian R. Levell***[1], *Henry W. Pauls[1], Yong-Mi Choi[1], William R. Ewing[1], Michael R. Becker[1], Daniel G. McGarry[1], C. J. Gardner[1], G. B. Poli[1], Mark Czekaj[1], Y. Gong[1], Aiwen Li[1], Roderick Davies[1], John Z. Jiang[1], Fung-Hwei V. Chu[1], Sébastien Maignan[2], Vincent Mikol[2], and Guyan Liang[3]. (1) Drug Innovation & Approval, Aventis Pharmaceuticals, 1041 Route 202-206, PO Box 6800, Mail Stop N-103B, Bridgewater, NJ 08807, Fax: 908-231-3576, Julian.Levell@aventis.com, (2) Structural Biology and Molecular Modeling, Aventis France, (3) Computational Chemistry, Aventis Pharmaceuticals*

Inhibition of the serine protease component of the prothrombinase complex, factor Xa, has been identified as a target for antithrombotic therapy. In previous publications we reported the discovery & SAR of benzamidine derived 3-amino-pyrrolidin-2-one factor Xa inhibitors & the replacement of the benzamidine with some isosteric heterocycles. Herein, we describe further benzamidine isosteres and 3-sulfonamide, amide, urea and alkyl derivatives, focusing on the effect of 3-haloheterocycle moieties on the binding mode of the compound in the active site. The binding is confirmed by xray crystallography. Synthesis of the aminoquinolines, aminoquinazolines, and aminoisoquinolines, and template functionalisation will be described.

78.

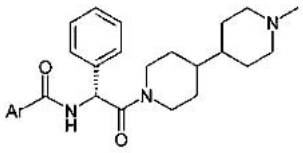
DISCOVERY OF BMS-561389/DPC 906, A HIGHLY POTENT, SELECTIVE AND ORALLY BIOAVAILABLE FACTOR XA INHIBITOR. ***Patrick Y. S. Lam**, Mimi Quan, Ming He, Renhua Li, Charles G. Clark, Donald J. P. Pinto, Christopher A. Teleha, Richard S. Alexander, Karen A. Rossi, Matthew R. Wright, Stephen A. Bai, Kan He, Joseph M. Luettgen, Pancras C. Wong, Robert M. Knabb, and Ruth R. Wexler, Pharmaceutical Research Institute, Bristol-Myers Squibb Co, P.O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3550, patrick.lam@bms.com*

Coumadin is the current drug of choice for oral anticoagulant therapy. It is a highly effective but narrow therapeutic index drug that requires careful patient monitoring. There is thus an unmet-medical need to discover safer and orally bioavailable anticoagulants. We would like to describe that using structure-based drug-design tools and molecular recognition principles, a series of pyrazole inhibitors, with 1-aminobenzisoxazole as benzamidine mimic, was discovered as novel Factor Xa inhibitors. These inhibitors are potent, selective and orally-bioavailable. Optimization led to the discovery of the Phase II clinical candidate, BMS-561389/DPC 906, as novel anticoagulant. DPC 906 is currently the most advance FXa inhibitor in clinical studies.

79.

SAR INVESTIGATION INTO THE USE OF 1-R-PHENYLETHYLENEDIAMINE DIAMIDES AS INHIBITORS OF HUMAN FXA. *Michael R. Wiley[1], **Peter R. Guzzo**[2], John W. Liebeschuetz[3], Nickolay Y Chirgadze[1], Ronald S Foster[1], Larry L. Froelich[4], Valentine J. Klimkowski[1], Trelia J. Craft[4], Donetta S. Gifford-Moore[4], John J. Masters[1], Jeffrey K. Smallwood[1], Gerald F. Smith[4], Richard D. Towner[4], Michael J. Wyle[2], and Stephen C. Young[5]. (1) Discovery Chemistry Research and Technology, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-651-6509, wileymr@lilly.com, (2) Albany Molecular Research Inc, 21 Corporate Circle, PO Box 15098, Albany, NY 12212, peter@albmolecular.com, (3) Computational Chemistry, Tularik Ltd, (4) Cardiovascular Research, Eli Lilly and Company, (5) Medicinal Chemistry, Tularik Ltd*

As part of our program to explore the structure activity relationships of fXa inhibitors such as D-phenylglycine amides (series 1), we have explored 1-R-phenylethylenediamine amides (series 2) as a scaffold which is not susceptible to racemization in the amide coupling step. In this presentation, we will highlight the exploration of substituent effects in the S4 binding element via a small library made via parallel reductive amination, as well as selected SAR results from the S1 binding element (Ar) in this series. The X-ray structure of a compound from series 2 bound in the active site of fXa will also be presented and contrasted with the binding orientation of compounds from series 1.



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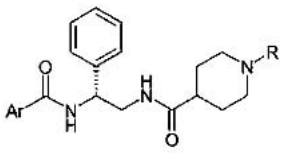

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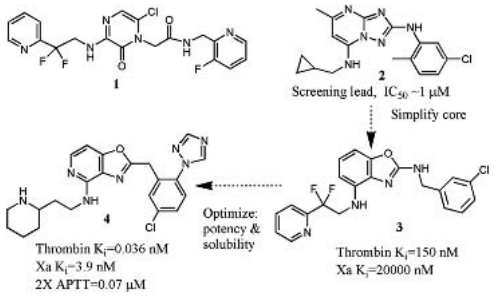
80.

BENZOXAZOLE THROMBIN AND FACTOR XA INHIBITORS. ***James Zhengwu Deng**[1], Christophe S. Burgey[1], Phillippe M. A. Rabbat[1], S. Dale Lewis[2], Bobby J. Lucas[2], Julie A. Krueger[2], Rebecca B. white[3], Bradley Wong[3], Elizabeth A. Lyle[4], Daniel R. McMasters[5], Joseph J. Lynch[4], Youwei Yan[6], Zhongguo Chen[6], Lawrence Kuo[6], Joseph P. Vacca[1], and Terry A. Lyle[1]. (1) Medicinal Chemistry, Merck Research Laboratories, PO Box 4, West Point, PA 19486, (2) Biological Chemistry, Merck Research Laboratories, (3) Drug Metabolism, Merck Research Laboratories, (4) Pharmacology, Merck Research Laboratories, (5) Molecular System, Merck Research Laboratories, (6) Structural Biology, Merck Research Laboratories*

Thrombin and Factor Xa are key enzymes in the coagulation cascade that regulate the blood clotting process. Direct inhibition of thrombin and Factor Xa is a common approach for the development of treatments for thrombosis. Previous reports from our labs have detailed the development of pyrazinone based thrombin inhibitors, exemplified by 1. In our efforts to develop structurally novel thrombin inhibitors, a benzoxazole P2 scaffold was designed based on 2 (IC50 ~ 1 uM for thrombin), a lead from high throughput screening. A series of potent thrombin inhibitors (e.g. 3) was developed through SAR studies on the P2 benzoxazole scaffold. Replacing the benzoxazole core with an oxazolopyridine resulted in thrombin inhibitors with similar potency and improved efficacy. A series of potent dual thrombin and Factor Xa inhibitors was discovered (e.g. 4), by introducing a novel P3 piperidine into the P2 oxazolopyridyl scaffold. Structural and SAR studies suggested that an intramolecular H-bond between the P2 pyridine nitrogen and the P3 piperidine NH maybe pivotal for

the Factor Xa activity. These studies have produced some of Merck's most potent in vitro anticoagulants.



81.

KETENE AMINALS BASED LACTAM DERIVATIVES AS A NOVEL CLASS OF ORALLY BIOAVAILABLE FXA INHIBITORS. ***Yan Shi***[1], *Doree Sitkoff*[2], *Jing Zhang*[1], *Nyeemah Grazier*[1], *Philip D. Stein*[1], *Karnail Atwal*[1], *Gregory S. Bisacchi*[1], *Jack Zhang*[1], *Eddie C.-K. Liu*[3], *Steven M. Seiler*[3], *William A. Schumacher*[3], *Thomas E Steinbacher*[3], *Herbert E. Klei*[2], *Andrew T. Pudzianowski*[2], *Kevin Kish*[2], *and Joseph Yanchunas*[2]. *(1) Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P. O. Box 4000, Princeton, NJ 08543, Fax: 609-252-6804, yan.shi@bms.com, (2) Computer Aided Drug Design, Department of Macromolecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, (3) Department of Biology, Bristol-Myers Squibb Pharmaceutical Research Institute*

Inhibition of the trypsin-like serine protease Factor Xa (FXa) has emerged as key point of intervention in the blood coagulation cascade for the development of antithrombotic agents. We have been interested in the development of novel, orally bioavailable FXa inhibitors. In this poster, the design, synthesis of a novel series of ketene aminal-based FXa inhibitors will be presented. Their binding with FXa and biological activities will also be discussed.

82.

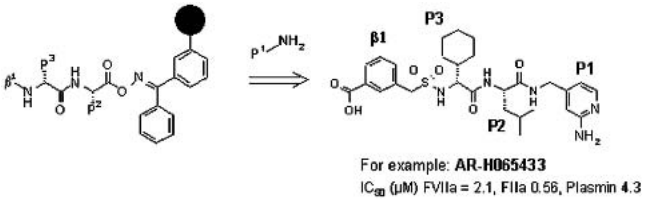
SAR INVESTIGATION ON THE IN-VITRO METABOLISM OF 1,2-AMINOETHANOL-DERIVED NON-COVALENT FACTOR XA INHIBITORS. *Scott M. Sheehan*[1], ***Brian M. Watson***[1], *Michael R. Wiley*[1], *J.W Liebeschuetz*[2], *Daniel J. Sall*[1], *Jeffry B. Franciskovich*[1], *Jothirajah Marimuthu*[1], *Jeffrey K. Smallwood*[1], *Nita J. Patel*[1], *Joseph Woodland*[1], *Robert Barbuch*[1], *Trelia J. Craft*[1], *Donetta Gifford-Moore*[1], *Mark W. Farmen*[1], *Richard D. Towner*[1], *and Gerald F. Smith*[1]. *(1) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-0715, sheehan_scott@lilly.com, watson_brian_m@lilly.com, (2) Computational Chemistry, Tularik Ltd*

The trypsin-like serine protease factor Xa (fXa) plays a key role in the coagulation cascade and is responsible for the conversion of prothrombin to thrombin. As a result, inhibition of fXa has emerged as a promising approach for the treatment of thrombotic disorders. We have recently discovered a series of novel 1,2-aminoethanol-derived factor Xa inhibitors and we investigated the surrogate metabolic profile of these derivatives. Metabolite identification studies have revealed sites of potential oxidative metabolism. In this presentation, the synthesis of these 1,2-aminoethanol-derived fXa inhibitors and their corresponding enzyme inhibitory activity will be disclosed. Discussion will focus on the impact of inhibitor structural modification on observed surrogate metabolism in human, rat, dog, and monkey microsomes.

83.

SEARCH FOR BENSAMIDINE P1-REPLACEMENT IN FVIIA DIPEPTIDE INHIBITORS. ***Fredrik R. Johansson***[1], ***Kenneth L. Granberg***[1], *Ulf E. Fahlander*[1], *Roger James*[2], *Andy Stocker*[2], *Pete Caulkette*[2], *Jens Petersen*[3], *Johanna Deinum*[4], *Frederico Nardi*[3], *and Kristina Nilsson*[1]. *(1) Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, 43183 Mölndal, Sweden, Fax: +46317763710, Fredrik.R.Johansson@astrazeneca.com, Kenneth.Granberg@astrazeneca.com, (2) Department of Cardiovascular, Gastro-Intestinal, AstraZeneca R&D Alderley Park, (3) Department of Structural Chemistry, AstraZeneca R&D Mölndal, (4) Department of Cell Biology and Biochemistry, AstraZeneca R&D Mölndal*

Free amidines usually render molecules poor permeability. The current investigation had the purpose to gather basic SAR for aminomethyl bensamidine replacement in a dipeptide lead. Solid phase parallel synthesis using an oxime based Kaiser resin, proved very efficient. First, construction of the β1-P3 fragments in solution followed by coupling to the resin bound P2 fragment, proceeded in good yields. Second, cleavage of the β1-P3-P2-resin using a range of P1 building blocks (amines) gave the desired β1-P3-P2-P1 dipeptides. The SAR for FVIIa activity was characterised by a strong preference for amidines while we observed moderate inhibition of FXIa and FIIa for various amidine replacements. The basis for these observations and the low level of selectivity against other serine proteases, when bensamidine was used as P1, will be discussed. This is supported by new in-house X-ray structures of des-Gla-FVIIa/sTF and FIIa in complex with β1-P3-P2-P1 inhibitors and by comparison of the S1 specificity pocket of other serine proteases.

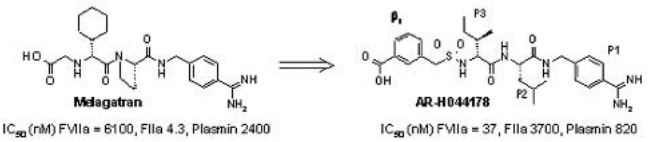


84.

SYNTHESIS OF POTENT AND SELECTIVE DIPEPTIDE INHIBITORS OF FVIIA. ***Ulf E. Fahlander***[1], ***Kenneth L. Granberg***[1], *Fredrik R. Johansson*[1], *Andy Stocker*[2], *Pete Caulkette*[2], *Roger James*[2], *Harji Rakesh*[2], *Susanne Alenfalk*[1], *Kristina Nilsson*[1], *Frederico Nardi*[3], *Jens Petersen*[3], *Tony Slater*[2], *and Johanna Deinum*[4]. *(1) Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, 43183 Mölndal, Sweden, Fax: +46317763724, ulf.fahlander@astrazeneca.com, kenneth.granberg@astrazeneca.com, (2) Department of Cardiovascular, Gastro-Intestinal, AstraZeneca R&D Alderley Park, (3) Department of Structural Chemistry, AstraZeneca R&D Mölndal, (4) Department of Cell Biology and Biochemistry, AstraZeneca R&D Mölndal*

Anticoagulant agents have proven to be clinically effective in the treatment of thrombotic disorders. Coagulation factor VIIa (FVIIa) is a serine protease that plays an important role in the initiation of blood coagulation. Herein, we report the investigation and synthesis of amidine based dipeptide derivatives, which led to the discovery of moderately selective and potent FVIIa inhibitors, as exemplified by AR-H044178.

Solid phase library production was based on traditional linear fmoc-peptide coupling. In solution, an optimised convergent route was devised employing an improved BSTFA one-pot procedure for preparation of sulfonated amino acid fragment (denoted β1-P3) in good yields. Coupling with P2-P1 followed by functional group interconversion gave the desired amidines e.g. AR-H044178. A rational for the observed SAR for selectivity and potency based on analysis of new X-ray structures of des-Gla-FVIIa/sTF in complex with the inhibitors is presented.



85.

X-RAY CRYSTALLOGRAPHIC STUDIES OF DES-GLA-FVIIA/STF COMPLEXES AND THEIR USE IN STRUCTURE BASED DESIGN. ***Kenneth L. Granberg***[1], *Jens Petersen*[2], *Marie Anderson*[2], *Frederico Nardi*[2], *Tony Slater*[3], *Fredrik R. Johansson*[1], *Andy Stocker*[3], *Pete Caulkette*[3], *John Preston*[3], *Johanna Deinum*[4], *and Ulf E. Fahlander*[1]. *(1) Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, 43183 Mölndal, Sweden, Fax: +46317763710, kenneth.granberg@astrazeneca.com, (2) Department of Structural Chemistry, AstraZeneca R&D Mölndal, (3) Department of Cardiovascular, Gastro-Intestinal, AstraZeneca R&D Alderley Park, (4) Department of Cell Biology and Biochemistry, AstraZeneca R&D Mölndal*

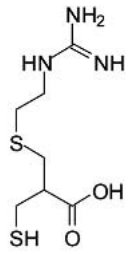
Coagulation factor VIIa (FVIIa), a trypsin like serine protease, is the prime initiator of the cascade of events that lead to activation of prothrombin. Thrombin (FIIa) can activate platelets and cleave fibrinogen to soluble fibrin,

which stabilise a growing thrombus. Tissue factor (TF) is the membrane bound co-factor that dramatically enhances the catalytic activation of factors IX and X by FVIIa. Consequently, FVIIa/TF is an important target for novel anticoagulants based on direct inhibition of FXa generation and hence indirect inhibition of FIIa generation. The new structures of des-Gla-domain FVIIa in complex with the soluble fragment of TF (sTF) and structurally diverse dipeptide and non-peptidic active site inhibitors have been determined by X-ray crystallography to a resolution of 2.0 Å. These X-ray structures were used in inhibitor design and the basis for this is presented.

86.

DESIGN OF PEPTIDE-BASED INHIBITORS OF THROMBIN ACTIVATED FIBRINOLYSIS INHIBITOR (TAFI). ***Douglas W. Beight***, *Yee Hoang Do, Donetta Gifford-Moore, Richard W. Harper, V. Joseph Klimkowski, Deshun Lu, Tianwei Ma, Rhadhakrishnan Rathnachalam, David L. Smiley, Sarah M. Smith, Alan Warshawsky, and Michael R. Wiley, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-276-1417, beight@lilly.com*

Thrombin Activated Fibrinolysis Inhibitor (TAFI) is a zinc metalloprotease that circulates as a plasma procarboxypeptidase B. TAFI is activated by a thrombin/thrombomodulin complex into TAFIa that has a half-life of 8-9 min at 37 °C. TAFIa specifically removes C-terminal amino acids from a number of peptides. This action diminishes tPA-mediated plasminogen activation by removing C-terminal lysine residues on partially degraded fibrin and thus prolongs clot lysis time. Inhibition of TAFIa would decrease clot lysis time and thus be useful in antithrombotic therapy. An early screen identified Plummer's compound, initially designed as a carboxypeptidase N inhibitor, as a potent inhibitor of TAFIa (Ki=100 nM). A preliminary SAR study based on this hit will be described.

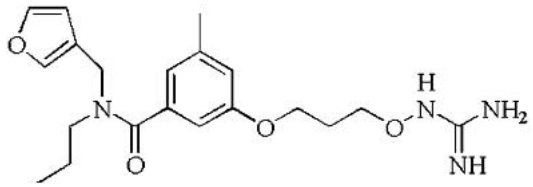


Plummer's compound

87.

OXYGUANIDINES: DISCOVERY OF NOVEL ORALLY ACTIVE THROMBIN INHIBITORS THROUGH STRUCTURE-BASED DRUG DESIGN AND PARALLEL SYNTHESIS. ***Thomas P. Markotan***, *Tianbao Lu, Frank Coppo, Bruce E. Tomczuk, Carl Crysler, Stephen Eisennagel, John Spurlino, Richard M. Soll, and Roger Bone, 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Dr., Suite 104, Exton, PA 19341, markotan@3dp.com*

Orally bioavailable antithrombotic agents, such as Warfarin, are of intense interest but possess a number of limitations, such as (a) their indirect mechanisms of action against thrombus formation, (b) the need for constant monitoring to assure effective drug plasma levels and avoidance of bleeding complications, and (c) their potential for drug-drug interactions. Other antithrombotics, such as heparin and the low-molecular-weight heparins (LMWH's), lack intrinsic oral bioavailability. We report here the discovery and development of novel, potent, selective, and orally active thrombin inhibitors (exemplified by **I**) through structure-based drug design and highly focused parallel syntheses. Structure activity relationships, x-ray crystal structures and pharmacokinetic data will be discussed.

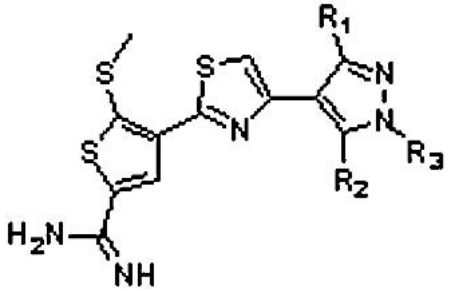


I

88.

SYNTHESIS AND BIOLOGICAL ACTIVITY OF POTENT AND SELECTIVE SMALL MOLECULE INHIBITORS OF C1S. ***Farah Ali***[1], *Carl R. Illig*[1], *M. Jonathan Rudolph*[1], *Scott Klein*[1], *Ehab Khalil*[1], *Richard Soll*[1], *Roger Bone*[1], *John Spurlino*[1], *Reneé DesJarlais*[1], *Carl Crysler*[1], *John M. Kilpatrick*[2], *Yarlagadda S. Babu*[2], *and Nalin L. Subasinghe*[1]. *(1) 3-Dimensional Pharmaceuticals, Inc, 665 Stockton Dr, Exton, PA 19341, farah.ali@3dp.com, (2) BioCryst Pharmaceuticals, Inc*

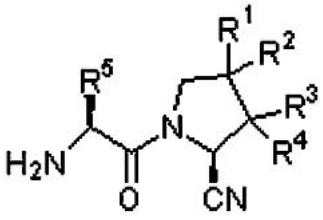
Activation of the classical pathway of complement has been implicated in disease states such as hereditary angioedema, ischemia-reperfusion injury and acute transplant rejection. C1s represents a pivotal upstream point of control in the classical pathway of complement activation and is likely to be a useful target in the therapeutic intervention of these disease states. The synthesis and enzyme activity of novel, potent, and selective small molecule inhibitors of C1s will be described.



89.

DPP-IV INHIBITORS (1) : SYNTHESIS AND EVALUATION OF 3- OR 4-SUBSTITUTED 2-CYANOPYRROLIDINES. *Hiroshi Fukushima, Akira Hiratate,* ***Masato Takahashi***, *Kiyokazu Kitano, and Koji Yamamoto, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403, Yoshino-cho, Kita-ku, Saitama-shi 331-9530, Japan, Fax: 048-652-7254*

Dipeptidyl peptidase IV (DPP-IV) is a widely distributed serine protease that cleaves N-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position. DPP-IV inhibitors attract attention as a drug for use in the treatment of Type 2 diabetes, by preventing degradation of glucagon-like peptide-1 (GLP-1) and extending the duration of action of GLP-1. A series of 2-cyanopyrrolidines is one of the most potent DPP-IV inhibitors. We focused attention on the substituents at 3 or 4 position of 2-cyanopyrrolidines, synthesized and evaluated these derivatives **1**. Among them, 4-fluoro derivative was found to show better DPP-IV inhibitory activity and higher plasma drug concentrations after oral administration to rats than 4-unsubstituted derivative. Synthesis, biological and physical data will be presented.



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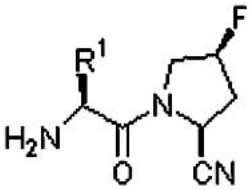
90.

DPP-IV INHIBITORS (2) : SYNTHESIS AND EVALUATION OF NOVEL 2-CYANO-4-FLUOROPYRROLIDINES. ***Hiroshi Fukushima***, *Akira Hiratate, Masato Takahashi, Kiyokazu Kitano, and Koji Yamamoto, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403, Yoshino-cho, Kita-ku, Saitama-shi 331-9530, Japan, Fax: 048-652-7254*

We found that 2-cyano-4-fluoropyrrolidines were potent DPP-IV inhibitors, but 1-isoleucyl derivative (**1**, R^1=sec-butyl) possesses unfavorable property about chemical stability. Chemical modification was made at the 1-position to give more stable compounds (**1** and **2**). As a result, we found several compounds, which have potent DPP-IV inhibitory activity, adequate chemical stability and

other properties as an oral hypoglycemic drug. Synthesis, biological and physical data will be presented.



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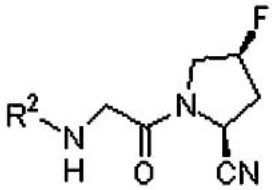


2

91.

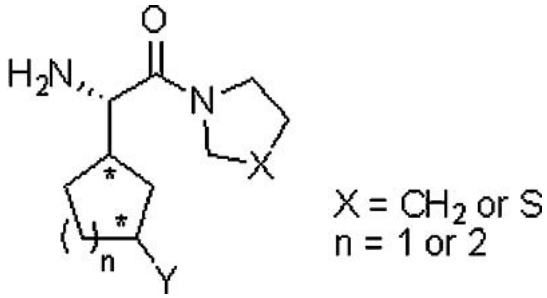
FLUROPYRROLIDINES AS NOVEL, POTENT DIPEPTIDYL PEPTIDASE INHIBITORS. ***Sab A. Randhawa***[1], *Curt D. Haffner*[1], *James M. Lenhard*[2], *Martin H. Osterhout*[3], *Brian Stephenson*[3], *Lois L. Wright*[4], *Dallas K. Croom*[2], *Jonathan Y. Bass*[1], *Richard D. Caldwell*[1], *David J. Cowan*[1], *David N. Deaton*[1], *Kate A. Dwornik*[1], *Jing Fang*[1], *Dennis O. Heyer*[1], *Istvan W. Kaldor*[1], *Andrew L. Larkin*[1], *Donovan J. McConn*[5], *Darryl L. McDougald*[1], *Robert B. McFadyen*[1], *Steven M. Reister*[1], *Melissa B. Secosky*[4], *Brian D. Thompson*[1], *Kevin J. Wells-Knecht*[5], *and Wenhai Zhang*[4]. *(1) MV CEDD Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Five Moore Drive, Research Triangle Park, NC 27709, Sab.A.Randhawa@gsk.com, (2) Metabolic Diseases, GlaxoSmithKline, (3) Synthetic Chemistry, Chemical Development, GlaxoSmithKline, (4) Department Of Biochemistry and Protein Chemistry, GlaxoSmithKline, (5) DMPK, GlaxoSmithKline*

Dipeptidyl peptidase IV (DPP-IV) is a glucagon-like peptide-1 (GLP-1) degrading enzyme. Inhibition of DPP-IV, a serine specific protease, represents a novel therapy for type-2 diabetes by extending the duration of action of GLP-1 and hence stimulate insulin secretion, inhibit glucagon release, slow gastric emptying, and promote β-cell recovery. Since GLP-1 effects are dependant on elevated blood glucose and diminish as glucose levels return to normal this form of treatment provides an advantage over many current therapies in lower incidents of hypoglycemia. Small molecule oral DPP-IV inhibitors in human clinical trials have demonstrated antidiabetic action with type-2 diabetic patients. Described is the synthesis, structure activity relationship (SAR) and evaluation *in vitro* and *in vivo* of several fluropyrrolidines as DPP-IV inhibitors. Nanomolar activity and good selectivity versus DPP-II is observed.

92.

DIASTEREOSELECTIVE SYNTHESIS AND CONFIGURATION-DEPENDENT ACTIVITY OF (3-SUBSTITUTED-CYCLOALKYL)GLYCINE PYRROLIDIDES AND THIAZOLIDIDES AS DIPEPTIDYL PEPTIDASE IV INHIBITORS. ***Wallace T. Ashton***[1], *Hong Dong*[1], *Rosemary M. Sisco*[1], *George A. Doss*[2], *Barbara Leiting*[3], *Reshma A. Patel*[3], *Joseph K. Wu*[3], *Frank Marsilio*[3], *Nancy A. Thornberry*[3], *and Ann E. Weber*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-5350, wally_ashton@merck.com, (2) Department of Preclinical Drug Metabolism, Merck Research Laboratories, (3) Department of Metabolic Disorders, Merck Research Laboratories*

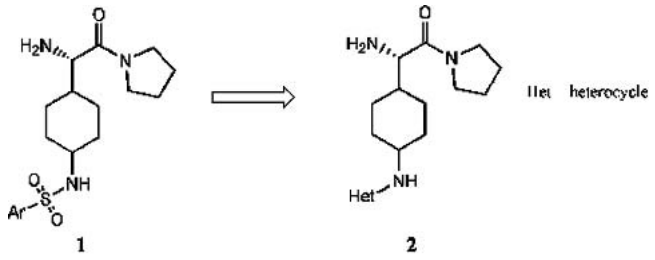
The incretin hormone glucagon-like peptide 1 (GLP-1), which stimulates glucose-dependent insulin secretion, has become a prominent target candidate for treatment of type 2 diabetes. However, therapeutic use of GLP-1 itself is severely compromised by lack of oral activity and rapid degradation by dipeptidyl peptidase IV (DP-IV). Inhibition of DP-IV represents a promising indirect approach to elevate endogenous GLP-1 levels, thereby improving glucose tolerance with minimal risk of hypoglycemia. Previous work from these laboratories has described (4-substituted-cyclohexyl)glycine pyrrolidides and thiazolidides as potent, selective, orally bioavailable inhibitors of DP-IV. We have now investigated corresponding cyclopentyl- and cyclohexylglycine derivatives bearing ring substitution at the 3-position. A diastereoselective route was used to generate the three asymmetric centers in a stereochemically unambiguous manner. Potent DP-IV inhibitors could be achieved in this series, depending on absolute configuration and choice of ring substituent.



93.

HETEROCYCLE LINKED CYCLOHEXYLGLYCINE DERIVATIVES AS NOVEL DIPEPTIDYL PEPTIDASE-IV INHIBITORS. ***Anthony Mastracchio***[1], *Scott D. Edmondson*[1], *Emma R. Parmee*[1], *Lawrence F. Colwell Jr.*[1], *Bahanu Halihaz*[1], *Huaibing He*[1], *Barbara Leiting*[2], *Kathryn Lyons*[1], *Frank Marsilio*[2], *Reshma A. Patel*[2], *Joseph K. Wu*[2], *Matthew J. Wyvratt*[1], *Michael H. Fisher*[1], *Nancy A. Thornberry*[2], *and Ann E. Weber*[1]. *(1) Department of Basic Chemistry, Merck & Co, P.O. Box 2000, Rahway, NJ 07065-0900, Fax: 732-594-5350, anthony_mastracchio@merck.com, (2) Department of Metabolic Disorders, Merck & Co*

Dipeptidyl peptidase-IV (DP-IV) is responsible for the rapid processing of incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which have a role in the biosynthesis and secretion of insulin. Inhibition of DP-IV increases circulating levels of GLP-1 and GIP leading to higher blood insulin levels and DP-IV inhibitors have been shown to lower fasting and post-prandial blood glucose levels in humans. Consequently, inhibition of DP-IV is emerging as a new approach for the treatment of type-II diabetes. Previous research from Merck laboratories led to the discovery of substituted cyclohexylglycines (1) as potent DP-IV inhibitors. In an effort to improve the in vitro and pharmacokinetic profile of this series, we replaced the cyclohexyl amides with nitrogen linked heterocycles (2) and fused heterocycles. This presentation will describe the synthesis and biological properties of these novel DP-IV inhibitors.



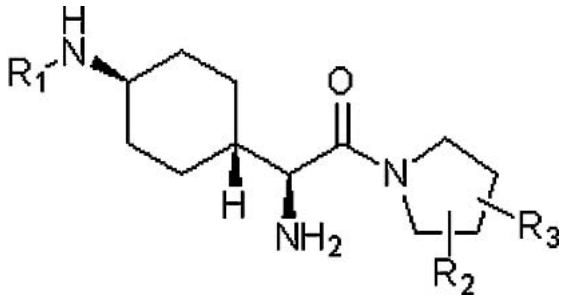
1 2

94.

SYNTHESIS AND EVALUATION OF FLUOROPYRROLIDINE AMIDES AS DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF DIABETES. ***Charles G. Caldwell***[1], *Ping Chen*[1], *Jiafang He*[1], *Emma R. Parmee*[1], *Barbara Leiting*[2], *Frank Marsilio*[2], *Reshma A. Patel*[2], *Joseph K. Wu*[2], *George J. Eiermann*[3], *Gerald J. Hickey*[3], *Margaret E. McCann*[3], *Huaibing He*[1], *Kathryn A. Lyons*[1], *Michael H. Fisher*[1], *Matthew J. Wyvratt*[1], *Nancy A. Thornberry*[2], *and Ann E. Weber*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, RY123-134, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-5790, chuck_caldwell@merck.com, (2) Department of Metabolic Disorders, Merck Research Laboratories, (3) Department of Animal Pharmacology, Merck Research Laboratories*

Glucagon-like peptide-1 (GLP-1), which is released in response to food intake, stimulates insulin biosynthesis and secretion while inhibiting hepatic glucose production. These effects would be of use in the treatment of diabetic patients, and continuous infusion of exogenous GLP-1 has been shown to reduce blood glucose levels. GLP-1 is rapidly inactivated *in vivo*, however, by dipeptidyl peptidase IV (DP-IV), a serine protease which cleaves a dipeptide from the *N*-terminus. Use of a small-molecule DP-IV inhibitor to extend the lifetime of endogenously secreted GLP-1 appears to be an attractive alternative to the administration of GLP-1. This presentation will describe the synthesis and biological activity of a series of fluoropyrrolidine amide derivatives which are

potent inhibitors of DP-IV having excellent oral bioavailability and pharmacokinetic properties.



95.
TARGETING THE ESSENTIAL PROTEINS OF HTLV-I MATURATION AND REPLICATION. ***Kelly J. Dennison***[1], *Bryan E. Herger*[1], *Michael D. Kulis Jr.*[2], *and Suzanne B. Shuker*[2]. *(1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332-0363, Fax: 404-894-2295, kelly.dennison@chemistry.gatech.edu, (2) Department of Chemistry and Biochemistry, Georgia Institute of Technology*

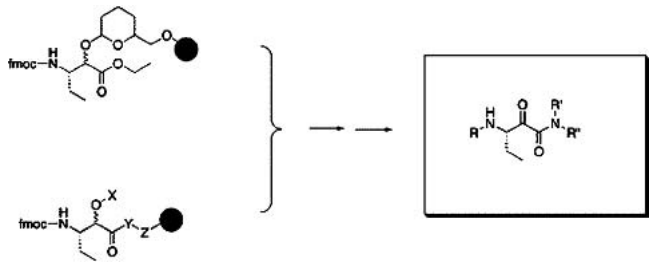
Human T-cell lymphotrophic virus (HTLV-I) is a retrovirus which is implicated in adult T-cell leukemia and TSP/HAM. Over 20 million people worldwide carry this virus, and of these, some 10% will die of HTLV-I-related disease. Like other retroviruses, HTLV-I requires a protease to process translated polyprotein precursors into functional proteins of the mature virion. This makes the protease a suitable target for drug therapies to treat HTLV-I infection. Structural and kinetic studies are essential for successful lead compound development. However, hydrophobic interactions lead to aggregation of the protease. In this work, we show the effects of C-terminal modification on activity and aggregation of HTLV-I protease.

96.
DESIGN AND SYNTHESIS OF NAPHTHALENE DERIVATIVES AS HCMV PROTEASE INHIBITORS. ***Ariamala Gopalsamy***[1], *Kitae Lim*[1], *John Ellingboe*[1], *Boris Mitsner*[1], *Antonia Nikitenko*[1], *Mathew Olson*[2], *Geri Bebernitz*[2], *Diane Grinberg*[2], *Boris Feld*[2], *and John O'Connell*[2]. *(1) Chemical Sciences, Wyeth, Pearl River, NY 10965, Fax: 845-602-3045, gopalsa@wyeth.com, (2) Infectious Diseases, Wyeth*

Human cytomegalovirus (HCMV), a herpesvirus, is an opportunistic pathogen in immunocompromised individuals and organ transplant recipients. The current antiviral agents for treating HCMV infection target the viral DNA polymerase, however they demonstrate sub-optimal efficacy and safety profiles. Hence drugs that act by different mechanism are highly desirable to combat this infection. HCMV protease is a viable target because of its critical role in capsid assembly and viral maturation. Through high throughput screening of various libraries, substituted styryl naphthalene was identified as HCMV protease inhibitor. Various regions of the lead molecule were optimized using parallel synthesis. Efforts to modify the styryl region of the molecule lead to the identification of naphthyl sulfonamide and naphthyl ether series. While the analogues had a wide range of activity, a number of analogues were identified with IC50 <5 M. The compounds showed selectivity against chymotrypsin (>5 fold) and trypsin (>15 fold). The parallel synthesis effort, optimization approach and the SAR will be discussed in detail.

97.
SOLID PHASE PARALLEL SYNTHESIS OF ALPHA-KETOAMIDE INHIBITORS OF NS3·4A HCV PROTEASE. ***John J. Court***, *Kevin C. Cottrell, Scott L. Harbeson, and Janos Pitlik, Department of Medicinal Chemistry, Vertex Pharmaceuticals Inc, 130 Waverly Street, Cambridge, MA 02139, Fax: 617-444-6766, john_court@vrtx.com*

Solid Phase parallel synthesis of a series of tetrapeptide based alpha-ketoamide inhibitors was used to explore the specificity for binding to the catalytic site of the NS3·4A HCV Protease. Three different linker strategies were employed to generate the compounds of interest. The syntheses, the isolation of the compounds, and the advantages of each route will be discussed.

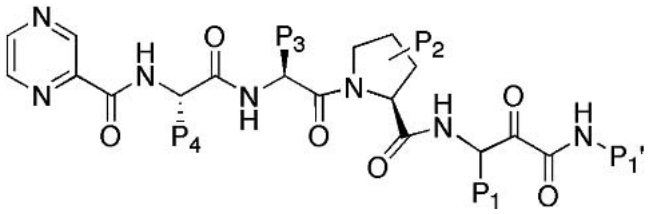


98.
HEPATITIS C NS3·4A PROTEASE INHIBITORS: DESIGN OF REVERSIBLE COVALENT WARHEADS. ***Robert B. Perni***, *Shawn D. Britt, John J. Court, Lawrence F. Courtney, David D. Deininger, Luc J. Farmer, Cynthia A. Gates, Scott L. Harbeson, Joseph L. Kim, Rhonda Levin, Young-Choon Moon, Yu-Ping Luong, Ethan O'Malley, Janos Pitlik, B. Govinda Rao, John H. Van Drie, Roger D. Tung, and John A. Thomson, Vertex Pharmaceuticals Inc, 130 Waverly Street, Cambridge, MA 02139, Fax: 617-444-6766, Robert_Perni@vrtx.com*

The design of inhibitors of the HCV NS3 serine protease has posed an exceptional challenge to medicinal chemists. Only recently has the first human trial of such a therapeutic been reported. The shallow, largely hydrophobic active site of this serine protease is the source of the difficulty. Nature has designed this protein with a natural recognition length of 10 amino acids. Numerous hydrophobic interactions and hydrogen bonds are required to effectively bind any potential inhibitor. In addition, either a charged terminus or a covalent attachment of the inhibitor to the catalytic serine is needed to anchor the assembly. In order to maximize binding while simultaneously maintaining an acceptable biological profile we have chosen to base our inhibitor scaffolds on a reversible covalent warhead motif to eliminate charged groups. One of the first observations from this approach is that most of the known, serine protease warhead moieties function poorly with NS3·4A enzyme. This poster will describe the evolution of the warhead concept leading to a potent series of inhibitors possessing good cellular activity.

99.
HEPATITIS C NS3·4A PROTEASE INHIBITORS: EXTENSIVE STRUCTURE-ACTIVITY RELATIONSHIP EXPLORATION OF POTENT, COVALENT KETOAMIDE BASED INHIBITORS. ***Janos Pitlik***, *Shawn D. Britt, Kevin C. Cottrell, John J. Court, Lawrence F. Courtney, David D. Deininger, Cynthia A. Gates, Chao Lin, Kai Lin, Yu-Ping Luong, Robert B. Perni, B. Govinda Rao, John A. Thomson, Roger D. Tung, and Yunyi Wei, Vertex Pharmaceuticals Inc, 130 Waverly Street, Cambridge, MA 02139, Fax: 617-444-6766, Janos_Pitlik@vrtx.com*

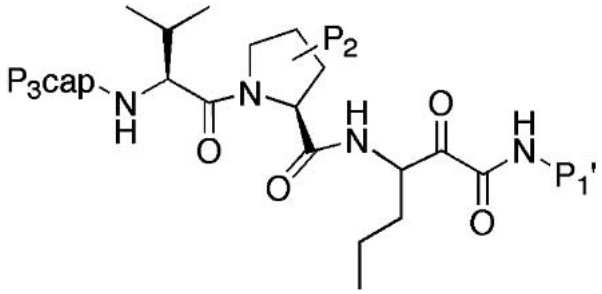
In our previous poster we reported that we have successfully identified ketoamide warhead based tetrapeptide scaffolds that are potent inhibitors of the HCV NS3/4A serine protease. Here we will detail a concerted effort how our original leads were optimized by using combinatorial, computational, and medicinal chemistry techniques. We prepared a small combinatorial library comprised of P1, P2, and P4 variants. We then chose several natural and non-natural amino-acids to optimize the S3 and S4 subsite binding of our inhibitors. Details of our findings and some intriguing structural observations will be presented.



100.

KETOAMIDE BASED INHIBITORS OF THE HCV NS3·NS4A PROTEASE: P3 TRUNCATION STUDIES. ***Janos Pitlik**, Shawn D. Britt, Kevin C. Cottrell, John J. Court, Lawrence F. Courtney, Cynthia A. Gates, Scott L. Harbeson, Yu-Ping Luong, Robert B. Perni, B. Govinda Rao, John A. Thomson, Roger D. Tung, and Yunyi Wei, Vertex Pharmaceuticals Inc, 130 Waverly Street, Cambridge, MA 02139, Fax: 617-444-6766, Janos_Pitlik@vrtx.com*

In our previous two posters we reported that we have successfully identified and further optimized ketoamide warhead based tetrapeptide inhibitors of the HCV NS3·4A serine protease. In this presentation we will summarize our work on a P3 truncated scaffold. A number of amide, carbamate, urea, and sulfonamide caps were examined. A small combinatorial library was assembled incorporating various caps in combination with P1′ and P2 variants. A summary of the resulting structure-activity relationships will be presented.



101.

DISCOVERY, ASSAY, AND X-RAY STRUCTURE OF NOVEL (CARBONYL-PIPERIDIN-4-YL) BENZYLAMINES AND BENZAMIDINES AS MAST CELL BETA-TRYPTASE INHIBITORS. ***Eric W. MacMillan**[1], Yong Gong[1], Guyan Liang[1], Julian R. Levell[1], Jennifer Cairns[1], Keith Sides[1], Jennifer Kwong[1], Magali Mathieu[2], Sebastien Maignan[2], Henry W. Pauls[1], and Joseph Tsay[1]. (1) Drug Innovation and Approval, Aventis Pharmaceuticals Inc, Bridgewater, NJ 08807, (2) Department of Structural Biology, Aventis Pharmaceuticals Inc, Vitry, France*

Mast cells degranulate upon antigen challenge, to release a number of proinflamatory mediators, including the serine protease beta-tryptase. This then cleaves numerous substrates, including the PAR-2 receptor (resulting in cellular activation and subsequent pro-inflammatory events). Specific beta-tryptase inhibitors are being developed as potential therapeutics for asthma, because they attenuate tryptase induced bronchoconstriction and microvascular leakage in mammalian lung, in addition to allergen-induced airway hyperreactivity.

We have previously disclosed a series of (carbonyl-piperidin-4-yl) benzylamines and benzamidine based tryptase inhibitors. Herein, we describe a related series of high molecular weight analogs. A detailed kinetic investigation indicated that these inhibitors are highly selective, sub-nanomolar inhibitors of beta-tryptase.

Competitive inhibitors would be expected to occupy all four active sites of the homotetramer (one inhibitor molecule per active site). However, our kinetic analysis, molecular modeling and X-ray analysis indicates that this new class of inhibitors binds only two molecules per tetramer.

102.

KETO-OXAZOLES AS CATHEPSIN S INHIBITORS. ***Vincent Leroy**[1], Joacy Aguiar[1], Dave Borcherding[1], Tieu-Binh Le[1], Sukanthini Thurairatnam[1], Andreas Timm[2], Elizabeth Allen[3], Nicholas J. Vitali[3], Jennifer Cairns[4], Dona M. Cramer[4], Keith Sides[4], Chao Zou[4], and David J Aldous[1]. (1) Medicinal Chemistry, Aventis Pharmaceuticals Inc, Route 202-206 Mail Code N-203A, PO Box 6800, Bridgewater, NJ 08807-0800, Fax: 908-231-3577, vincent.leroy@aventis.com, (2) High Throughput Medicinal Chemistry, Aventis Pharmaceuticals Inc, (3) RRADG-RA Pharmacology, Aventis Pharmaceuticals Inc, (4) Resp/RA Mol Biology & Genomics, Aventis Pharmaceuticals Inc*

The involvement of lysosomal cysteine protease cathepsin S in antigen presentation has triggered wide interest for the development of selective, reversible inhibitors. Cathepsin S processes the invariant chain blocking the MHC class II complex, thus allowing antigen presentation. Inhibitors of cathepsin S might be useful for the treatment of disorders resulting from excessive antigen presentation. Keto heterocycles have been shown to be cathepsin S inhibitors. The preparation and SAR of a series of 2-keto oxazoles will be described.

103.

SUCCINATE DERIVATIVES AS CATHEPSIN S INHIBITORS. ***Vincent Leroy**[1], Joacy Aguiar[1], Dave Borcherding[2], Brian S. Freed[3], Tieu-Binh Le[1], Jean-Philippe Letallec[1], Sukanthini Thurairatnam[1], Andreas Timm[3], Elizabeth Allen[4], Nicholas J. Vitali[4], Jennifer Cairns[5], Dona M. Cramer[5], Keith Sides[5], Chao Zou[5], and David J Aldous[2]. (1) Medicinal Chemistry, Aventis Pharmaceuticals Inc, Route 202-206 Mail Code N-203A, PO Box 6800, Bridgewater, NJ 08807-0800, Fax: 908-231-3577, vincent.leroy@aventis.com, (2) Medicinal Chemistry, Aventis Pharmaceuticals Inc, (3) High Throughput Medicinal Chemistry, Aventis Pharmaceuticals Inc, (4) RRADG-RA Pharmacology, Aventis Pharmaceuticals Inc, (5) Resp/RA Mol Biology & Genomics, Aventis Pharmaceuticals Inc*

The involvement of lysosomal cysteine protease cathepsin S in invariant chain processing as triggered interest to evaluate its inhibitors for the treatment of diseases characterized by excess antigen presentation. Keto-heterocycles have been shown to be cathepsin S inhibitors. The synthesis and SAR of a series of keto-heterocycles having alkyl succinate derived P2/P3 fragments will be described.

104.

POTENT INHIBITORS OF PROCOLLAGEN C-PROTEINASE. *Wen-Bin Ho[1], **Eric D. Turtle**[1], Nicholas Chow[1], Udo Bauer[2], Mitch Brenner[3], Charles Yang[3], and Sergio Sosa[3]. (1) Medicinal Chemistry Group, FibroGen Inc, 225 Gateway Boulevard, South San Francisco, CA 94080, Fax: 650-866-7207, eturtle@fibrogen.com, (2) Medicinal Chemistry, AstraZeneca R&D Mölndal, (3) Small Molecule Evaluation Group, FibroGen Inc*

Procollagen C-Proteinase (PCP) is a zinc metallo proteinase responsible for cleaving procollagen types I-III to initiate the formation of extracellular collagen fibrils. Excessive collagen deposition contributes to numerous medical conditions including fibrotic disorders and scarring; therefore, inhibitors of PCP may lead to useful therapeutic agents. This poster describes the discovery and preliminary optimization of several classes of compounds that have led to potent selective inhibitors of PCP.

105.

STRUCTURAL MODELS AND MODIFICATIONS OF HTLV-I PROTEASE. ***Kelly J. Dennison**[1], Bryan E. Herger[1], and Suzanne B. Shuker[2]. (1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332-0363, Fax: 404-894-2295, kelly.dennison@chemistry.gatech.edu, (2) Department of Chemistry and Biochemistry, Georgia Institute of Technology*

Human T-cell lymphotrophic virus (HTLV-I) is a retrovirus which is implicated in adult T-cell leukemia and TSP/HAM. Over 20 million people worldwide carry this virus, and of these, some 10% will die of HTLV-I-related disease. Like other retroviruses, HTLV-I requires a protease to process translated polyprotein precursors into functional proteins of the mature virion. This makes the protease a suitable target for drug therapies to treat HTLV-I infection. Structural and kinetic studies are essential for successful lead compound development. However, hydrophobic interactions lead to aggregation of the protease. In this work, we show the effects of C-terminal modification on activity and aggregation of HTLV-I protease.

106.

STRUCTURE-BASED DISCOVERY OF NON-PEPTIDE, SMALL MOLECULE INHIBITORS OF XIAP. ***Zaneta Nikolovska-Coleska**[1], Zengjian Hu[1], Xueliang Fang[1], York Tomita[2], Manchao Zhang[3], Liang Xu[3], Dajun Yang[3], Marc E Lippman[3], Peng Li[4], Peter P. Roller[4], and Shaomeng Wang[1]. (1) Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109-0934, (2) Lombardi Cancer Center, Georgetown University, (3) Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, (4) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health*

XIAP has a key function in the negative regulation of apoptosis and overexpression of XIAP renders the cell resistant to a wide variety of apoptotic stimuli. Smac-based peptide inhibitors effectively could overcome apoptosis-resistance

in different types of cancer cells with high levels of XIAP protein. Using the computer screening approach based on X-ray structure of XIAP, we discovered several classes of small molecule inhibitors of XIAP. One such inhibitor, SMXI-56, was studied in detail. SMXI-56 was shown to bind to the XIAP BIR3 domain, compete with the Smac peptide, and effectively inhibit cell growth and induce apoptosis in human prostate cancer cell lines with a high level of XIAP protein. SMXI-56 was shown to have minimal effect on normal epithelial prostate cells and other normal cells with low level of XIAP, showing selectivity. SMXI-56 was further shown to activate caspase-9 and -3. Our studies demonstrate that non-peptide, small molecules can directly and potently inhibit the anti-death function of XIAP and may be ultimately developed as new anticancer drugs by overcoming apoptosis-resistance in cancer cells.

107.

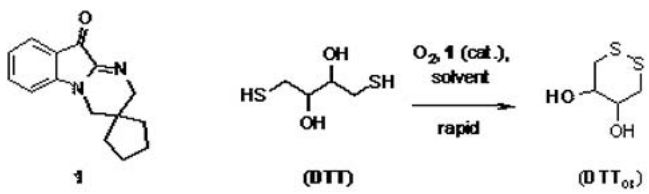
ANTITUMOR 1,4-ANTHRACENEDIONES INDUCE APOPTOSIS IN HL-60 CELLS BY A FAS-INDEPENDENT MECHANISM WHICH IS PARTIALLY MEDIATED BY CASPASE-2. ***Jean-Pierre H. Perchellet***[1]*, Elisabeth M. Perchellet*[1]*, Yang Wang*[1]*, Rebeka L. Weber*[1]*, Kaiyan Lou*[2]*, Justin Crossland*[2]*, and Duy H. Hua*[2]*. (1) Anti-Cancer Drug Laboratory, Kansas State University, Division of Biology, Ackert Hall, Manhattan, KS 66506-4901, Fax: 785-532-6653, jpperch@ksu.edu, (2) Department of Chemistry, Kansas State University*

Among synthetic analogs of 1,4-anthraquinone (AQ code number), 6-methyl-1,4-anthracenedione (AQ8) and 6-bromomethyl-1,4-anthracenedione (AQ9) induce the release of mitochondrial cytochrome *c*, the activation of initiator caspases 2, 8 and 9 and effector caspase 3 and the cleavage of poly(ADP-ribose) polymerase-1 at 6 h and internucleosomal DNA fragmentation at 24 h before inhibiting HL-60 tumor cell viability (IC_{50}: 79-87 nM at day 4). In contrast to the caspase-8 inhibitor z-IETD-fmk, the caspase-2 inhibitor z-VDVAD-fmk totally blocks the activation of other caspases by AQ8, suggesting that caspase-2 is required to mediate AQ-induced caspase-9, -3 and -8 activities. But z-VDVAD-fmk and z-IETD-fmk do not prevent AQ8 from inducing cytochrome *c* release, suggesting that AQs might directly target mitochondria. Moreover, the FasL/Fas signaling pathway is not involved in the mechanism by which AQs induce apoptosis since AQ9 triggers cytochrome *c* release and caspase-2, -9, -3 and -8 activations in the presence of antagonistic anti-Fas and anti-FasL monoclonal antibodies.

108.

CHEMICAL STRATEGIES FOR IDENTIFYING FALSE POSITIVES: APPLICATIONS TO CASPASE-3 SCREENING. ***Dean G. Brown****, Rebecca A. Urbanek, Robert T. Jacobs, David Aharony, Frances M. McLaren, Reed W. Smith, Gary B. Steelman, Sally A. Walsh, Smita Ghanekar, Donald E. Mathisen, James B. Campbell, Gajendran Sundarababu, Don E. Pivonka, and Andrew T. Maynard, Medicinal Chemistry, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19803, Fax: 302-886-5382, dean.brown@astrazeneca.com*

A series of dihydropyrimido[1,2-*a*]indolones **1** was identified which initially gave rise to apparent potent activities in a caspase-3 inhibition assay. However, it was determined that a catalytic reduction-oxidation (red-ox) cycle of these compounds with dithiothreitol (**DTT**, a common reducing agent in cysteine protease assays) and molecular oxygen was a likely cause of caspase-3 inhibition. This reaction could be easily monitored by quantifying the amount of dithiane-4,5-diol (**DTTox**) produced under modified assay conditions using either NMR or Raman spectroscopy. A detailed mechanistic explanation is given as well as strategies for identifying compounds that may be behaving in a similar manner.



1 **(DTT)** **(DTT_{ox})**

109.

DESIGN AND SYNTHESIS OF PEPTIDYL AZA-EPOXIDE INHIBITORS FOR CASPASES. ***Özlem Dogan Ekici***[1]*, Juliana L. Asgian*[2]*, Karen E. James*[2]*, Zhao Zhao Li*[2]*, and James C. Powers*[2]*. (1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332, Fax: 404-894-2295, gte538r@prism.gatech.edu, (2) Department of Chemistry and Biochemistry, Georgia Institute of Technology*

Caspases, cysteine aspartate specific proteases, are members of clan CD cysteine proteases and are highly specific for Asp at the P1 residue. In humans, there are more than 15 members of the caspase family. Some caspases are important mediators of inflammation, while others are involved in apoptosis. Excessive apoptosis has been associated with neurodegenerative disorders such as stroke, ALS, Alzheimer's disease and Parkinson's disease. Therefore, potent and specific caspase inhibitors could lead to the development of potential drugs. Peptidyl aza-epoxide inhibitors are potent and highly specific inhibitors of clan CD proteases. We report the synthesis and kinetic data on several dipeptidyl aza-epoxide inhibitors for caspases. These results should be valuable for the design of more potent inhibitors.

110.

DISCOVERY OF 3-ARYL-5-ARYL-[1,2,4]-OXADIAZOLE AS POTENT APOPTOSIS INDUCER. ***Han Zhong Zhang****, Jared Kuemmerle, Kristin Ollis-Mason, Hong Zhang, Bill Kemnitzer, John Drewe, Shailaja Kasibhatla, Ling Qiu, Shannon Archer, Sergei Maliartchouk, Ben Tseng, and Sui Xiong Cai, Maxim Pharmaceuticals, 6650 Nancy Ridge Dr, San Diego, CA 92121, Fax: 858-202-4000, hzhang@maxim.com*

Apoptosis or programmed cell death is a normal cellular process and the failure of cells to undergo apoptosis plays an important role in the development of cancer. We are interested in the discovery and development of apoptosis inducers as new chemotherapeutical agents. Through our cell-based high throughput screening technology, we have identified 3-aryl-5-aryl-[1,2,4]-oxadiazole as a novel apoptosis inducer. It has high activity against cancer cell lines but is inactive in normal cells. Additional studies showed it induces apoptosis in the G1 phase of cell cycle with a novel mechanism. We will report the synthesis, structure-activity relationship and biological characterization of this novel series of apoptosis inducers.

111.

DISCOVERY OF INDOLE-2-CARBOXYLIC ACID BENZYLIDENE-HYDRAZIDES AS POTENT APOPTOSIS INDUCERS USING CELL-BASED HIGH THROUGHPUT SCREENING ASSAY. ***Han Zhong Zhang****, John Drewe, Shailaja Kasibhatla, Ben Tseng, and Sui Xiong Cai, Maxim Pharmaceuticals, 6650 Nancy Ridge Dr, San Diego, CA 92121, Fax: 858-202-4000, hzhang@maxim.com*

The discovery and development of apoptosis inducers as potential anti-cancer agents is an attractive approach since many anticancer drugs are known to kill tumor cells via apoptosis. By applying our cell-based high throughput screening technology, we have identified indole-2-carboxylic acid benzylidene-hydrazides as a new class of apoptosis inducer. To explore the preliminary SAR, analogs with substitution in the indole ring and phenyl ring have been prepared. We will report in detail the chemistry, SAR and biological characterization of indole-2-carboxylic acid benzylidene-hydrazides as inducers of apoptosis.

112.

DISCOVERY OF SUBSTITUTED 2-ARYL-4-ARYLAMINOPYRIMIDINES AND ANALOGS AS POTENT APOPTOSIS INDUCERS AND ACTIVATORS OF CASPASES. ***Azra Pervin****, Bao Nguyen, Nilantha Sirisoma, Sanjeeva Reddy, John Drewe, Ben Tseng, Shailaja Kasibhatla, and Sui Xiong Cai, Maxim Pharmaceuticals Inc, 6650 Nancy Ridge Drive, San Diego, CA 92121, Fax: 858-202-4000, apervin@maxim.com*

Apoptosis is a physiological cell suicide mechanism involved in developing embryo, immune system, and in adult animal during tissue turnover. Many anti-cancer drugs are known to kill cancer cells through the induction of apoptosis. As part of our ongoing effort to discover and develop novel inducers of apoptosis as potential anticancer agents, we have discovered a series of substituted 2-aryl-4-arylaminopyrimidines as a new class of potent inducers of apoptosis through our caspase and cell based HTS assay. These 2-aryl-4-arylaminopyrimidines have been found to induce apoptosis in cancer cells derived from a range of human solid tumors including breast, prostrate, and

colon. EC50 values as measured by caspase activation, range from 50 nM to 1500 nM for different cells. Several analogs showed sub-micromolar or better potency against most cell lines testes in the growth inhibition assay. We will report in detail the chemistry and SAR of substituted 2-aryl-4-arylaminopyrimidines as inducer of apoptosis.

113.

DESIGN, SYNTHESIS AND ANTITUMOR RESEARCH OF PEPTIDOMIMETIC MATRIX METALLOPROTEINASE INHIBITORS. ***Wenfang Xu**, and Zhen Zhang, College of Pharmacy, Shandong University, West Wenhua Road 44#, Jinan, Shandong Province 250012, China, xuwenf@sdu.edu.cn*

Matrix metalloproteinases (MMPs) plays a pivotal role in the invasion and metastasis process of malignant tumor. Inhibition and regulation of the activity of MMPs will probably control the progression of malignant tumor. Therefore, the inhibitors of MMPs as a class of new antitumor agent that are developed very rapidly. In our study, 3 series of peptidomimetic matrix metalloproteinase inhibitors (MMPIs) were designed and synthesized. The chemical structure of designed compounds was identified by IR, ESI-MS and 1H-NMR spectra. Antitumor activity screening was carried out by in vitro and in vivo experiments. MTT method was used in vitro to test the inhibition of target compounds on Hepatocarcinoma Bel-7402 cell. In vivo experiment was carried out on a H22 bearing mice anti-metastasis model to evaluate the inhibition of target compounds on H22 tumor cell metastasis through blood vessels. From the result of experiments we can see that some compounds could inhibit the growth and metastasis of the tumor cell with a high inhibit rate, among which compound ZX-18 and ZX-5 had a inhibit rate of 59.67% and 42.47%, respectively, in vivo. And there is a correlation between in vitro and in vivo experiments.

114.

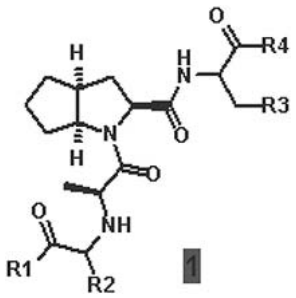
DESIGN, SYNTHESIS, AND EVALUATION OF SULTAM HYDROXAMATES AS NOVEL MMP INHIBITORS. ***Robert J. Cherney**, Dayton T. Meyer, Zelda R. Wasserman, Karl D. Hardman, Rui-Qin Liu, Maryanne B. Covington, Mingxin Qian, David D. Christ, James M. Trzaskos, Robert C. Newton, Ronald L. Magolda, and Carl P. Decicco, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000*

Matrix metalloproteinases (MMPs) are zinc dependent endopeptidases belonging to the metzincin superfamily. The MMPs are involved in the proteolysis of the extracellular matrix where they assist in the maintenance, development, and repair of tissues. Under normal conditions they are expressed in small amounts and are controlled by endogenous inhibitors. However, uncontrolled MMP expression leads to tissue damage which has been linked to arthritis, angiogenesis, periodontal disease, restenosis, and multiple sclerosis. This association has created an intense search for selective inhibitors of disease relevant MMPs. As a result, we initiated a search to find new templates that may aid in the development of selective MMP inhibitors. Toward this end, we describe sultam hydroxamates as novel MMP inhibitors.

115.

OCTAHYDROCYCLOPENTA[B]PYRROLE-2-CARBOXYLIC ACID CONTAINING TRIPEPTIDES AS INHIBITORS OF NEUROLYSIN. ***Stephen J. Shimshock**[1], Brian Whiteley[2], Gregory, H. Merriman[2], Jian Shen[3], Elaine Powers[4], Richard Knapp[5], Ann Marie Szczepanik[4], and Inder Patel[6]. (1) Department of Medicinal Chemistry, Aventis Pharmaceuticals, Rt 202/206N, P.O. Box 6800, Bridgewater, NJ 08807-0800, Fax: 908-231-3605, Stephen.Shimshock@aventis.com, (2) HTMC, Aventis Pharmaceuticals, (3) Aventis Pharmaceuticals Inc, (4) Department of Neurochemistry, Aventis Pharmaceuticals, (5) DMPK, Aventis, (6) Protein Production, Aventis Pharmaceuticals*

Neurolysin is a zinc-dependent member of the M3 metalloprotease family, widely distributed in mammalian tissues. In vitro, neurolysin has been shown to degrade biologically active peptides, such bradykinin and neurotensin. These data suggest that neurolysin plays a role in the physiological regulation of neuropeptide metabolism, and hence is involved in brain function. High throughput screening identified several tripeptide-like analogs as promising hits, which were amenable to further exploration by parallel synthesis. A series of novel, potent, and selective peptide analogs 1 were prepared by solution and solid phase parallel synthesis. The synthesis and in vitro SAR of the series will be described.



1

116.

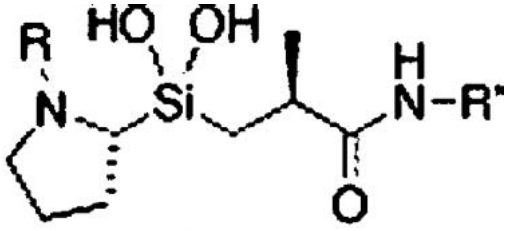
THIOMORPHOLINE SULFONAMIDE HYDROXAMIC ACID-BASED TACE INHIBITORS. ***Leif M. Laakso**[1], Jeremy I. Levin[1], Mila Du[1], Guixian Jin[1], Rebecca Cowling[1], Stacey Skala[1], Terri Cummons[1], Jun Xu[1], Dauphine Barone[2], and Jerauld S. Skotnicki[1]. (1) Chemical Sciences, Wyeth Research, 401 North Middletown Road, Pearl River, NY 10965, laaksol@wyeth.com, (2) Amgen Inc*

TNF-α is a pro-inflammatory cytokine implicated in rheumatoid arthritis and other disease conditions. To discover orally active compounds which arrest or retard connective tissue breakdown, efforts have concentrated on sulfonamide hydroxamic acids which act as inhibitors of TNF-α converting enzyme (TACE). Recent work has focused on the design and synthesis of a series of thiomorpholine sulfonamide hydroxamic acid TACE inhibitors. We found the thiomorpholine 6-position to be a preferred site for modification. A diastereoselective synthesis of 3, 6- disubstituted thiomorpholines was devised which offers convenient access to several classes of 6-substituted thiomorpholines. The thiomorpholine sulfonamide hydroxamic acids presented are potent inhibitors of cell free TACE enzyme and MMPs, potent inhibitors of induced TNF-α production in cells and efficacious in the mouse CIA model.

117.

SILANEDIOL-BASED INHIBITORS OF ANTHRAX LETHAL FACTOR. ***Madhusudhan Purushotham**, and Scott McN. Sieburth, Department of Chemistry, Temple University, 1901 N. 13th Street, Philadelphia, PA 19122, pmadhu@temple.edu*

The appropriately named metalloprotease, Anthrax Lethal Factor (LF), is the cause of mortality from infection by the anthrax bacterium, even after antibiotics have dispatched the microorganism. An inhibitor of LF could thereby save lives. Silanediol-based inhibitors have been shown to be effective against a number of metalloproteases. The current status of the design of LF inhibitors around silanediol (I) will be described.



I

118.

DESIGN AND SYNTHESIS OF NEW POTENT STATINE-LIKE INHIBITORS OF THE MALARIA ASPARTYL PROTEASES PLASMEPSIN I AND II USING SOLID PHASE LIBRARY SYNTHESIS. ***Per-Ola Johansson**[1], Yantao Chen[1], Anna Karin Belfrage[1], Ingemar Kvarnström[1], Lotta Vrang[2], Elizabeth Hamelink[2], Anders Hallberg[3], Åsa Rosenquist[2], and Bertil Samuelsson[2]. (1) Department of Chemistry, Linköping University, S-58183 Linköping, Sweden, Fax: +46-13-281399, perjo@ifm.liu.se, (2) Medivir AB, (3) Department of Organic Pharmaceutical Chemistry, BMC, Uppsala University*

Malaria is considered as one of the most serious infectious diseases in the world, affecting approximately 500 million people yearly and it is estimated that

the annual mortality from malaria is 2 million people. The malaria parasite degrades human hemoglobin as a source of nutrients for growth and development with the help of aspartic, cysteine and metallo proteases. We have identified new potent statine-like inhibitors of plasmepsin I and II, the aspartic proteases of the malaria parasite *Plasmodium falciparum*, by synthesis of libraries of compounds using solid phase chemistry. The reaction route starts by synthesis of a general scaffold which is attached to solid support and the diversifications are then made by the use of parallel chemistry. The best inhibitors identified exhibit K_i values between 0.5-74 nM for both Plm I and II and up to 1000-fold selectivity over human cathepsin D.

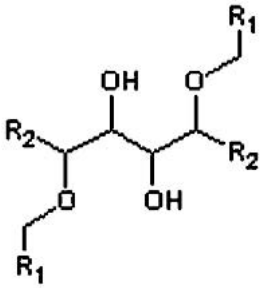
119.

POTENT INHIBITORS OF THE *P. FALCIPARUM* ENZYMES PLASMEPSIN I AND II. ***Karolina Ersmark***, *Isabella Feierberg, Sinisa Bjelic, Johan Åqvist, and Anders Hallberg, Department of Medicinal Chemisrty, Uppsala University, BMC, Box 574, Uppsala 751 23, Sweden, Fax: +46 18 471 44 74, karolina@orgfarm.uu.se*

Resistance to current antimalarial drugs is spreading rapidly resulting in an urgent need for new, effective drugs. The aspartic proteases plasmepsin I and II have been acknowledged as potential targets for development of new antimalarials.[1]

We have identified inhibitors of plasmepsin I and II based upon a C_2-symmetric mannitol-derived scaffold. These inhibitors were also found to be essentially devoid of inhibitory activity against the highly homologous human enzyme cathepsin D.

Predictions of binding affinity to plasmepsin II were carried out using the linear interaction energy (LIE) method. The results were compared to experimental measurements with plasmepsin II in a standardized assay.



120.

ANALOGUES OF CAFFEIC ACID PHENYLETHYL ESTER (CAPE) AS AFFINITY COVALENT MODIFIERS OF HIV-1 INTEGRASE. ***Sachindra S. Patil***[1], *Xuechun Zhang*[1], *Godwin C. G. Pais*[1], *Mamuka Kvaratskhelia*[2], *Evguenia S. Svarovskaia*[3], *Christophe Merchand*[4], *Vinay K. Pathak*[3], *Y. Pommier*[5], *Stuart Le Grice*[2], *and Terrence R Burke Jr.*[1]. *(1) Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, sachin@helix.nih.gov, (2) HIV Drug Resistant Program, NIH, (3) NCI- Frederick, NIH, (4) Laboratory of Molecular Pharmacology, National Cancer Institute, NIH, (5) Laboratory of Molecular Pharmacology, NCI, NIH*

Integrase is an enzyme found in human immunodeficiency virus that while being required for the viral life cycle has no human homologue. For this reason HIV integrase (IN) has become an important target for the development of new AIDS therapeutics. Although efforts toward this end have spanned more than ten years, only two viable clinical candidates have emerged and these are in phase II trials. One difficulty in developing IN inhibitors is the lack of X-ray crystal structures of enzyme/ligand complexes. Although substantial progress has been made in understanding the structure and function of HIV IN and in the design of HIV IN inhibitors, failure to clearly understand the locations and basis of enzyme-inhibitor interactions limits structure-based design. The caffeoyl moiety has figured prominently in a variety of catecol-containing HIV-1 IN inhibitors. Caffeic acid phenylethyl ester (CAPE) is a prototypical member of this family. In order to define sites of interaction of CAPE with HIV-1 integrase we designed a variety of CAPE analogues as affinity covalent modifiers. Presented here are aspects of this work, with emphasis on O-acetyl CAPE derivatives that function as site-specific acetylating agents.

121.

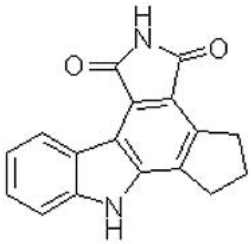
DESIGN, SYNTHESIS AND SAR EVALUATION OF NOVEL INHIBITORS OF POLY(ADP-RIBOSE)POLYMERASE (PARP). ***Kwon Yon Musick***[1], *Philip M. Weintraub*[1], *Paul Eastwood*[2], *Shujaath Mehdi*[3], *Jack Koehl*[3], *Dorothea Kominos*[4], *and Herman Schreuder*[5]. *(1) Medicinal Chemistry, Aventis, Inc, P.O. Box 6800, N-203-A, Route 202/206, Bridgewater, NJ 08807-0800, Fax: 908-231-3605, kwon.musick@aventis.com, (2) Argenta Discovery, (3) CNS Neurochemistry, Aventis, Inc, (4) Molecular Modeling, Aventis, Inc, (5) Aventis Pharma*

PARP-1 is a member of a family of ADP-ribosylating enzymes found in the nucleus of most eukaryotic cells. It is part of the cell's extensive DNA surveillance network involved in repairing DNA damage. Several studies have shown that in vivo administration of a PARP-1 inhibitor decreases infarct volume in rats after either transient or permanent focal cerebral ischemia. High-throughput screening identified a novel class of PARP-1 inhibitors. The synthesis, structure-activity relationship and biological activity of these compounds will be described. An X-ray co-crystal structure of one of the compounds soaked into the inhibitor is shown.

122.

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NOVEL POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS. ***Ming Tao***, *Chung Ho Park, Ron Bihovsky, Gregory Wells, Jean Husten, Mark A. Ator, and Robert L. Hudkins, Cephalon, Inc, 145 Brandywine Parkway, West Chester, PA 19380, mtao@cephalon.com*

Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme implicated in pathogenesis of stroke, myocardial ischemia, diabetes, shock and traumatic CNS injury. PARP inhibition in tumor cells may potentate radiotherapy and cancer chemotherapeutic agents targeting DNA due to the involvement in processes related to DNA damage. A screening of our internal database identified carbazole 1 (IC50=36 nM) as a potent PARP inhibitor. The synthesis and SAR optimization of this novel PARP template will be presented.



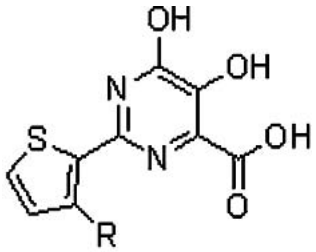
1

123.

SYNTHESIS AND SAR OF 2-(4,5-DIHYDROXY-6-CARBOXY-PYRIMIDINYL) THIOPHENES AS INHIBITORS OF THE HEPATITIS C VIRUS NS5B POLYMERASE. ***Savina Malancona***[1], *Barbara Attenni*[1], *Stefania Colarusso*[1], *Immacolata Conte*[1], *Steven Harper*[1], *Vincenzo Summa*[1], *Sergio Altamura*[2], *Uwe Koch*[1], *Victor G. Matassa*[1], *and Frank Narjes*[1]. *(1) Medicinal Chemistry, IRBM, via Pontina Km 30,600, 00040 Pomezia (Roma) NÅ, Italy, Savina_Malancona@Merck.com, (2) Biochemistry, IRBM*

The Hepatitis C virus (HCV), a (+)-strand RNA virus, infects nearly 3% of the world population. The RNA dependent RNA polymerase, essential for viral replication, is located in the non-structural 5B region of the viral polyprotein. Inhibition of the HCV NS5B polymerase represents an attractive target for the treatment of viral infection. From an initial lead, the 2-pyrimidinyl-thiophene scaffold (1) was developed. SAR in the 3-position of the thiophene led to potent inhibitors of the enzyme in vitro. Details of the discovery, a brief summary of

SAR studies and biological data on this compound and its analogues will be presented.



(1)

124.

STRUCTURE ACTIVITY RELATIONSHIP STUDIES AND PHARMACOLOGICAL EVALUATION OF 3,5-DISUBSTITUTED THIOPHENE-2-CARBOXYLIC ACID DERIVATIVES: POTENT INHIBITORS OF HCV NS5B POLYMERASE AND HCV SUBGENOMIC RNA REPLICATION. ***Carl Poisson***[1], *Laval Chan*[1], *Sanjoy Kumar Das*[1], *Thumkunta J. Reddy*[1], *Oswy Zeno Pereira*[1], *Mélanie Proulx*[1], *Liliane Halab*[1], *Marc Courchesne*[1], *Caroline Roy*[1], *Constantin Yannopoulos*[1], *Arshad Siddiqui*[1], *Wuyi Wang*[1], *Nghe P Nguyen-Ba*[1], *Ming-Qiang Zhang*[1], *Richard Bethell*[2], *Lucille L'Heureux*[2], *Maud David*[2], *Jean Bédard*[2], *Martine Hamel*[2], *Darius Bilimora*[2], *Olivier Nicolas*[2], *Nicolas Morin*[2], *Philippe Asselin*[2], *Bettina Hamelin*[3], *Kelly Dong*[3], *Nathalie Rioux*[3], *Annie Richard*[3], *Michael N. G. James*[4], *Meitian Wang*[4], *Kenneth K.-S. Ng*[4], *and Maia M. Cherney*[4]. *(1) Department of Medicinal Chemistry, Shire BioChem Inc, 275 Armand-Frappier Blvd., Laval, QC H7V 4A7, Canada, Fax: 450-978-7777, cpoisson@ca.shire.com, (2) Department of Virology, Shire BioChem Inc, (3) Department of Pharmacology, Shire BioChem Inc, (4) Department of BioChemistry, Canadian Institutes for Health Research Group in Protein Structure and Function / University of Alberta*

Hepatitis C Virus (HCV) is a blood–borne pathogen and has infected approximately 170 million people worldwide. Close to 60% of these infected people develop a chronic infection that leads to cirrhosis, fibrosis and in some cases, to hepatocellular carcinoma. It is estimated that by the year of 2010, the total deaths from HCV-related disease may overtake the current death toll due to AIDS. So far the only available therapy requires the use of interferon-α in conjunction with ribavirin. The utility of this therapy is limited by serious side effects and low response against HCV genotype 1. Therefore, there remains a significant unmet medical need for a safe and well-tolerated oral therapy for the treatment of HCV. Of several attractive viral enzyme targets, the RNA-dependent RNA polymerase has been shown to be critical for viral replication; thus this enzyme represents an important target for the discovery of novel antiviral agents. Recently, we have discovered a novel class of 3,5-disubstituted thiophene-2-carboxylic acid derivatives as HCV NS5B polymerase inhibitors. Structure activity relationship studies were then undertaken and have yielded several potent inhibitors. This poster will outline the detailed SAR studies, pharmacological and biological evaluation of these thiophene-2-carboxylic acid derivatives as potent inhibitors of HCV NS5B polymerase as well as of HCV subgenomic RNA replication.

125.

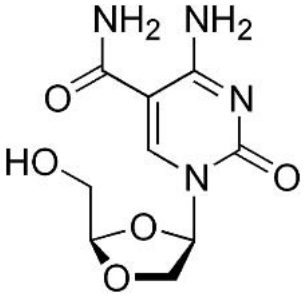
NOVEL GUANIDINE CONTAINING HETEROBICYCLIC [2.2.1] SCAFFOLD MOLECULES: APPLICATION TOWARDS HIV-1 TAR RNA. ***Ruben M. Savizky***[1], *Sergey N. Savinov*[2], *Dafna Nathan*[1], *Donald M. Crothers*[3], *and David J. Austin*[1]. *(1) Department of Chemistry, Yale University, 225 Prospect Street, New Haven, CT 06511, Fax: 203-432-6144, ruben.savizky@yale.edu, (2) Department of Chemistry, Pennsylvania State University, (3) Departments of Chemistry and Molecular Biophysics and Biochemistry, Yale University*

RNA-protein interactions constitute a rapidly growing area of research, especially because of their prevalent role in many cellular processes. A series of molecules have been designed to interact with the HIV-1 Tat/TAR system. The basic arrangement makes use of a hetero-bicyclic [2.2.1] scaffold to allow for diversity both in terms of the position and type of functionality incorporated. The proposed pharmacophore, a guanidinium group, has been systematically located at different positions throughout the molecule to better understand the structural and geometric requirements for in vitro biological activity. The objectives of this project include: combinatorial synthesis of these small molecules using solution phase organic synthesis and screening of this library based on the affinity of the inhibitor for the RNA or RNA/protein complex using various fluorescence based assays.

126.

SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-CARBOXAMIDO-2′,3′-DIDEOXY-3′-OXACYTIDINE. ***Xingang Fang***, *Department of Chemistry, Emory Univeristy, 1515 Pierce Drive, Atlanta, GA 30322, xfang2@emory.edu, Raymond F. Schinazi, Veterans Affairs Medical Center, Emory University, and Dennis C. Liotta, Department of Chemistry, Emory University*

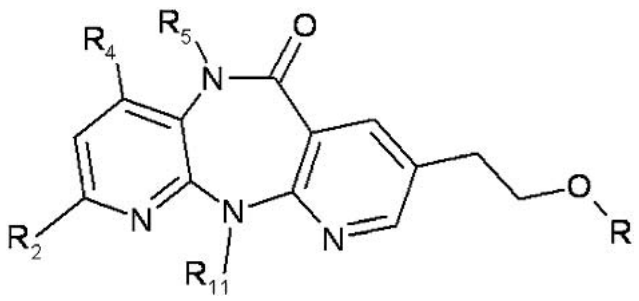
5-Carboxamido-2′,3′-dideoxy-3′-thiacytidine exhibits an interesting profile of modest anti-HIV activity, good anti-HBV activity and low toxicity. This suggests an alternative structure-activity mechanism that differs from the one observed for 3TC and FTC (i. e., only small 5-substituents (H or F) exhibit antiviral activity in oxathiolane nucleosides). One hypothesis for this comes from the novel intramolecular hydrogen bonding pattern associated with 5-carboxamidocytosines which creates a hybrid pyrimidine / purine motif. In this report, we synthesized 5-carboxamido-2′,3′-dideoxy-3′-oxacytidine as a potential representative of this type of the structure / function relationship. The synthesis of this novel agent and the results of our biological assessments of it will be discussed. These results are important to develop better understanding of the origin of the surprising activity and determine whether this interesting profile can be translated to other analogs.



127.

TOWARDS A SECOND GENERATION NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS) OF HIV-1 WITH BROAD SPECTRUM OF ACTIVITY. ***Bounkham Thavonekham***[1], *Pierre R Bonneau*[2], *Charles L. Cywin*[3], *Robert Deziel*[1], *Louise Doyon*[2], *Jianmin Duan*[2], *Ingrid Guse*[1], *Bruno Haché*[1], *Susan E. Hattox*[3], *Serge Landry*[1], *Eric Malenfant*[1], *Julie Naud*[1], *William W. Ogilvie*[1], *Jeff A. O'Meara*[1], *John R. Proudfoot*[3], *Raymond Plante*[1], *Bruno Simoneau*[1], *Mehran Yazdanian*[3], *Christiane Yoakim*[1], *Peter M. Grob*[3], *Michael Bös*[1], *and Michael G. Cordingley*[2]. *(1) Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, bthavonekham@lav.boehringer-ingelheim.com, (2) Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Research & Development, (3) Department of Chemistry, Boehringer Ingelheim Pharmaceuticals Inc. Research & Development Center*

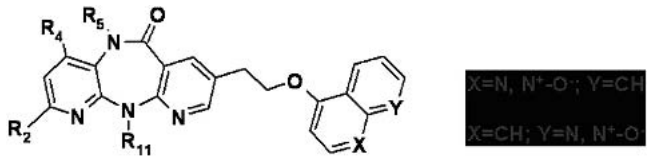
Treatment with nevirapine (like all NNRTIs) often results in the development of resistance due to mutation (s) in the RT enzyme. A pre-requisite for the next generation of NNRTI is potent antiviral activity against clinical prevalent NNRTI-resistant variants. Using C-8 substituted nevirapine analogues as a starting point, novel 8-heteroaryloxyethyl derivatives with broad antiviral activity have been identified. We will report herein the synthesis, the activity and the biopharmaceutical profile of these new derivatives.



128.

IDENTIFICATION OF A NOVEL SERIES OF NEVIRAPINE-LIKE NNRTIS WITH BROAD ANTIVIRAL POTENCY AGAINST MUTANT GENOTYPES ASSOCIATED WITH TREATMENT FAILURE. ***Serge Landry***[1], *Pierre R Bonneau*[2], *Robert Deziel*[1], *Louise Doyon*[2], *Jianmin Duan*[2], *Ingrid Guse*[1], *Bruno Haché*[1], *Eric Malenfant*[1], *Julie Naud*[1], *William W. Ogilvie*[1], *Jeff A. O'Meara*[1], *Raymond Plante*[1], *Bruno Simoneau*[1], *Bounkham Thavonekham*[1], *Christiane Yoakim*[1], *Michael Bös*[1], *and Michael G. Cordingley*[2]. *(1) Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, slandry@lav.boehringer-ingelheim.com, (2) Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Research & Development*

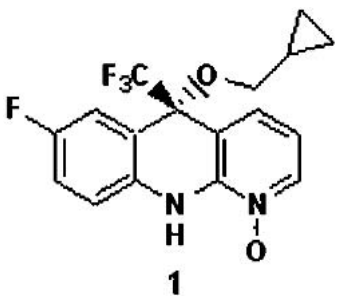
HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a potent component of highly active anti-retroviral therapies (HAART). With the currently approved NNTRIs, patients who fail treatment and develop resistance can not expect efficacy from any other NNRTIs, since all approved NNRTIs exhibit broad cross-resistance. There is therefore a therapeutic need for a second generation NNRTI having potent antiviral activity against HIV-1 wild-type and the most prevalent mutant genotypes associated with treatment failure. Using C-8 substituted analogs of Nevirapine as starting point, a series of potent inhibitors possessing a quinoline moiety were found to be highly potent against wild-type virus, as well as prevalent single and double mutants. The biological activities, biopharmaceutical profile and the syntheses of these inhibitors will be discussed.



129.

NOVEL 5,10-DIHYDROBENZO[B][1,8]NAPTHYRIDINE N-OXIDES AS NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS OF HIV-1 WITH HIGH POTENCY AGAINST CLINICALLY RELEVANT MUTANTS VARIANTS. ***Barry L. Johnson***[1], *Christine M. Tarby*[1], *Anurag Srivastava*[1], *Rajagopal Bakthavatchalam*[2], *Qiyan Lin*[2], *Anthony J. Cocuzza*[1], *Donna M. Bilder*[1], *Lee T. Bacheler*[2], *Sharon Diamond*[1], *Susan Jeffrey*[2], *Ronald M. Klabe*[2], *Beverly C. Cordova*[2], *Sena Garber*[2], *Kelly Logue*[2], *Susan K. Erickson-Viitanen*[2], *George L. Trainor*[1], *Paul S. Anderson*[2], *and James D. Rodgers*[2]. *(1) Department of Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702, barry.johnson@bms.com, (2) N/A*

The design, synthesis and SAR of 5,10-dihydrobenzo[*b*][1,8]-naphthyridine N-oxides as potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) of human immunodeficiency virus type one (HIV-1) are described. The compounds were optimized to exhibit improved activities against a panel of clinically relevant single and double-mutant isolates of HIV-1 as demonstrated by **1** (IC_{90}s: WT 4.2 nM, K103N 1.6 nM, Y188L 23 nM, K103N/L100I 42 nM). The potencies, protein binding free fractions and pharmacokinetic properties were considered simultaneously in selecting compounds for further development. These agents have superior resistance profiles over efavirenz and other currently marketed NNRTIs. The new compounds were designed for use as durable components of HIV combination therapies and may function as constituents of salvage therapy for antiretroviral-experienced patients failing their current regimens.



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130.

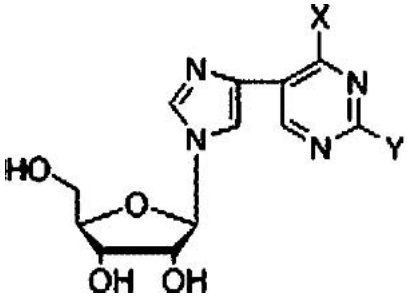
NOVEL NEVIRAPINE-LIKE INHIBITORS WITH IMPROVED ACTIVITY AGAINST NNRTI-RESISTANT HIV: 8-HETEROARYLTHIOMETHYLDIPYRIDODIAZEPINONES DERIVATIVES. ***Jeff A. O'Meara***[1], *Pierre R Bonneau*[2], *Robert Deziel*[1], *Louise Doyon*[2], *Jianmin Duan*[2], *Ingrid Guse*[1], *Bruno Haché*[1], *Serge Landry*[1], *Eric Malenfant*[1], *Julie Naud*[1], *William W. Ogilvie*[1], *Raymond Plante*[1], *Bruno Simoneau*[1], *Bounkham Thavonekham*[1], *Christiane Yoakim*[1], *Michael Bös*[1], *and Michael G. Cordingley*[2]. *(1) Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, 2100 Cunard Street, Laval, QC H7S 2G5, Canada, jomeara@lav.boehringer-ingelheim.com, (2) Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Research & Development*

Reverse transcriptase of HIV-1 is a key target for the inhibition of viral replication. However, upon treatment with a regiment containing non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistance often occurs due to drug-specific mutations. Advanced derivatives of the NNRTI nevirapine were used as a starting point for the identification of new inhibitors with broader antiviral profile. Synthesis, activity and biopharmaceutical profile of these 8-heteroarylthiomethyl analogues will be described.

131.

"FLEXIMERS". COMPUTATIONAL MODELING, DESIGN AND SYNTHESIS OF NOVEL SHAPE-MODIFIED NUCLEOSIDES. ***Samer Salim***, *Liang Zhang, Peter I. O'Daniel, and Katherine L. Seley, School of Chemistry and Biochemistry, Georgia Institute of Technology, 770 State St, Atlanta, GA 30332, Fax: 404-894-2295, gte438k@prism.gatech.edu*

"Fleximers" mimic purine bases by separation of the imidazole and pyrimidine moieties with a C-C single bond. This structural modification serves to introduce flexibility into the nucleoside while maintaining the necessary elements for molecular recognition. As a result these fleximers could be used as dimensional probes for investigation of enzyme-coenzyme binding sites specifically S-Adenosylhomocysteine hydrolase. The design, synthesis and molecular modeling of the proximal fleximers are reported herein.



132.

TETRAPEPTIDES THAT SPECIFICALLY INHIBIT THE DIMER FORM OF MOUSE RIBONUCLEOTIDE REDUCTASE. ***Ying Gao***, *Chiheng Tan, and Barry S. Cooperman, Chemistry Department, University of Pennsylvania, Philadelphia, PA 19104, gaoying@sas.upenn.edu*

Mouse ribonucleotide reductase (mRR), which is composed of two subunits mR1 and mR2, has two major active forms in vivo, R12R22 and R16(R22)j (j=1 – 3). R12 formation is induced by dATP, dTTP, dGTP or ATP binding to the specificity site (s-site), whereas R16 formation requires ATP binding to the hexamerization site (h-site). AcFTLDDADF (P7), the heptapeptide corresponding to the C-terminus of R2, inhibits both R12R22 and R16(R22)3 with close to equivalent Ki values. In contrast, FmocWVFF and FmocWFDF, selected from FmocWX1X2F libraries, were found to show specific, high inhibitory activity toward R12R22, with much lower activity against R16R26. This specificity results from preferential binding to R1 monomer, which does not form an enzymatic active complex with R22.The possible utility of selective R12R22 inhibitors for chemotherapeutic applications will be discussed.

133.

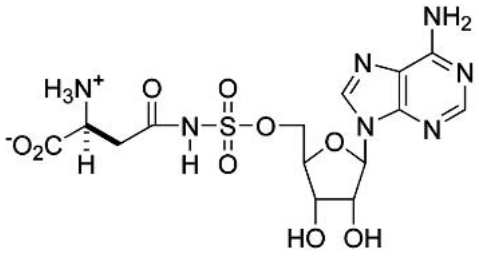
SYNTHESIS OF 8-[^{11}C]METHOXYGANCICLOVIR AND 8-[^{11}C]METHOXYPENCICLOVIR AS NOVEL POTENTIAL PET HSV-TK GENE REPORTER PROBES. ***Ji-Quan Wang***, *Qi-Huang Zheng, Xiangshu Fei, and Gary D. Hutchins, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L-3, Rm. 202, Indianapolis, IN 46202-2111, Fax: 317-278-9711, jiqwang@iupui.edu*

Gene transfer technology has shown significant potential in treating several common cancers. Among several gene therapy clinical trails using a variety of viral and non-viral vectors, the use of virally delivered herpes simplex virus thymidine kinase (HSV-tk) has attracted much attention. HSV-tk provides a potential target for the development of positron emission tomography (PET) gene reporter probes. Radiolabeled ganciclovir (GCV, 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine) and penciclovir (PCV, 9-[4-hydroxy-3(hydroxymethyl-)butyl]guanine) analogs such as 8-[^{18}F]fluoroganciclovir ([^{18}F]FGCV), 9-[(3-[^{18}F]fluoro-1-hydroxy-2-propoxy)methyl]guanine ([^{18}F]FHPG); and 8-[^{18}F]fluoropenciclovir ([^{18}F]FPCV), 9-(4-[^{18}F]fluoro-3-hydroxymethylbutyl)guanine ([^{18}F]FHBG) have shown great potential as PET imaging agents to detect HSV-tk gene expression. In our previous work, we have synthesized [^{18}F]FHPG and [^{18}F]FHBG. In this ongoing study, we report the synthesis of 8-[^{11}C]methoxyganciclovir and 8-[^{11}C]methoxypenciclovir starting from GCV and PCV.

134.

SYNTHESIS AND BIOLOGICAL EVALUATION OF AN *N*-ACYLSULFONAMIDE INHIBITOR OF HUMAN ASPARAGINE SYNTHETASE. ***Lukasz Koroniak***, *Jemy A. Gutierrez, Mihai Ciustea, and Nigel G. J. Richards, Department of Chemistry, University of Florida, Box 117200, Gainesville, FL 32611-7200, Fax: 352-392-7918, lkoron@chem.ufl.edu*

In humans, asparagine is biosynthesized from aspartic acid by asparagine synthetase (AS). Several lines of evidence suggest that over-expression of asparagine synthetase in human T-cells results in metabolic changes that underpin the appearance of drug resistant forms of acute lymphoblastic leukemia (ALL). Hence it is widely believed that, in combination with other drugs, potent AS inhibitors will provide new clinical approaches for the treatment of ALL and other solid tumors. The synthesis of *N*-acylsulphonamide **1**, which is an analog of β-aspartyl-AMP, is described. This compound appears to be the first potent inhibitor of human asparagine synthetase, exhibiting time-dependent inhibition kinetics. Preparation and characterization of two additional *N*-acylsulphonamide analogs has demonstrated the importance of hydrogen bonding interactions in the recognition of the AS inhibitor with the enzyme. These observations provide the basis for the discovery of new compounds with application in the treatment of drug resistant leukemia.



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135.

NANOMOLAR INHIBITORS OF CNS PHENYLETHANOLAMINE N-METHYL TRANSFERASE (PNMT). ***F. Anthony Romero***, *and Gary L. Grunewald, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, fromero@ku.edu*

To aid in defining the role of epinephrine within the CNS, an inhibitor of PNMT would be a useful pharmacological tool. We have previously prepared a small library of racemic 3-fluoromethyl-7-N-(aryl- or alkyl-aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines (1), of which several are predicted to cross the blood-brain barrier, show very little affinity for other binding sites (e.g., the a2-adrenoceptor), and some are highly potent and selective inhibitors of PNMT. Examination of the crystal structure revealed that the (R)-1 should be more potent than the (S)-1. Therefore, a small series of (R)-1 was synthesized and evaluated. Several of these compounds are the most potent and selective PNMT inhibitors yet reported. An interpretation of SAR results using the crystal structure of hPNMT co-crystallized with SK&F 29661 and S-adenosyl-L-homocysteine will also be described.

136.

STRUCTURE-BASED DESIGN, SYNTHESIS, AND EVALUATION OF MULTISUBSTRATE INHIBITORS OF PHENYLETHANOLAMINE N-METHYLTRANSFERASE. ***Jian Lu***, *Kevin R. Criscione, and Gary L. Grunewald, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, lujian@ku.edu*

Phenylethanolamine N-Methyltransferase (PNMT) catalyzes the final step in epinephrine (Epi) biosynthesis by the transfer of a methyl group from the cofactor S-adenosyl-L-methionine to the amino group of norepinephrine. A selective inhibitor of PNMT could be used to regulate Epi levels without significant effect on the biosynthesis of other catecholamines. Although PNMT has been studied as a potential target for multisubstrate inhibitors, no lead structure has been reported. The recent determination of the crystal structure of PNMT as a complex with S-adenosyl-L-homocysteine and inhibitor SK&F 29661 has provided an opportunity for the rational design of multisubstrate inhibitors. Based on the crystal structure and previous QSAR studies from our laboratory, a series of multisubstrate inhibitors were designed, synthesized and evaluated for their PNMT inhibitory activity. Some of these new compounds are potent inhibitors of PNMT.

137.

SYMMETRY RELATED ELEMENTS OF NEUROTRANSMITTER RECEPTOR AGONISTS AND INHIBITORS. ***Nikolay Azar***, *and Alexander Greer, Department of Chemistry and The Graduate Center, The City University of New York (CUNY), Brooklyn College, Brooklyn, NY 11210, agreer@brooklyn.cuny.edu*

We have developed a theoretical approach for studying relationships that exist between ligands and neurotransmitter receptors found in parts of the brain. We provide a guiding principle using B3LYP/D95** calculations to elucidate a preferred binding action for bisamine molecules possessing bilateral symmetry. The term bilateral symmetry is used here to correlate C2 (plane or axis), Cs, and C2v symmetry elements in molecules. Bilateral symmetry elements are found in many natural products and drug molecules, e.g., barbituates (5,5-diethyl barbituric acid, 5-ethyl-5-isopentylbarbituric acid, brevital, pentothal, phenobarbital), anesthetics (ether, sevoflurane, propofol, 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane), and narcotics (pethidine, meprobamate, ethinamate, fentanil), which also tend to occupy sites on protein targets. It is evident that some neurotransmitter active sites bind bilaterally symmetrical molecules, but do not possess an apparent "bivalent" complementary cavity. Molecules possessing bilateral symmetry are composed of two like parts with a proposed entropic advantage (twofold in form) to interact the molecule's appendage with the receptor site. Ligand-neurotransmitter receptor interactions were modeled with density functional theory by positioning the molecule juxtaposed to the active site to predict the protein's potential to carry out a recognition task.

138.

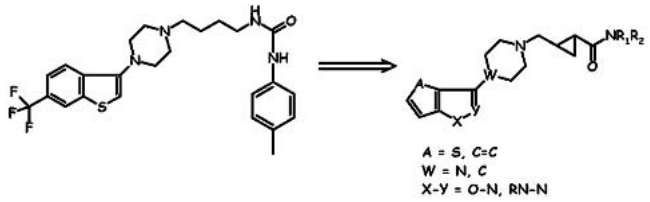
DESIGN AND SYNTHESIS OF AGENTS THAT MIMIC CLOZAPINE'S BINDING AT DOPAMINE RECEPTORS. ***Donald Sikazwe***[1], *Anne Schmidt*[2], *A. Vanase-Frawley*[2], *A. Shrihkande*[2], *A. Villalobos*[2], *and Seth Y. Ablordeppey*[1]. *(1) College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, Fax: 850-599-3934, seth.ablordeppey@famu.edu, (2) Central Research Division, Pfizer Inc*

Typical antipsychotics are limited by their debilitating side effects in the form of extra pyramidal symptoms or EPS. Haloperidol, the most widely used typical antipsychotic, non-selectively binds to both D2 and D4 receptors with high affinities and induces disabling EPS. On the other hand, clozapine, an effective atypical antipsychotic binds to D2 receptors with low affinity and with high affinity to D4 receptors, and is without EPS. Our working hypothesis is that clozapine's therapeutic efficacy is related to its D2/D4 affinity ratio. To this end, agents incorporating 8-azabicyclo[3.2.1]octane and pyrrolidine moeities have been designed, synthesized and evaluated for D2 and D4 binding. Because these analogs cannot be biotransformed to the quaternary pyridinium species (BCPP+) suggested to be involved in haloperidol's long term side effects, we anticipate that they should have improved pharmacological profiles (i.e., lack EPS symptoms).

139.

(HETEROARYL-PIPERAZIN-1-YLMETHYL)-CYCLOPROPANECARBOXAMIDES: SYNTHESIS AND SAR OF POTENT AND SELECTIVE HUMAN DOPAMINE D3 RECEPTOR ANTAGONISTS/PARTIAL AGONISTS. ***John G. Jurcak***[1], *David M. Fink*[1], *James A. Hendrix*[1], *Horst Hemmerle*[1], *Matthias Urmann*[1], *Felicia Messing*[2], *Thomas J. Corbett*[2], *Sharon Kafka*[2], *David Rampe*[3], *Norman Huebert*[4], *Richard Knapp*[4], *Yulin Chiang*[1], *Nicola Collar*[1], *John Z. Jiang*[1], *Michael R. Becker*[1], *Eric MacMillan*[1], *Jean-François Sabuco*[1], *and Sathapana Kongsamut*[2]. *(1) Medicinal Chemistry, Aventis, Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800, john.jurcak@aventis.com, (2) CNS Disease Group, Aventis, (3) Drug Safety, Aventis, (4) DMPK, Aventis*

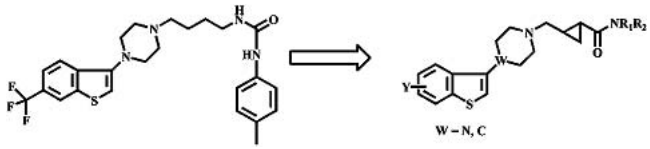
Schizophrenia is a debilitating neuropsychiatric illness. The treatment of schizophrenia with dopamine D2 antagonists is well documented. Unfortunately, the use of traditional D2 antagonists is linked with extrapyramidal side effects (EPS), which in turn are associated with D2 antagonism in the striatum. Dopamine D3 receptors are preferentially located in limbic brain regions where dopamine receptor antagonism is associated with antipsychotic activity. AVE5997 represents a new class of potent dopamine D3 antagonist and was advanced to human clinical trials. Modification of AVE5997 lead to a series of cyclopropyl amides. The synthesis of these analogs will be discussed, along with SAR studies exploring the effect of modifying the heterocyclic portion of the molecules.



140.

2-(4-BENZO[B]THIOPHEN-3-YL-PIPERAZIN-1-YLMETHYL)-CYCLOPROPANECARBOXAMIDES: SYNTHESIS AND SAR OF POTENT AND SELECTIVE DOPAMINE D3 RECEPTOR ANTAGONISTS. ***David M. Fink***[1], *James A. Hendrix*[1], *Horst Hemmerle*[1], *Matthias Urmann*[1], *John G. Jurcak*[1], *Felicia Messing*[2], *Nicola Collar*[1], *Rowena Naeseth*[2], *Deirdre DeSteno*[2], *Thomas J. Corbett*[2], *Sharon Kafka*[2], *David Rampe*[3], *Norman Huebert*[4], *Richard Knapp*[4], *Yulin Chiang*[1], *John Z. Jiang*[1], *Michael R. Becker*[1], *Eric MacMillan*[1], *Jean-François Sabuco*[1], *and Sathapana Kongsamut*[2]. *(1) Medicinal Chemistry, Aventis, Bridgewater, NJ 08833, david.fink@aventis.com, (2) CNS Disease Group, Aventis, (3) Drug Safety, Aventis, (4) DMPK, Aventis*

Schizophrenia is a debilitating neuropsychiatric illness. The treatment of schizophrenia with dopamine D2 antagonists is well documented. Unfortunately, the use of traditional D2 antagonists is linked with extrapyramidal side effects (EPS), which in turn are associated with D2 antagonism in the striatum. Dopamine D3 receptors are preferentially located in limbic brain regions where dopamine receptor antagonism is associated with antipsychotic activity. AVE5997 represents a new class of potent dopamine D3 antagonist and was advanced to human clinical trials. Modification of AVE5997 lead to a series of cyclopropyl amides. The synthesis of these analogs will be discussed, along with SAR studies exploring the effect of modifying the amide portion of the molecules.



141.

DOPAMINE RECEPTOR ANTAGONIST. ***Joyce Smith***, *Department of Computer Science, New York Institute of technology, Old westbury, NY 11563, and Ann Holder, Department of Computer Science, California Institute of Technology*

Historic, old-world style buildings surrounded by acres of majestic trees and bushes that bloom with bright pinks and reds in the spring and summer, flame with autumn's oranges and golds, and glisten with the gentle white of a winter snowfall. The Dorothy and Alexander Schure Old Westbury Campus will excite and inspire you with its beauty. And you'll be equally impressed with all there is to do and see. Take a look??EYour college experience will be more rewarding if you spend your free time making friends, developing new interests and experiencing local culture. NYIT has more than 100 clubs, activities and organizations, and you can participate on any campus!

142.

SYNTHESIS AND SAR OF A POTENT, SELECTIVE AND ORALLY ACTIVE HUMAN DOPAMINE D3 RECEPTOR ANTAGONIST: AVE5997. ***James A. Hendrix***, *Sathapana Kongsamut, Kenneth J. Bordeau, Joseph T. Strupczewski, Horst Hemmerle, Matthias Urmann, Felicia Messing, Thomas J. Corbett, Sharon Kafka, David Rampe, and Norman Huebert, Medicinal Chemistry, Aventis Pharmaceuticals, Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800, Fax: 908-231-3577, james.hendrix@aventis.com*

The effective treatment of schizophrenia with dopamine D2 antagonists is well documented. Unfortunately, treatment with traditional D2 antagonists is associated with debilitating side effects such as extrapyramidal syndrome (EPS) and tardive dyskinesia. A new class of potent dopamine D3 antagonists was discovered with selectivity over dopamine D2 and alpha-1 adrenoceptor. Screening our compound collection provided a lead compound. The structure-activity relationships in four regions of the lead molecule were explored. The synthesis of these analogs will be discussed. The SAR studies showed that increased steric bulk at the 6-position of the benzo[b]thiophene gave improved selectivity over alpha-1 while maintaining D3 potency. Multiple analogs with greater than 100-fold selectivity for D3 over D2 and alpha-1 were discovered. Data characterizing the lead such as solubility, ADME, HERG binding and in vivo activity will be presented. These efforts lead to the discovery of AVE5997, a selective, orally active dopamine D3 antagonist that advanced to human clinical trials.

143.

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF A SERIES OF 4-(2-QUINOLYL)-2-METHYLPIPERIDINES AND 4-(2-BENZOTHIAZOLYL)-2-METHYLPIPERIDINES AS DUAL 5HT 1A ANTAGONISTS/5HT UPTAKE INHIBITORS. ***John X. He***, *Vincent P. Rocco, Daniel J. Koch, Patrick G. Spinazze, Kumiko Takeuchi, David L.G. Nelson, David B. Wainscott, Janice L. Shaw, Penny G. Threlkeld, Laura Dreshfield, and David T. Wong, Eli Lilly and Company, Indianapolis, IN 46285*

A series of 4-(2-quinolyl)piperidines and 4-(2-benzothiazolyl) piperidines was prepared as part of a search for dual 5HT 1A antagonist and serotonin uptake inhibitors. The synthesis and biological activity of these compounds will be presented.

144.

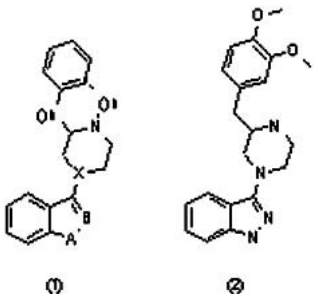
NOVEL, POTENT 5HT2A ANTAGONISTS. ***Keith J. Harris***, *Mark Palermo, Julie Knight, Steven Shimshock, Kenneth J. Bordeau, David M. Fink, Raymond Kosley, Veronica Wolf, Yulin Chiang, George Lee, Barbara S. Rauckman, Ronald Bernotas, Lily Sing, Janice Hitchcock, Stephen Sorensen, Sam Kongsamut, Joachim E. Roehr, Yaw Senyah, and Dorothea Kominos, Chemistry, Aventis, N2314, Route 202/206, PO Box 6800, Bridgewater, NJ 07039, Fax: 973-231-3577, Keith.Harris@Aventis.com*

The synthesis and biological evaluation of novel, potent 5HT2A antagonists will be described. These 1-heterocyclic-3-substituted piperazine compounds (1) exhibit potent 5HT2A binding *in vitro*. Several compounds were tested for *in vivo* 5HT2A antagonism (DMT mouse head twitch). Compound (2) below possessed oral activity in the DMT head twitch model.

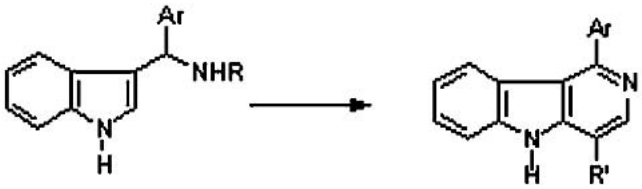
145.

DESIGN, PREPARATION AND COMPARISON OF POTENTIAL CARDIOVASCULAR AGENTS AND 5-HT$_3$ ANTAGONISTS. ***Samuel D. Jensen***[1], *Christopher T. Lloyd*[2], *Wayne M. Stalick*[1], *and James H. Wynne*[2]. *(1) Department of Chemistry, George Mason University, Fairfax, VA 22030, Fax: 202-767-0594, sjensen2@gmu.edu, (2) Chemistry Division, Naval Research Laboratory*

In recent years, much attention has been devoted to the preparation of novel effective cardiovascular agents. Despite the many diverse approaches reported,



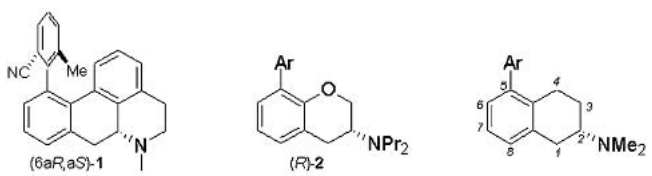
the utility of alkaloid systems have proven quite effective. Our efforts have lead to the preparation of a variety of indole alkaloid systems, which are analogues to those previously reported. It is anticipated that our ability to adjust both polarity and binding ability by simple manipulation of substituted groups will allow a more targeted approach. Likewise it is believed that this library of compounds will also function as 5-HT3 antagonists. We have design a convenient multiple approach to the target molecules. The design and preparation of these novel compounds will be presented along with a comparison to existing compounds of this class.



146.

5-ARYL SUBSTITUTED (S)-2-(DIMETHYLAMINO)-TETRALINS: NOVEL SEROTONIN 5-HT7 RECEPTOR LIGANDS. ***Anette M. Johansson***[1]*, Magnus Brisander*[2]*, Andrei Sanin*[3]*, Susanne Rosqvist*[4]*, Nina Mohell*[5]*, and Åsa Malmberg*[4]*. (1) Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, JOHANSSON_ANETTE@Lilly.com, (2) BioVitrum AB, (3) Biolipox, (4) Dept of Lead Generation, AstraZeneca R&D, (5) ACADIA Pharmaceuticals Inc*

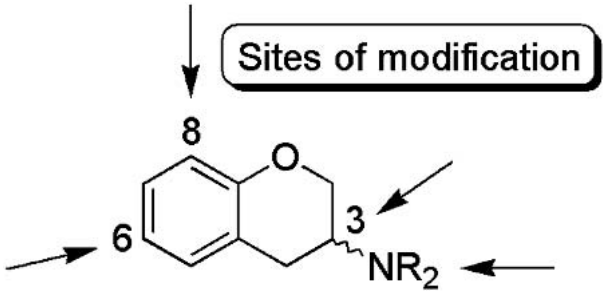
The family of serotonin receptors consists of 14 subtypes, 13 G-protein coupled receptors and one ion channel. The least studied receptor of the 5-HT-receptor family is the most recently discovered 5-HT_7 receptor. This is most probably caused by the absence of selective ligands. We have recently described some 11-aryl (R)-aporphines as selective 5-HT_7 antagonists as well as some non-selective 3-aminochromans with agonistic activity at 5-HT_7 receptors. We have extended our search for ligands for the 5-HT_7 receptors to also include derivatives of 2-aminotetralin and we here present the synthesis of 5-aryl substituted derivatives of (*S*)-2-(dimethylamino)tetralin. The in vitro binding of the novel derivatives to 5-HT_7 and 5-HT_{1A}receptors as well as the efficacy of selected compounds at the 5-HT_7 receptors will be presented.



147.

TOWARDS SELECTIVE SEROTONIN 5-HT_7 LIGANDS: ENANTIOMERICALLY PURE 3-AMINOCHROMANS. ***Pär Holmberg***[1]*, Patrizia Caldirola*[2]*, Pavel Zlatoidsky Zlatoidsky*[3]*, Adolf Gogoll Gogoll*[4]*, Nina Mohell*[2]*, Susanne Rosqvist*[5]*, Lena Unelius*[5]*, and Anette M. Johansson*[6]*. (1) Organic Pharmaceutical Chemistry, Uppsala University, BMC, Box 574, SE-751 23 Uppsala, Sweden, holmberg@orgfarm.uu.se, (2) BioVitrum AB, (3) AstraZeneca R&D, (4) Dept of Organic Chemistry, Uppsala University, (5) Dept of Lead Generation, AstraZeneca R&D, (6) Lilly Research Laboratories, Eli Lilly and Company*

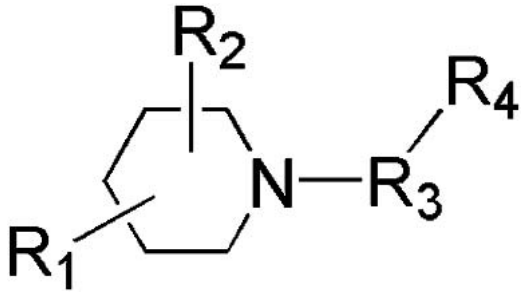
The serotonin 5-HT_7receptor is the most recent addition to the family of G-protein coupled 5-HT receptors. A few selective antagonists are available, but no selective agonists have so far been reported. A series of enantiomerically pure 3-aminochromans have been synthesized2 and evaluated for their interaction with 5-HT_{1A}, 5-HT_7 and D_{2A} receptors. The effects of substitution in the 6- and 8-position with different aryl substituents as well as the stereochemistry and different N-alkyl substituents were investigated. The aryl substituents were introduced by various Pd catalyzed cross-coupling reactions. Trends in the structure-activity relationships (SARs) will be presented.



148.

RAPID DISCOVERY OF POTENT G-PROTEIN COUPLED RECEPTOR LIGANDS USING A RATIONALLY DESIGNED DRUG-LIKE COMBINATORIAL LIBRARY. ***Yuefei Shao***, *Gang Qian, Tao Guo, and Doug W. Hobbs, Pharmacopeia, Inc, CN 5350, Princeton, NJ 08543-5350, yshao@pharmacop.com*

The majority of marketed drugs are administered via the oral route and therefore the goal of many drug discovery programs is to identify a candidate compound with good oral bioavailability. More than ten years old, combinatorial chemistry is now an integral part of the drug discovery process. One challenging task facing medicinal/combinatorial chemists today is to build drug-likeness into combinatorial libraries. A number of empirical rules and computational methods have been developed for this purpose. In this presentation, the rational design and chemical synthesis of a drug-like 19,470-member combinatorial library targeting G-protein coupled receptors (GPCRs) will be described. Screening of this library resulted in the rapid discovery of potent and selective GPCR ligands.



149.

HOMOLOGY MODELING OF THE MU-OPIOID RECEPTOR BUILT IN A COMPLETE MEMBRANE SYSTEM. ***Yan Zhang***[1]*, Yuk Y. Sham*[2]*, Ramkumar Rajamani*[3]*, Jiali Gao*[3]*, and Philip S. Portoghese*[1]*. (1) Department of Medicinal Chemistry, University of Minnesota, 308 Harvard St SE, 8-115 WDH, Minneapolis, MN 55455, Fax: 612-626-6891, zhang192@umn.edu, (2) Minnesota Supercomputing Institute, University of Minnesota, (3) Department of Chemistry, University of Minnesota*

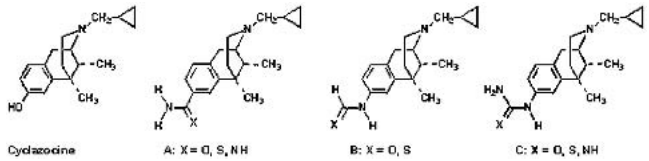
Three types of opioid receptors, mu, delta and kappa, belong to the rhodopsin subfamily in the G-protein-coupled receptor superfamily. With the recently

solved x-ray crystal structure of rhodopsin, considerable attention has been focused on molecular modeling of these transmembrane proteins. In the present study, a homology model of the mu-opioid receptor was constructed based on the X-ray crystal structure of bovine rhodopsin. A Phospholipid bilayer was built around the receptor and two water layers were placed on both surfaces of the lipid bilayer. Molecular dynamic simulations were carried out using CHARMM for the entire system consisting of 316 amino acid residues, 92 phospholipid molecules, 8327 water molecules and 11 chloride counter-ions (altogether 40,931 atoms). The whole system was equilibrated for 2 ns followed by another 2 ns dynamic simulation. Opioid ligands were docked into the model and the critical amino acid residues for binding were identified.

150.

THIOFORMAMIDO AND THIOCARBOXAMIDO DERIVATIVES OF CYCLAZOCINE: SYNTHESES AND OPIOID RECEPTOR BINDING PROPERTIES. *Mark P. Wentland[1], **Xufeng Sun**[1], Rongliang Lou[1], and Jean M. Bidlack[2]. (1) Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, (2) Department of Pharmacology and Physiology, University of Rochester*

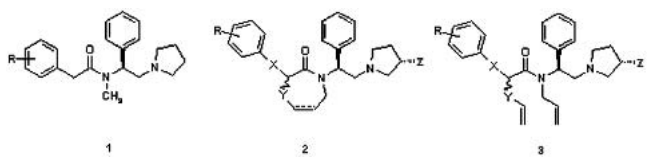
We recently reported that replacement of the phenolic-OH group of cyclazocine with carboxamido (8-CAC; A: X=O) and formamido (B: X=O) groups gave derivatives having similar opioid receptor binding affinities as cyclazocine. In in vivo studies, 8-CAC showed high antinociception activity and a much longer duration of action than cyclazocine (15 h vs 2 h) when both were dosed at 1 mg/kg ip in mice. Within this small series of carboxamide and formamide derivatives, preliminary SAR studies revealed that both H-bond donor (NH) and acceptor (C=O) groups are required for binding to opioid receptors. To further explore this SAR, we have made and evaluated the corresponding thioamides (A: X=S and B: X=S) which we found to have comparable binding affinities to their amide counterparts. The syntheses and SAR of these and related derivatives (A: X=NH; C: X=O, S, NH) will be presented. (Supported by NIDA DA12180, DA03742, and KO5-DA00360).



151.

NOVEL 3–ARYL–1–(1–PHENYL–2–PYROLIDIN–1–YL–ETHYL)AZEPIN–2–ONES AS CONSTRAINED KAPPA OPIOID RECEPTOR AGONISTS. ***Paul A. Tuthill Sr.***[1], *Pamela Seida[1], Roland E. Dolle[1], Joel A. Cassel[2], and Robert N. DeHaven[2]. (1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, Fax: 484-595-1551, pat@adolor.com, (2) Department of Pharmacology, Adolor Corporation*

Kappa opioid receptor agonists display potent antinociceptive activity in vivo. A novel series of constrained kappa opioid agonists 2 based on archetypal arylacetamides 1 was synthesized to enhance activity and to target peripheral receptors. The key step in their construction was a ring closing metathesis (RCM) reaction via diene intermediates 3. Details for the synthesis and biological activity of these novel constrained kappa opioid agonists will be presented.



152.

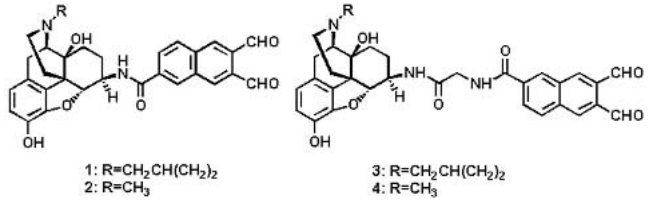
PHENYLALKYL DIAMINE AS SIGMA RECEPTOR LIGANDS : STRUCTURE-ACTIVITY RELATIONSHIP AND POTENTIAL ANTI-DEPRESSANT ACTIVITY. *Yong-Kil Kim, **Sung-Yong Seo**, Joon Heo, and Yong-Moon Choi, Bio-Pharm Research Lab, SK Corporation, 140-1, Wonchon-Dong, Yusung-gu, Taejon, South Korea, Fax: 82-42-866-7702, seosy@skcorp.com*

The physical and pharmaceutical nature of the sigma receptor has not been fully defined. However, various evidence indicate that sigma receptors have a number of biological functions. Potential applications of sigma ligands are the treatment of depression, psychosis, etc. Phenylalkylamine derivatives, such as diamine or amide compounds, are one important class of therapeutic medicines that is useful in managing central nervous system (CNS) disease. Accordingly, agents potently acting on the sigma receptors may be useful in the therapy of these conditions. Also, creating the specific drug for sigma receptor interaction and finding the novel pharmacological effect are important for developing new type of drugs. As a result of intensive research, we have found that phenylalkyl diamine and amide compounds are strongly bind to the sigma receptors and have potential anti-depressant effect. The synthesis and biological activities of these series will be presented.

153.

SYNTHESIS AND KINETIC STUDIES OF AGONIST AND ANTAGONIST REPORTER AFFINITY LABELS FOR OPIOID RECEPTORS. ***Yan Zhang**, Christopher R. McCurdy, and Philip S. Portoghese, Department of Medicinal Chemistry, University of Minnesota, 308 Harvard St SE, Minneapolis, MN 55455, Fax: 612-626-6891, zhang192@umn.edu*

Reporter affinity labels have been introduced as a new approach to labeling opioid receptors. The concept involves the use of an aromatic ortho-dialdehyde to cross-link neighboring lysine and cysteine residues at the recognition site followed by the generation of a highly fluorescent isoindole moiety that can be studied by flow cytometry. Based on this principle, compounds 1-4 were synthesized and the kinetics of covalent binding to wild type and mutant opioid receptors was studied to verify the cross-linking residues in the opioid receptors recognition site. While 1 covalently bound wild type opioid receptors with the concomitant generation of fluorescence, the finding that mutant mu-K233R and mu-C235S receptors afforded no specific fluorescence suggested that the conserved K233 and C235 are the cross-linking residues at the recognition site. The results of similar kinetic studies with 2-4 will be presented to compare possible differences in cross-linking of agonists and antagonists to opioid receptors.



154.

DESIGN OF A NEOCEPTOR AND COMPLEMENTARY NEOLIGAND DERIVED FROM THE A2A ADENOSINE RECEPTOR. ***Soo-Kyung Kim**[1], Zhan-Guo Gao[1], Philippe Van Rompaey[2], Ariel S. Gross[1], Aishe Chen[1], Serge Van Calenbergh[2], and Kenneth A. Jacobson[1]. (1) Molecular Recognition Section, NIDDK, NIH, Bldg. 8A, Rm. 1A-20, Bethesda, MD 20892-0810, Fax: 301-402-0008, Soo-KyungK@intra.niddk.nih.gov, (2) Laboratorium voor Medicinale Chemie (FFW), Harelbekestraat 72 B-9000 Gent, Belgium*

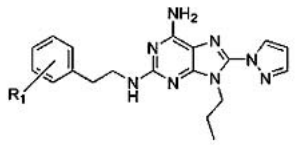
The neoceptor approach to engineer GPCRs for unique activation is based on use of molecular modeling to alter the recognition elements of a GPCR binding site, such that only synthetic, small molecular agonists (neoligands) that are selectively matched on the basis of molecular complementarity will activate the mutant receptor. The ligand recognition profile of neoceptors need not correspond to the profile of the parent, native receptor. We have designed neoceptors of the human A2A adenosine receptor (AR), in which key residues of the binding site are replaced with negatively charged residues in proximity to interact with positively-charged agonist ligands. A three-dimensional model of the human A2AAR built by homology to rhodopsin and its docked ligands suggested locations for possible new electrostatic interaction as the basis of neoceptor-neoligand pairs. Adenosine derivatives were synthesized to contain a positively charged ammonium group on ribose. Adenosine neoligands had

selectively enhanced affinity at mutant receptors expressed in COS7 cells that contain Asp and Glu residues in TMs 3, 7, e.g. a 5′-2-aminoethyluronamide derivative at the T88D mutant receptor.

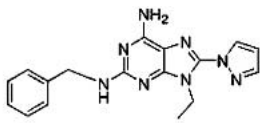
155.

STRUCTURE AFFINITY RELATIONSHIP OF 8-PYRAZOLYL ADENINE DERIVATIVES FOR THE A1 AND A2B ADENOSINE RECEPTORS. ***Rao V Kalla***[1], *Venkata Palle*[1], *Vaibhav M Varkhedkar*[1], *Dengming Xiao*[2], *Anthony D. Piscopio*[2], *Uerica Wang*[3], *Tenning Maa*[3], *Yuzhi Wu*[3], *Dewan Zeng*[3], *and Jeff A. Zablocki*[1]. *(1) Department of Bioorganic Chemistry, CV Therapeutics, Inc, 3172 Porter Drive, Palo Alto, CA 94304, Fax: 650-858-0390, rao.kalla@cvt.com, (2) Department of Process, Array BioPharma Inc, (3) Department of Pharmacological Sciences, CV Therapeutics, Inc*

In our search for new adenosine receptor ligands, we designed a novel 8-pyrazolyl-9-propyladenine derivative, **1**, which has modest affinity for both A_1 and A_{2B} adenosine receptors (AdoR). Varying substitution on the phenyl ring of compound **1**, led to the m-fluoro derivative **2** that has enhanced affinity for both receptor subtypes. Compound **3**, obtained through structural modifications of both C-2- and N9-substituents, had high affinity for the A_1 AdoR and selectivity versus the A_{2B} AdoR. Further SAR studies will be described that include substitution on the 8-pyrazolo ring and N^6-amino groups. Members of this class of compounds have been demonstrated to be functional antagonists for the A_{2B} AdoR using the cAMP readout (**1** and **3**, HEK 293 cells).



1 R_1= H; K_i (A_1) = 113 nM; K_i (A_{2B}) = 500 nM
2 R_1= m-F; K_i (A_1) = 28 nM; K_i (A_{2B}) = 165 nM



3 K_i (A_1) = 18 nM; K_i (A_{2B}) = 1000 nM

156.

2-SUBSTITUTION OF ADENINE NUCLEOTIDE ANALOGUES CONTAINING A BICYCLO[3.1.0]HEXANE RING SYSTEM LOCKED IN A NORTHERN CONFORMATION: ENHANCED POTENCY AS P2Y1 RECEPTOR ANTAGONISTS. ***Michihiro Ohno***[1], *Hak Sung Kim*[2], *Bin Xu*[3], *Hea Ok Kim*[4], *Yongseok Choi*[5], *Xiao-duo Ji*[6], *Savitri Maddileti*[7], *Victor E. Marquez*[8], *T. Kendall Harden*[7], *and Kenneth A. Jacobson*[9]. *(1) Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, Fax: 301-480-8422, michihiroo@intra.niddk.nih.gov, (2) Molecular Recognition Section, NIDDK, NIH, Bethesda, MD 20892-0810, (3) Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, (4) Division of Chemistry and Molecular Engineering, Seoul National University, (5) Laboratory of Medicinal Chemistry, Center for Cancer Research, (6) Molecular recognition Section, LBC, NIDDK, National Inst. of Health, (7) School of Medicine, University of North Carolina, (8) Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health, (9) Molecular Recognition Section, NIDDK, NIH*

Preference for the Northern (N) ring conformation of the ribose moiety of adenine nucleotide 3′,5′-bisphosphate antagonists of P2Y1 receptor was established by using a ring-constrained methanocarba (a bicyclo[3.1.0]hexane) ring as a ribose substitute. We have now combined the ring-constrained (N)-methanocarba modification with other functionalities at the adenine 2-position. Within the series of analogues, a (N)-methanocarba N6-methyl-2-iodo analogue (MRS2500), which displayed Ki value in competition for binding of [3H]MRS2279 (corresponding 2-chloro analogue) of 0.79 nM and a functional KB value of 1.74 nM, is the most potent antagonist selective for the P2Y1 receptor yet reported. The (N)-methanocarba N6-methyl-2-methyl analogue exhibits similar affinity as MRS2279 at P2Y1 receptor, whereas the 2-methylthio, 2-methylseleno, 2-hexyl, 2-(1-hexenyl), and 2-(1-hexynyl) analogues bound less well, exhibiting micromolar affinity at P2Y1 receptors. The 2-iodo group of MRS2500 was substituted with trimethyltin, thus providing a precursor for generation of a radioiodinated ligand of high affinity.

157.

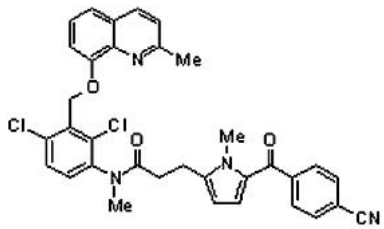
STRUCTURAL COMPARISON OF P2Y RECEPTORS BASED ON HOMOLOGY MODELING. ***Stefano Costanzi***, *and Kenneth A. Jacobson, Molecular Recognition Section, NIDDK, NIH, 9000 Rockville Pike, Bldg. 8A, Rm. B1A-23, Bethesda, MD 20892-0810, stefanoc@intra.niddk.nih.gov*

P2Y receptors encompass at least eight subtypes of G protein-coupled receptors (GPCRs), which respond to adenine and/or uracil nucleotides and show different preference for di- and triphosphates. Performing a BLAST search against the Homo sapiens subset of the SWISS-PROT and TrEMBL databases, we were able to identify a GPCR family to which P2Y receptors belong and to delineate two different subfamilies. By means of sequence alignment and homology modeling techniques, using a rhodopsin template, we constructed complete models of all human P2Y receptor subtypes, showing minimal deviation from the template. Furthermore, we performed automatic docking experiments guided by mutagenesis results to gain an insight into the binding sites for preferred and structurally varied agonists or antagonists at each subtype. This comparative modeling study is intended to aid in understanding the molecular mechanisms involved in ligand recognition and receptor activation and to serve as the basis of rational structure-based drug design.

158.

BRADYKININ (BK2) ANTAGONISTS AS ANALGESICS: NOVEL PYRROLE ALKYLAMIDE ANALOGS. *Mark A. Youngman,* ***Michele C. Jetter****, Scott L. Dax, John R Carson, Ellen E. Codd, Raymond W. Colburn, Dennis J. Stone, and Sui-Po Zhang, Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Roads, Spring House, PA 19477-0776, Fax: 215-628-4985, myoungma@prdus.jnj.com, mjetter@prdus.jnj.com*

Bradykinin is an endogenous nonapeptide that is thought to play an important role in a variety of inflammatory diseases and pain. The biological effects of bradykinin are mediated through two distinct receptor subtypes, BK_1 and BK_2. Both receptors are members of the G-protein coupled receptor superfamily. Antagonists at the BK_2 receptor may be useful for the treatment of pain and inflammation. We have designed and synthesized several series of novel pyrrole alkylamide analogs that are potent antagonists at the BK_2 receptor. Compounds such as **1** have nanomolar affinity for the BK_2 receptor and also show activity in an *in vivo* analgesic model. This poster will highlight the synthesis, SAR and biological data of these compounds.



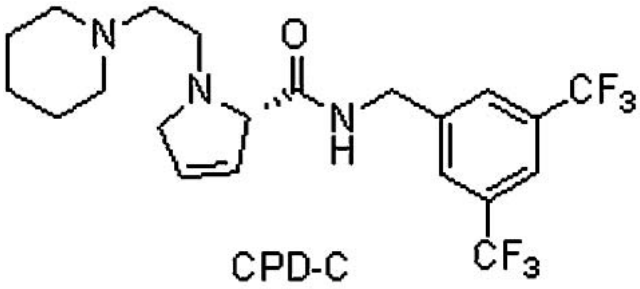
1
BK_2 Ki = 4 nM

159.

CYCLIC L-AMINO ACIDS AS CORES FOR THE IDENTIFICATION OF POTENT SMALL MOLECULE CCR2 ANTAGONISTS. ***Changyou Zhou***[1], *Liangqin Guo*[1], *William H. Parsons*[1], *Sander G. Mills*[1], *Pasquale P. Vicario*[2], *Hans Zweerink*[2], *Shefali Goyal*[2], *Margaret A. Cascieri*[2], *Martin S. Springer*[2], *and Lihu Yang*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, RY50G-340, Rahway, NJ 07065, Fax: 732-594-3007, changyou_zhou@merck.com, (2) Department of Immunology/Rheumatology, Merck Research Laboratories*

Monocyte chemoattractant protein (MCP-1), which binds to CC chemokine receptor 2 (CCR2), is involved in monocyte migration to the site of inflammation. CCR2 antagonism is recognized as an approach for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. To further improve the potency and reduce molecular weight of the 3,3-bis(trifluoromethyl)benzyl L-arylglycinamide based CCR2 antagonists disclosed in the previous poster, we systematically introduced restrictions to the central amino acid. A new class of lower molecular weight and potent CCR2 antagonists emerged. A representative is CPD-C, which incorporates L-3,4-dehydroproline

with good binding potency (IC50=37 nM, hCCR2) and excellent functional activity (IC50=3 nM, chemotaxis, human monocyte).



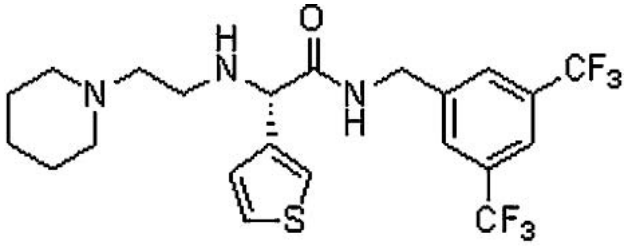
CPD-C

160.

DISCOVERY OF 3,3-BIS(TRIFLUOROMETHYL)BENZYL L-ARYLGLYCINAMIDE BASED POTENT CCR2 ANTAGONISTS. ***Lihu Yang***[1], *Changyou Zhou*[1], *Liangqin Guo*[1], *Gregori J. Morriello*[1], *William H. Parsons*[1], *Sander G. Mills*[1], *Malcolm MacCoss*[1], *Pasquale P. Vicario*[2], *Hans Zweerink*[2], *Shefali Goyal*[2], *William A. Halon*[2], *Margaret A. Cascieri*[2], *and Martin S. Springer*[2]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, R50G-301 PO Box 2000, Rahway, NJ 07065-0900, Fax: 732 594 3007, lihu_yang@merck.com, (2) Department of Immunology/Rheumatology, Merck Research Laboratories*

Chemokines, or chemotactic cytokines, are a large family of small (~8-15 kDa) structurally related proteins that play an important role in leukocyte migration and activation. Chemokines mediate their effect through the binding to the specific cell-surface seven-transmembrane spanning G-protein coupled receptors. Monocyte chemoattractant protein (MCP-1) belongs to the CC chemokine family and binds to CC chemokine receptor 2 (CCR2), which is most abundantly expressed on monocytes. Murine data from peptide CCR2 antagonists, monoclonal antibodies and deletion of either CCR2 or MCP-1 suggesting interruption of the MCP-1/CCR2 interaction, through small molecule antagonists, may provide potential therapies for a variety of diseases including rheumatoid arthritis, multiple sclerosis and atherosclerosis.

In this presentation, we will discuss the Structure-activity relationship (SAR) studies that lead to the discovery of potent 3,3-bis(trifluoromethyl)benzyl L-arylglycinamide based CCR2 antagonists from a screening hit. The best compound in this series, CPD-B, demonstrated good binding affinity to the human CCR2 receptor (IC50=30 nM) and in vitro functional antagonism of MCP-1 mediated chemotaxis of human monocytes (IC50=10 nM).

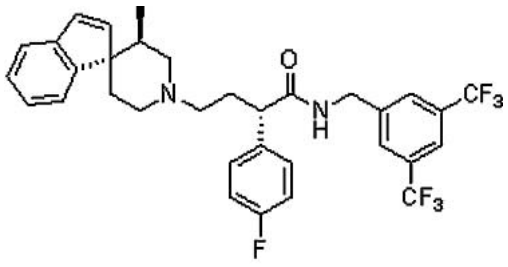


CPD-B

161.

ORALLY BIOAVAILABLE GAMMA-AMINOAMIDE CCR2 ANTAGONISTS. ***Alexander Pasternak***[1], *Dominick Marino*[1], *Pasquale P. Vicario*[2], *Julia M. Ayala*[2], *Margaret A. Cascieri*[2], *William H. Parsons*[1], *Sander G. Mills*[1], *Malcolm MacCoss*[1], *and Lihu Yang*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, alexander_pasternak@merck.com, (2) Department of Immunology/Rheumatology, Merck Research Laboratories*

Monocyte chemoattractant protein-1 (MCP-1), included within the CC class of chemokines, mediates chemotaxis of monocytes to inflammatory sites primarily through interactions with its receptor, CCR2. Recent studies have linked MCP-1 and CCR2 to various inflammatory diseases, including rheumatoid arthritis (RA) and atherosclerosis. Consequently, the therapeutic potential of CCR2 antagonists in treating inflammatory diseases has stimulated considerable interest. This presentation will describe the modification of a screening lead from our sample collection to afford a structurally distinct new lead, (2*S*)-*N*-[3,5-bis(trifluoromethyl)benzyl]-2-(4-fluorophenyl)-4-(4-phenylpiperidin-1-yl)butanamide (binding [I^{125}-MCP-1]: IC_{50}=150 nM), which has subsequently served as the departure point for an ongoing program targeting CCR2 antagonists. Further optimization by modifications to the 4-phenylpiperidine moiety leading to more potent and orally bioavailable CCR2 antagonists will also be discussed. Compound CPD-F (binding [I^{125}-MCP-1]: IC_{50}=59 nM, chemotaxis: IC_{50}=41 nM, human CCR2 (monocytes) will be highlighted.

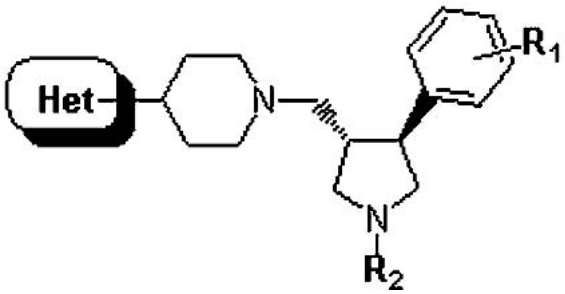


CPD-F

162.

DESIGN, ANTIVIRAL AND PHARMACOKINETIC PROFILES OF POTENT 1,3,4-TRISUBSTITUTED PYRROLIDINE CCR5 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF HIV-1 INFECTION. ***Dooseop Kim***[1], *Liping Wang*[1], *Jeffrey J. Hale*[1], *Christopher Lynch*[1], *Richard J. Budhu*[1], *Malcolm MacCoss*[1], *Sander G. Mills*[1], *Lorraine Malkowitz*[2], *Sandra L. Gould*[2], *Julie A. DeMartino*[2], *Martin S. Springer*[2], *Daria Hazuda*[3], *Joseph Kessler*[3], *Renee Danzeisen*[3], *Anthony Carella*[3], *Karen Holmes*[3], *Janet Lineberger*[3], *William A. Schleif*[3], *and Emilio A. Emini*[3]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, Fax: 732-594-7877, dooseop_kim@merck.com, (2) Department of Immunology Research, Merck Research Laboratories, (3) Department of Antiviral Research, Merck Research Laboratories*

Since the discovery that the β–chemokine receptor CCR5, a cell-surface G-protein coupled receptor, can function as a co-receptor along with CD4 for cell entry of M-tropic HIV-1 strains, the potential development of CCR5 antagonists that inhibit entry of HIV-1 into host cells has emerged as a new approach for the treatment of HIV-1 infection. Recent reports described a series of 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists as novel anti-HIV agents. Our continuing efforts focused on the heterocyclic modifications at the 4-piperidine position in this series with the goal of developing potent antagonists. After an exhaustive SAR study of a variety of heterocycles, some bicyclic structures were found to boost potency into the sub-nanomolar range both for receptor binding and in two cell-based assays. The synthesis and the biological activities of these compounds will be discussed in this presentation.



163.

SYNTHESES AND SAR STUDIES OF PYRROLIDINEACETIC ACID ANTAGONISTS OF THE CCR5 CHEMOKINE RECEPTOR. ***K. Shankaran***[1], *Karla F. Donnelly*[1], *Shrenik K. Shah*[1], *Ravindra N. Guthikonda*[1], *Sander G. Mills*[1], *Malcolm MacCoss*[1], *L. Malkowitz*[2], *Martin S. Springer*[2], *J. DeMartino*[2], *Salvatore J. Siciliano*[2], *Margaret A. Cascieri*[2], *Sandra L. Gould*[2], *William A. Schleif*[3], *Daria Hazuda*[3], *Renee Danzeisen*[3], *Anthony Carella*[3], *Gwen Carver*[3], *Janet Lineberger*[3], *Joseph Kessler*[3], *Karen Holmes*[3], *and Emilio A. Emini*[3]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, (2) Department of Immunology Research, Merck Research Laboratories, (3) Department of Antiviral Research, Merck Research Laboratories*

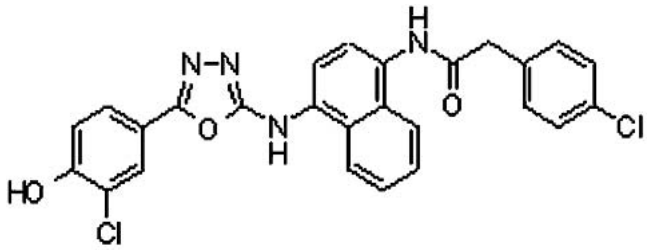
CCR5, a seven-transmembrane receptor for the chemokines RANTES and MIP-1 (alpha) has been identified as a primary co-receptor with CD4 for cell entry of

M-tropic HIV-1 strains. Individuals homozygous for a 32-pair deletion in the gene for CCR5 lack this receptor on cell surfaces and are highly resistant to HIV-1 infection, while infected heterozygous individuals show significantly delayed progression to AIDS. These results suggest that, modulations in the CCR5 receptors might provide a potential for the treatment of AIDS. Our continuing efforts towards this end have led to the preparation of series of pyrrolidineacetic acid derivatives that display high affinity for CCR5 receptor, good antiviral activity and oral bio-availibility. This presentation will discuss the syntheses and the biological activities of such compounds with a heterocyclic appendage on the piperidine ring.

164.

GLUCAGON RECEPTOR ANTAGONISTS FOR THE TREATMENT OF TYPE 2 DIABETES. ***Anthony L. Handlon***, *Adwoa Akwabi-ameyaw, Kathleen Brown, Felix De Anda, David Drewry, Jing Fang, Orlando Irsula, Guo Li, James A; Linn, Naphtali O. Milliken, and Joshi Ramanjulu, Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709-3398, Fax: 919-315-0430, tony.l.handlon@gsk.com*

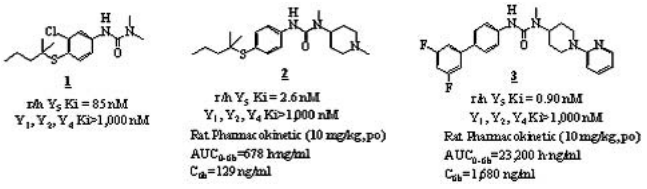
Glucagon and insulin are hormones that tightly control plasma glucose concentrations. For patients with Type 2 diabetes glucagon is elevated relative to insulin, and this imbalance is thought to contribute to the hyperglycemia of these patients. Antagonists of the glucagon receptor are expected to attenuate endogenous glucose production and may be useful in the treatment of Type 2 diabetes. We have discovered a series of glucagon receptor antagonists based on an aminooxadiazole template. Optimization of the aminooxadiazole lead series has resulted in functional antagonists with IC_{50} values in the 2-30 nanomolar range. One member of this series, GW4123X, when dosed IV to rats at 3 mg/Kg, decreased fasting plasma glucose and inhibited the rise in plasma glucose in response to a glucagon bolus. Synthetic methods and SAR will be discussed.



165.

DEVELOPMENT OF THE SUBSTITUTED PHENYL UREAS AS ORALLY ACTIVE NPY Y5 RECEPTOR ANTAGONISTS. ***Yusheng Wu***, *Andrew W. Stamford, Xiaoping Hou, Jianping Pan, Joseph Kelly, Stuart McCombie, Mahua Manna, Predeep Pushpavanam, Sundeep Dugar, Michael Czarniecki, William J. Greenlee, Deborra Mullins, Mario Guzzi, Xiaoping Zhang, Joyce J. Hwa, Jun Gao, Lorraine Ghibaudi, Matthew Bryant, and Sam Weihaus, Schering-Plough Research Institute, Kenilworth, NJ 07033-0359, yusheng.wu@spcorp.com*

Neuropeptide Y (NPY) is a 36 amino acid peptide and a member of the family of neurotransmitter peptides. Much attention recently has been focused on it since several lines of evidence suggest NPY is a key modulator in the control of body weight and NPY receptor antagonists might be useful antiobesity agents. To date, there are at least six distinct G protein –coupled receptors of NPY identified as Y1, Y2, Y3, Y4, Y5, Y6. The NPY Y5 receptor, located primarily in the hypothalamus, is believed to be one of the receptors that NPY interacts with to affect its feeding response. Therefore compounds that antagonize neuropeptide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia. Screening of our in-house chemical library identified a novel thiophenyl urea, 1 with modest NPY Y5 binding affinity (Ki=85 nM) and good selectivity against other NPY receptors, Y1, Y2, Y4. To improve the in vitro potency, the SAR development from 1 was carried out and led us to discover the thiophenyl urea 2 with more than 10 fold improved in vitro potency. However, the thiophenyl urea 2 and other thiophenyl urea analogs had very poor pharmacokinetic in rat. The later on SAR development was then focused on the improvement of pharmacokinetic of the compounds. The biphenyl urea 3 was identified with sub- nanomolar potency against Y5 receptor and displayed good to excellent pharmacokinetic across species (rat, dog and monkey). The compound significantly reduces D-Trp34 NPY stimulated food intake in rat.



166.

SYNTHESIS AND EVALUATION OF NOVEL SMALL-MOLECULE CGRP ANTAGONISTS. ***C. Blair Zartman***[1], *Ian M. Bell*[1], *Steven N. Gallicchio*[1], *Samuel L. Graham*[1], *Stefanie A. Kane*[2], *Yvonne M. Leonard*[3], *John Mallee*[2], *Cynthia Miller-Stein*[4], *Ruth Rutledge*[2], *Christopher Salvatore*[2], *Joseph P. Vacca*[1], *Audrey Wallace*[3], *and Theresa M. Williams*[1]. *(1) Department of Medicinal Chemistry, Merck Research Laboratories, Sumneytown Pike, P.O. Box 4, West Point, PA 19486, Fax: 215-652-7310, blair_zartman@merck.com, (2) Department of Molecular Pharmacology, Merck Research Laboratories, (3) Department of Pharmacology, Merck Research Laboratories, (4) Department of Drug Metabolism, Merck Research Laboratories*

Calcitonin Gene-Related Peptide (CGRP) is a 37-amino acid neuropeptide which is widely distributed in various tissues including the CNS. CGRP-containing nerves are closely associated with blood vessels and CGRP's most pronounced effect is vasodilation. This vasodilatory effect and the elevated levels of CGRP associated with migraine headache attacks initiated the investigation of antagonists of the CGRP receptor as a possible treatment for migraine and pain. Recently, Boehringer Ingelheim reported the first selective small molecule CGRP antagonist for the human CGRP receptor. This compound has entered human clinical trials as an iv agent for the treatment of migraine. Our project team is attempting to identify an orally bioavailable CGRP antagonist and a structurally novel non-peptide lead was identified from screening. Extensive SAR studies defined the key pharmacophoric elements and provided insight into the bioactive conformation. These compounds are competitive with CGRP but, in contrast to other non-peptide antagonists, their activity is affected by the presence of divalent cations. Ultimately, optimization of this series produced a low molecular weight CGRP receptor antagonist with excellent pharmacokinetic properties in both rat and dog.

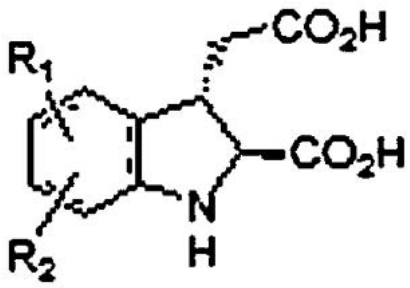
167.

SAR AND BONE ANABOLIC ACTIVITY OF EP4 RECEPTOR SELECTIVE PROSTAGLANDIN E2 AGONISTS. ***Kimberly O. Cameron***[1], *Bruce A. Lefker*[1], *Margaret Y. Chu-Moyer*[1], *David T. Crawford*[1], *Paul DaSilvaJardine*[1], *Sandra Gilbert*[1], *William A. Grasser*[1], *HuaZhu Ke*[1], *Bihong Lu*[1], *Thomas A. Owen*[1], *Vishwas M. Paralkar*[1], *Hong Qi*[1], *Dennis O. Scott*[2], *David D. Thompson*[1], *Christina M. Tjoa*[1], *and Michael P. Zawistoski*[1]. *(1) Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, Fax: 860-715-4706, kimberley_o_cameron@groton.pfizer.com, (2) Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Global Research and Development*

PGE2 is a non-selective agonist at its four known receptor subtypes (EP1-EP4). PGE2 is known to stimulate bone formation and increase bone mass and strength in animal models. We have previously demonstrated that EP4 selective heptanoic acid lactams produce significant new bone in an osteopenic rat model. To improve EP4 potency, we surveyed a range of acid linkers and identified the propylbenzoic acid and propylthiophene acid as optimum side-chains. Chemical optimization led to the identification of CMP-1, a potent and selective EP4 agonist. After s.c. administration at 0.3 mg/kg in an osteopenic rat model, CMP-1 produced significant new bone. EP4 selective agonists therefore have potential clinical utility for the treatment of skeletal disorders such as osteoporosis.

168.
DESIGN AND SYNTHESIS OF CONFORMATIONALLY CONSTRAINED ANALOGUES OF KAINIC ACID AS IONOTROPIC GLUTAMATE RECEPTOR LIGANDS. ***Xiaohong Shou**, and A. Richard Chamberlin, Department of Chemistry, University of California, Irvine, Irvine, CA 92697, shoux@uci.edu*

(–)-α-Kainic acid, a rigid analogue of glutamate, is recognized as an agonist for the kainate (KA) subclass of ionotropic glutamate receptors (GluR). In search for receptor sub-type selective ligands, a series of conformationally constrained kainic acid analogues has been designed. One class of analogues is based on the indoline structure intended to mimic the found conformation of kainic acid complexed with the binding domain of GluR5. Synthesis of these ligands along with the evaluation of their docking in the GluR5 crystal structure will be presented.



169.
DESIGN, SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NOVEL TRIAZINONES AS NON-COMPETITIVE AMPA RECEPTOR ANTAGONISTS. ***Yoshihiko Norimine**[1], Satoshi Nagato[1], Kohshi Ueno[1], Koki Kawano[1], Koichi Ito[1], Takahisa Hanada[1], Masataka Ueno[1], Shinji Hatakeyama[1], Makoto Ohgoh[1], Hiroyoki Amino[1], Toshihiko Yamauchi[1], Naoki Tokuhara[1], Terence Smith[2], Anthony Groom[2], Leanne Rivers[2], and Masahiro Yonaga[1]. (1) Tsukuba Research Laboratories, Eisai Co., Ltd, Tokodai 5-1-3, Tsukuba-shi, Ibaraki 300-2635, Japan, Fax: +81-29-847-2037, y-norimine@hhc.eisai.co.jp, (2) Eisai London Research Laboratories .Ltd*

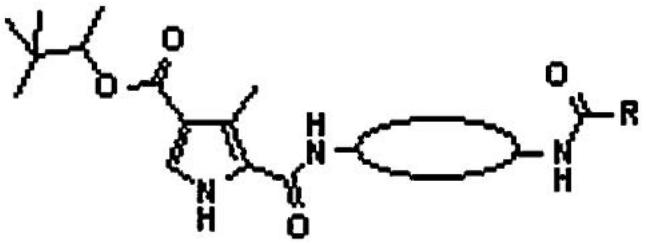
Glutamate plays a significant role of the excitatory neurotransmission in the central nervous system. Recently, a lot of published reports suggest that alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptor antagonists within the ionotropic class of glutamate antagonists have shown the ameliorative effect in the animal models of the various neurodegenerative and demyelinating diseases. In the present work, novel triazinone derivatives were synthesized and examined for their ability to inhibit the excitatory neurotransmission via AMPA receptor. These compounds showed a potent non competitive inhibitory activity against AMPA in vitro (calcium influx in rat cortical neurons) and in vivo (mice seizure model, p.o. administration). The synthesis and structure-activity relationships of the series of compounds will be presented.

170.
SYNTHESIS, SARS AND BIOLOGICAL ACTIVITIES OF POTENT AND SELECTIVE GROUP II MGLUR ANTAGONISTS: NOVEL 2-AMINO-6-FLUOROBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID DERIVATIVES. ***Atsuro Nakazato**, Akito Yasuhara, Kazunari Sakagami, Hiroshi Ohta, Ryoko Yoshikawa, Manabu Itoh, Masato Nakamura, and Shigeyuki Chaki, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 1-403, Yoshino-cho, Kitaku, Saitama-shi, Saitama 331-9530, Japan, Fax: +81-48-652-7254, atsu.nakazato@po.rd.taisho.co.jp*

Metabotropic glutamate receptors (mGluRs) consist of at least eight different subtypes (1-8) that are classified into three groups (I-III) based on sequence homology, signal transduction mechanisms, and pharmacology. Group II mGluRs (mGluR2 and mGluR3) are negatively coupled to adenylyl cyclase. Recently, 2-amino-3 or 6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acids (MGS0008 or MGS0028) has been reported as selective and potently oral active group II mGluR agonists. As part of an effort to develop group II mGluR antagonists, we chemically modified 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid. This study resulted in the discovery of novel group II mGluR antagonists. In this meeting, the synthesis and biological activities of 2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives will be presented.

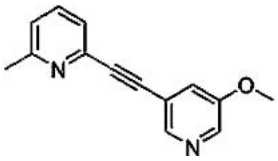
171.
SOLID PHASE SYNTHESIS OF PYRROLE DERIVATIVES SUITABLE AS MGLUR1 ANTAGONISTS. ***Fabio M. Sabbatini**, Tommaso Messeri, Fabrizio Micheli, Romano Di Fabio, and Daniele Donati, Via A. Fleming, 4, 37100, GlaxoSmithKline Research Center, Verona, Italy, Fax: +39-045-9218196, fabio.m.sabbatini@gsk.com*

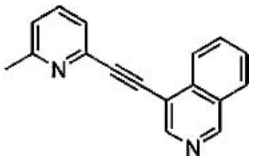
The mGluR1 receptor, according to data reported in the literature, might offer therapeutic opportunities for the treatment of pain and CNS/injuries. A new non-competitive antagonist pyrrole template has been recently disclosed. A solid phase library of amides at C-2 position of this scaffold has been synthesized using Argogel MB-CHO resin. The aim of this work was to exploit the possibility to obtain compounds of acceptable potency by varying the size and lipophilicity of the substituent of the amidic moiety at C-2. 8 Symmetric diamines and 10 acid chlorides have been used to prepare 80 different derivatives. The best compounds have been re-prepared as discretes and their potency as mGluR1 antagonists has been assayed.



172.
SYNTHESIS AND SAR OF AROMATIC-ETHYNYL-AROMATIC DERIVATIVES WITH POTENT MGLUR5 ANTAGONIST ACTIVITY. ***David Alagille**, Ronald M Baldwin, and Gilles D Tamagnan, VA CT HCS (116A2), Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516*

The heterogeneous family of receptors for L-glutamate, the principal excitatory neurotransmitter in the CNS, can be divided into two major types: ionotropic (iGluR) and metabotropic (mGluR). Compared to the thoroughly investigated roles of the iGluR, functional studies showing the importance of mGluR have just emerged in recent years. Non-competitive antagonists of subtype 5 (mGluR5) are potential therapeutics for CNS disorders including pain, anxiety and drug addiction. To discover novel non competitive mGluR5 antagonists, we synthesized 13 derivatives of the known lead phenyl pyridyl acetylenes MPEP and M-MPEP by transition metal coupling of substituted aromatic synthons, in 33–90 % yield. Our SAR results showed the critical role of the substitution pattern of the two aromatic rings to retain activity. Two of the new compounds were potent mGluR5 antagonists, with IC_{50}=21 nM and IC_{50}=22 nM.

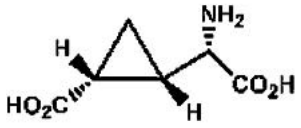




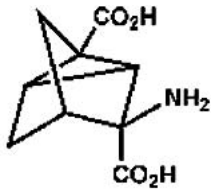
173.
ATHD-III (WAY-855): A NOVEL EAAT-2 SELECTIVE INHIBITOR OF GLUTAMATE RE-UPTAKE. ***Gary Stack**[1], John Dunlop[2], Alexander Greenfield[1], Scott Eliasof[3], H. Beal McIlvain[2], Dianne Kowal[2], Karen Marquis[2], Robert Petroski[3], Tikva Carrick[2], Zheng Wang[1], and Jonathan Gross[1]. (1) Chemical Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, stackg@wyeth.com, (2) Neuroscience Discovery Research, Wyeth Research, (3) Neurocrine Biosciences*

EAAT-2 is a member of the family of high-affinity Na+-dependent glutamate transporters. It is expressed principally in astroglia and is believed to be responsible for the clearance of extracellular glutamate by mediating the cellular uptake of glutamate in a process driven by the transmembrane Na+ gradient. (1R*,2R*,3R*,4S*,6S*)-3-Amino-tricyclo[2.2.1.02,6]heptane-1,3-dicarboxylic acid (ATHD-III, WAY-855) is a fully constrained, bridged tricyclic analog of glutamic acid and its 2-(carboxycyclopropyl)glycine analog, L-CCG-III. ATHD-III was designed and prepared as part of a program to identify agonists of the metabotropic glutamate receptors (mGluRs), but was found instead to be a potent (IC50=2.2 uM) and selective inhibitor of EAAT-2 glutamate uptake.

Herein, we describe the chemistry and biological data for this selective tool for the exploration of glutamate transporter pharmacology.



L-CCG-III



ATHD-III

174.

STRUCTURE ACTIVITY STUDIES OF NOVEL CONFORMATIONALLY CONSTRAINED 3, 6 DISUBSTITUTED PIPERIDINE ANALOGS: IN SEARCH FOR MEDICATION FOR COCAINE ABUSE. ***Rohit Kolhatkar***[1]*, Maarten Reith*[2]*, and Aloke K Dutta*[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, rbkolhatkar@wayne.edu, (2) Department of Biomedical and Therapeutic Sciences, University of Illinois*

In our previous report we have demonstrated 3,6-disubstituted piperidine derivatives as a novel template for binding to the dopamine transporter (DAT). These derivatives represent structurally constrained version of our previously developed flexible piperidine analogues. In that study, different substitutions at the exocyclic N-atom at the 3-position have shown to influence the affinity of these compounds for the DAT. Also the enantiomers of the most potent compound cis 4-[(6-Benzhydryl-piperidin-3-ylamino)-methyl]-benzonitrile, have shown differential activity. In an effort to further optimize the binding affinity of these analogs, we have further explored the structure activity relationship study through further modification of the piperidine ring. These new molecules with modified piperidine ring structure and with different substitutions at the exocyclic nitrogen will help us to provide more insights about the bioactive conformation of these molecules for their interaction with the monoamine transporters and in developing a medication for cocaine addiction. Design, synthesis and biological characterization of these molecules will be presented.

175.

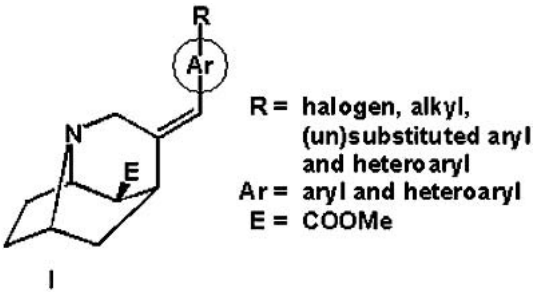
TUNING THE SERT/NET SELECTIVITY OF CONFORMATIONALLY CONSTRAINED ARYL TROPANES: ADDITIONAL ARYL SUBSTITUENTS CAUSE DRAMATIC CHANGES IN SELECTIVITY AND LEAD TO PICOMOLAR ACTIVE LIGANDS. ***Thomas Kläß***[1]*, Jia Zhou*[1]*, Ao Zhang*[1]*, Pavel A. Petukhov*[1]*, Kenneth M. Johnson*[2]*, Cheng Z. Wang*[2]*, Yanping Ye*[2]*, and Alan P. Kozikowski*[1]*. (1) Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3970 Reservoir Road, NW, Washington, DC 20057, Fax: 202-687-0738, tk77@georgetown.edu, (2) Department of Pharmacology and Toxicology, University of Texas Medical Branch*

According to the dopamine theory of addiction, cocaine is believed to elicit its behavioral and pharmacological effects primarily by binding to the dopamine transporter (DAT). Recent studies suggest that both the serotonin (SERT) and the norepinephrine (NET) transporters may also play a prominent role in cocaine addiction. In order to gain a better understanding of the pharmacology of cocaine a series of conformationally constrained aryl tropane (**I**) analogues of cocaine were synthesized and their ability to inhibit reuptake of dopamine, serotonin, and norepinephrine by DAT, SERT, and NET were evaluated. It was found that substituents at the aromatic ring (Ar) have a tremendous influence on both selectivity and affinity of these compounds towards the SERT and NET. Some ligands in this series show affinities in the picomolar range. The synthesis of compounds **I** and their SAR will be presented.

176.

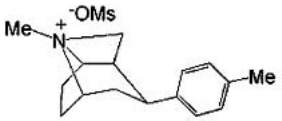
SYNTHESIS AND MONOAMINE TRANSPORTER AFFINITY OF 6-AZABICYCLO[3.2.2]NONANE (REARRANGED TROPANE) ETHERS. ***David Alagille***[1]*, Ronald M Baldwin*[1]*, Lionel ogier*[1]*, Nora S. Kula*[2]*, Ross J. Baldessarini*[2]*, and Gilles D Tamagnan*[1]*. (1) VA CT HCS (116A2), Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516, (2) Department of Psychiatry, Harvard Medical School and McLean-Mailman Research Center*

A series of novel 6-azabicyclo[3.2.2]nonane (rearranged tropane) ether analogs **2** was synthesized by nucleophilic displacement of the tricyclic quaternary

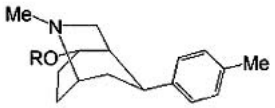


I

ammonium salt **1** with an appropriate alcohol. The potency of these rearranged tropanes was evaluated by competition against radiolabeled ligands selective for serotonin (5-HTT), dopamine (DAT), and norepinephrine (NET) transporters in rat forebrain tissue and human cell membranes. High affinity for 5-HTT and DAT was maintained compared to the corresponding 8-azabicyclo[3.2.1]octane (tropane) analogs, and selectivity for 5-HTT vs. DAT increased significantly in one compound.



1



2

177.

DESIGN, SYNTHESIS, AND SAR EXPLORATION OF ANALOGS OF CIS-3,6-DISUBSTITUTED PYRAN AT EITHER 3- AND 6-POSITION AS POTENTIAL DOPAMINE TRANSPORTER BLOCKER. ***Shijun Zhang***[1]*, Maarten Reith*[2]*, and Aloke K Dutta*[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, ai2434@wayne.edu, (2) Department of Biomedical and Therapeutic Sciences, University of Illinois*

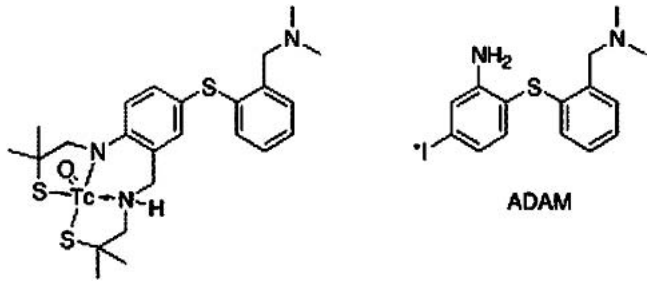
Our further exploration of structure activity relationship study on new cis-3,6-disubstituted pyran template developed recently in our laboratory led to design and development of novel analogues. Compounds developed from our studies exhibited interesting binding activity with much more affinity for the norepinephrine transporter compared to their piperidine counterparts. This might indicate existence of different interaction modes with the monoamine transporter systems compared with the corresponding piperidine analogs developed in our laboratory before. This may be due to the fact that the exchange of a nitrogen atom with a less basic oxygen atom can introduce shuttle differences in interactions with the transporter molecules. It is also possible that since physiochemical properties of pyran derivatives may differ from piperidines, these molecules might exhibit different in vivo properties as a result of their different pharmacokinetics and pharmacodynamic properties. To further understand the optimum pharmacophoric structural requirement of this new template, a series of 3,6-disubstituted pyran analogs with structural expansion on either side of 3- and 6-positions were synthesized and biologically tested. Our goal is to explore the effects of separation of space between diphenyl moiety and side chain nitrogen atom on the binding activity and selectivity. The synthesis and bioactivity will be presented.

178.

SYNTHESIS AND CHARACTERIZATION OF A TC-99M LABELED BIPHENYLTHIOL AS SEROTONIN TRANSPORTER IMAGING AGENT. ***Shunichi Oya****, Seok-Rye Choi, and Hank F. Kung, Department of Radiology, University of Pennsylvania, 3700 Market St. Suite 305, Philadelphia, PA 19104, Fax: 215-349-5035, oya@sunmac.spect.upenn.edu*

Serotonin transporters (SERT) are implicated in various psychiatric disorders. Previously we reported that Iodine-123/125 labeled SERT ligand 2-((2-((dimethylamino)methyl) phenyl)thio)-5-iodophenylamine (ADAM) showed highly specific binding to SERT rich site in the brain by SPECT. Technetium-99m labeled imaging agent is desirable since Tc-99m is the most widely used isotope in diagnostic nuclear medicine. We designed a Tc-99m labeled SERT imaging agent base on the structure of ADAM. The ligand was synthesized by a straightforward reaction scheme with excellent yield. The ligand was labeled with

Technetium-99m successfully. We herein report chemical synthesis and initial biological evaluation of a novel Tc-99m labeled SERT imaging agent.



179.

***GINKGO BILOBA* TERPENE TRILACTONES ATTENUATED EXTRACELLUAR ACIDIFICATION IN CHO CELLS EXPRESSING THE PLATELET-ACTIVATING FACTOR RECEPTOR.** *Sonja Krane, **So Ra Kim**, Leif M. Abrell, and Koji Nakanishi, Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, Fax: 212-932-8273, sorakim@chem.columbia.edu*

Microphysiometry was used to evaluate the effect of terpene trilactone and flavonoid constituents of *Ginkgo biloba* on CHO cells transfected with human platelet-activating factor receptor (PAFR). Inhibition of the platelet-activating factor response by terpene trilactones was confirmed using this functional assay. Ginkgolide B (GB) and 10-*O*-benzyl-GB showed the strongest inhibition (77% and 91%, respectively) of the PAFR response. However, rutin and quecertin showed negligible response inhibition.

180.

AMPHIPHILIC PYRIDINIUM SALTS SUPPRESS PRODUCTION OF THE PROINFLAMMATORY CYTOKINE IL-8 IN CYSTIC FIBROSIS LUNG EPITHELIAL CELLS. ***Susanna Tchilibon***[1]*, J. Zhang*[2]*, Harvey P. Pollard*[2]*, and Kenneth A. Jacobson*[3]*. (1) Molecular Recognition Section, NIDDK, National Inst. of Health, Bldg 8A, Rm B1A-17, Bethesda, MD 20892/0810, Fax: 301-480-8422, susannat@intra.niddk.nih.gov, (2) Department of Anatomy, Institute of Molecular Medicine, F. Edward Hebert School of Medicine, University of the Health Sciences, (3) Molecular Recognition Section, NIDDK, NIH*

Cystic fibrosis (CF) is the most common, lethal autosomal recessive disease affecting children in the United States and Europe. CF airways are phenotypically inundated by inflammatory signals, primarily contributed by sustained secretion of the proinflammatory cytokine interleukin 8 (IL-8) from mutant CFTR airway epithelial cells. The production of IL-8 is controlled by genes from the TNF-alphaR/NFkappaB pathway, and it is possible that the CF phenotype is due to dysfunction of genes from this pathway. Previous studies of genetically defective CF cells have shown that both gene therapy with CFTR and pharmacological rescue substantially suppress IL-8 secretion. From library screening, we have identified a series of amphiphilic pyrdinium salts that suppressed spontaneously-elevated IL-8 secretion in IB-3 CF lung epithelial cells. The structure activity relationships of these derivatives have been explored, leading to MRS 2481, an (R)-1-phenylpropionic acid ester which had an IC50 of 0.35 µM. A hydrophobic moiety present on the pyrdinium derivatives displayed highly specific structural requirements in suppression of IL-8 production. The enantiomer, MRS 2485, was nearly inactive in effect on IL-8 production.

181.

DESIGN, SYNTHESIS AND EVALUATION OF CONSTRAINED TYROSINE ANALOGUES AS POTENT A4 INTEGRIN ANTAGONISTS. ***Li Chen***[1]*, Jefferson W. Tilley*[1]*, Richard Trilles*[1]*, Fotouhi Nader*[1]*, David Fry*[1]*, Karen Rowan*[2]*, David Jackson*[3]*, Sherman Fang*[3]*, and Lou Renzetti*[4]*. (1) Discovery Chemsitry, Hoffmann-La Roche Inc, 340 Kingsland Street, Nutley, NJ 07110, Fax: 973-235-6084, li.chen@roche.com, (2) Discovery Technology, Hoffmann-La Roche Inc, (3) Chemistry, Genentech Inc, (4) Discovery Pharmacology, Hoffmann-La Roche Inc*

The constrainted tyrosine containing cyclic peptide RO0270253 is a potent antagonist of VCAM/VLA-4 and MadCAM/a4b7 interactions. It has an IC50 of 0.2 nM in Ramos cell/VCAM and 1.5 nM in RPMI cell/MacCAM assays respectively. RO0270253 inhibits VCAM mediated human T-cell proliferation with an IC50 of 1 nM and is active after aerosol administration in a mouse lung allergy model. In the present work, we show the exquisite sensitivity of analogues of RO0270253 to structural changes, particularly in stereochemistry and aryl ring substitution. The preferred conformation of RO0270253 was determined by NMR and can serve as a starting point for the design of novel non-peptidic alpha-4 integrin antagonists.

182.

NON-PEPTIDE AVB3 RECEPTOR ANTAGONISTS: IDENTIFICATION OF POTENT, ORALLY ACTIVE RGD MIMETICS FOR THE TREATMENT AND PREVENTION OF OSTEOPOROSIS. ***Karen M. Brashear***[1]*, Paul J. Coleman*[1]*, John H. Hutchinson*[1]*, Mark E. Duggan*[1]*, George D. Hartman*[1]*, David B. Whitman*[1]*, Garry R. Smith*[1]*, Sevgi B. Rodan*[2]*, Gideon A. Rodan*[2]*, Chih-Tai Leu*[2]*, Lei Duong*[2]*, Donald Kimmel*[2]*, Thomayant Prueksaritanont*[3]*, Carmen Fernandez-Metzler*[3]*, Bennett Ma*[3]*, and Joseph J. Lynch*[4]*. (1) Departments of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, karen_brashear@merck.com, (2) Bone Biology and Osteoporosis Research, Merck Research Laboratories, (3) Drug Metabolism, Merck Research Laboratories, (4) Pharmacology, Merck Research Laboratories*

The vitronectin receptor avb3 is a heterodimeric glycoprotein complex that is highly expressed in osteoclasts. Bone resorption by osteoclasts is thought to involve avb3 through its role in the adhesion and migration of osteoclast cells on the bone surface. Antagonists of this integrin receptor in the form of antibodies, RGD-containing peptides and small molecule RGD-mimetics have been shown to inhibit bone resorption in vivo. avb3 antagonists may therefore be suitable for the prevention and treatment of osteoporosis. A series of novel avb3 receptor antagonists based on a 9-(tetrahydro-[1,7]naphthyridine)-nonanoic acid scaffold was prepared in which the 3-aryl substituent was varied in order to examine effects on potency, pharmacokinetics, and in-vivo efficacy. The synthesis of these compounds, as well as their in vitro, in vivo, and pharmacokinetic data, will be presented.

183.

SHEAR EXPERIMENTS OF MIMICKED AND REAL CARTILAGE IN THE SURFACE FORCE APPARATUS. ***Marcel Benz**, Jacob Israelachvili, and Nianhuan Chen, Department of Chemical Engineering, University of California, Santa Barbara, CA 93106, Fax: 805-893-7870, mbenz@engineering.ucsb.edu*

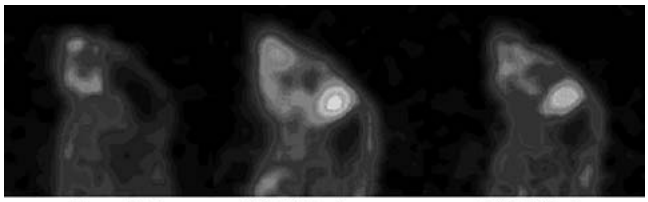
The role of hyaluronan (HA), a polysaccharide and major component of synovial fluid, in the joint lubrication of articular cartilage is investigated. The Surface Force Apparatus (SFA) is ideally suited to measure normal and shear forces between surfaces in different solutions. We first mimicked the cartilage surface by covalently attaching HA to the surfaces. The chemically bound HA provided high wear protection but did not show any lubrication ability (friction coefficient of ~0.2). Next, we will study the friction of micrometer thick animal cartilage attached to the surfaces in the SFA. Preliminary measurements show friction coefficients smaller than 0.01. The surfaces will be sheared in different media as well as treated with trypsin and hyaluronidase prior to friction measurements to test for the absence of lubricin (a glycoprotein believed to be responsible for the boundary lubrication) and HA, respectively.

184.

POSITRON EMISSION TOMOGRAPHY IMAGING OF α_v-INTEGRIN EXPRESSION IN BRAIN TUMORS. ***Xiaoyuan Chen***[1]*, James R. Bading*[1]*, Peter S. Conti*[1]*, Vazgen Khankaldyyan*[2]*, Rex Moats*[2]*, and Walter E. Laug*[2]*. (1) Department of Radiology, University of Southern California Keck School of Medicine, 1510 San Pablo St, HCC 350, Los Angeles, CA 90033, Fax: 323-442-3253, xchen@usc.edu, (2) Department of Pediatrics, Childrens Hospital Los Angeles*

Brain tumors are angiogenesis dependent. Anti-angiogenic therapies that either block expression of tumor angiogenesis related proteins, or directly prevent endothelial cells from migration and induce apoptosis have proven effective in brain tumor. EMD 121974, a peptide antagonist of α_v-integrins has produced favorable effects in phase I/II clinical trials of brain tumor patients. Quantitative imaging of α_v-integrin expression level will facilitate individualized anti-α_v-integrin treatment using EMD 121974 and/or other integrin inhibitors. We labeled cyclic RGD peptide c(RGDyK) with the positron emitter ^{18}F ($t_{1/2}$=110 min) through a prosthetic 4-[^{18}F]fluorobenzoyl moiety. The [^{18}F]FB-RGD tracer

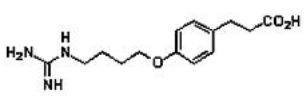
showed very rapid blood clearance and tumor specific uptake in subcutaneous U87MG glioblastoma model. MicroPET and autoradiographic imaging with an orthotopic U251T brain tumor model revealed very high tumor-to-brain (T/B) ratio, with virtually no uptake in the normal brain. Further study to correlate the α_v-integrin expression level with magnitude of tumor uptake is in progress. (Supported by 5P20 CA86532 and ACS-IRG-58007-42)

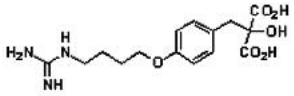


185.

REPLACEMENT OF ASPARTIC ACID IN RGD MIMETICS. ***Diane B. Hauze***[1], *Charles W. Mann*[1], *Kenneth L. Kees*[1], *Horace Fletcher III*[1], *Richard J. Murrills*[2], *Jeanne Yoon*[2], *and Frederick J. Bex*[2]. *(1) Chemical Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426-3930, hauzed@wyeth.com, (2) Women's Health Research Institute, Wyeth Research*

An aspartic acid replacement was incorporated into arginine-glycine-aspartic acid (RGD) mimetics and the resulting compounds were tested for their vitronectin receptor ($\alpha_v\beta_3$) affinity. Incorporation of a tartronic acid (hydroxy malonic acid) unit into a VnR antagonist template afforded a compound which both retained VnR activity, and showed affinity for hydroxyapatite, a major constituent of bone. The synthesis, receptor binding, and hydroxyapatite affinity will be presented for the tartronic acid analogs.





186.

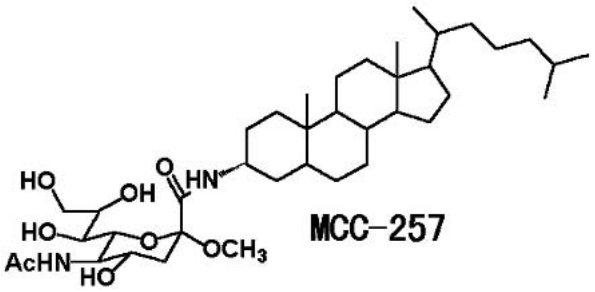
SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF NOVEL VLA-4 ANTAGONISTS. ***Satoru Ikegami***, *Yoichiro Hoshina, Akihiko Okuyama, Hideto Fukui, Kiyoshi Inoguchi, Kyoko Fujimoto, Tatsuya Maruyama, Tatsuhiro Harada, and Tsutomu Nakamura, Central Research Laboratories, Kaken Pharmaceutical Co.,Ltd, 14,Shinomiya,Minamikawara-cho,Yamashina-ku, Kyoto 607-8042, Japan, Fax: +81-75-594-0790, ikegami_satoru@kaken.co.jp*

VLA-4(*f¿4f*À1 integrin) plays a key role in physiologic and pathologic responses in inflammation and autoimmune diseases. We have been working on drug discovery research for our VLA-4 inhibitor program, and consequently our efforts to develop orally-available small molecule inhibitors have led to the successful introduction of a unique template 2,3-diphenylpropionic acid. Some compounds with the template inhibited the VLA-4 dependent adhesion with IC50 < 3.0nM. The compounds showed a more potent inhibitory activity than VLA-4 antagonists disclosed by other companies and also drug-like favorable properties. In this poster, we report on the design, synthesis, and structure-activity relationships of these compounds.

187.

MCC-257: A NOVEL NEUROPROTECTIVE SIALIC ACID DERIVATIVE. *Haruyuki Chaki*[1], ***Naoko Ando***[2], *Rie Yoshida*[3], *Tomoko Yugami*[3], *Yasuhiro Morinaka*[3], *and Kenichi Saito*[3]. *(1) Technology & Production Division, Mitsubishi Pharma Corporation, 14 Sunayama, Hasaki-machi, Kashima 314-0255, Japan, Fax: +81-479-46-6113, Chaki.Haruyuki@ma.m-pharma.co.jp, (2) Research & Developement Division, Mitsubishi Pharma Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan, Fax: +81-45-963-4437, Ando.Naoko@mh.m-pharma.co.jp, (3) Research & Developement Division, Mitsubishi Pharma Corporation*

Neurotrophins, e.g., nerve growth factor, play important roles in differentiation, development and survival of neurons. The therapeutic uses of them for treatment of neurodegenerative diseases, cerebral stroke and chronic neuropathic pain have not succeeded because of their difficulties applying large polypeptides as drugs. To find alternative approaches, we challenged to create a small molecule like neurotrophins starting from gangliosides, well-known sialic acids-containing glycoconjugates which promote neuronal survival. As we thought that sialic acids moiety of gangliosides played an important role, we designed several types of sialic acid derivatives and found that sialic acid amides prevented decrease of choline acetyltransferase activity of cholinergic neurons in septal primary culture. Among them, MCC-257 increased the number of acetylcholinesterase-positive neurons. These results show that MCC-257 might be used as a drug for neurodegenerative disorders. The detailed synthesis and structure-activity relationship of these amide derivatives will be presented.



188.

SOLID PHASE SYNTHESIS OF C-GLYCOSIDE ANALOGS OF SIALIC ACIDS. ***Sultan Nacak Baytas***[1], *Qun Wang*[2], *Xuejun Yuan*[1], *and Robert J. Linhardt*[1]. *(1) Department of Chemistry, Rensselaer Polytechnic Institute, Cogswell, 110 8th Street, Troy, NY 12180, Fax: 319-335-6634, sbaytas@blue.weeg.uiowa.edu, (2) Division of Medicinal and Natural Products Chemistry, University of Iowa*

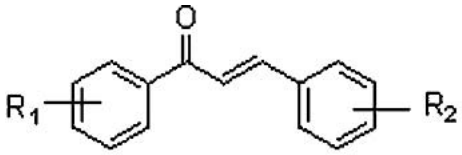
Glycoconjugates are major components on the surface of mammalian cells that play a key role in the transmission of biological information at the cellular level. These activities can be lost on catabolism when the glycan linkages are enzymatically hydrolyzed. A carbon-linked analog (C-glycoconjugate) should show enhanced stability in vivo and may have applications in modern medicine for the control of bacterial and viral diseases, cancer therapy, and treating inflammatory processes. Sialic acid residues, localized on the non-reducing termini of gycoconjugates, may be the single most important monosaccharide component. Based on diastereocontrolled synthesis of sialic acid based alpha-C-glycosides, using smarium iodide mediated coupling reaction, we have set out to synthesize C-glycoside analogs. This chemistry has been successfully performed on solid support which should facilitate the construction of a combinatorial library for screening as inhibitors of sialidase activity and hemagglutinin interaction.

189.

DESIGN AND SYNTHESIS OF NOVEL CHALCONES AS POTENTIAL TREATMENT FOR ASTHMA. ***Liming Ni***, *Charles Q. Meng, M. David Weingarten, Kimberly J Worsencroft, Zhihong Ye, Jacob E. Simpson, Jason W. Skudlarek, Elaine M. Marino, Fei-Hua Qiu, Cynthia L. Sundell, Randy B. Howard, Martin A. Wasserman, and James A. Sikorski, AtheroGenics, Inc, 8995 Westside Pkwy, Alpharetta, GA 30004, Fax: 678-336-2501, lni@atherogenics.com*

Interactions between vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells and its receptors on leukocytes are known to result in the recruitment of inflammatory cells into tissues. Molecules that inhibit the expression of VCAM-1 may prevent the inflammatory cell infiltration and thus could be used to treat chronic inflammatory diseases such as asthma. We designed and synthesized a series of novel chalcone derivatives which effectively inhibited TNF-α inducible VCAM-1 expression on endothelial cells. After optimization lead compound, AGI-2048, demonstrated not only potent inhibition of VCAM-1 expression (IC_{50}=0.6 μM), but also reduction of airway eosinophils in a mouse model of

allergic asthma. The synthesis, SAR studies and biological effects of this new series will be reported.



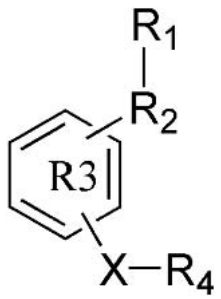
R_1 = alkoxy, carboxy, halides
R_2 = alkoxy, carboxy, heterocycles, halides

190.
POOR SOLUBILITY IS ASSOCIATED WITH POOR DATA QUALITY IN IN VITRO ADME SCREENS. ***Yun W. Alelyunas****, DMPK, AstraZeneca, 1800 Concord Pike, CRDL 123, Wilmington, DE 19803*

Purpose: To investigate the impact of aqueous solubility on the quality of in-vitro ADME screening data including lipophilicity (logD), Caco2, protein binding, and human microsomal stability. Methods: In-vitro ADME screening data generated in-house through automation and LC/MS/MS quantitation were examined for about 900 compounds covering a number of projects and diverse chemical series. Spotfire and other visualization and statistical tools were employed for the analysis. Results: Poor aqueous solubility is associated with poor data reproducibility in logD measurement. Poorly soluble compounds generally have lower upper limit of permeability in Caco2 and % free in protein binding. When solubility is at or below the measurement concentration, there is a high tendency of low recovery in Caco2 data, indicating potential under estimate of permeability. For microsomal stability results, the measurement error is higher at the measurement concentration, indicating less reliability of the data. Conclusions: Solubility is generally associated with poor data quality in other in vitro ADME screens. It is important to consider solubility when interpretating these data, especially when the reported value is undesirable. A cutoff value of 0.5 uM at pH 7.4 has been proposed as the CNS solubility limit for either compound selection or data interpretation.

191.
RAPID LEAD OPTIMIZATION THROUGH FOCUSED COMBINATORIAL LIBRARIES. ***Ruiyan Liu****, K.Kan Ho, Steven G. Kultgen, Guizhen Dong, Peng Geng, Kurt W. Saionz, and Tao Guo, Department of Chemistry, Pharmacopeia,Inc, P.O.Box 5350, Princeton, NJ 08543, Fax: 732-422-0156, rliu@pharmacop.com*

Combinatorial chemistry has become a key component of the drug discovery process in the biotechnology and pharmaceutical industries. Since the founding of the company in 1993, Pharmacopeia chemists have prepared over 200 combinatorial libraries containing over 7.5 million drug-like compounds using a proprietary ECLiPS technology. This large compound collection has enabled Pharmacopeia and its collaboration partners to rapidly discover and optimize lead compounds for numerous enzyme and receptor targets. In this presentation, the design and synthesis of two focused libraries containing 34,441 compounds for a lead optimization program will be discussed. The ability of these focused libraries to aid in the rapid establishment of a combinatorial SAR and the discovery of optimized compounds will be described.



192.
BUSPIRONE, A CASE STUDY: INTEGRATING IN SILICO PREDICTION OF METABOLISM AND ACTIVITY INTO DRUG DISCOVERY. *Manish Tandon,* ***Mark A. Ashwell****, Alan Beresford, Alex Porte, Stuart Russell, and Donglai Yang, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, MAshwell@arqule.com, MAshwell@arqule.com*

There can be little doubt that early incorporation of ADME into the drug discovery process is a worthy goal. However, there are a few road maps to follow for the best way to achieve this. Buspirone, (BUSPAR TM), a marketed anxiolytic drug, is metabolized primarily by human CYP3A4 and has low bioavailability (approximate 4%) in man and was selected as a model compound for the demonstration of our ability to combine our in silico predictive metabolism, experimental ADME and activity prediction with our high throughput synthesis, purification and analysis capabilities. This poster will describe the combination of our proprietary CYP3A4 regioselectivity model with our activity models in the selection of the compounds to be synthesized using our high throughput synthesis, purification and analysis platform. In vitro results will be presented for CYP3A4 stability and radiolabelled-ligand displacement against the 5HT1A receptor. Finally a local CYP3A4 metabolism model for the Buspirone analogs will be described.

193.
GENERATING HIGHER QUALITY LEADS FOR LEAD OPTIMIZATION. ***Mark A. Ashwell****, Jean-Marc Lapierre, and Syed Ali, ArQule Inc, 19 Presidential Way, Woburn, MA 01801, MAshwell@arqule.com*

The identification and selection of suitable leads for optimization strategies lies at the heart of increasing the pace of drug discovery. The application of in silico prediction of human ADME early on in discovery projects has resulted in the need to develop tools and approaches, which can be readily harnessed by medicinal chemists. The continuing use and integration of these models with computational models of activity and experimental data was applied to our sodium channel blocker program to decrease CYP450 liabilities and CNS penetration. The combination and application of predictive tools, high-throughput synthesis, purification and analysis capability with in vitro ADMET profiling technology platform led to the rapid identification of a series of compounds showing good biological activity and ADME properties.

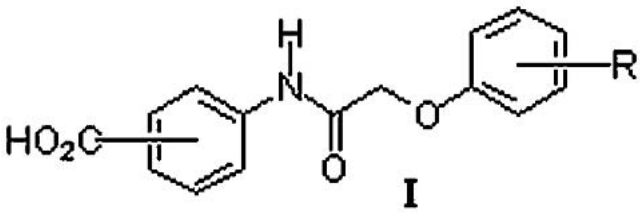
194.
INFORMATICS CHALLENGES IN PHARMACEUTICAL ADME/TOX EVALUATION. ***Gregory M. Banik****[1], Deborah Kernan[2], and Dan Hirshout[1]. (1) Bio-Rad Laboratories, Informatics Division, 3316 Spring Garden Street, Philadelphia, PA 19104, gregory_banik@bio-rad.com, (2) Informatics Division, Bio-Rad Laboratories*

Nearly 75% of the cost of bringing a new drug to the market is associated with failures. The vast majority of the failed compounds have problems associated with their Absorption, Distribution, Metabolism, Excretion, or Toxicity (ADME/Tox) profiles. The evaluation of ADME/Tox properties earlier in the drug discovery process, while clearly bringing about increased productivity through the "fail-early, fail-often" approach, poses numerous informatics challenges. This paper describes the integration of ADME/Tox Informatics™ tools with MS Informatics™ tools, creating a unified, integrated informatics environment to predict, evaluate, and track the ADME/Tox profiles of compounds early in the drug discovery process.

195.
SMALL-MOLECULE MODULATION OF READ-THROUGH (SMMRT): DISCOVERY OF 2-PHENOXYACETANILIDES AS PROMOTERS OF PROTEIN EXPRESSION FROM RNA WITH NONSENSE CODONS. ***Richard G. Wilde****, Stephen W. Jones, Hongyu Ren, Neil G. Almstead, Ellen M. Welch, Jin Zhuo, Westley J. Friesen, Yuki Tomizawa, John Babiak, and Stuart W. Peltz, PTC Therapeutics Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, rwilde@ptcbio.com*

A series of 2-phenoxyacetanilide benzoic acids (I) was discovered which modulate the read-through of a premature termination codon present in a reporter mRNA resulting in protein expression. This effect may be beneficial for the treatment of certain genetic diseases caused by the presence of premature

stop codons in the RNA sequence. Synthesis and structure-activity relationships of the series will be presented.



I

196.

SMALL-MOLECULE MODULATION OF READ-THROUGH (SMMRT): MODIFICATION OF 2-PHENOXYACETANILIDES TO IMPROVE SOLUTION STABILITY. ***Richard G. Wilde***, *James J. Takasugi, Stephen W. Jones, Haiqing Hu, Bryan A. Vining, Neil G. Almstead, Ellen M. Welch, Jin Zhuo, Westley J. Friesen, Yuki Tomizawa, John Babiak, and Stuart W. Peltz, PTC Therapeutics Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, rwilde@ptcbio.com*

A program was begun to discover small molecules that modulate read-through of a premature termination codons in mRNAs that are associated with a myriad of genetic disorders. Increased protein expression resulting from readthrough represents a novel approach to treat certain genetic diseases. A series of 2-phenoxyacetanilide benzoic acids was identified through high-throughput screening. These compounds were modified by incorporating an additional ring in an effort to improve stability in buffer and serum solutions. Synthesis and structure-activity relationships of the new series will be presented.

197.

SYNTHESIS AND C-ELONGATION OF A NEW ROTAXANE BUILDING BLOCK: PEPTIDE [2]ROTAXANES AS POTENTIAL PRODRUG SYSTEMS. ***Stéphanie Potok***[1], *David A. Leigh*[1], *and Frédéric Coutrot*[2]*. (1) School of Chemistry, Edinburgh University, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom, S.Potok@sms.ed.ac.uk, (2) Laboratoire de Chimie Biomoléculaire, Ecole Nationale Supérieure de Chimie de Montpellier*

Involved in a wide range of biological processes, peptides are potential therapeutic agents. Despite their degradation in vivo and their poor membrane transport permeability, peptides derivatized into rotaxanes using a five-component hydrogen-bond assembly can possibly be used as novel prodrug delivery systems. The presence of the tetraamide macrocycle around the peptide thread acts as a protective shield against peptidases and modifies its cell membrane transport characteristics. However, this clipping method of encapsulation is mainly limited to dipeptide sequences since the presence of intramolecular hydrogen bonds in longer peptide threads causes folding of the backbone, thus preventing good interactions with the precursor to the macrocycle. To remedy this problem, we present here the synthesis of a glycylglycine [2]rotaxane building block terminated by an activated ester. Its further C-elongation is then applied to the synthesis of oligopeptide [2]rotaxanes and especially to the protected leucine enkephalin as a biological example.

198.

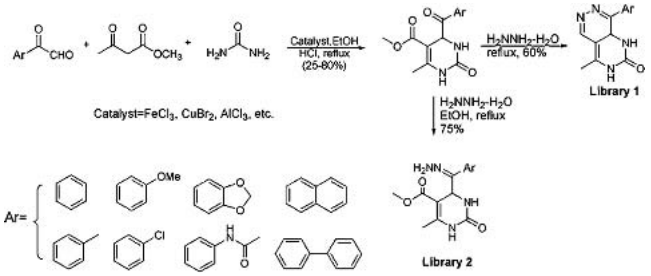
DENSE GAS PROCESSES FOR DRUG FORMULATION. ***Neil R. Foster***[1], *Fariba Dehghani*[1], *and Hubert L. Regtop*[2]*. (1) School of Chemical engineering, University, The University of New South Wales, Sydney 2052, Australia, Fax: 612 9385 5966, n.foster@unsw.edu.au, (2) Company*

The product quality of pharmaceutical compounds can be significantly influenced by their physical properties such as particle size, size distribution and morphology. Fine particles of pharmaceuticals with a narrow particle size distribution are essential for the development of inhalation aerosols, injectable suspensions, controlled release dosage forms, and other specialised drug delivery systems. In addition, particle size is a critical parameter that determines the rate of dissolution of the drug in the biological fluids and hence has a significant effect on the bioavailability of poorly water-soluble drugs for which the dissolution is the rate-limiting step in the absorption. Dense gas techniques utilising the properties of fluids in the vicinity of the critical point has been used for particle design purposes. Dense gases such as carbon dioxide (with critical temperature of 31.1°C and critical pressure of 72.9 bar) are commonly used in these processes. Therefore, the processes can be undertaken at moderate temperature, and are thus suitable for many heat labile compounds such as proteins and biocompatible polymers. Micronisation and recrystallisation of pharmaceutical compounds using dense gases has many advantages over conventional techniques, such as minimum product contamination, reduced waste streams, enabling the processing of thermolabile, shock- and chemically-sensitive compounds, and the possibility of producing particles with narrow size distribution in a single step operation. In this study examples of particle formation by dense gas techniques are presented to demonstrate the broad application of this technique for drug formulation purposes. The compounds selected include anti-inflammatory drugs, proteins, steroids and antibiotics. In vitro analysis of the processed powders demonstrates enhancement in dissolution rate of poorly water soluble drugs and the potential for administration of the drug by inhalation system.

199.

GENERATION OF TWO READY TO SCREEN LIBRARIES VIA BIGINELLI THREE COMPONENT CONDENSATION WITH NOVEL SUBSTRATES. *Qiang Yu,* ***Min Yang***, ***Zhiqiang Fang***, *Liangfu Huang, and Wuping Ma, SynChem, Inc, 1700 Mount Prospect Rd., Des Plaines, IL 60018, qyu@synchem.com, yangmin@synchem.com, df@synchem.com*

Previously, we have reported the first application of arylglyoxals as substrates in the Biginelli multi-component reactions (MCRs) with low to moderate yields. Extensive studies using various combinations of Lewis acids and solvents, led to significant improvements in the reaction yields and we have developed a scalable isolation procedure. The obtained dihydropyrimidine products thus possess an extra ketone functional group, which provides a potential site for further transformation. We have applied a combinatorial chemistry approach to exploit this extra ketone functionality to generate two sets of ready-to-screen libraries for anti-cancer and anti-AIDS purposes.



200.

EVALUATION OF *SACCHAROMYCES CEREVISIAE* REDUCTASES AS PRACTICAL CATALYSTS FOR KETONE REDUCTIONS. ***Iwona A. Kaluzna***, *and Jon D. Stewart, Department of Chemistry, University of Florida, 127 Chemistry Research Building, Gainesville, FL 32611*

Saccharomyces cerevisiae has been the most widely used whole-cell catalyst for the asymmetric reduction of carbonyl compounds. There are over 40 potential carbonyl reductases in the yeast genome. A number of those reductases may have overlapping substrate specificities, but differing stereoselectivities yield a mixture of stereoisomeric alcohols when using whole-cell yeast as a biocatalyst. A rapid and convenient method to overcome this problem involves isolation of individual enzymes by tag affinity purification. We constructed a library of glutathione S-transferase (GST) fused yeast reductase open reading frames in an *E. coli* expression vector. A subset of those reducatses have been purified and screened for activity toward a variety of α- and β- keto esters. This work demonstrates applications of these fusion proteins in stereoselective reductions. One example is the production of ethyl (*R*)-2-hydroxy-4-phenylbutyrate, which is chiral intermediate for the synthesis of inhibitors containing the L-homophenylalanine substructure.

201.

DESIGN, SYNTHESIS AND EVALUATION OF β-AMINO HYDROXAMIC ACIDS AS SELECTIVE TUMOR NECROSIS FACTOR-α CONVERTING ENZYME INHIBITORS. ***James J.-W. Duan**, Gregory R. Ott, Bryan W. King, Thomas P. Maduskuie, Chu-Biao Xue, Lihua Chen, Zhonghui Lu, John L. Gilmore, Naoyuki Asakawa, Stephen E. Mercer, Meizhong Xu, Cathy M. Harris, Zelda R. Wasserman, Rui-Qin Liu, Maryanne B. Covington, Mingxin Qian, Krishna G. Vaddi, David D. Christ, Karl D. Hardman, Maria D. Ribadeneira, Robert C. Newton, James M. Trzaskos, and Carl P. Decicco, Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000, Fax: 609-252-7199, james.duan@bms.com*

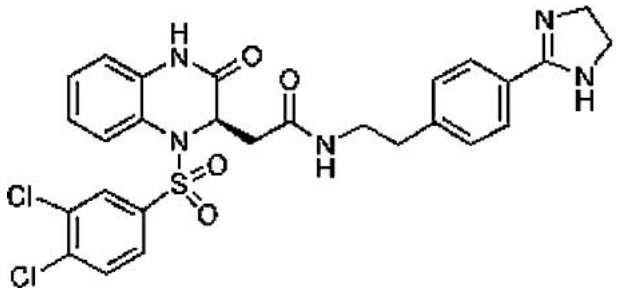
Tumor necrosis factor-α converting enzyme (TACE) is the principal metalloprotease that processes the pro-form of tumor necrosis factor-α (TNFα) to the soluble form. With the clinical success of anti-TNFα biologics in diseases such as rheumatoid arthritis, TACE has attracted significant interest as an intervention point for small molecules to suppress the amount of circulating TNFα. Most of the early TACE inhibitors were derived from inhibitors of structurally related matrix metalloproteinases (MMPs) and hence suffered from lack of TACE selectivity. In an effort to discover selective TACE inhibitors, a series of β-amino hydroxamates was found to be highly potent and selective for TACE relative to MMPs. The design, synthesis and evaluation of these inhibitors will be presented.

202.

DISCOVERY OF A POTENT, NON-PEPTIDE BRADYKININ B1 RECEPTOR ANTAGONIST. ***Dai-Shi Su**, M. Kristine Markowitz, Robert M. DiPardo, Kathy L. Murphy, C. Meacham Harrell, Stacy S. O'Malley, Rick W. Ransom, Ray S. Chang, Sookhee Ha, Fred J. Hess, Douglas J. Pettibone, Glenn S. Mason, Susan Boyce, Roger M. Freidinger, and Mark G. Bock, Department of Medicinal Chemistry, Merck & Co, WP14-3, P. O. Box 4, West Point, PA 19486, Fax: 215-652-3971, daishi_su@merck.com*

Bradykinin (BK) plays an important role in the pathophysiological processes accompanying pain and inflammation. Selective bradykinin B1 receptor antagonists have been shown to be anti-nociceptive in animal models and could be novel therapeutic agents for the treatment of pain and inflammation.

We have explored chemical modifications in a series of dihydroquinoxalinone sulfonamides in order to evaluate the effects of various structural changes on biological activity. The optimization of a screening lead compound, facilitated by a homology model of the BK B1 receptor, culminated in the discovery of a potent human BK B1 receptor antagonist. Results from site directed mutagenesis studies and experiments in an animal pain model are presented.



203.

DISCOVERY OF POTENT AND SELECTIVE CYTOSOLIC PHOSPHOLIPASE A2A INHIBITORS. ***Steve Tam**[1], John C McKew[1], James D. Clark[2], Mark Behnke[1], Lihren Chen[1], Megan Foley[1], katherine Lee[1], Nevena Mollova[3], Elizabeth Murphy[2], Cheryl Nutter[2], Marina Shen[2], Jaechul Shim[1], Weiheng Wang[1], Xin Xu[3], and Wen Zheng[2]. (1) Department of Chemical and Screening Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, Fax: 617-665-5685, stam@wyeth.com, (2) Department of Inflammation, Wyeth Research, (3) Department of Discovery Pharmacokinetics, Wyeth Research*

Cytosolic phospholipase A2 alpha (cPLA2a catalyzes the release of arachidonic acid from phospholipid membranes to initiate the generation of prostaglandins, leukotrienes and platelet-activating factor (PAF). The importance of cPLA2a in lipid mediator biosynthesis has been demonstrated using cPLA2a-deficient mice, where leukotriene, prostaglandin and PAF production were reduced by >90%. Moreover, these "knockout (KO) mice" are healthy, validating cPLA2a as a safe target.

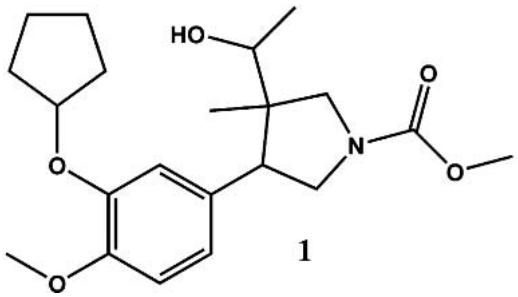
NSAIDs and COX-2 selective inhibitors have validated the clinical utility of inhibiting prostaglandin production in the treatment of pain and inflammation. Thus, a cPLA2a inhibitor, by blocking arachidonic acid release, should also be analgesic and anti-inflammatory. Moreover, the additional inhibition of leukotrienes may yield enhanced efficacy since leukotrienes are pro-inflammatory and have been implicated in dental pain, dysmenorrhea and various animal models of hyperalgesia.

This presentation will cover the identification and characterization of specific inhibitors of cPLA2a as well as our effort in optimizing in vivo efficacy using pharmacokinetic support.

204.

DISCOVERY OF POTENT, SELECTIVE, NON-EMETIC PDE4 INHIBITORS BASED ON A PYRROLIDINE CORE. ***Joshua O. Odingo**[1], Amy R. Oliver[1], Edward A. Kesicki[1], Laurence E. Burgess[2], John J. Gaudino[2], Zachary S. Jones[2], Bradley J. Newhouse[2], Stephen T. Schlachter[2], Susan Wang[1], Carmen Hertel[1], Thomas E. Stephan[1], Timothy J. Martins[1], and Kerry W. Fowler[1]. (1) ICOS Corporation, 22021 20th Avenue SE, Bothell, WA 98021, Fax: 425-635-4183, jodingo@icos.com, (2) Array BioPharma*

Phosphodiesterases are a family of enzymes that hydrolyze cyclic nucleotide intracellular second messengers, cAMP and cGMP. It has been demonstrated that inhibition of the type 4 phosphodiesterase (PDE4), a cAMP-specific enzyme, results in elevation of cAMP in a variety of pro-inflammatory cells, leading to alterations in cytokine release (e.g. TNFalpha) and downregulation of inflammatory response in these cells. Additionally, clinical success of biologically-derived anti-TNFalpha therapeutics validates targeting TNF-alpha. PDE4 has, therefore, become an important molecular target for the development of novel anti-inflammatory therapies including asthma, COPD and rheumatoid arthritis. Despite intense efforts towards the development of PDE4 inhibitors, progress of prototype inhibitors has been hampered by dose-limiting side effects such as nausea and emesis. We present the refinement of our lead compound (1) into highly potent, selective and non-emetic PDE4 inhibitors with good PK properties. A compound from this program is entering Phase 2 clinical trials for COPD.



205.

SELECTIVE ESTROGEN RECEPTOR-BETA AGONISTS ARE POTENT ANTIINFLAMMATORY AGENTS. ***Michael S. Malamas**[1], Heather A Harris[2], James C. Keith[3], Bob McDevitt[1], Iwan Gunawan[1], Christopher P. Miller[1], Leo M. Albert[3], Yelena Leathurby[3], and Eric S Manas[1]. (1) Department of Chemical Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, malamam@wyeth.com, (2) Women's Health Research Institute, Wyeth Research, (3) Department of Musculoskeletal Sciences, Wyeth Research*

The discovery of a second subtype of the estrogen receptor (ERb) in 1996 caused considerable excitement within the scientific community and impetus to identify its physiological role in mediating estrogen action. However, despite extensive use of currently available tools, ERb's physiological role remains unclear and controversial. The approach that has not yet been fully exploited is the use of highly selective ERb selective agonists. Toward this end, we have designed a series of highly potent and selective agonists for ERb and have characterized their activity in several clinically relevant rodent models. This presentation will be the primary disclosure of a ERB-041, a highly selective ERb agonist and clinical candidate. Our design strategy, which included a structure-based approach (using X-ray crystallography data and molecular modeling), will also be discussed. In particular, it will be detailed how these tools allowed us to exploit a single amino acid difference between the two ERs (ERb Ile373 to ERa

Met421). ERB-041 binds to ERb with an IC50 of 3-5 nM, similar to 17b-estradiol, but it is ^{3} 200 fold selective. ERB-041 is inactive in several animal models (uterotrophic, osteopenia, mammotrophic, and ovulation) where nonselective estrogens (e.g. 17b-estradiol) are known to have robust effects. Taken together, our data suggest that ERB-041 has little or no utility in hormone therapy or as a contraceptive agent. However, ERB-041 has a dramatic beneficial effect in the HLA-B27 transgenic rat model of inflammatory bowel disease and the Lewis rat adjuvant-induced arthritis model. Daily oral doses as low as 1 mg/kg reverse the chronic diarrhea of the HLA-B27 transgenic rats and dramatically improve histological disease scores in the colon. The same dosing regimen in the therapeutic adjuvant-induced arthritis model reduces joint scores from 12 (maximal inflammation) to 1 over a period of 10 days. Synovitis and Mankin (articular cartilage) histological scores are also significantly lowered (50-75%). These data suggest that one function of ERb may be to modulate the immune response and that ERB-041 may offer a novel therapy to treat chronic inflammatory conditions.

206.
SIGNAL TRANSDUCTION GENE FAMILIES REGULATING PROTEIN PHOSPHORYLATION: THERAPEUTIC TARGETS AND DRUG DISCOVERY. ***Tomi K Sawyer**, Ariad Pharmaceuticals, 26 Landsdowne Street, Cambridge, MA 02129, tomi.sawyer@ariad.com*

Significant advances in genomics and proteomics related to signal transduction pathways intimately involved in regulating protein phosphorylation have been recently achieved. The genes-to-drug paradigm is especially promising in such efforts to identify, validate and exploit a plethora of promising therapeutic targets (e.g., kinases, phophatases, adapter proteins, and transcription factors), which functionally use phosphorylation to regulate complex cellular processes, to enable drug discovery. This presentation will focus on unraveling the complex biology of such multifunctionalized protein phosphoryation with particular emphasis on dysregulated signal transduction pathways known to exist in a wide range of cancers. Smart chemistry approaches using structure-based as well as mechanism-based drug design for key therapeutic targets will be highlighted.

207.
GENE FAMILY-BASED APPROACHES TO DRUG DISCOVERY. ***Woods Wannamaker**, Department of Chemistry, Vertex Pharmaceuticals, 130 Waverly St, Cambridge, MA 02139, Fax: 617-444-6920, woods_wannamaker@vrtx.com*

Following the sequencing of the human genome, the gene family-based approach to target validation and drug discovery has become widely employed throughout the pharmaceutical industry. A key advantage of this approach is the ability to accelerate the process of medicinal chemistry with subsequent targets within a family by the reuse of chemical and biological information derived with previous targets. The challenge for medicinal chemistry is to design novel, drug-like molecules of "appropriate" selectivity for relevant targets. This presentation will outline how Vertex has approached medicinal chemistry within the kinase gene family keying on the use of structure-based design and biochemical and cellular compound profiling methods to drive the discovery of novel kinase inhibitors.

208.
DESIGNING ARRAYS FOR THE NUCLEAR RECEPTOR GENE FAMILY. ***Peter J. Brown**, High Throughput Chemistry, GlaxoSmithKline, 3030 Cornwallis Road, Research Triangle Park, NC 27709, Fax: 919-315-0430, pjb5890@gsk.com*

The nuclear receptor (NR) gene family comprises 48 proteins, 25 of which have natural or synthetic ligands identified. Many of these targets are high-value, clinically validated targets for the treatment of diseases such as diabetes and asthma. In an effort to optimize the efficiency of chemistry resources, we are interested in developing array design techniques which combine the advantages of parallel synthesis (chemical diversity) with screening against multiple nuclear receptor targets (biological diversity).

One method involves calculating 3D molecular descriptors for known ligands, and using this information to define NR chemical space. Proposed virtual arrays are profiled against this targeted space, enabling the prioritization of different chemistries.

In another method, X-ray crystallography data is available for 19 ligand-binding domains out of 28 protein sub-groups, and this structural data can be used in docking experiments with virtual arrays.

209.
MINING INFORMATION FROM THE STEROID HORMONE BINDING SUBFAMILY OF NUCLEAR RECEPTORS: PROTEIN MODELING AND LIGAND BINDING STUDIES ON GR AND ERR-γ. ***Wendy D. Cornell**, Central Technologies, Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, NJ 07936, wendy.cornell@pharma.novartis.com, Kiyean Nam, Department of Molecular Genetics, Microbiology, and Immunology, University of Medicine and Dentistry of New Jersey, and Paul Marshall, Arthritis and Bone Metabolism, Novartis Institutes for Biomedical Research*

Members of the NR3 or steroid hormone binding subfamily of nuclear receptors serve as targets for a number of drugs on the market. A wealth of protein structure and ligand data is available for this subfamily. Using this protein structure data, a homology model was developed for the protein Glucocorticoid Receptor (GR) and applied to virtual screening studies aimed at identifying non-steroid ligands. An approach which combined docking and pharmacophore screening was found to yield superior results to one based on 2D descriptors derived from Estrogen Receptor (ER) ligands. A homology model was also built for the orphan nuclear receptor Estrogen Related Receptor ERR-γ. Molecular dynamics simulation studies of the ERR-DES and ER-DES complexes provided insight into the opposing pharmacological effects of this ligand on the two related receptors. Finally, we compare the GR and ERR-γ homology models with recently available x-ray crystal structures of these targets.

210.
GRID/CPCA METHOD: A COMPUTATIONAL TOOL TO ANALYZE PROTEIN FAMILIES AND TO DESIGN SELECTIVE LIGANDS. ***Thomas Fox**[1], Mika A. Kastenholz[1], Manuel Pastor[2], Gabriele Cruciani[2], and Eric E. J. Haaksma[1]. (1) Department of Lead Discovery / Computer Aided Molecular Design, Boehringer-Ingelheim Pharma GmbH & Co, 88397 Biberach, Germany, Fax: 49 07351 83 7585, thomas.fox@bc.boehringer-ingelheim.com, (2) Laboratory of Chemometrics, Department of Chemistry, University of Perugia*

A new method has been developed which helps in obtaining ligands with the ability to interact more selectively with a certain receptor among a set of related ones. The GRID/CPCA method starts from a set of protein structures, ideally complexed with some ligand or inhibitor. The proteins are then superimposed and the binding sites are described with the use of GRID, a program which generates for each receptor a set of molecular interaction fields (MIF) between the protein and some "probes" representing relevant chemical groups. In a second stage, the MIF are analyzed using Consensus Principal Component Analysis (CPCA). This analysis highlights the regions in the receptor which are more interesting to target selective interactions, and points to the interesting interaction types. This methodology also allows the comparison of a large number of proteins from a protein family, thus defining similarity from a ligand point of view.

The GRID/CPCA method was applied to a set of serine proteases as well as to matrix-metalloproteases, producing interesting results which will be shown and discussed.

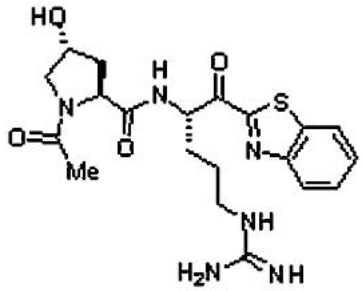
211.
POTENT, ORALLY ACTIVE AND NON-EMETIC PHOSPHODIESTERASE-4 INHIBITORS. ***Daniel Guay**, Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, P. O. Box 1005, Pointe Claire-Dorval, QC H9R 4P8, Canada, Fax: 514-428-4900, daniel_guay@merck.com*

Following a number of findings in basic research associated with inflammation, it has been proposed that intracellular modulation of cAMP levels by selective phosphodiesterase type 4 (PDE4) inhibitors might be a promising novel approach for the treatment of chronic inflammatory diseases such as asthma COPD and rheumatoid arthritis. Indeed, compounds such as CDP-840 have been reported to reduce the bronchoconstriction induced by antigen in asthmatic patients. We will report on our efforts to discover potent PDE4 inhibitors by optimizing the lead compound CDP-840 and by exploring new structural series. The resolution of issues related to metabolism and to side effects such as emesis and QTc interval prolongation will be discussed. This work led to the identification of inhibitor L-869,298 which exhibits excellent in vitro and in vivo

activity. Also, compounds reported in the literature, as development candidates for asthma, will be discussed.

212.
POTENT, SMALL-MOLECULE INHIBITORS OF HUMAN MAST CELL TRYPTASE. ANTI-ASTHMATIC ACTION OF A DIPEPTIDE-BASED TRANSITION-STATE ANALOGUE CONTAINING A BENZOTHIAZOLE KETONE. ***Michael J. Costanzo***[1], *Steven C. Yabut*[1], *Harold R. Almond Jr.*[1], *Patricia Andrade-Gordon*[1], *Thomas W. Corcoran*[1], *Lawrence de Garavilla*[1], *Jack A. Kauffman*[1], *William M. Abraham*[2], *Rosario Recacha*[3], *Debashish Chattopadhyay*[3], *and Bruce E. Maryanoff*[1]. *(1) Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh and McKean Roads, P.O. Box 0776, Spring House, PA 19477, Fax: 215-628-4985, mcostanz@prdus.jnj.com, (2) Department of Research, Mount Sinai Medical Center, (3) Centre for Macromolecular Studies, University of Alabama at Birmingham*

While exploring analogues of potent α-ketoheterocycle thrombin inhibitors, we discovered interesting low-molecular-weight β-tryptase inhibitors. Inhibitors of human mast cell β-tryptase have therapeutic potential for the treatment of allergic or inflammatory disorders, such as asthma. We have investigated a series of reversible, transition-state mimetic inhibitors that possess a heterocycle-activated ketone group, resulting in RWJ-56423 (Ki=10 nM). In preclinical studies with sheep, the advanced lead was effective in preventing both the early and late phases of asthma, as well as the airway hyperreactivity response, after three days of aerosol dosing. RWJ-56423 has since advanced into human clinical study. The design, synthesis, structure-activity relationships (SAR), and biological properties of this promising series will be presented.



RWJ-56423
tryptase K_i = 10 nM

213.
NOVEL ANTI-ASTHMA DRUGS BASED ON ADENOSINE. ***John R. Fozard****, Institute of Biomedical Research, Novartis Pharma Ltd, CH-4002 Basel, Switzerland, Fax: +41613242733, john_r.fozard@pharma.novartis.com*

Compelling evidence for a role for adenosine in the pathophysiology of asthma, the plurality of its receptor mechanisms and the advent of lead agonist and antagonist ligands conspire to make novel therapeutics based on adenosine a growth area in the pharmaceutical industry. Endogenous adenosine acting through A2A receptors is an essential part of the physiological feedback mechanism for limitating inflammation. Selective agonists at this site powerfully suppress pulmonary inflammation induced by allergen in rodent models of asthma and could provide a viable alternative to glucocorticosteroids as anti-inflammatory agents in asthma. A2B receptors mediate the synergistic effects of adenosine and allergen on human mast cells. Selective A2B receptor antagonists could provide an improved theophylline of particular relevance to the treatment of allergen/exercise-induced asthma. Agonists or antagonists at the A3 receptor could provide therapeutic benefit. Compounds designed to activate the A2A receptor or block the A2B receptor and are in clinical development.

214.
ALPHA4 INTEGRIN ANTAGONISTS: A NEW CLASS OF ANTIINFLAMMATORY AGENTS FOR TREATMENT OF AUTOIMMUNE DISEASES. ***David Y. Jackson****, Medicinal Chemistry, Genentech, 1 DNA Way, South San Francisco, CA 94080, Fax: 650-225-2061*

The accumulation of leukocytes in various organs contributes to the pathogenesis of a number of human autoimmune diseases such as asthma, rheumatoid arthritis, Crohn's disease, ulcerative colitis, hepatitis C, and multiple sclerosis. The inflammatory processes leading to tissue damage and disease are mediated in part by the a4 integrins, a4b1 and a4b7, expressed on the leukocyte cell surface. These receptors modulate cell adhesion via interaction with, vascular cell adhesion molecule (VCAM) and mucosal addressin cell adhesion molecule (MAdCAM), expressed in the affected tissue. Elevated cell adhesion molecule (CAM) expression in various organs has been linked with a number of autoimmune diseases. Monoclonal antibodies specific for a4 integrins or their cell adhesion molecule ligands can moderate inflammation in animal models suggesting such inhibitors may be useful for treating human autoimmune diseases. This paper reviews our efforts to identify and develop alpha4 antagonists as therapeutic agents.

215.
COMBINATORIAL LIBRARIES TARGETING PROTEIN–PROTEIN OR PROTEIN–DNA INTERACTIONS. ***Dale L. Boger****, Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, Fax: 858-784-7550, boger@scripps.edu*

Recent studies on the solution-phase synthesis of combinatorial libraries and the development of techniques for their examination against a series of protein–protein or protein–DNA targets will be described including (1) EPO agonists that act by promoting cell surface EPO receptor dimerization, (2) inhibitors of MMP2/$\alpha_v\beta_3$, (3) inhibitors of paxillin/α_1, (4) inhibitors of Myc/Max dimerization, and (5) inhibitors of LEF-1/β-catenin DNA binding.

216.
TOOL COMPOUNDS TO BLOCK INTRACELLULAR PROTEIN-PROTEIN INTERACTIONS. ***Carlos Garcia-Echeverria****, Oncology Research, Novartis Pharma AG, WKL-136.4.84, CH-4002 Basel, Switzerland, Fax: 41 61 696 62 46, carlos.garcia-echeverria@pharma.novartis.com*

Our ability to select therapeutically relevant protein-protein interactions is going to be challenged by the number of new proteins identified by genomics and proteomics. Parallel to our efforts to establish generic approaches to discover potent and effective antagonists of protein-protein interactions, we will have to be able to provide up-front tool compounds to assess and validate the "right" interaction. One potential avenue in this extremely demanding endeavour can be the use of functional antagonists linked to molecular transporters. Polymers containing cationic motifs have been shown to translocate across cell membranes and deliver a covalently linked "molecular cargo" to cytoplasmic and/or nuclear targets. The intracellular delivery of exogenous compounds by this noninvasive method can be an effective approach to study intracellular natural interactions, and validate this class of therapeutic targets in cellular settings and/or animal models before substantial investments are made in drug discovery. New molecular transporters and their potential applications in this area of research will be presented.

217.
CHEMICAL BIOLOGY OF PROGRAMMED CELL DEATH AND HIV-1 ENTRY: STUDYING AND INHIBITING THEIR PROTEIN-PROTEIN INTERACTIONS WITH NOVEL SYNTHETIC MOLECULES. ***Ziwei Huang****, Departments of Biochemistry and Chemistry, University of Illinois at Urbana-Champaign, 407 South Goodwin Avenue, MC-119, Urbana, IL 61801, z-huang@life.uiuc.edu*

Two representative areas of our research will be presented in this talk: Bcl-2 family proteins and chemokine receptors. Bcl-2 family proteins play a key role in regulating apoptosis or programmed cell death and are implicated in cancer and other diseases. We have discovered and studied synthetic molecules that act as antagonists of the Bcl-2 family. Progress in using these molecules as leads to develop a new class of anticancer drugs and probes to study basic mechanism of Bcl-2-regulated signaling pathways are discussed. Chemokine receptors such as CXCR4 are essential co-receptors required for the cellular entry of HIV-1 and thus represent important targets for anti-HIV drug development. We have synthesized unnatural ligands of CXCR4 and used them to probe the mechanism of ligand-CXCR4 interaction and signal transduction. The implications of these studies for the development of new anti-HIV agents are discussed.

218.
CAPTURING THE SAR OF PROTEINS IN THE SEARCH FOR ANTAGONISTS OF PROTEIN PROTEIN INTERACTIONS. ***Thomas R. Gadek****, Department of Bioorganic Chemistry, Genentech, Inc, One DNA Way, South San Francisco, CA 94080, Fax: 650-225-2061, trg@gene.com*

Alanine mutagenesis data coupled with structural studies of interacting proteins has enabled the definition of each protein's structure activity relationship (SAR),

their individual epitopes and the energetics of their protein-protein interaction. Consequently, a rational search for antagonists of a protein interaction can begin with considerations of the SAR of one of the protein partners. Mimicry of aspects of a protein epitope can identifying small molecule leads which bind to and antagonize that protein's cognate partner. This presentation will discuss the successful application of this approach to the identification of potent immunosuppressive agents which mimic ICAM-1 and antagonize LFA-1.

219.

SYNTHETIC APPROACHES TO DISRUPTING PROTEIN-PROTEIN INTERACTIONS. ***Andrew D. Hamilton**, Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520-8107, Fax: 203-432-3221, andrew.hamilton@yale.edu*

In this lecture we will describe a program aimed at the design of synthetic agents that can recognize the exterior surface of proteins and block protein-protein interactions involved in oncogenic signaling pathways. The unique distribution of charged, hydrophobic and hydrophilic groups on the surface of proteins offers the potential that well-designed artificial receptors will bind strongly and selectively. By analogy to the antigen combining site of the antibody FAB fragment, we have constructed a family of synthetic agents in which multiple recognition regions are attached to a core scaffold to form a complementary surface to the protein-protein interface. The strategy will be exemplified with two examples. The first involves the design of synthetic agents that can recognize the exterior surface and antagonize the function of growth factors that are critically involved in oncogenesis. In particular, we have identified molecules that bind to PDGF, prevent it from binding to its receptor tyrosine kinase, and block PDGF-induced receptor autophosphorylation and activation of Erk1 and Erk2. These leads are potent (IC50 <250nM) and selective for PDGF over EGF, IGF-1, aFGF, and bFGF and show significant inhibition of tumor growth and angiogenesis a nude mouse model. In a second example we will describe synthetic mimics of alpha-helical domains involved in protein-protein interactions. In particular we have designed terphenyl-based mimics of the BH3 helix of Bak and shown by fluorescence polarization and NMR that they bind to BclxL with a Kd of 100nM and disrupt the Bak/BclxL complex.

220.

INTERFERING WITH PROTEIN-PROTEIN IN RAS MEDIATED CELL SIGNALING PATHWAYS. ***Lutz Weber**, Morphochem AG, Gmunder Str. 37-37a, Muenchen 81379, Germany, Fax: 49-89-78005-555, lutz.weber@morphochem.de*

The mitogen activated Ras-Raf-Mek-Erk signaling pathway is one of the better studied MAPK-pathways. Mutated Ras protein has been identified as an oncogenein several cancer types, working through an overtly enhanced MAPK signaling.The discovery of inhibitors of Ras signaling is aiming at a new therapy for Ras dependent cancers. Various concepts have been followed: farnesyltransferase inhibitors as well as ATP mimetic kinase inhibitors for the Raf, Mek and Erk kinase have been developed and are currenly in clinical trials. Morphochem's drug discovery approach targets to inhibit the protein-protein interaction of Ras with Raf, aiming at molecules with more specificity and less general toxicity. Using a yeast 2-hybrid screening technology we identified molecules that block the interaction of H-Ras with c-Raf. A range of biological assay technologies was used to both establish and study the mode-of-action of these novel protein-protein interaction inhibitors: protein expression arrays, gene-reporter cell lines as well as phenotypic cell based assays. The use of our protein interaction inhibitors as "chemical genomic" tools lead to a better understanding of the Ras-Raf signaling pathway and possible therapeutic applications. Contrary to known kinase inhibitors, and as a result of their mode-of-action our protein interaction inhibitor are not generally cytotoxic. However, significant inhibition of Ras down-stream gene expression as well as inhibition of anchorage independent growth was observed in a range of Ras dependent cell lines.

221.

BIOTOPOLOGY OF ANDROGEN RECEPTOR. *Demet Gurel, Chemistry and Physics, Touro College, 27-33 West 23rd Street, New York, NY 10010, Fax: 212-684-0597, protein@attglobal.net, and **Okan Gurel**, IBM, 630 First Avenue, New York, NY 10016, Fax: 212-684-0597, protein@attglobal.net*

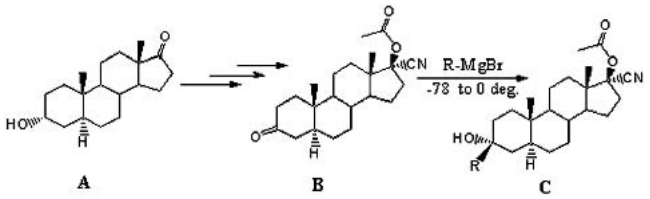
The human androgen receptor (AR) with 919 amino acid residues folds as DO(18-9). We analyze the topology of the activation function (AF1) (residues 142-337) and AF2 in the ligand binding domain (LBD residues 676-919), [Fig.1]. We also show that the motifs WXXLF (residues 433-437) and FXXLF (residues 23-27) fall on a topologically significant positions revealed by the topology of the folded DO(18-9). In addition, chiralities of the DNA binding site alters between the two possible isomers of the folded AR.

222.

SYNTHESIS OF NEUROSTEROIDS : 3-β-SUBSTITUTED,17-α-CYANO-17-β-ACETYL-5-α-ANDROSTAN-3-α-OLS. *David Y.W. Lee, Bio-Organic and Natural Products Lab, McLean Hospital, Harvard Medical School, 115 Mill Street, Fax: 617-855-2040, dlee@mclean.harvard.edu, and **Leelakrishna Kondaveti**, Bioorganic and Natural Products/Dept of Psychiatry, McLean Hospital/Harvard Medical School, MRC-311, 115 Mill Street, Fax: 617-855-2040, krishna_kondaveti@hms.harvard.edu*

$GABA_A$ receptor- chloride ion channel complex is a target for several therapeutically useful anticonvulsants, anxiolytics and sedatives such as benzodiazepines and barbiturates. There is a large body of evidence suggesting a distinct modulatory site on $GABA_A$ receptor that binds to neuroactive steroids. Previous *in vitro* and *in vivo* SAR studies indicated that steroidal $GABA_A$ receptor modulators must possess a 3-α hydroxylated A ring. Naturally occurring neuroactive steroids have therapeutic limitations because they are rapidly metabolized *in vivo* presumably by oxidation of 3-α hydroxyl to corresponding ketones. Recent studies show that certain modifications by blocking the metabolic sites at 3-β and 17-α positions resulted in greater *in vitro* potencies compared to the naturally occurring neuroactive steroid (3-α , 5-α THP). Ganaxalone is a synthetic neurosteroid and is undergoing clinical trials for the treatment of Epilepsy.

In the present report, we describe the synthesis of a series of novel 3-α Hydroxy, 3-β and 17-substituted steroids to study their $GABA_A$ binding interaction. Oxidation of compound **A** followed by selective protection of 3-ketone and hydrocyantion of 17-oxo steroid yields 17-α cyanohydrin. Acetylation of 17 hydroxy group and deprotection of 3-ketal results in compound **B** . Compound **B** on reaction with appropriate Grignard reagents yields the target 3-α hydroxy Compound **C** along with the inactive 3-β hydroxy diastereomer.

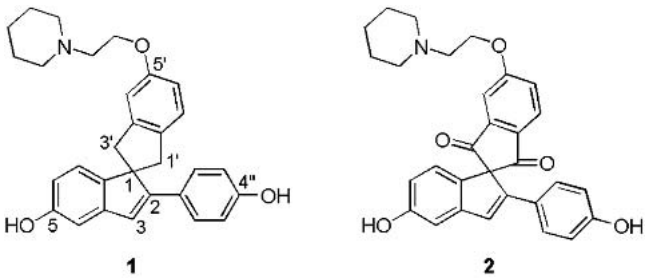


R = CH_3, C_6H_5, C_2H_5, CH=CH, CH=CH-CH_3, HC≡CH

223.

COMPARISON OF 2-PHENYLSPIROINDENES AND 2-PHENYLSPIROINDENEDIONES AS ESTROGEN RECEPTOR LIGANDS. ***Timothy A. Blizzard**, Ralph T. Mosley, Elizabeth T. Birzin, Wanda Chan, and Milton L Hammond, Merck Research Laboratories, RY800-B116 P.O. Box 2000, Rahway, NJ 07065, tim_blizzard@merck.com*

A series of 2-phenylspiroindenediones (e.g. 2) was prepared. The spiroindenediones were found to be less active than the corresponding spiroindenes (e.g. 1) as estrogen receptor ligands and failed to demonstrate the receptor subtype selectivity that molecular modelling predicted.

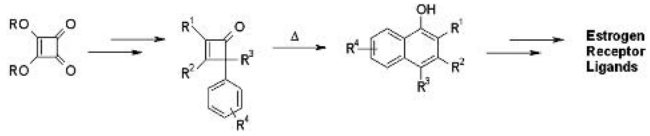


1 **2**

224.

CYCLOBUTENONE-BASED SYNTHESIS OF LIGANDS FOR THE ESTROGEN RECEPTOR. ***Philip Turnbull**, Department of Medicinal Chemistry, GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709, Fax: 919-315-5668, philip.s.turnbull@gsk.com*

Organolithium additions to squarate esters afforded highly substituted cyclobutenones. Thermolytic ring opening of these cyclobutenones and subsequent 6-π electrocyclization gave highly substituted naphthols that are difficult to access through standard aromatic substitution methods. Further functionalization of the naphthol scaffolds furnished highly potent ligands for the estrogen receptor.



225.

DESIGN AND SYNTHESIS OF NOVEL ESTRADIOL ANALOGUES TARGETING THE MEMBRANE ESTROGEN RECEPTOR. ***Trevor T. Charvat**[1], Ali Pedram[2], Mahnaz Razandi[2], Ellis R. Levin[2], and A. R. Chamberlin[1]. (1) Department of Chemistry, University of California, Irvine, Irvine, CA 92697-2025, tcharvat@uci.edu, (2) Division of Endocrinology, Veterans Affairs Medical Center, Long Beach*

The transcriptional effects of estradiol (E_2) are traditionally considered to be mediated exclusively via the nuclear estrogen receptor (*n*ER). However, emerging evidence suggests that E_2 may elicit both genomic and non-genomic effects via a putative membrane-bound estrogen receptor (*m*ER). These findings prompted the search for novel ligands that can selectively bind the *m*ER. We present the design, synthesis, and biological evaluation of a series of 17α-substituted E_2 analogs in an effort to probe the intracellular signal transduction pathways implicated in E_2 promoted *m*ER activation.

226.

DESIGN, SYNTHESIS, AND IN VITRO BIOLOGICAL EVALUATION OF A CLASS OF DOXORUBICIN-FORMALDEHYDE CONJUGATES TARGETED TO ESTROGEN RECEPTOR-POSITIVE BREAST CANCER. ***Patrick J. Burke**, and Tad H. Koch, Department of Chemistry and Biochemistry, University of Colorado, Campus Box 215, Boulder, CO 80309, Fax: 303-492-5894, Patrick.Burke@colorado.edu*

The anthracycline antitumor drug, doxorubicin, is one of the most effective chemotherapeutic agents employed in the treatment of breast cancer. Although the cytoxic mechanism is not entirely understood, DNA is clearly a target and formaldehyde-mediated DNA alkylation plays a role in the cytotoxic action of the drug. Recent results indicate that induction of oxidative stress culminating in the production of formaldehyde is an important event in the activation of doxorubicin. Some of the formaldehyde is trapped by doxorubicin and used to alkylate DNA at 5′-NGC-3′ sequences which, in rapidly dividing cells, plays a role in cell death. A 12-step synthesis of doxorubicin-formaldehyde conjugates chemically tethered to a derivative of 4-hydroxytamoxifen, an antiestrogen that tightly binds the estrogen receptor, will be reported. The tether includes a group that releases the doxorubicin-formaldehyde conjugate from the hydroxytamoxifen targeting group. Estrogen receptor binding and in vitro growth inhibition of breast cancer cells as a function of estrogen receptor and multidrug resistance expression will also be presented.

227.

SYNTHESIS OF QUINAZOLIN-4-ONE ANALOGUES OF RALOXIFENE AS POTENTIAL BONE-SPARING AGENTS. ***Arthur A. Santilli**, and Marci C. Koko, Chemical Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, Fax: 484 -865- 9398, Santila@wyeth.com*

Our research,directed toward the discovery of tissue-specific antiestrogenic bone-sparing compounds, led us to consider substituting a quinazolin-4-one scaffold in replacement of the benzo[b]thiophene-3-keto template present in the antiestrogenic bone-sparing agent raloxifene. Raloxifene(Evista®)is currently being marketed by Lilly for this indication. Raloxifene has been found not to be free of undesirable uterotrophic effects in an ovx rat model. We were interested in the possibility of identifying a bone-sparing agent that is less uterotrophic in this model with an improved overall biological profile to that of raloxifene. We now report an early approach in attempting to achieve this goal. We have synthesized in several steps three novel isomeric quinazolin-4-ones having various structural features in common with raloxifene. The syntheses, rationale for their design and biological test results of these compounds will be presented.

228.

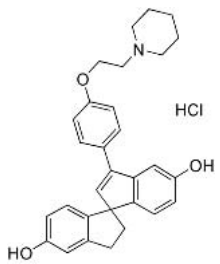
OS-0689üF A NOVEL SELECTIVE ESTROGEN RECEPTOR MODULATOR WITH UNIQUE BIOLOGICAL PROFILES IN HOT FLUSH MODEL. ***Akihisa Ikeno**[1], Hisao Minato[1], Chie Kohayakawa[1], Nobuhide Watanabe[2], Hiroshi Nakagawa[2], and Jun-ichi Tsuji[1]. (1) Pharmacology & Microbiology Researchü@Laboratories, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita, Osaka 564-0053, Japan, akihisa-ikeno@dainippon-pharm.co.jp, (2) Chemistry Research Laboratories, Dainippon Pharmaceutical Co., Ltd*

Hot flushes are the most common symptom of climacteric and occur in up to 80% of perimenopausal and postmenopausal women of whom 10-20% experience severe symptom. Given the increased risk of breast cancer associated with hormone replacement therapy (HRT), the most effective treatment for hot flushes, there seems to be an urgent need for new treatments that retain HRT effectiveness without the associated side effects. Although nonsteroidal selective estrogen receptor modulators (SERMs) have been reported to have no beneficial effect on hot flushes, we assumed that OS-0689, a novel SERM, might be imparted an unprecedented biological profile due to its unique structure characteristics. In this study, we examined the effects of OS-0689 on hot flush using a rat model. Indeed, like β-estradiol (E2), OS-0689 improved temperature change in rat tail skin and had no antagonistic effect on E2-induced temperature change. Additionally, like other SERMs, OS-0689 inhibited the reduction of bone mineral density in ovariectomized (OVX) rats and, unlike E2, had marginal effects on uterine weight compared to OVX controls. Detail of the results will be discussed.

229.

SPIRO[INDENE-1,1′-INDANE]-5,5′-DIOLS: A NOVEL CLASS OF SELECTIVE ESTROGEN RECEPTOR MODULATORS. ***Nobuhide Watanabe**[1], Hiroshi Nakagawa[1], Akihisa Ikeno[2], Hisao Minato[2], Chie Kohayakawa[2], Jun-ichi Tsuji[2], and Katsumi Chiba[1]. (1) Chemistry Research Laboratories, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita, Osaka 564-0053, Japan, nobuhide-watanabe@dainippon-pharm.co.jp, (2) Pharmacology & Microbiology Researchü@Laboratories, Dainippon Pharmaceutical Co., Ltd*

Tamoxifen and raloxifene have been widely used in the treatment of breast cancer and osteoporosis and as selective estrogen receptor modulators (SERMs) have shown potential benefits for women′s health. Despite numerous efforts for the development of novel classes of SERMs that have all the beneficial effects of estrogens but not their adverse effects, little success has been reported. Recently, we have found spiro[indene-1,1′-indane]-5,5′-diol as a promising motif for estrogen receptor ligands. Extensive structure-activity relationship (SAR) studies on this class of compounds led to the discovery of OS-0689 ((+)-enantiomer), a new SERM with highly potent in vivo effects on bone and lipid metabolism. The asymmetric synthesis and SAR of the compounds will be presented.



OS-0689

230.

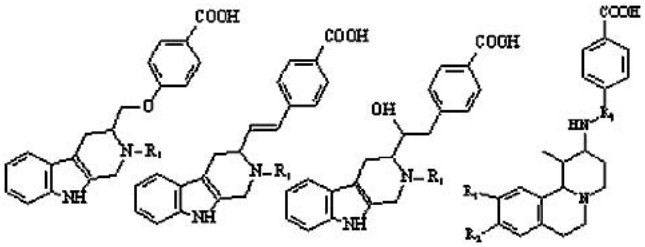
NOVEL PYRROLE-CONTAINING PROGESTERONE RECEPTOR MODULATORS. ***Jay Wrobel***[1], *Mark A. Collins*[2], *Valerie Hudak*[2], *Reinhold Bender*[2], *Andrew Fensome*[2], *Puwen Zhang*[2], *Lori Miller*[2], *Richard Winneker*[3], *Zhimming Zhang*[3], *Yuan Zhu*[3], *and Rayomond J. Unwalla*[2]. *(1) Chemical and Screening Sciences, WyethResearch, 500 Arcola Rd, Collegeville, PA 19426, wrobelj@wyeth.com, (2) Chemical and Screening Sciences, Wyeth Research, (3) Women's Health and Bone, Wyeth Research*

A series of 1,4-dihydro-2H-[d][3,1]-benzoxazin-2-one and 1,3-dihydro-[3H]-indol-2-one containing 6- or 5-respectively appended substituted pyrrole moieties were synthesized and evaluated for their ability to modulate the biology of the progestin receptor. Key structural changes in the pyrrole moieties of these molecules were shown to have a predictive influence as to whether the compounds behaved as PR receptor agonists or antagonists.

231.

DESIGN, SYNTHESIS AND EVALUATION OF SUBTYPE SELECTIVE RETINOID RECEPTOR LIGANDS. ***Weilin Sun***[1], *Huri Piao*[1], *Maureen Feege*[1], *Shyam Desai*[1], *Jerome L. Gabriel*[2], *and Daniel J Canney*[1]. *(1) Dept of Pharmaceutical Sciences, Temple University, Philadelphia, PA 19140, canney@temple.edu, (2) Dept of Biochemistry, School of Medicine, Temple University*

Retinoids regulate many important biological processes including growth and differentiation of cells and modulation of apoptosis. Retinoids have been used in the treatment of dermatological disorders and certain types of cancer. The toxicity of these agents may be due to their ability to bind and activate various subtypes of retinoic acid receptors (RARs; a, b, g subtypes). Accordingly, ligands that exhibit subtype selectivity provide valuable tools for receptor characterization and ultimately, may lead to useful therapeutic agents. Novel ligands for RARs were designed based on molecular modeling studies and structure-activity relationship (SAR) data. Synthetic routes to the proposed ligands were devised based on precedented procedures. Ligands were evaluated in binding studies for the ability to inhibit the specific binding of [3H]-ATRA. Promising ligands (ki < 100 nM) were evaluated further for activity in transactivation assays to determine whether the compounds display agonist or antagonistic activity.



232.

SYNTHESIS AND MAMMARY CANCER CHEMOPREVENTIVE ACTIVITY OF A NEW CONFORMATIONALLY DEFINED RETINOIC ACID ANALOG, UAB76. ***Venkatram R. Atigadda***[1], *Wayne J Brouillette*[1], *Clinton J. Grubbs*[2], *and Donald D. Muccio*[1]. *(1) Department of Chemistry, University of Alabama at Birmingham, 901 14th Street South, Birmingham, AL 35294, Fax: 205-934-2543, venkatra@uab.edu, (2) Chemoprevention Center, University of Alabama at Birmingham*

Retinoids are a group of natural and synthetic vitamin A analogs and are promising agents for the prevention and treatment of a variety of cancers and diseases. The anti-cancer effects of these retinoids are mainly mediated by their nuclear receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). Each of these receptors has three sub-types α, β and γ. Retinoids that activate the RXRs display potential for chemoprevention of breast cancer. Here we will present the synthesis and biological activity of conformationally constrained retinoid 9cUAB76. 9cUAB76 is an RXR selective agonist that is very effective in the prevention of MNU-induced mammary cancers in rats (68% reduction at 200mg/kg of diet) without overt signs of toxicity.

233.

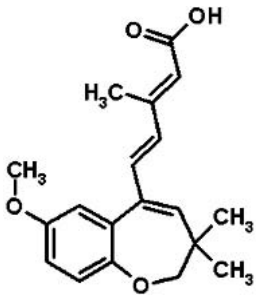
COMPETITIVE BINDING OF RETINOIDS TO CELLULAR RETINOIC ACID-BINDING PROTEIN TYPE I. ***Amy Marie Waligorski***[1], *Jeffrey R. Kovacs*[2], *Karl Anderson*[2], *Wilson S. Meng*[2], *and Jeffrey D. Evanseck*[3]. *(1) Center for Computational Sciences, Duquesne University, Department of Chemistry and Biochemistry, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, waligor805@duq.edu, (2) Division of Pharmaceutical Sciences, Duquesne University, (3) Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

Synthetic retinoids (Vitamin A derivatives) and retinoic acid (RA) have shown promise for the treatment and prevention of several cancers. Retinoic acid receptors (RARs), and cellular retinoic acid-binding proteins (CRABPs) are two classes of proteins that play roles in mediating the biological effects of RA. The exact mechanism by which these proteins interact with retinoids in order to invoke an immune response is not known. Docking studies and molecular dynamics simulations have been carried out in order compare the interactions of known retinoids, retinol and fenretinide, and the details of the interactions occurring within these complexes have been analyzed. We also used the simulations in order to evaluate the competitive binding of retinoids to the CRABP I protein. Modified retinoids are predicted to create more effective anti-cancer agents.

234.

EMD 336340, A SUBSTITUTED PENTADIENOIC ACID, AS A NOVEL BALANCED ACTIVATOR OF PPAR ALPHA AND GAMMA. *Michel Brunet,* ***Jean-Jacques Zeiller****, Jean-Jacques Berthelon, Francis Contard, Valérie Guyard-Dangremont, Hervé Dupont, and Daniel Guerrier, Research and Development Center, MERCK SANTE, 115 avenue Lacassagne, 69424 Lyon Cedex 03, France, Fax: 33-4-72-68-30-99, jean-jacques.zeiller@merck.fr*

A new series of substituted pentadienoic acids was synthesized as potential hypoglycemic and hypolipidemic agents. The synthesis of one representative of this new chemical family, EMD 336340 (LM 4156), is described. EMD 336340 activated both PPAR α and γ receptors in an in vitro cellular model using Gal4-hPPAR chimera. In vivo the activity has been shown in db/db mouse, a predictable model of Type 2 diabetes. This balanced effect offers a potential monotherapy in the management of hyperglycemia and dyslipidemia in type 2 diabetic patients.



235.

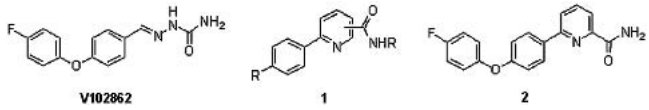
SYNTHESIS AND EVALUATION OF SUBSTITUTED PHENYLPROPANOIC ACIDS AS STRUCTURALLY NEW PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS: THE DISCOVERY OF POTENT AND HUMAN PPAR ALPHA SUBTYPE-SELECTIVE AGONIST. ***Hiroyuki Miyachi****, Masahiro Nomura, Takahiro Tanase, Tomohiro Ide, Masaki Tsunoda, Masahiro Suzuki, Michiaki Nagasawa, Hideharu Uchiki, and Koji Murakami, Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd, 2399-1 Mitarai, Nogi-machi, Shimotsuga-gun, Tochigi 329-0114, Japan, Fax: 81-0280-57-1293, hiroyuki.miyachi@mb2.kyorin-pharm.co.jp*

A series of substituted-phenylpropanoic acids was prepared for the creation of PPAR alpha agonists. SAR studies indicated that the nature of the substituent at the alpha position of the carboxyl group, the distance between the carboxyl group and the right side benzene ring, the linking group between the right side benzene ring and the left side benzene ring, and the substituent at the distal hydrophobic tail all play key roles in determining the potency and the selectivity. Transactivation study using chimera-PPAR alpha indicated that the species-selectivity of these compounds was mediated via the specific interaction between these compounds and the side chain of a crucial amino acid (Ile272)

located in the helix 3 region of PPAR alpha. This study has led to the identification of potent and human PPAR alpha-selective optically active derivative (KCL), which will be useful as candidate drug for the treatment of altered metabolic homeostasis.

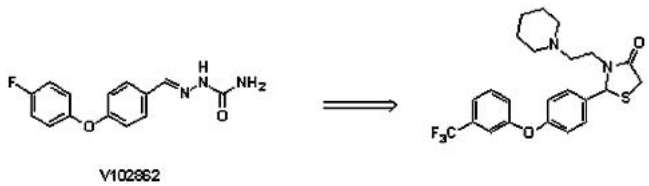
236.
DESIGN AND SYNTHESIS OF NOVEL PYRIDINECARBOXAMIDE SODIUM CHANNEL BLOCKERS. ***Sam F. Victory***, *Qun Sun, R. Richard Goehring, Bin Shao, Derk Hogenkamp, Phong Nguyen, Deyou Sha, Chongwu Zhang, Khondaker Islam, Donald J. Kyle, Jim Limberis, Victor I. Ilyin, and Silvia Robledo, Discovery Research, Purdue Pharma, L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, sam.victory@pharma.com*

V102862 is a potent state-dependent sodium channel blocker (Ki=370 nM, rBIIa) that has been shown to be efficacious in the Chung model of neuropathic pain. Toward the discovery of a second-generation compound having an improved pharmaceutical profile, we embarked on a systematic structure–activity investigation aiming to replace the semicarbazone moiety of V102862 with various heterocycles as bioisosteric replacements. In this effort, the synthesis of compounds containing a pyridine ring as a replacement was carried out. Analogues of type 1 were prepared using the Suzuki coupling reaction as a means of forming the biaryl pyridine unit, utilizing both solution-phase and solid-phase strategies. Compound 2 was identified as a potent state-dependent sodium channel blocker (Ki=101 nM, DRG, TTX-S) and also shown to be effective in the Chung model of neuropathic pain. Details of the synthesis, SAR, and in vivo data of analogues will be presented.



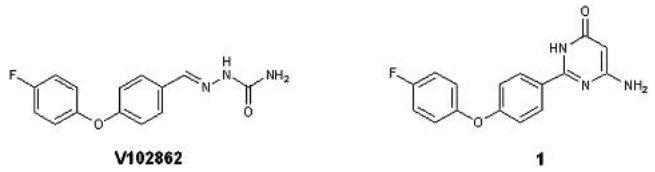
237.
PARALLEL SYNTHESIS OF A BIASED LIBRARY OF THIAZOLIDINONES AS A NOVEL SODIUM CHANNEL ANTAGONISTS. ***Laykea Tafesse***[1], *Qun Sun*[1], *James T. Limberis*[2], *Khondekar Islam*[1], *and Donald J. Kyle*[1]. *(1) Purdue Pharma LP, 6 Cedar Brook Drive, Cranbury, NJ 08512, laykea.tafesse@pharma.com, (2) Pharmacia*

A biased chemical library containing 91 differentially substituted thiazolidinones was prepared in an effort to improve the pharmacology and to overcome certain development liabilities of a known anticonvulsant agent V102862. The collection was prepared in a single step multi-component condensation reaction that produced good yields and very high crude purity (75%-85%). Seven compounds, identified within the library were shown to be more potent than V102862, our parent reference compound, in an electrophysiological assay measuring sodium channel antagonism. The most potent compound, 3-(2-piperidinylethyl)-2-(3-(3-trifluoromethylphenoxy)phenyl)thiazolidinone, has a Ki of 90 nM.



238.
SYNTHESIS AND EVALUATION OF PYRIMIDINE AND PYRIMIDINONE LIBRARIES AS VOLTAGE-GATED SODIUM CHANNEL BLOCKERS. ***Sam F. Victory***, *Bin Shao, R. Richard Goehring, Deyou Sha, Donald J. Kyle, Jim Limberis, Victor I. Ilyin, George Sakellaropoulos, and Silvia Robledo, Discovery Research, Purdue Pharma, L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, sam.victory@pharma.com*

Voltage-gated sodium channels are essential for the initiation and propagation of neuronal impulses and appear to be dynamically involved in mediating neuropathic pain states. One approach toward treating neuropathic pain is the suppression of the abnormal, repetitive firing that is common in damaged neurons. Previously, the semicarbazone V102862 was identified as a potent voltage-gated sodium channel blocker. In a program aimed at optimizing the profile of V102862, a systematic structure–activity investigation was carried out in which the semicarbazone moiety was replaced with various heterocycles. As part of this strategy, a parallel synthesis effort of alkyl- and amino-substituted pyrimidines and pyrimidinones was carried out. Evaluation of these series identified compound 1 as a potent sodium channel blocker (Ki=470 nM, rBIIa), which was shown to be effective in the Chung model of neuropathic pain. Details of the parallel synthesis effort as well as the in vitro and in vivo activity of 1 will be presented.

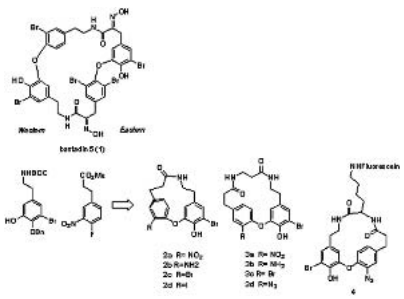


239.
PYRAZOLE DERIVATIVES AS NOVEL POTENT AND SELECTIVE CA^{2+} RELEASE-ACTIVATED CA^{2+} CHANNEL INHIBITORS. ***Hirokazu Kubota***, *Yasuhiro Yonetoku, Yoji Miyazaki, Yoshinori Okamoto, Masashi Funatsu, Noriko Ishikawa, Jun Ishikawa, Makoto Takeuchi, Mitsuaki Ohta, and Shin-ichi Tsukamoto, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd, 21, Miyukigaoka, Tsukuba, Ibaraki 3058585, Japan, Fax: +81-29-852-2971, kubota@yamanouchi.co.jp*

A sustained Ca^{2+} influx through Ca^{2+} release-activated Ca^{2+} (CRAC) channels plays an important role in various immune and inflammatory responses by activating T lymphocytes, and by stimulating the production of cytokines. We conducted a chemical-file screening, and found some pyrazole derivatives to inhibit CRAC channel selectively. To examine the structure-activity relationships (SARs), we prepared a series of pyrazole derivatives, and evaluated for its CRAC channel inhibitory activity and selectivity over voltage-operated Ca^{2+} (VOC) channel. Among them, some derivatives were found to inhibit Ca^{2+} influx through CRAC channels in Jurkat T cells with IC_{50} values at submicromoler and to exhibit high selectivity to CRAC channel over VOC channel. In addition, some compounds also inhibited interleukin-2 production in Jurkat T cells with IC_{50} values at the level of 10^{-8} M. The SARs and the biological activities of the pyrazole derivatives will be discussed.

240.
SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF CYCLIC ANALOGS OF BASTADIN 5, A MODULATOR OF SKELETAL MUSCLE FKBP12/ CALCIUM CHANNEL COMPLEX. *Tadeusz F. Molinski*[1], ***Makoto N Masuno***[1], *and Isaac N. Pessah*[2]. *(1) Department of Chemistry, University of California, Davis, 1 Shields Ave, Davis, CA 95616, Fax: 530-752-8995, tfmolinski@ucdavis.edu, mnmasuno@ucdavis.edu, (2) Department of Molecular Biosciences, School of Veterinary Medicine, UC Davis*

Bastadin 5 (**1**), isolated from the marine sponge *Ianthella basta* is a potent agonist of the skeletal muscle FKBP12/ Ca2+ channel complex. Synthesis of structural analogs of **1** will help determine its mode of action and binding site. We report here the synthesis of 18- and 14-membered ring analogs of **1** (macrolactams **2** and **3**) and their structure-activity relationships. Analogs **2** exhibit atropisomerism. The finding that better activity is correlated with the conformational flexibility present in **3** prompted the design of second-generation analogs (e.g. **4**) that contain both a fluorescent tag and a photoaffinity label. Recent results on the synthesis of enantiomers of **2**, and investigation of dependence of activity upon the Ar-O-Ar torsional angle will be presented.



241.

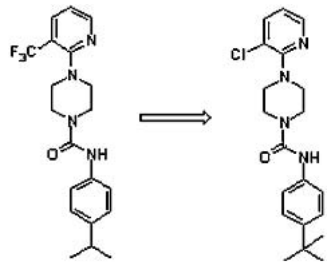
TYPE III PEPTIDOMIMETICS OF SHK TOXIN AS MOLECULAR PROBES FOR THE KV1.3 ION CHANNEL. ***Andrew J. Harvey**, and Jonathan B. Baell, Structural Biology Division, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3050, Australia, Fax: +61393452211, aharvey@wehi.edu.au*

Blockade of the Kv1.3 ion channel of T-lymphocytes has been identified as a target for the regulation of T-cell replication and consequently the suppression of immune function. The peptide toxin, ShK, isolated from the sea anemone *Stichodachyla helianthus*, blocked Kv1.3 expressed in *Xenopus* oocytes in the picomolar range. Binding studies of single-residue-variant ShK analogs suggested that residues Arg-11, Lys-22, Tyr-23, and Arg-24 were major contributors to binding stabilization, although there were discrepancies between reports over the relative contributions of the two arginine residues. We have designed two three-point peptidomimetics; one mimicking a continuous epitope (Lys-22, Tyr-23, Arg-24) and the other mimicking a discontinuous epitope (Arg-11, Lys-22, Tyr-23) as molecular probes to investigate the effect of the arginine side chains on the binding energy of ShK. The peptidomimetics were synthesized and both were found to be weak binders of the Kv1.3 ion channel.

242.

4-(2-PYRIDYL)PIPERAZINE-1-CARBOXAMIDES: POTENT VANILLOID RECEPTOR 1 ANTAGONISTS. ***Laykea Tafesse**, Qun Sun, Khondaker Islam, Xiaoming Zhou, Sam F. Victory, Chongwu Zhang, Mohamed Hachicha, Lori A. Schmid, Aniket Patel, Yakov Rotshteyn, Kenneth J. Valenzano, and Donald J. Kyle, Discovery Research, Purdue Pharma L.P, 6 Cedar Brook Drive, Cranbury, NJ 08512, laykea.tafesse@pharma.com*

A series of 4-(2-pyridyl)piperazine-1-carboxamide analogues based on the lead compound 1 was synthesized and evaluated for VR1 antagonist activity in capsaicin-induced (CAP) and pH (5.5)-induced (pH) FLIPR assays in a rat VR1-expressing HEK293 cell line. Potent VR1 antagonists were identified through SAR studies. From these studies, 18 was found to be very potent in the in vitro assay [IC50=4.8 nM (pH) and 35 nM (CAP)] and orally available in rat (F%=15.1).



1

243.

STRUCTURE-ACTIVITY RELATIONSHIP TO INVESTIGATE LIGAND SELECTIVITY FOR THE ACETYLCHOLINE BINDING SITE OF THE RAT $\alpha4\beta2$ AND $\alpha3\beta4$ NICOTINIC SUBTYPES. ***William H. Bisson**[1], Gerrit Westera[1], P. August Schubiger[1], and Leonardo Scapozza[2]. (1) Department of Chemistry and Applied Biosciences, Center for Radiopharmaceutical Science, Swiss Federal Institute of Technology (ETH), Raemistrasse 100, 8091 Zuerich, Switzerland, william.bisson@dmr.usz.ch, (2) Department of Chemistry and Applied Biosciences, Biopharmaceutical Chemistry, Swiss Federal Institute of Technology (ETH)*

Neuronal nicotinic acetylcholine receptor ligands (nAChR) may have important therapeutic and diagnostic potential for a variety of neurological diseaseas, but their subtype selectivity remains a problem to overcome. Recently, the first high-resolution structure of the acetylcholine binding protein (AChBP), a homologous of the ligand extracellular binding domain of nAChR, has been determined. Based on this structure, homology-models of the extracellular domain of the neuronal $\alpha4\beta2$ and ganglionic $\alpha3\beta4$ rat nAChR subtypes were built, energetically minimized and their stability was assessed using molecular dynamics. A series of 16 nicotinic ligands known from literature were docked into the modeled binding site cavity of both receptors. Structure-activity relationship was investigated to understand the selectivity of the ligands for the acetylcholine binding site of the rat $\alpha3\beta4$ and $\alpha4\beta2$. The resulting models indicate how to design specific and selective $\alpha4\beta2$ nAChR subtype ligands overcoming toxicity due to interaction with ganglionic $\alpha3\beta4$ receptor.

244.

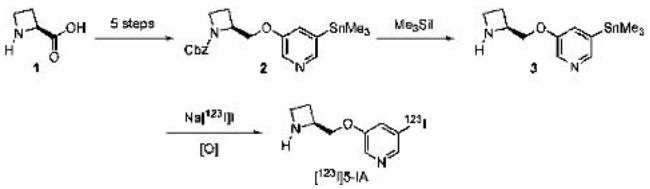
SYNTHESIS AND EVALUATION OF 3-PYRIDYL ETHERS CONTAINING 7-AZABICYCLO[2.2.1]HEPTYL MOIETIES AS LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTORS. ***Andrei O. Koren**, and Edythe D. London, Neuroimaging Research Group, David Geffen School of Medicine, University of California, Los Angeles, 760 Westwood Plaza, C8-532 NPI, Los Angeles, CA 90024, Fax: 310-825-0812, akoren@mednet.ucla.edu*

Nicotinic acetylcholine receptor (nAChR) ligands based on the structure of epibatidine (2-(3-pyridyl)-7-azabicylo[2.2.1]heptanes) feature advantageous characteristics, such as picomolar affinities for central nAChRs, low temperature dependence of affinity, rapid penetration into the brain, and low nonspecific binding *in vivo*. The use of these compounds as probes for studying nAChRs *in vivo* is, however, problematic because of their high toxicity. The latter is attributable, at least partially, to the combination of high affinity and high intrinsic activity at peripheral nAChRs. Based on the analysis of recent SAR studies of 3-pyridyl azacyclic nAChR ligands, we hypothesized that placing an ether-motif spacer between the heteroaromatic and azabicyclic moieties of the epibatidine structure could provide ligands that possess enhanced central-*vs.*-peripheral nAChR subtype selectivity and less toxicity while retaining the favorable characteristics. The synthesis and initial *in vitro* evaluation of a series of such compounds (bridged analogs of 3-(2-pyrrolidinylmethoxy)pyridine) will be presented. (Supported by PMERP).

245.

SYNTHESIS AND LABELING OF A NEW 5-IA PRECURSOR. ***Eric Brenner**, Ronald M Baldwin, Louis Amici, and Gilles D Tamagnan, VA CT HCS (116A2), Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516*

The iodinated analog of A-85380, (S)-5-[123I]iodo-3-(2-azetidinylmethoxy)pyridine ([123I]5-IA) is a new SPECT tracer studied in human subjects because of its affinity for a4b2 nicotinic acetylcholine receptors, which play an important role in neurodegenerative diseases and in tobacco dependence. At present the methods described in the literature require two steps to afford [123I]5-IA, one step to label an N-protected precursor and another one to release the amino group. We realized the synthesis of a new precursor 3, obtained in 64% overall yield in six steps starting from (S)-2-azetidinecarboxylic acid 1. The key step of this synthesis is the last one with the selective removal of the amine function without loss of the stannyl substituent. Acid catalyzed cracking resulted in destannylation and catalytic hydrogenolysis failed to remove the amide. However, we found that iodotrimethylsilane afforded 3 in 92% yield without affecting the stannyl moiety. This new precursor, accessible in good overall yield, presents the advantage to lead directly to [123I]5-IA in one step, rather than requiring deprotection after the labeling step.

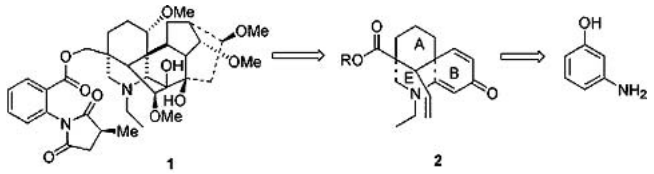


246.

STUDIES DIRECTED TOWARD A TOTAL SYNTHESIS OF METHYLLYCACONITINE. ***Sarathy Kesavan**, Department of Chemistry, Iowa State University, Ames, IA 50011, sarathy@iastate.edu, and George A Kraus, Chemistry Department, Iowa State University*

Methyllycaconitine (1) is an alkaloid isolated from Delphinium brownii Rydberg in 1938. It is the principal insecticidal toxin of several delphinium species that has a long history of use as an insecticide. It inhibits acetylcholine and anatoxin induced whole-cell currents in cultured fetal rat hippocampal neurons at Pico

molar concentration. Construction of ABE segment 2 and further studies towards the synthesis of 1 will be discussed.

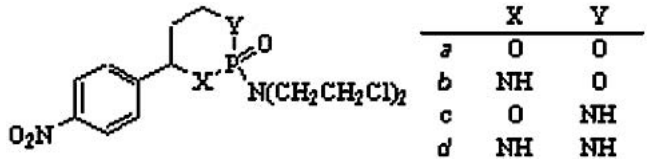


1 2

247.

DESIGN, SYNTHESIS, AND EVALUATION OF NOVEL CYCLOPHOSPHAMIDE PRODRUGS FOR REDUCTIVE ACTIVATION. ***Yongying Jiang***[1], *Chengzhi Yu*[1], *Jiye Han*[1], *Patrick Browne*[2], *Richard J. Knox*[2], *and Longqin Hu*[1]. *(1) Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, (2) Enact Pharma PLC, Porton Down Science Park, Salisbury, Wiltshire, SP4 0JQ, UK*

Tumor tissues become hypoxic, or oxygen-deficient, due to insufficient blood supply as a result of the primitive nature of their vasculature. Hypoxic tumor tissues could, therefore, be targeted selectively by bioreductive drugs. In addition, a reductive enzyme such as E. coli nitroreductase could be delivered site-specifically to tumor tissues by gene-directed or antibody-directed enzyme delivery systems. Cyclophosphamide is a clinically useful drug that is activated by cytochrome P-450 enzyme in the liver. The activated cytotoxic metabolites are then distributed to various body compartments including tumor tissues. In order to increase tumor selectivity and to decrease systemic toxicity, we designed p-nitrophenyl substituted cyclophosphamide congeners that could potentially be activated site-specifically in hypoxic tumor cells or by a reductase enzyme delivered to tumor cells. Central to their activation pathway is a cleavage reaction which occurs at the aromatic benzylic carbon upon bioreduction. The design, synthesis, nitroreductase substrate activity and cell culture activity of these cyclophosphamide compounds will be presented. Supported by a grant from the New Jersey Commission on Cancer Research to L.H.

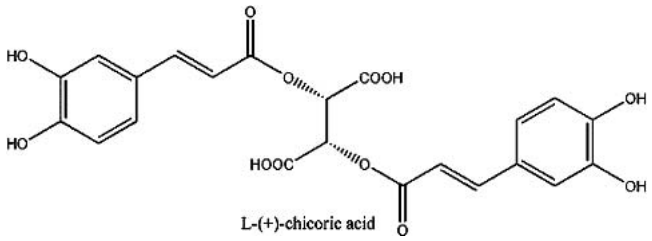


	X	Y
a	O	O
b	NH	O
c	O	NH
d	NH	NH

248.

DETERMINATION OF THE EFFECT OF ECHINACEA ANGUSTIFOLIA PHENOLICS ON THE PROLIFERATION OF CANCER CELLS. ***Eric D Huntimer***, *and Fathi T. Halaweish, Chemistry & Biochemistry, South Dakota State University, Shepard hall 121, Brookings, SD 57007, jazzman36b@hotmail.com*

Several studies regarding the use of herbal medicines revealed that a growing number of people use herbal medicine before undergoing surgery. However, over 70% do not reveal to their physicians that they use herbal medicines. This has raised concerns over herb-related adverse reactions. The indigenous plant Echinacea angustifolia remains one of the most common herbal extracts on the market. It possesses anti-inflammatory activity, which was shown to inhibit hyaluronidase. This enzyme has played a role in the degradation of the protective layer surrounding cancer cells. Thus, inhibition of the enzyme may prevent the destruction of cancer cells. Fractionation of an alcoholic extract of E. angustifolia provided two anti-inflammatory fractions, the butyl acetate and ethyl acetate fractions. These fractions were separated and their constituents were identified using HPLC and LC-MS. Chicoric acid, an anti-inflammatory compound present in Echinacea, was synthesized using literature methods. Cell cultures were used in analyzing the effect of the Echinacea fractions and chicoric acid on cancer cells. HeLa cells were grown and exposed to the fractions or compounds and hyaluronidase for 24 hours followed by doxorubicin for one hour. Further studies are in progress.

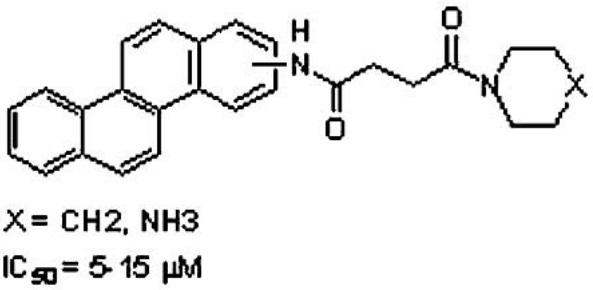


L-(+)-chicoric acid

249.

ISOMERIC CHRYSENES AS NEW ANTICANCER AGENTS: EFFECTS OF ELECTRON DONATING AND WITHDRAWING GROUPS. ***Bimal K. Banik***, *Indrani Banik, Linda Hackfeld, and Frederick F. Becker, Department of Molecular Pathology, Box # 89, UT MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, Fax: 713-792-5940, bbanik@mail.mdanderson.org*

In our earlier studies, we demonstrated a systematic SAR study of a number of derivatives prepared from 6-amino chrysene and 1-amino pyrene against different cancer cells *in vitro*. These derivatives had a side chain with a terminal heterocyclic system. Encouraged by these results, we prepared several isomeric chrysene derivatives using 1-amino, 2-amino, 3-amino chrysenes. In addition electrophilic substitution of 6-substituted derivative was accomplished to examine the effects of electron donating and electron withdrawing groups on the bioactivity. The derivatives which had electron donation groups were more potent than the compounds which had electron withdrawing groups. However, the activity of isomeric chrysene derivatives was comparable.



X = CH2, NH3

IC_{50} = 5-15 μM

250.

NUCLEAR TARGETING IN BORON NEUTRON CAPTURE THERAPY. *Stephen B. Kahl*[1], *Myoung Koo*[1], ***Paola Dozzo***[1], *Eleanor A. Blakely*[2], *Kathleen A. Bjornstad*[2], *Gosia Pellarin*[3], *Bert Feuerstein*[3], *and Dennis F. Deen*[4]. *(1) Department of Pharmaceutical Chemistry, University of California at San Francisco, 513 Parnassus Ave., San Francisco, CA 94143, sbkahl@itsa.ucsf.edu, paoladozzo@hotmail.com, (2) Life Sciences Division, Lawrence Berkeley National Laboratory, (3) Department of Laboratory Medicine, University of California at San Francisco, (4) Brain Tumor Research Center, University of California at San Francisco*

Boron neutron capture therapy (BNCT) is a binary cancer treatment based on the cytotoxicity of alpha particles, which are generated in the nuclear reaction of a B-10 isotope and a thermal neutron. Nuclear targeting of boron-containing drugs has long been a primary objective, since localization of B-10 in the nucleus should increase the killing efficiency of the treatment by 10-100 fold. Novel porphyrin-NLS conjugates were synthesized by coupling various nuclear localization sequences (NLS) to the boron containing porphyrin m-BOPP. The m-BOPP-NLS were incubated with the human brain tumor cell line SF-767 and imaged using fluorescence and confocal microscopy. These experiments strongly support nuclear or abundant perinuclear localization.

251.

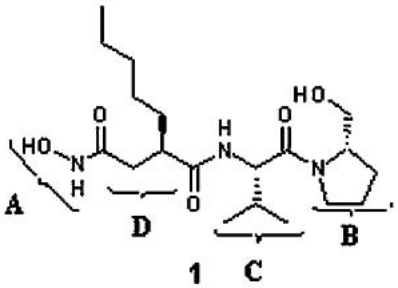
SYNTHESIS AND IN VITRO STUDIES OF TRANSITION METAL PENDENT GLUCOSE DERIVATIVES. ***Cécile Dumas***[1], *Roger Schibli*[1], *Jeannine Petrig*[1], *Elisa Garcia-Garayoa*[1], *Loredana Spadola*[2], *Leonardo Scapozza*[2], *Judith Stahel*[1], *and P. August Schubiger*[1]. *(1) Center for Radiopharmaceutical Science of the ETH, PSI, USZ, Paul Scherrer Institut, Villigen PSI 5232, Switzerland, Fax: 00-41-563102849, cecile.dumas@psi.ch, (2) Department of Chemistry and Applied Biosciences, Biopharmaceutical Chemistry, Swiss Federal Institute of Technology*

Tumor growth is heavily related to increased glucose metabolism. Thus, there is a considerable interest to develop innovative glucose derivatives for medicinal purposes. With regard to build on metal-based, radiopharmaceuticals for diagnostic purpose, different methods were set up to functionalize glucose at C-1, C-2, C-3 and C-6 positions, with various linkers (alkyl or polyethylene glycol) and chelating moieties containing amines and carboxylic acids functionalities. These glucoses analogues labeled with the organometallic precursor $[M(OH_2)_3(CO)_3]^+$ (M=^{99m}Tc or Re) yielded highly stable and water-soluble organometallic complexes. The complexes have been tested for affinity towards yeast hexokinase (HK) and Glut1 transportation. They revealed all low internalization in colon carcinoma cell line HT29 (0.1-0.3% total radioactivity) and variable inhibitory activity of HK dependent of the functionalization position and the length and nature of the linker. Best results have been observed for C-2 derivatives with a polyethylene glycol spacer (K_i=0.25mM).

252.

DESIGN, SYNTHESIS AND SAR OF ACTINONIN ANALOGS. ***Christopher Paul Borella***[1], *William G. Bornmann*[2], *David A. Scheinberg*[3], *Francis Sirotnak*[2], *and Mona Lee*[2]. *(1) Organic Synthesis Core Facility, Memorial Sloan Ketering Cancer Center, New York, NY 10021, Fax: 212-717-3655, borellac@mskcc.org, (2) Sloan Kettering Institute, Memorial Sloan-Kettering Cancer Center, (3) Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center*

Actinonin (1), which was initially developed as an anti-bacterial agent, has recently been discovered to have anti-cancer properties associated with it including the inhibition of tumor cell invasion and cytotoxicity. Since the cellular target of actinonin is still unknown traditional medicinal chemistry has been used to develop a structure activity relationship (SAR) and create compounds with improved pharmacological profiles. Initial results have shown that a metal binding group (A) is required for activity. Modification at the terminal amine (B) was also found to have significant effects on activity. The further development of this SAR as well as preliminary animal studies will be discussed.



253.

GENE EXPRESSION DRIVEN DISCOVERY OF NOVEL ANTI-CANCER COMPOUNDS. *Wieslaw M. Cholody,* ***Valentina Petukhova****, Norman Ohler, Sean A. O'Brien, Jeff Strovel, Tamara Tatunchak, Ade Majolagbe, and Stanislaw Pikul, Avalon Pharmaceuticals, Inc, 20358 Seneca Meadows Parkway, Germantown, MD 20876, mcholody@avalonrx.com, vpetukhova@avalonrx.com*

As a new approach to discover potential small molecule anticancer drugs, we have established unique signature sets of genes for various tumor types, and screened for compounds that can reverse the gene expression profile from patterns typical for cancer cells to patterns seen in normal cells. Here, we wish to disclose our discovery of novel, pyrrole-based compounds which modify gene expression in colon cancer cells in a very unique way, namely, they change the expression of genes involved in the Wnt pathway. Analysis of our gene expression pattern database suggests that these molecules have a novel MOA as they cannot be clustered with any known anticancer compound. The most active compounds in the series exhibit potent cytotoxic activity against HT29, Colo205 and other colon tumor cells. Transcriptional and cytotoxic activities of these novel compounds will be presented.

254.

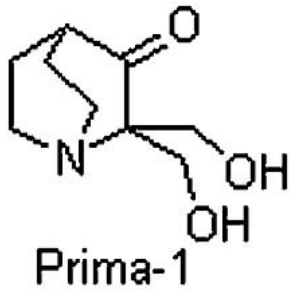
DESIGN, SYNTHESIS, AND EVALUATION OF NEW INHIBITORS OF HSP90. *Brian S. J. Blagg, and* ***Gang Shen****, Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Malott 4077, Lawrence, KS 66045-7582, Fax: 785-864-5326, bblagg@ku.edu, gangshen@ku.edu*

The 90 kDa Heat Shock Proteins (Hsp90) are responsible for the refolding of denatured proteins following heat shock, as well as the maturation of several key regulatory enzymes/receptors involved in cancer. Inhibition of Hsp90 results in the ubiquitination of bound client proteins, and subsequent proteolysis by the proteosome. As a result, Hsp90 is a target for the development of therapeutics for the treatment of cancer. New inhibitors of Hsp90 have been carefully designed based on the previously reported co-crystal structures of Radicicol and Geldanamycin bound to Hsp90. The design, synthesis, and biological evaluation of these molecules will be presented.

255.

SYNTHESIS AND EVALUATION OF PRIMA-1 AND ITS ANALOGS AS COMPOUNDS CAPABLE OF RESTORING NORMAL ACTIVITY TO MUTANT P-53. ***Athanasios Glekas***[1], *Tatiana Bersten*[2], *Mikhail Doubrovin*[2], *Vladimir Ponomarev*[2], *William P Tong*[3], *William G. Bornmann*[1], *and Juri Gelovani*[2]. *(1) Organic Synthesis Core, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 93, New York, NY 10021, Fax: 212-717-3655, (2) Radiology, Memorial Sloan Kettering Cancer Center, (3) Pharamcology Analytical Laboratory, Memorial Sloan Kettering Cancer Center*

More than half of all human cancers lose p53 function due to mutations. p53 is an integral part of an apoptosis pathway that responds to DNA damage. Recently, several small molecular compounds have been identified as potential mutant p53-binding agents (PRIMA-1 and CP31398), which induce restoration of normal p53 structure and function, resulting in profound apoptosis of tumor cells. A series of analogs have been synthesized using PRIMA-1 as a lead compound and assessed in vitro for their p53 binding (EMSA) and pro-apoptotic activity in tumor cell lines with either the wild-type p53, different mutant p53s, and in p53 -/- (null) cell lines. A significant pro-apoptotic activity of PRIMA-1 and several analogs was observed in vitro in different tumor cell lines (low ìM to nM IC50). However, the p53 specificity of pro-apoptotic activity of these compounds still remains to be determined. With the same aims, the co-crystallization studies of the wild-type or mutant p53s with PRIMA-1 and the newly developed analogs have been initiated.



256.

STRUCTURAL CHARACTERIZATION OF CELL SURFACE HEPARAN SULFATE GLYCOSAMINOGLYCANS IN TUMOUR PROGRESSION. ***Wenjun Mao***[1], *Yi Li*[2], *Guangli Yu*[1], *Fuming Zhang*[3], *and Xia Zhao*[1]. *(1) Marine Drugs and Foods Institute, Ocean University of China, 5 Yushan Road, Qingdao 266003, China, wenjunmqd@hotmail.com, (2) Navy 401 Hospital, (3) Chemistry, University of Iowa*

Heparan sulfate glycosaminoglycans are complex polysaccharides with enormous structural diversity that are ubiquitous in nature. Every heparan sulfate glycosaminoglycans contains a core backbone that consists of a disaccharide repeat unit of a glucosamine linked to either an iduronic or glucuronic acid. The structural complexity arises from the differential modification of individual disaccharide units within an oligosaccharide chain. Heparan sulfates glycosaminoglycans have been identified in all animal tissues, where they are located mainly at cell-surface membranes or in the extracellular matrix. Heparan

sulfate glycosaminoglycans regulate several aspects of cancer biology, including tumorigenesis, tumour progression and metastasis. The current study investigated the structural characterization of cell surface heparan sulfate glycosaminoglycans with liver tumour-mice. NMR analysis has been performed as preliminary characterization of the isolated heparan sulfate glycosaminoglycans. We will further study the structural differences of heparan sulfate glycosaminoglycans during the tumour progression. Gaining better insight into the structure-function relationships of complex polysaccharides is key to understanding how these molecules regulate different aspects of cancer biology and to developing targeted therapeutics.

257.

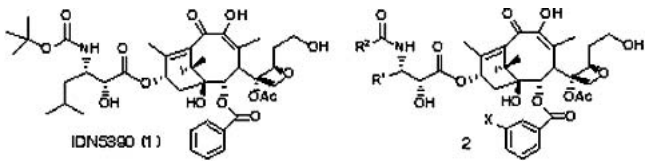
NOVEL INHIBITORS OF STAT SIGNALING: POTENTIAL SELECTIVE ANTI-CANCER THERAPEUTICS. ***Matthew P. Glenn***[1], *Joon S. Kim*[2], *James Turkson*[3], *Said M. Sebti*[4], *Richard Jove*[3], *and Andrew Hamilton*[1]. *(1) Department of Chemistry, Yale University, 225 Prospect St, New Haven, CT 06511, Fax: 203-432-6144, matthew.glenn@yale.edu, (2) Department of Chemistry, Yale, (3) Moffitt Cancer Center and Research Institute, University of South Florida, (4) Department of Biochemistry and Molecular Biology, University of South Florida*

Current models of anti-cancer therapy based on inhibitors of tyrosine kinase signaling, or other upstream effectors of kinase activity, disrupt multiple downstream signaling pathways, and may ultimately fail due to toxicity. The need for selective, non-toxic anti cancer agents has prompted us to investigate downstream proteins as preferred anti-cancer targets. The STAT (Signal Transducers and Activators of Transcription) proteins represent a point of convergence in tyrosine kinase signaling, where constitutively activated STATs drive oncogenesis via up-regulation of anti-apoptotic and cell survival proteins (Bcl-x_L, Cyclin D1, and c-Myc) in malignancies that include breast cancer, head and neck cancer, melanoma, and multiple myeloma. Here we describe a series of STAT3 dimerization inhibitors that decrease STAT3-DNA binding in a dose dependant manner, and thereby suppress constitutive STAT3 activation and transcriptional activity in human breast and lung carcinoma cells that expressed constitutively active STAT3, and ultimately induce apoptosis in transformed cells.

258.

DESIGN, SYNTHESIS AND SAR STUDY OF NOVEL C-SECO-TAXOIDS. ***Ioana Maria Ungureanu***[1], *Antonella Pepe*[1], *Larissa Kuznetsova*[1], *Andrew Sturm*[1], *Dansu Li*[1], *Paula Pera*[2], *Ralph J. Bernacki*[2], *Gabriele Fontana*[3], *Antonella Riva*[3], *Ezio Bombardelli*[3], *Cristiano Ferlini*[4], *Giovanni Scambia*[4], *and Iwao Ojima*[1]. *(1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, (2) Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, (3) Indena S.p.A, (4) Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart*

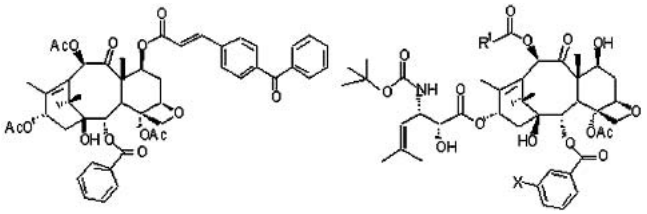
Recently it was disclosed that cytotoxic taxane anticancer drugs, paclitaxel and docetaxel, are potent inhibitors of endothelial cell migration, and their antiangiogenic activity is observed at much lower concentration than that exerting their cytotoxicity. This finding led to the drug candidate selection aiming at identifying taxoids in which the two activities are even further apart. Then, the screening of taxoids for high activity to inhibit endothelial cell motility with low cytotoxicity selected the lead compound IDN5390 (1), which is a novel C-seco-taxoid wherein the C-ring of the normal taxane skeleton is cleaved. This rather serendipitously discovered novel C-seco-taxoid 1 is at the late stage preclinical studies and will be advanced to human clinical trials shortly. However, it is reasonable to assume that much better drug candidates can be discovered and developed based on the extensive SAR studies of this novel class of taxanes. In this paper, we will present our preliminary SAR studies for optimization of 1 as well as investigation into the mechanism of action(s) based on the design, synthesis, and biological activity assays of novel C-seco-taxoids (2).



259.

DESIGN, SYNTHESIS, AND EVALUATION OF TAXANES AS POTENTIAL ANTIMALARIAL AGENTS. ***Jin Chen***[1], *Larissa Kuznetsova*[1], *Kelly Chibale*[2], *Cailean Clarkson*[3], *Peter Smith*[3], *Simon L. Croft*[4], *and Iwao Ojima*[1]. *(1) Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794, jinchen2@ic.sunysb.edu, (2) Department of Chemistry, University of Cape Town, (3) Division of Pharmacology, Department of Medicine, University of Cape Town, (4) Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine*

Malaria is the most widespread tropical disease and approximately 300 million cases occur annually and over 1.1 million people die due to this disease each year. The emergence of chloroquine-resistant strains has made this disease even more lethal. Accordingly, new antimalarial drugs with different mechanism of action, which can overcome multidrug resistance are desperately needed. Paclitaxel, a microtubule-stabilizing anticancer agent, has been shown to block the replication of *Plasmodium falciparum*. Because of the good homology between the human β-tubulin and that of *P. falciparum*, the parasitic tubulin should be an excellent target for potential antimalarial drugs. However, to treat these parasitic diseases, the drug should not affect the human host cells, which requires the differentiation of the human tubulin and the parasite tubulin. We have found that some non-cytotoxic taxanes as well as some second-generation taxoids exhibit high potency as antimalarial agents. These taxanes and taxoids serve as a promising lead compounds for further development. Our preliminary results on the efficacy of these taxanes and taxoids as potential antimalarial agents will be discussed.



260.

DEVELOPMENT OF TAXOIDS FOR USE AS IMMUNOCONJUGATES. ***Michael L. Miller***, *Elizabeth E. Roller, Erkan Baloglu, Barbara A. Leece, Victor S Goldmacher, and Ravi V.J. Chari, Department of Chemistry, ImmunoGen, Inc, 128 Sidney Street, Cambridge, MA 02139, Fax: 617-995-2510, michael.miller@immunogen.com*

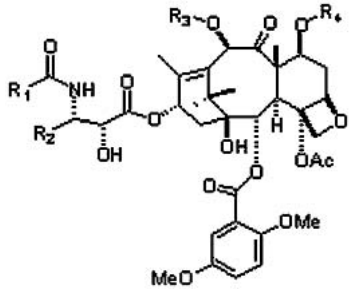
Taxol® and Taxotere® are considered to be two of the most important drugs in modern cancer chemotherapy, being one of the standard treatments for breast cancer, non-small cell lung cancer, and ovarian cancer. Despite their widespread use in the treatment of these cancers, the therapeutic efficiency of these drugs is limited due to their non-specific toxicity to healthy tissues. One method to potentially overcome this lack of specificity is with the use of monoclonal antibodies directed against specific tumor-associated antigens. In our studies, we have focused on the development of novel taxoids that possess high potency, aqueous solubility, and a handle allowing them to be linked to antibodies useful in targeted delilvery. The synthesis, biological applications, and development of a lead taxoid will be reviewed.

261.

STUDIES TOWARD NOVEL TAXOID-MONOCLONAL ANTIBODY CONJUGATES. ***Erkan Baloglu***, *Michael L. Miller, Elizabeth E. Roller, Barbara A. Leece, Victor S. Goldmacher, and Ravi V. J. Chari, ImmunoGen Inc, 128 Sidney Street, Cambridge, MA 02139, Fax: 617-995-2510, erkan.baloglu@immunogen.com*

The use of drug-antibody conjugates affords a method for the targeted delivery of anticancer drugs specifically to cancer cells. Monoclonal antibodies alone usually do not posses high therapeutic efficacy, however, they are capable of targeting tumor markers selectively. Although both paclitaxel (Taxol®) and docetaxel (Taxotere®) are known to be highly effective anticancer agents in the clinic today, neither is sufficiently potent to be utilized as the cytotoxic component of the conjugate for antibody-mediated delivery. We have prepared taxoids with significantly higher cytotoxicity than paclitaxel and docetaxel while possess-

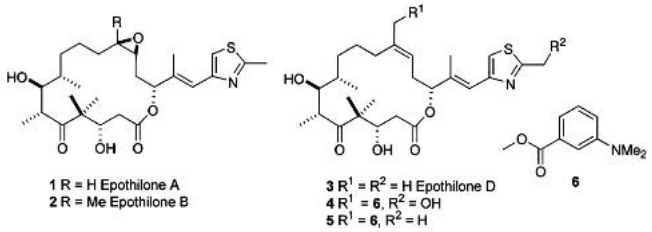
ing a linking group that allows their attachment to the antibody. The design, synthesis and biological evaluation of these taxoids will be reported.



262.

SYNTHESIS AND BIOLOGICAL EVALUATION OF FLUORESCENTLY LABELED EPOTHILONE ANALOGS FOR TUBULIN BINDING STUDIES. ***Thota Ganesh***[1], *David G. I. Kingston*[1], *Susan Bane*[2], *Natasha Shanker*[2], *and Jennifer K. Schilling*[1]. *(1) Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, tganesh@vt.edu, (2) Department of Chemistry, State University of New York*

Epothilones such as epothilones A, B, and D (1-3) are natural products which have a similar tubulin polymerization activity to paclitaxel. Despite their structural differences with paclitaxel, epothilones are found to bind to the same binding site as paclitaxel on microtubules. They also have better water solubility than paclitaxel and are active against MDR tumor cell lines. All these properties suggest that they could be potential successors to paclitaxel, and some epothilone analogs are currently in clinical trials as anticancer agents. A clear understanding of the nature of the binding of epothilones to tubulin polymer is essential. Significant information can be obtained from fluorescence studies (FRET measurements), and from REDOR NMR studies. We have synthesized several epothilone analogs and their fluorescent congeners (4, 5). Compound 4 induces tubulin polymerization in vitro and is about 20-fold less cytotoxic than paclitaxel in PC-3 cells. Microtubule binding causes an increase in emission intensity and a blue shift in its emission maximum. The synthesis, cytotoxicities, and tubulin polymerization activities of these compounds will be presented.



263.

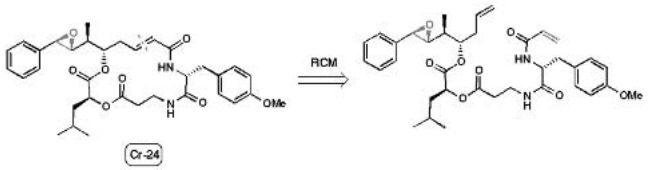
SYNTHESIS AND ANTI-TUBULIN ACTIVITY OF A NOVEL INDOLE BASED PHOSPHATE PRODRUG VASCULAR TARGETING AGENT. ***Mallinath B. Hadimani***[1], *Raymond J. Kessler*[1], *Anupama R. Shirali*[1], *Heather O'Dell*[1], *Anjan Ghatak*[1], *Charles M. Garner*[1], *Klaus Edvardsen*[2], *and Kevin G. Pinney*[1]. *(1) Department of Chemistry and Biochemistry, Baylor University, P O Box 97348, Waco, TX 76798-7348, Fax: 254-710-4272, Mallinath_Hadimani@baylor.edu, (2) Department of Cell and Molecular Biology, University of Lund, Lund, Sweden*

The discovery and development of potent vascular targeting agents (VTAs) for cancer chemotherapy is paramount since compounds of this new class of anti-cancer agents show remarkable selectivity for tumor vasculature. VTAs are often prepared as phosphate prodrug salts, and in this form, they have diminished interaction with tubulin. Following dephosphorylation, the parent phenol (or amine) drug analog is an inhibitor of tubulin assembly. Interaction with the endothelial cells lining tumor vasculature results in morphology changes (flat to round), which occlude blood flow and result in tumor necrosis. We have designed and developed a wide variety of novel VTAs. A leading member of this library is an indole-based phosphate prodrug which, in parent phenolic form, is a strong inhibitor of tubulin assembly (IC_{50}=1-2 μm) and as a phosphate prodrug, demonstrates nearly quantitative blood flow cessation to tumors within 24 hours and dose dependent tumor growth delay. We herein report the design, synthesis and biological activity of this novel prodrug.

264.

RCM APPROACH TOWARDS THE TOTAL SYNTHESIS OF ANTI-CANCER AGENT CRYPTOPHYCIN-24. ***Narendra K Tripathy***, *and Gunda I Georg, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, narendra@ku.edu*

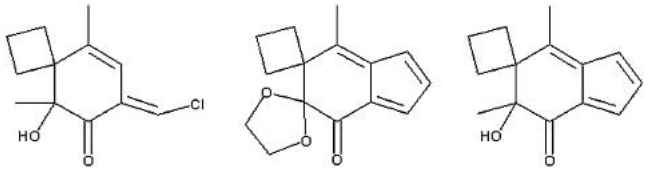
Cryptophycin A and its family of compounds are currently considered one of the most exciting new leads in cancer therapy. Their selective anti-cancer activity and effectiveness against MDR cancers made them a prime target for drug development. Even though several total and partial synthesis of the cryptophycins have been accomplished, we like to present the first RCM approach towards the total synthesis of cryptophycin-24 (arenastatin).



265.

SAR STUDIES OF ILLUDINS: ANALOGS POSSESSING A SPIRO-CYCLOBUTANE RING. *Trevor C. McMorris*[1], ***Qiang Cong***[1], *and Michael J. Kelner*[2]. *(1) Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California, 9500 Gilman drive, La Jolla, CA 92093-0506, mcm@chem.ucsd.edu, qcong@ucsd.edu, (2) Department of Pathology, UCSD Medical School, San Diego*

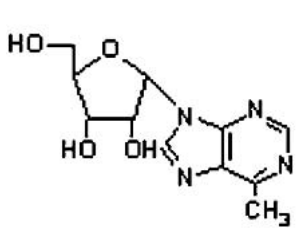
Bicyclic and tricyclic analogs of anticancer sesquiterpene illudin S have been synthesized. These contain a spiro-cyclobutane instead of spiro-cyclopropane structure. The toxicity of the former is less than that of the corresponding cyclopropane containing compounds.



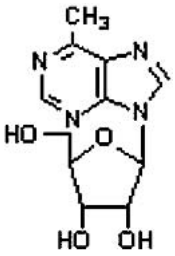
266.

IMPROVED SYNTHESIS OF B-D-6-METHYLPURINE RIBOSIDE AND ANTITUMOR EFFECTS OF THE B-D- AND A-D-ANOMERS. ***Canio J. Marasco Jr.***[1], *Paula J. Pera*[2], *Arthur J. Spiess*[2], *Ralph Bernacki*[2], *and Janice R. Sufrin*[2]. *(1) Department of Math and Natural Sciences, D'Youville College, 320 Porter Ave, Buffalo, NY 14201, marascoc@dyc.edu, (2) Grace Cancer Drug Center, Roswell Park Cancer Institute*

6-Methylpurine (6-MP) nucleoside analogs are often prepared by fusion of 6-MP to an appropriate O-acylated sugar. This synthetic approach consistently produces product mixtures of a- and b-anomers. For example, 6-methylpurine-D-riboside, when prepared by fusion of 6-MP with tetra-O-acetyl-b-D-ribofuranose gives a 10/1 mixture of b/a anomers and requires a tedious chromatographic separation of the closely eluting a- and b-anomers to obtain pure b-anomer. Recently, we have developed an improved synthesis of 6-methylpurine-b-D-riboside (b-D-MPR) that yields the b-anomer exclusively. The conditions for coupling 6-MP to 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribose to produce only the b-D-anomer will be reported. Furthermore, the in vitro antitumor effects of b-D-MPR and 6-methylpurine-a-D-riboside (a-D-MPR) in 5 human tumor cell lines will be described. In brief, b-D-MPR was highly active (IC50 values ranging from 6 to 34 nM), while a-D-MPR, although less active than b-D-MPR, also exhibited significant antitumor effects (IC50 values ranging from 1.47 to 4.83 mM).



α-D-MPR

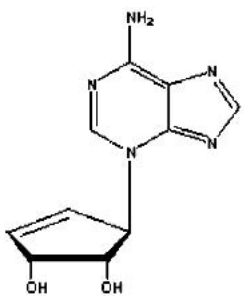


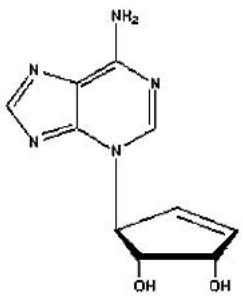
β-D-MPR

267.
WITHDRAWN.

268.
CARBOCYCLIC ISOADENOSINE ANALOGUES OF NEPLANOCIN A. ***Sylvester L. Mosley***[1]*, Fanxing Zeng*[2]*, and Katherine L. Seley*[1]*. (1) Department of Chemistry and Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, Fax: 410-455-2608, sylvester_mosley@yahoo.com, (2) School of Chemistry and Biochemistry, Georgia Institute of Technology*

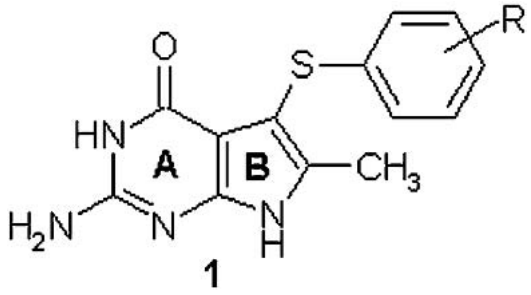
The inhibition of critical enzymes in nucleotide metabolism and DNA synthesis can be used as a chemotherapeutic approach to treating many diseases. DNA encodes information by forming specific patterns of methylation, and since gene expression is determined by "reading" these patterns during DNA-protein interactions, disruption of DNA methylation becomes an attractive target for therapy. Disruption of DNA methylation can be accomplished in several ways, in particular, by inhibition of DNA methyltransferase (DNA Metase) and/or S-adenosylhomocysteine hydrolase (SAHase), both established cellular targets for antiviral, antiparasitic and anticancer agents. Modified nucleosides, in particular the carbocylic nucleosides, have exhibited significant inhibitory activity against SAHase and DNA Metase. Isoadenosine was shown to possess interesting anticancer activity, however due to inherent problems with stability was not pursued further. Herein we report the synthesis, structural elucidation and biological activity of two enantiomerically pure analogues of isoadenosine.



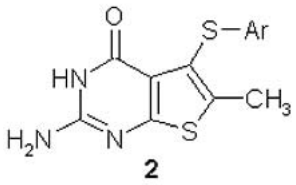


269.
DESIGN AND SYNTHESIS OF 5-ARYLTHIO-SUBSTITUTED 2-AMINO-4-OXO-6-METHYLTHIENO[2,3-D]PYRIMIDIN AS THYMIDYLATE SYNTHASE INHIBITORS. *Aleem Gangjee*[1]*,* ***Yibin Qiu***[1]*, and Roy L. Kisliuk*[2]*. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Department of Biochemistry, Tufts University School of Medicine*

The thymidylate synthase (TS) inhibitors 5-FU, ZD1694 and LY231514 induce the synthesis of new TS protein which could result in tumor resistance. Gangjee *et al.* have reported the nonclassical 6-5 ring fused systems **1** as potent TS inhibitors that allow the inhibitor-TS complex to bind to TS mRNA thus preventing new TS protein synthesis. We replaced the NH in the B ring of **1** with a sulfur to determine the effect of a thiophene rather than a pyrrole. Thus, the 5-substituted 2-amino-4-oxo-6-methylthieno[2,3-*d*]pyrimidines of general structure **2** were designed and synthesized. The synthesis and biological activities of the nonclassical analogs **2a-i** will be reported.



1



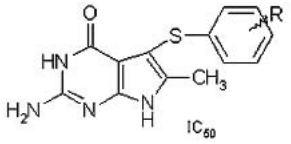
2

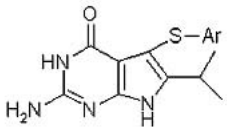
Ar
a Phenyl
b 4'-Chlorophenyl
c 4'-Nitrophenoyl
d 2',5'-Dimethoxyphenyl
e 3',4'-Dichlorophenyl
f 3',5'-Dichlorophenyl
g 2'-Naphthalene
h 4'-Pyridine
i 4'-Fluorophenyl

270.
DESIGN AND SYNTHESIS OF CLASSICAL AND NONCLASSICAL 6-ISOPROPYL-5-ARYLTHIO-SUBSTITUTED PYRROLO[2,3-D]PYRIMIDINES AS NON-INDUCIVE TS INHIBITORS. *Aleem Gangjee*[1]*,* ***Yibin Zeng***[1]*, John J. McGuire*[2]*, Roy L. Kisliuk*[3]*, and Edward Chu*[4]*. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Grace Cancer Drug Center, Roswell Park Cancer Institute, (3) Department of Biochemistry, Tufts University School of Medicine, (4) Yale Cancer Center, Yale University School of Medicine*

N-[4-[(2-Amino-6-methyl-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)thio] benzoyl]-*L*-glutamic acid (**1a**) and its corresponding nonclassical analogues (**1b-d**) were previously described from our laboratory as potent inhibitors against recombinant human (rh) thymidylate synthase (TS) with IC_{50} values in the 10^{-7} M range or less. Recent biological studies indicated that unlike TS inhibitors 5FU, ZD1694 and LY231514 binding of these novel antifolates with TS did not abrogate the binding of TS protein to its mRNA thus preventing TS protein synthesis. The potential use of these novel antifolates against tumor resistance associated with induced over-expression of TS protein prompted the synthesis of **2a-h**. Molecular modeling suggested that extending the C6-methyl moiety to an isopropyl could enhance the hydrophobic interaction with the Trp 109 in hTS and perhaps increase the potency against TS. Thus compounds

2a-h, the C6-isopropyl analogues of **1a-d**, were designed. The synthesis and biological activity of compounds **2a-h** will be presented.



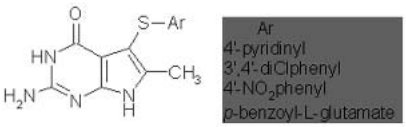


1a. R = 4-CO-L-glu	(42 nM)	**2a**. Ar = 4-benzoyl-L-glu	**2e**. Ar = 4-pyr
1b. R = 4-Cl	(1000 nM)	**2b**. Ar = 4-Cl-Ph	**2f**. Ar = 1-Naph
1c. R = 3,4-diCl	(130 nM)	**2c**. Ar = 3,4-diCl-Ph	**2g**. Ar = 2-Naph
1d. R = 4-NO_2	(150 nM)	**2d**. Ar = 4-NO_2-Ph	**2h**. Ar = 2,6-diCl-Ph

271.

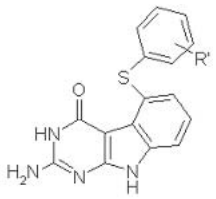
DESIGN AND SYNTHESIS OF TRICYCLIC 2-AMINO-5-(SUBSTITUTED-PHENYLTHIO)-3,9-DIHYDRO-4*H*-PYRIMIDO[4,5-*B*]INDOL-4-ONES AS THYMIDYLATE SYNTHASE INHIBITORS. *Aleem Gangjee[1], **Jie Yang**[1], and Roy L. Kisliuk[2]. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, Fax: 412-396-5593, gangjee@duq.edu, (2) Department of Biochemistry, Tufts University School of Medicine*

Gangjee *et al*. reported that both classical and non-classical 5-subsituted 2-amino-4-oxo-6-methylpyrrolo[2,3-*d*]pyrimidines of general structure **1** possess significant thymidylate synthase (TS) inhibitory activity. Recent biological data further indicated that unlike other antitumor TS inhibitors, such as 5-FU, ZD1694 and LY231514, compound **1** does not induce new TS protein synthesis, a regulatory mechanism that tumor cells use to develop resistance to TS inhibitors. Molecular modeling indicated that the 6-methyl moiety influences the conformation of the 5-substituted side chain and makes hydrophobic contact with human TS at Trp109. Thus, we designed tricyclic analogues of general structure **2**, whose benzene ring can increase the hydrophobic interaction of the 6-methyl of compound **1**, and also influence the conformation of the 5-substituent. The synthesis and biological activities of compounds of general structure **2** will be presented.



1

Ar
4'-pyridinyl
3',4'-diClphenyl
4'-NO_2phenyl
p-benzoyl-L-glutamate



2

272.

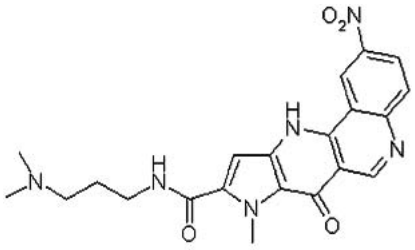
ANTITUMOR 1,4-ANTHRACENEDIONES INDUCE THE LOSS OF MITOCHONDRIAL MEMBRANE POTENTIAL IN CELL AND CELL-FREE SYSTEMS. ***Yang Wang***[1], *Mary M. Ward[1], Elisabeth M. Perchellet[1], Kaiyan Lou[2], Justin Crossland[2], Duy H. Hua[2], and Jean-Pierre H. Perchellet[1]. (1) Anti-Cancer Drug Laboratory, Kansas State University, Division of Biology, Ackert Hall, Manhattan, KS 66506-4901, Fax: 785-532-6653, yangwang@ksu.edu, (2) Department of Chemistry, Kansas State University*

Fluorescent probes of transmembrane potential have been used to determine whether synthetic analogs of 1,4-anthraquinone (AQ code number), which induce cytochrome *c* release without caspase activation, might directly target mitochondria to cause the loss of mitochondrial membrane potential ($\Delta\psi_m$) indicative of mitochondrial permeability pore transition (MPPT). Using JC-1 dye, the abilities of various AQs to induce the loss of $\Delta\psi_m$ in HL-60 cells are rapid, irreversible after drug removal, concentration-dependent in the 0.1-10 μM range, and correlated to their antitumor activities. The loss of $\Delta\psi_m$ caused by 6-hydroxymethyl-1,4-anthracenedione (AQ10), which is more potent than mitoxantrone, staurosporine and the reference depolarizing agent CCCP, is not prevented by catalase, z-VDVAD-fmk and z-IETD-fmk, suggesting that reactive O_2 species and apical caspase activation are not involved in this process. The losses of $\Delta\psi_m$ caused by 1.6 μM AQ10 and 100 μM $CaCl_2$ in mitochondria isolated from mouse liver and loaded with Rhodamine 123 dye are similarly blocked by cyclosporine A, which prevents MPPT.

273.

DESIGN AND SYNTHESIS AND OF A 7H,5,8,11-TRIAZA-CYCLOPENTA[B]PHENANTHRENE ANALOGUE : POTENTIAL DNA BENDING AGENT. ***Jaipal Hooda***, *and Steven M. Firestine, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5599, jai_hooda@hotmail.com*

DNA bending has been shown to be one of the mechanisms by which genes are regulated. In an attempt to control the expression of genes, our lab is interested in the synthesis of agents, which have the potential to bend DNA. To accomplish this, we have chosen to utilize bulky molecules that widen the minor groove of DNA resulting in bending. In an effort to develop a sequence specific DNA bending agent, polyamide-based DNA binding agent that should form a 2:1 complex upon binding to DNA are being studied. A key intermediate in our design is compound **1**. The synthesis of 1 along with DNA binding data and DNA bending data will be presented.



1

274.

DEVELOPMENT AND TESTING OF NEW SEQUENCE-SPECIFIC DNA BENDING AGENTS. ***Anne Loccisano***, *Center for Computational Sciences, Duquesne University, Department of Chemistry and Biochemistry, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, aloccisano@hotmail.com, Steven M. Firestine, Graduate School of Pharmaceutical Sciences, Duquesne University, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

Studies on the control of gene expression by DNA bending have indicated that bends in DNA can cause activation or inhibition of gene expression depending on the phase of the bend. Bending by external agents has been attributed to groove widening or contraction either by steric or ionic interactions. Sequence-specific agents that bind to and bend DNA are being developed and tested. These agents are polyamide-based drugs that bind in a 2:1 complex with DNA, and they contain sterically bulky groups that widen the minor groove of DNA. In order to evaluate the sequence specificity and the ability to bend DNA, parameters for the new molecules have been created for the CHARMM force field in order to perform molecular dynamics simulations with DNA and the bending agents. The information gained from these simulations will provide a detailed picture of how these new drugs bend DNA.

275.

DNA BENDING BY INSERTION OF A BULKY AMINE INTO THE MINOR GROOVE. ***Sarah A. Mueller-Stein***, *Department of Chemistry and Biochemistry, Center for Computational Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5683, mueller971@duq.edu, Steven M. Firestine, Graduate School of Pharmaceutical Sciences, Duquesne University, and Jeffrey D. Evanseck, Department of Chemistry & Biochemistry and Center for Computational Sciences, Duquesne University*

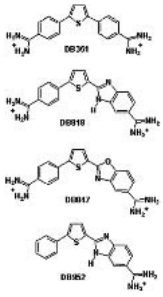
A experimental and computational approach has been undertaken to investigate the hypothesis that guanine derivatives with bulky amines positioned in the minor groove can cause DNA bending. Insertion of sterically bulky amines has been accomplished by modification of a guanine base at the C2 position. The modification is projected into the minor groove to mimic the forces of small, nonpeptide DNA bending drugs. A 24 base pair oligonucleotide with a 3-bp overhang has been synthesized using 2-fluoro-2-deoxyinosine in place of one internal guanine residue. The oligonucleotides have been treated with t-butylamine and adamantanamine to generate the substituted oligonucleotides. Bending has been analyzed using gel assays in which the ligated modified oligonucleotides were compared to the non-modified oligonucleotides. Preliminary results indicate that the modified oligonucleotides migrate more slowly

through the gel than non-modified oligonucleotides. Oligonucleotides synthesized experimentally have been modeled using molecular dynamics simulations to examine bending at the molecular level.

276.

THERMODYNAMIC AND STRUCTURAL STUDIES ON A NOVEL CLASS OF BENZIMIDAZOLE DERIVATIVES THAT BIND TO THE MINOR GROOVE OF DNA. ***Sirish Mallena***, *Arvind Kumar, Adalgisa Batista-Parra, Chad E. Stephens, David W. Boykin, and W. David Wilson, Department of Chemistry, Georgia State University, 50 Decatur Street, Atlanta, GA 30303, chesm@langate.gsu.edu*

The human genome project as well as sequencing of the genomes of other organisms offers a wealth of DNA targets for both therapeutic and diagnostic applications and it is important to develop additional DNA binding motifs to fully exploit the potential of this new information. We have recently found that an aromatic dication, DB293, with an amidine-phenyl-furan-benzimidazole-amidine structure can recognize specific sequences of DNA by binding in the minor groove as a dimer. The heterocyclic dimer represent only the second small molecule class that can recognize mixed sequences of DNA. In order to test the structural limits on the new type of complex, it is important to probe the influence of compound charge, chemical groups and structural features. We have synthesized several related derivatives that are based on a central thiophene system instead of the parent furan. As an initial step in the evaluation of these compounds, we have conducted detailed studies on their complexes with different sequences such as AATT, ATAT, CGCG in DNA oligomers as well as with alternating and non-alternating copolymer DNA duplexes. The effects of compound molecular variations on DNA complex formation have been evaluated by CD and UV spectroscopy, thermal melting, and quantitative analysis with surface plasmon resonance biosensor, isothermal titration calorimetry and differential scanning calorimetry methods. The thiophene heterocycle is found to have a very pronounced influence on the AATT interactions when coupled with a benzimidazole heterocycle. The terminal cationic amidine groups are both very important to binding but both amidines do not make the same contribution to the binding energetics. The results show that formation of the minor-groove complexes is very sensitive to compound structure in this series. These results offer new opportunities to enhance the specificity and expand the range of applications of compounds that target DNA. The analysis of the results on the spectroscopic and the thermodynamic investigations will be discussed in detail.



277.

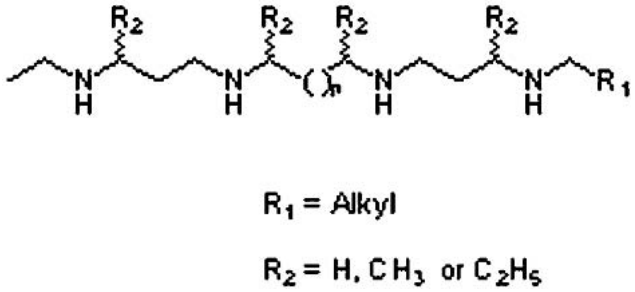
ANTITUMOR TRIPTYCENE BISQUINONES INHIBIT BOTH DNA TOPOISOMERASE I AND II ACTIVITIES. *Buna Wang[1], **Jean-Pierre H. Perchellet**[1], Elisabeth M. Perchellet[1], Yang Wang[1], Masafumi Tamura[2], and Duy H. Hua[2]. (1) Anti-Cancer Drug Laboratory, Kansas State University, Division of Biology, Ackert Hall, Manhattan, KS 66506-4901, Fax: 785-532-6653, jpperch@ksu.edu, (2) Department of Chemistry, Kansas State University*

Synthetic triptycene analogs (TT code number) mimic the antitumor effects of daunorubicin in the nM range *in vitro* but have the advantage of blocking nucleoside transport and retaining their efficacy in multidrug-resistant tumor cells. Since TT bisquinones induce caspase-9 and -3 activities and poly(ADP-ribose) polymerase-1 cleavage at 6 h and internucleosomal DNA fragmentation at 24 h, which are, respectively, early and late markers of apoptosis, these lead antitumor drugs were tested for their ability to trigger the DNA topoisomerase (Topo) inhibitions responsible for the initial and massive high molecular weight cleavage of DNA required for tumor cells to commit apoptotis. Interestingly, antitumor TTs have the unusual ability to inhibit, in a concentration-dependent manner and in relation to their cytotoxicity and quinone functionality, the relaxation of supercoiled plasmid DNA catalyzed by both purified human Topo I and II enzymes. Moreover, one of the most cytotoxic TT bisquinone, 6-bromo-7-methoxy- or 7-bromo-6-methoxy-2-*N*-methylamino-1*H*,4*H*,5*H*,8*H*-9,10-dihydro-9,10-[1′,2′]benzenoanthracene-1,4,5,8-tetraone (TT24), inhibits Topo II activity more effectively than amsacrine and matches the Topo I inhibitory effect of camptothecin.

278.

COMPARISON OF STRAIGHT CHAIN AND ALPHA METHYL POLYAMINES AS METABOLICALLY STABLE ANTITUMOR AGENTS. ***D.H. Eranda Jayamaha***[1], *Tracey Ward[1], Robert A. Casero[2], and Patrick M. Woster[1]. (1) Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, djayamah@chem.wayne.edu, (2) Department of Oncology, Johns Hopkins University*

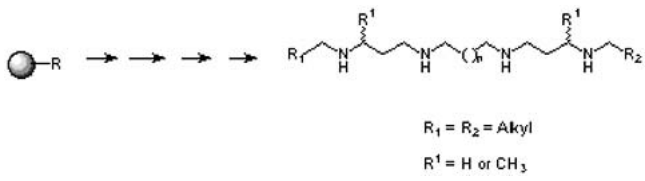
The precise functions of polyamines in cell physiology are not well understood at the molecular level. The polyamine biosynthetic and metabolic pathways leading to the natural polyamines via enzyme catalyzed reactions are now well established. The back-conversion of polyamines proceeds through an N-acetylation followed by oxidative deamination catalyzed by spermidine/spermine-N1-acetyltransferase (SSAT) and polyamine oxidase (PAO) respectively. To date, a number of symmetrically substituted straight chain polyamine analogues have been synthesized. There is evidence that these analogues can also serve as substrates for polyamine oxidase, and that the resulting metabolites may be involved in the mechanism of analogue cytotoxicity. For these reasons, we have undertaken the synthesis of the _–methyl homologues that are metabolically stable to oxidation which would possess activity comparable to the parent analogues. In this paper we will discuss synthesis and biological activity of some of the _ –methyl analogues with their corresponding straight chain analogues.



279.

SOLID-PHASE SYNTHESIS OF UNSYMETRICALLY SUBSTITUTED ANTINEOPLASTIC ALKYLPOLYAMINES. ***D.H. Eranda Jayamaha***[1], *Robert A. Casero[2], and Patrick M. Woster[1]. (1) Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, djayamah@chem.wayne.edu, (2) Department of Oncology, Johns Hopkins University*

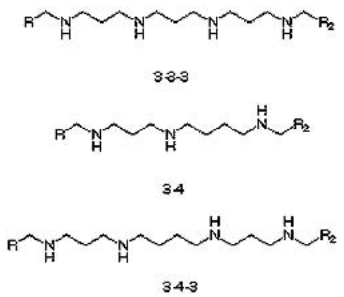
The polyamines putrescine, spermidine and spermine are naturally occurring polycationic alkylamines. They have been shown to be required in normal and neoplastic cell proliferation, and in some cases effect cell survival. Much work has been done in the area of blocking the biosynthesis of polyamines, but more recent work is directed towards the regulatory properties of polyamine metabolism by active polyamine analogues. Along thess lines our lab has made quite a large number of active symmetrical and unsymmetrical polyamine analogues using solution phase techniques. In drug discovery combinatorial approaches are attractive because they speed up the process of lead finding and the optimization of a lead compound up to the final drug as compared to traditional medicinal chemistry. The preferred method for combinatorial chemistry is synthesis on a solid support. In this paper we will discuss the synthesis and biological evaluation of polyamine analogues using solid phase techniques as potential antitumor agents.



280.

STRUCTURE ACTIVITY RELATIONSHIPS OF ANTINEOPLASTIC BIS-SUBSTITUTED ALKYLPOLYAMINES. *Tracey Ward[1], Amy Hacker[2], Erin Hager[2], Robert A. Casero[2], and* ***Patrick M. Woster***[1]*. (1) Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, Fax: 313-577-2033, tward@wizard.pharm.wayne.edu, pwoster@wayne.edu, (2) Department of Oncology, Johns Hopkins University*

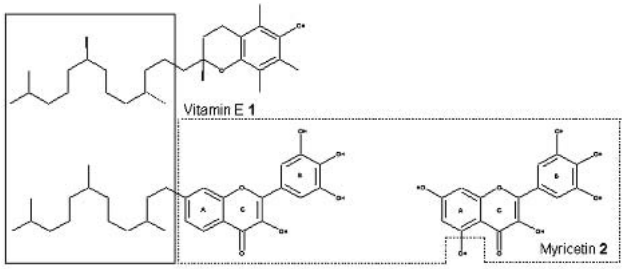
A series of symmetrically- and unsymmetrically substituted alkylpolyamines were synthesized containing 3-3-3, 3-4 and 3-4-3 polyamine backbones. Analogues were tested in vitro against H157 (nonSCLC) and H82 (SCLC) lung tumor cells and/or 231, 243 and MCF7 breast cancer cells both in vivo and in vitro. A number of compounds have been found to show extremely promising IC50 values as low as 0.4μM. This poster will describe the synthesis, in vitro assay and in vivo characterization of these analogues.



281.

MYRICETIN-VITAMIN E HYBRIDS: POTENTIAL THERAPEUTIC ANTIOXIDANTS. ***Christopher J. Bennett***[1]*, Donald B. McPhail[2], Peter T. Gardner[2], Garry G. Duthie[2], and Richard C. Hartley[3]. (1) Department of Chemistry, OxyProTec, University of Glasgow, Glasgow G12 8QQ, United Kingdom, Fax: +44-141-330-4888, chrisb@chem.gla.ac.uk, (2) Rowett Research Institute, (3) Department of Chemistry, University of Glasgow*

Reactive oxygen species (ROS) such as hydroxyl radicals and peroxyl radicals can damage lipid membranes, and this oxidative damage is involved in many clinical conditions including ischaemia-reperfusion injury and neurological disorders. Vitamin E **1** is the primary lipid-soluble antioxidant used in the body's defence against ROS. Many dietary flavonols are powerful reducing agents: myricetin **2** reacts 28 times faster than vitamin E with oxygen-centred radicals and each molecule can destroy twice as many ROS. However, it is a poor biological antioxidant due to its low solubility in lipids. Myricetin-vitamin E hybrid **3** and related compounds combine the radical defence qualities of flavonols with the lipid solubility of vitamin E and are excellent biological antioxidants.

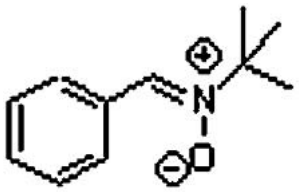


Vitamin E - myricetin hybrid **3**

282.

NOVEL NITRONE ANTIOXIDANTS. ***Alison Hay***[1]*, Richard C. Hartley[1], Donald B. McPhail[2], and Garry G. Duthie[2]. (1) Department of Chemistry, University of Glasgow, University Avenue, Glasgow G12 8QQ, United Kingdom, alisonh@chem.gla.ac.uk, (2) Rowett Research Institute*

Reactive oxygen species (ROS) have increasingly been demonstrated in recent years as contributing towards a variety of pathologies most notably stroke, arteriosclerosis, diabetes and organ transplantation. ROS irreversibly modify polyunsaturated membrane lipids due to lipid peroxidation which in turn, affects essential cellular functions. Natural antioxidant defences can be overwhelmed when the body is placed under high oxidative stress. Therefore, intervention by synthetic antioxidants should be beneficial. *N*-(benzylidene)-*tert*-butylamine *N*-oxide (PBN), commonly used as an ESR reagent, has previously been shown to protect neurones from ROS damage. Novel nitrone antioxidants designed to protect membranes from ROS damage have been synthesised in 5 steps, with good yield and have demonstrated excellent ROS trapping ability using electron spin resonance spectroscopy (ESR). The results of *in vitro* tests will also be presented.



PBN

283.

PHOTOCHEMILUMINESCENCE- BASED ANALYSIS OF ANTIOXIDATIVE CAPACITY IN BLOOD FOR BIOLOGICAL RESEARCH AND MEDICAL ROUTINE DIAGNOSTICS. ***Andreas Sterner****, and Scott Wallace, Analytik Jena USA, Inc, 26009 Budde Rd., Suite D-100, The Woodlands, TX 77380, Fax: 281-367-6130, a.sterner@analytik-jena.de*

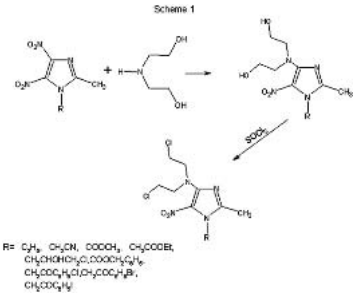
Various diseases and damaging processes in the body coincide with sharply enhanced exposition of body cells to so-called reactive oxygen species (ROS). These intrinsic compounds, which are always present to a certain scale, are balanced in healthy persons by a group of compounds, the Antioxidants. Among these are ascorbic acid (vitamin C), tocopherols (vitamin E), bilirubin, polyphenols etc, which act as scavangers, therefore neutralizing harmful radicals in processes like cancer, inflammation and arthrithis, just to name some. In literature, many positive effects to the health status are direcly related to Antioxidants, e.g. the French Paradox, stating that a small but regular intake of red wine leads to a significant reduction of the risk of cardiac infarction. A most interesting objective in medical research is the linkage of the antioxidative status (sum parameter) to diseases, thus making it possible to monitor disease progression or recovery and develop new methods of prophylaxis. Because of the most divergent chemical nature of Antioxidants, it is still expensive and time-consuming to monitor them together in classic medical routine diagnostics. Therefore a quick, reliable but universal method is now available to state the efficacy of Antioxidants in its collectivity.

284.

SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF 4-[BIS(2-CHLOROETHYL)AMINO]-5-NITROIMIDAZOLE. ***Stanisaw Sobiak****, and Iwona Weidlich, Department of Chemical Technology of Drugs/Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 68-780 Poznañ, Poland, Fax: 865-9566, ssobiak@amp.edu.pl*

Combination of two chemical functionalities nitroimidazole and bis(2-chloroethyl)amine arises hopes to synthesize a compound showing selective activity on neoplasmic cells, which would be expected of a combination of the nitric group and nitrogen of nitrogen mustard. A low yield of 1-alkyl-4-bromo-2-methyl-5-nitroimidazole in accordance with literature data, prompted us to make 4-[bis(2-chloroethyl)amino]-5-nitroimidazole derivatives in different manner (Scheme 1). The N-substituted derivatives of 4,5-dinitro-2-methylimidazole were obtained as a result of reactions with appropriate alkyl chloride. The compounds obtained were treated with bis(2-hydroxyethyl)amine in an appropriate solvent at a proper temperature. Chlorination of the diols with thionyl chloride in pyridine, yielded the desired products. The compounds obtained were identified by the 1H and 13C NMR, spectra MS and elemental analyses.

Scientific research was supported by Center of Committee of Scientific Investigations(Poland) –project 0321/P05/2002/23

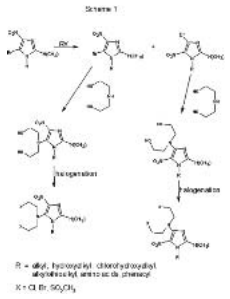


285.

SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF 5(4)-[BIS(2-CHLORETHYL)AMINO]-4(5)-NITROIMIDAZOLE BEING NEW GROUP OF ANTICANCER DRUGS. ***Iwona Weidlich***, *and Stanis*[3]*aw Sobiak, Department of Chemical Technology of Drugs/Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 68-780 Poznañ, Poland, Fax: 865-9566, iweidlic@amp.edu.pl*

Particular abilities nitroimidazoles to accumulate in living cells in the state of hypoxy stimulated us to make an attempt to synthesize compounds showing cytostatic activity. Derivatives of p-halogeno-5-bromo-4-nitroimidazole have shown a promising ability to inhibit growth of Hel cells. In the leading compound (5-bromo-1(4-chlorophenacyl)-2-methyl-4-nitroimidazole) the bromine atom has been replaced by a bis(2-chloroethyl)amino group. The nitric group coupled with the amine group of nitrogen mustard leads to an electron deficit and finally to a decrease in the cytotoxic activity. N-alkylation of 5(4)-bromo-2-methyl-4(5)-nitroimidazole was made in DMF/NaHCO3 leading to a mixture of isomers in which derivatives of 4-nitroimidazole were dominant. Substitution of bromide at C-5 of nitroimidazole bis(2-hydroxyethyl)amine and halogenation of the product resulted in formation of N-substituted derivatives of bis(2-chloroethyl)aminonitroimidazole. The compounds obtained were identified by the 1H and 13C NMR, spectra MS and elemental analyses.

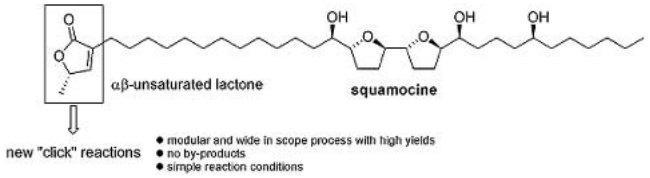
Scientific research was supported by Center of Committee of Scientific Investigations(Poland) –project 0321/P05/2002/23



286.

LIBRARY OF SQUAMOCIN ANALOGS BY "CLICK CHEMISTRY". ***Erwan Poupon***, *Romain Duval, Guy Lewin, and Reynald Hocquemiller, Laboratoire de Pharmacognosie - UMR CNRS 8076, University, 5, rue Jean-Baptiste Clément, 92260 Châtenay-Malabry, France, Fax: +33-1-46-83-53-99, erwan.poupon@cep.u-psud.fr*

Among the new methodologies for rapid access to chemical diversity and complexity developed recently, Sharpless "click chemistry" constitutes an original and exciting direction. As a way of quickly making large numbers of molecules, it offers an attractive alternative in medicinal chemistry. We believe that a unique high level of diversity can be reached very easily when combining "click chemistry" strategies with the preexisting and often tremendous complexity of natural products. We want to use and further expand the set of highly reliable reactions, the essence of the concept, to synthesize libraries of natural product-like molecules. Squamocin, a highly active secondary metabolite from Annonaceae with promising anticancer activities (blockage of mitochondrial complex I), has been selected for this purpose. Along with the discovery of new reactivities, a library of complex squamocin derivatives has been successfully prepared using short and modular "click chemistry" sequences. First results of biological screening will be reported.



287.

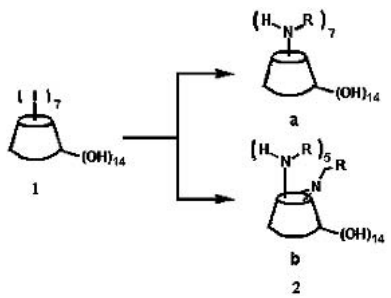
[^{18}F]XELODA AS A NOVEL POTENTIAL PET IMAGING AGENT FOR CANCER DETECTION. *Xiangshu Fei, Qi-Huang Zheng,* ***Ji-Quan Wang****, and Gary D. Hutchins, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L-3, Rm. 202, Indianapolis, IN 46202-2111, Fax: 317-278-9711, xfei@iupui.edu, jiqwang@iupui.edu*

Xeloda (5′-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine, capecitabine) (Hoffman LaRoche) is the first and only fluoropyrimidine to be approved for use as second-line therapy in metastatic breast cancer, colorectal cancer, and other malignancies. Xeloda labeled with positron emitting radionuclide fluorine-18 may enable non-invasive monitoring of cancer thymidine phosphorylase (TP) levels and cancer response to Xeloda therapy using positron emission tomography (PET) imaging techniques. To develop novel PET cancer imaging agents, we initialed a synthetic endeavor of [^{18}F]Xeloda. The key intermediate 5-deoxy-1,2,3-tri-O-acetyl-β-D-ribofuranoside was prepared from D-ribose via six steps, which was coupled with 5-nitrocytosine to give 2′,3′-di-O-acetyl-5′-deoxy-5-nitrocytidine. After the acylation of N^4-amino group of 2′,3′-di-O-acetyl-5′-deoxy-5-nitrocytidine produced the precursor 5-nitro-Xeloda analogue, it was radiolabeled with K[^{18}F]/Kryptofix2.2.2 followed by a quick deprotection to afford the target molecule [^{18}F]Xeloda.

288.

PER-6-SUBSTITUTED-PER-6-DEXOY-β-CYCLODEXTRINS INHIBIT THE FORMATION OF β-AMYLOID-PEPTIDE(Aβ) DERIVED, SOLUBLE OLIGOMERS. ***Zhiqiang Wang***[1]*, Lei Chang*[2]*, Lara Bakhos*[2]*, William L. Klein*[2]*, and* ***Duane L. Venton***[1]*. (1) Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612-7231, (2) Department of Neurobiology and Physiology, Northwestern University*

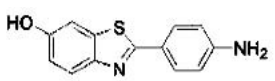
Recent studies have indicated that the most important role of Aβ in the etiology of Alzheimer's Disease (AD) may not be in plaque formation, but in the formation of soluble, metastable $A\beta_{1\text{-}42}$ neurotoxic intermediates (called ADDLs). Direct interference with the assembly or activity of ADDLs may represent an attractive strategy for the treatment of AD. Using a high throughput dot blot assay, recently developed in our laboratories for measuring Aβ oligomerization, we describe the preparation, isolation and evaluation of certain β-CD derivatives which inhibit ADDLs formation *in vitro*. We are presently exploring these and other β-CD derivatives as a means of controlling *in vivo* ADDLs formation in the treatment of AD.



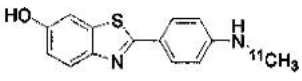
289.

SYNTHESIS AND EVALUATION OF [11C]-2-(4-METHYLAMINOPHENYL)BENZOTHIAZOL-6-OL: A POTENTIAL PET TRACER FOR AMYLOID PROTEINS. ***J. S. Dileep Kumar***[1], *Theodore S. Wang*[2], *Victoria Arango*[3], *Mark D. Underwood*[3], *Ramin V. Parsey*[3], *Norman R. Simpson*[2], *Suham Kassir*[3], *Anna R. Cooper*[3], *Julie Arcement*[3], *Ronald L. Van Heertum*[2], *and J. John Mann*[3]. *(1) Department of Psychiatry and Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, Fax: 212-543-6017, dk2038@columbia.edu, (2) Department of Radiology, Columbia University, (3) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute*

Small molecule based imaging agents have been sought for the detection of beta-amyloid in Alzheimer's Disease (AD) in vivo. Synthesis of [11C]-2-(4-Methylaminophenyl)-benzothiazol-6-ol (6-hydroxy-BTA-1), a potential imaging agent for amyloid protein with positron emission tomography has been described. We have synthesized [11C]-2-(4-methylaminophenyl)benzothiazol-6-ol with over 1000 Ci/ mmol specific activity by the reaction of 2-(4-aminophenyl)benzothiazol-6-ol (6-hydroxy-BTA-0) with [11C]MeOTf at 60 °C with an average radiochemical yield of 33% (EOS). The radioligand was found to be selective for the labeling of amyloid proteins in slide mounted sections of AD postmortem brain using a phosphor imager. Details of the synthesis, radiosynthesis, in vitro autoradiography and PET imaging in rats and baboons will be presented. [11C]-2-(4-Methylaminophenyl)-benzothiazol-6-ol is a promising PET ligand for in vivo imaging of Alzheimer's disease.



6-Hydroxy-BTA-0

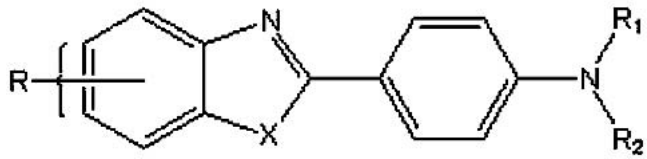


[11C]-6-Hydroxy-BTA-1

290.

SYNTHESIS OF CYCLOPENTADIENYL RHENIUM TRICARBONYL SUBSTITUTED BENZOXAZOLES AND THEIR BIOLOGICAL EVALUATION. ***Sven H Hausner***, *Ronald M Baldwin, and Gilles D Tamagnan, VA CT HCS (116A2), Yale University School of Medicine, 950 Campbell Ave, West Haven, CT 06516*

Benzoxazole and benzothiazole (X=O, S) derivatives of the structure shown below have been used with promising results in the PET imaging of amyloid plaque implicated in the development of Alzheimer's disease, as well as in the selective treatment of tumors. We synthesized arylamide substituted benzoxazoles (R=ArCONH), employing a boric acid induced condensation as the key step, as well as an alkyne analogue. Ethyl polyphosphate induced condensation was explored, as well. The benzoxazoles (Ar=CpRe$(CO)_3$) can be viewed as metal complex analogues of IBOX (2-(4′-dimethylaminophenyl)-6-iodobenzoxazole), whose radioiodinated form shows promise for imaging. The cyclopentadienyl rhenium tricarbonyl compounds serve as models for the corresponding technetium-99m compounds, which would be advantageous for imaging.



291.

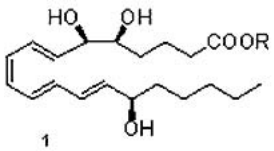
SYNTHESES AND NEUROPROTECTIVE EFFECTS OF THE CYCLIC ANALOGS OF COMPLESTATIN. *Sung-Hwa Yoon*[1], ***Ho Joon Park***[1], *Haeun Lee*[1], *and ByoungJoo Gwag*[2]. *(1) Department of Molecular Science and Technology, Ajou University, PaldalGu WonchunDong, Suwon 442-749, South Korea, Fax: 31-214-8918, shyoon@madang.ajou.ac.kr, pkhead99@ajou.ac.kr, (2) Department of Pharmacology, College of Medicine, Ajou University*

It has been found by our group that complestatin, a bicylcic peptide derived from actinomycete, Streptomyce sp. WK-3419, protects the cultured cortical neurons from excitotoxicity induced by NMDA, AMPA, or kainates. Since excess activation of NMDA or AMPA/kainate receptors produces neuronal death and has been implicated as a major cause of hypoxic-ischemic neuronal injuries such as Alzheimer's diseases and Parkinson's diseases, complestatin can be used as a lead compound for the development of new peptide-typed neuroprotectants. For the purpose of symplifying the bicyclic structure of complestatin, we previously reported that various linear peptide analogs of complestatin showed weak antagonistic activities against NMDA neurotoxicity. In this study, we extended our investigation to the cyclic peptide analogs of complestatin to understand the structure-activity relationship of complestatin. The syntheses and biological evaluations of the cyclic peptide analogs of complestatin will be discussed in detail. Supported by NRL program and BK21 program.

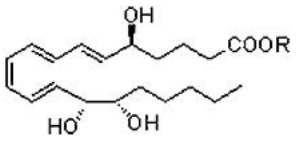
292.

DESIGN AND SYNTHESIS OF NOVEL LIPOXIN ANALOGUES. *Nicos A. Petasis*[1], ***Raquel Keledjian***[1], *and Charles N. Serhan*[2]. *(1) Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, 837 West 37th Street, Los Angeles, CA 90089-1661, Fax: 213-740-6684, petasis@usc.edu, keledian@usc.edu, (2) Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Harvard Medical School*

Unlike prostaglandins and leukotrienes that are pro-inflammatory lipid mediators, the lipoxins (LXA4, **1** and LXB4, **2**) and the corresponding 15-epi lipoxins which are generated via the action of COX-2 in the presence of aspirin, display potent anti-inflammatory properties. We have recently designed, synthesized and studied a number of lipoxin analogues that suppress the rapid metabolic inactivation of the natural lipoxins, while they retain a lipoxin-like anti-inflammatory profile. Our most recent studies on lipoxin analogues will be presented, including analogues that have structural modifications at the tetraene moiety and/or the terminal alkyl chain.



1

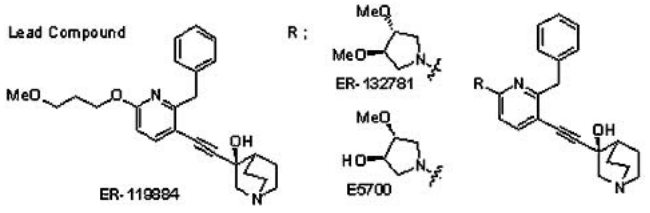


2

293.

DISCOVERY AND SAR OF NOVEL TRI-SUBSTITUTED PYRIDINE DERIVATIVES AS INHIBITORS OF SQUALENE SYNTHETASE. ***Toshimi Okada***, *Daisuke Shinmyo, Keigo Tanaka, Nobuyuki Kurusu, Kazuki Miyazaki, Hiroyuki Sugumi, Hironori Ikuta, Masashi Ito, Mamoru Yanagimachi, Hironobu Hiyoshi, Takao Saeki, and Shinya Abe, Tsukuba Research Laboratories, Eisai Co., Ltd, Tokodai 5-1-3, Tsukuba-shi, Ibaraki 300-2635, Japan, Fax: +81-29-847-2037, t5-okada@hhc.eisai.co.jp*

Squalene synthase catalyzes the first step committed to sterols in the pathway of cholesterol biosynthesis. Inhibition of this enzyme has been recognized as a novel approach for the treatment of hyperlipidemia. In this study, we report a series of tri-substituted pyridine derivatives as potent squalene synthase inhibitors. Firstly, we discovered ER-119884 by modification of 3-(o-benzylpyridyl)ethynyl-3-quinuclidinol derivatives. ER-119884 potently inhibited cholesterol biosynthesis in rats (ED50, 0.73 mg/kg). Through the screening of ER-119884 derivatives in normolipidemic rhesus monkeys, we found that pyrrolidine derivatives (E5700, ER-132781, etc.) potently reduced plasma cholesterol and triglyceride levels. These compounds may provide a novel approach to treat patients with mixed dyslipidemia.



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294.

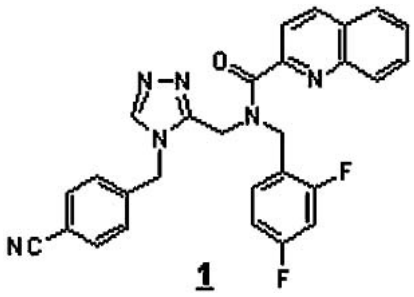
DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF POTENT AND SELECTIVE PEPTIDOMIMETIC GERANYLGERANYLTRANSFERASE-I INHIBITORS. ***Dora Carrico***[1], *Hairuo Peng*[1], *Michelle A. Blaskovich*[2], *Said M. Sebti*[2], *and Andrew D Hamilton*[1]. *(1) Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520, Fax: 203-432-6144, dora.carrico@yale.edu, (2) Department of Biochemistry and Molecular Biology, University of South Florida*

Peptidomimetic inhibitors of protein geranylgeranyltransferase-I (GGTase-I) based on the C-terminal CAAX (X=L, F) sequence found in many geranylgeranylated proteins were designed and synthesized. Using novel scaffolds as mimetics for the central dipeptide (AA), we have developed potent inhibitors that selectively block the activity of GGTase-I over the very closely related enzyme protein farnesyltransferase (FTase). The findings that geranylgeranylated proteins RhoC, RhoA, Rac-1, Cdc42 and R-Ras play a critical role in tumorigenesis and metastasis, make GGTase-I a promising target for the development of anticancer agents. Details of the syntheses, SAR studies and enzyme inhibition activity will be presented.

295.

NOVEL TRIAZOLE BASED INHIBITORS OF FARNESYL TRANSFERASE. ***Li Liu****, Ashis K. Saha, Bart L. De Corte, Richard L. Simoneaux, Henry J. Breslin, Michael J. Kukla, and David W. End, Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, L.L.C, Welsh & McKean Roads, P.O.Box 776, Spring House, PA 19477, lliu@prdus.jnj.com*

Farnesyl transferase inhibitors represent a new class of antitumor agents. A synthetic effort exploring the potential of triazole containing compounds as anti-infective and antiproliferative agents led to the discovery of 1, a potent and selective farnesyl transferase inhibitor. The synthesis and biological activity of 1 and a number of triazole containing analogues will be discussed.



1

296.

PARALLEL LIQUID SYNTHESIS OF N,N′-DISUBSTITUTED 3-AMINO AZEPINES AS POTENT FARNESYL TRANSFERASE INHIBITORS. ***Jean-Claude Ortuno***[1], *Thierry Le Diguarher*[2], *Gilbert Dorey*[2], *Nicolas Guilbaud*[3], *Jean-Luc Fauchère*[1], *John Hickman*[3], *Gordon Tucker*[3], *and Patrick J. Casara*[2]. *(1) Combinatorial Chemistry, Institut de Recherches SERVIER, 125 Chemin de Ronde, Croissy sur Seine 78290, France, Fax: 33-1-55-72-24-70, jean-claude.ortuno@fr.netgrs.com, (2) Medicinal Chemistry, Institut de Recherches SERVIER, (3) Oncology, Institut de Recherches SERVIER*

Protein Farnesyl Transferase (FTase) is a zinc dependent enzyme that catalyses the attachment of a farnesyl lipid group to the sulfur atom of a cysteine residue of numerous proteins involved in cell signalling, including the oncogenic H-Ras protein. This lipid side chain is critical for the cell membrane anchoring of these proteins, and therefore FTase inhibition has been recognised as a valuable antitumour therapeutic approach. We wish to report the solution phase parallel synthesis of N,N′-disubstituted-3-amino Azepines a new class of FTase Inhibitors. Activities in both in vitro and in vivo assays will be presented.

297.

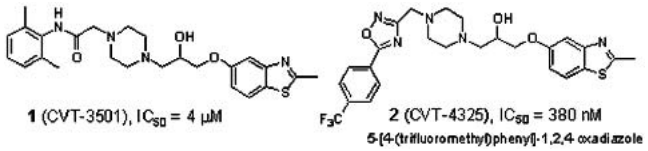
SYNTHETIC AND BIOLOGICAL STUDIES OF PRESQUALENE DIPHOSPHATE AND ITS ANALOGUES. *Nicos A. Petasis*[1], *Raquel Keledjian*[1], *and Charles N. Serhan*[2]. *(1) Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, 837 West 37th Street, Los Angeles, CA 90089-1661, Fax: 213-740-6684, petasis@usc.edu, (2) Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Harvard Medical School*

Abstract text not available.

298.

STRUCTURE ACTIVITY RELATIONSHIPS OF NOVEL INHIBITORS OF FATTY FCID OXIDATION. ***Kevin Shenk***[1], *Elfatih Elzein*[2], *Dmitry Koltun*[2], *Bob Jiang*[3], *Prabha Ibrahim*[2], *Tim Marquart*[2], *Ken Rehder*[4], *Yuan Li*[5], *Suresh Kerwar*[5], *Marie Nguyen*[5], *Dewan Zeng*[5], *Nancy Chu*[6], *Dan Soohoo*[6], *Jia Hao*[6], *Kwan Leung*[7], *and Jeff Zablocki*[3]. *(1) BioOrganic Chemistry, CV Theraputics, 3172 Porter Drive, Palo Alto, CA 94304, kevin.shenk@cvt.com, (2) Department of Bioorganic Chemistry, CV Therapeutics, (3) Department of Bio-Organic Chemistry, CV Therapeutics, (4) PPD Discovery, (5) Department of Pharmacological Sciences, CV Therapeutics, (6) Department of Pre-clinical Development, CV Therapeutics, (7) Department of Pre-Clinical Development, CV Therapeutics*

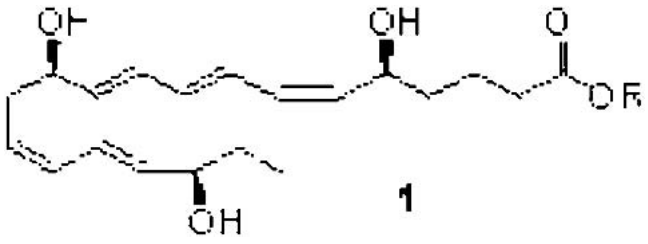
Inhibitors of fatty acid oxidation as potential metabolic modulators for the treatment of ischemic syndromes including angina, congestive heart failure, and intermittent claudication have been identified. Compound **1** showed moderate inhibitory activity (IC_{50}=4 μM) against 1-^{14}[C]-Palmitoyl-CoA (Palm-CoA) oxidation in isolated rat heart mitochondria, good oral bioavailability, but a relatively poor half-life *in vivo* (dog). Replacement of the metabolically labile amide moiety in compound **1** with different 1,2,4-oxadiazoles as amide bioisosteres resulted in significant enhancement in inhibitory activity against Palm-CoA oxidation (compound **2**, IC_{50}=0.380 μM), and a reduction in plasma clearance. The synthesis of this new series of compounds along with detailed SAR around the 3- and 5-phenyl groups on the oxadiazole moiety will be presented.



299.

SYNTHESIS OF TRIHYDROXY POLYUNSATURATED LIPID MEDIATORS. *Nicos A. Petasis*[1], ***Rong Yang***[1], *and Charles N. Serhan*[2]. *(1) Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, 837 West 37th Street, Los Angeles, CA 90089-1661, Fax: 213-740-6684, petasis@usc.edu, rongyang@usc.edu, (2) Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Harvard Medical School*

Dietary ω-3 polyunsaturated fatty acids (PUFA), including eicosapentaenoic acid (EPA)and docosahexaenoic acid (DHA) are known to have many beneficial effects in human health and in the prevention of various diseases, including inflammation, cancer and cardiovascular diseases. Despite numerous studies in this area, however, the molecular mechanisms for many of the actions of PUFA remain unknown. A new series of PUFA-derived hydroxylated derivatives termed Resolvins was recently discovered and it was shown that these compounds behave as potent bioactive lipid mediators. Herein we present our synthetic studies towards the development of efficient strategies for the total synthesis of molecules of this type, including compound **1** (Resolvin E1).



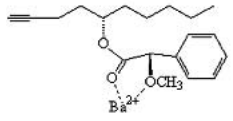
1

300.

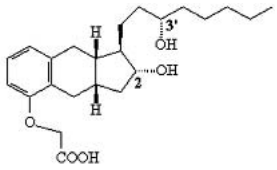
ABSOLUTE CONFIGURATION DETERMINATION OF STEREOGENIC CENTERS IN TREPROSTINIL USING 1H NMR ON BARIUM (II) COMPLEX. *Robert M. Moriarty*[1], ***Anca Hirtopeanu***[1], *Rajesh Naithani*[1], *Ileana Dragutan*[1], *Kuanquiang Gao*[1], *Liang Guo*[2], *Raju Penmasta*[2], *James P. Staszewski*[2], *Neena Rani*[2], *Sudersan M. Tuladhar*[2], *David Crich*[1], *Livia A. Enache*[3], *and Om Prakash*[1]. *(1) Department of Chemistry, University of Illinois, 845 W Taylor St, Chicago, IL 60607, Fax: 312-996-0431, ancah@uic.edu, (2) Research and Development, United Therapeutics, (3) deCODE Genetics, Inc*

Treprostinil (**2**) is a benzindene prostacyclin used for the treatment of pulmonary hypertension and its synthesis involves the introduction of a chiral

side-chain using 1-decyn-5-ol. As for all biologically important compounds, absolute stereochemistry has a major impact on the activity. The absolute configuration of the 1-decyn-5-ol was determined by NMR using derivatization with alpha-methoxyphenylacetic acid and in situ complexation with barium (II), a fast and reliable method for assignment of configuration. Having established the absolute configuration of the side-chain synthon, the method was extended to the configuration of both hydroxyl groups (C_2 and $C_{3'}$) in **2**. The application of this approach to related benzindene prostacyclins will be presented.



1

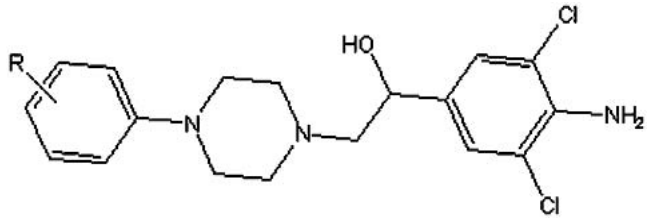


2

301.

ARYL PIPERAZINES: A NEW CLASS OF STEROID SULFATASE INHIBITORS FOR THE TREATMENT OF HORMONE-DEPENDENT BREAST CANCER. ***Wendy Lee***[1], *Mary DeRome*[2], *Joanna DeBear*[2], *Stephen Noell*[2], *David Epstein*[3], *Cathy Mahle*[4], *Lynn DeCarr*[4], *Kristine Woodruff*[4], *Zimei Huang*[4], *and Jacques Dumas*[1]. *(1) Department of Chemistry Research, Bayer Corporation, 400 Morgan Lane, West Haven, CT 06516, wendy.lee.b@bayer.com, (2) Department of Cancer Research, Bayer Corporation, (3) Archemix Corporation, (4) Department of Diabetes and Obesity Research, Bayer Corporation*

Compounds targeting the estrone sulfatase pathway (E1-STS) may be potential therapeutic agents for the treatment of hormone-dependent breast cancer tumors. A high-throughput screening effort led to the discovery of certain aryl piperazines exhibiting potent STS activity. Early optimization focused on the aniline moiety and the stereocenter of the hydroxy link. Using high-speed parallel solution-phase chemistry, a library of aryl piperazines was prepared and evaluated, resulting in the identification of several new compounds having STS activity. Since aryl piperazine derivatives are known to modulate serotoninergic and dopaminergic neurotransmission, the selectivity profile of novel compounds was evaluated against a panel of neurotransmitter receptor binding assays.



302.

COMPARISON OF PHOSPHONOTHIOIC ACIDS WITH PHOSPHONIC ACIDS AS INHIBITORS OF PHOSPHATASE. ***Krzysztof J. Swierczek****, and Alvan C. Hengge, Department of Chemistry and Biochemistry, Utah State University, 0300 Old Main Hill, Logan, UT 84322, krzys123@yahoo.com*

Protein phosphorylation plays a crucial role in the regulation of many biochemical processes, including the regulation of metabolism and signal transduction. The phosphorylation levels are controlled by the balancing actions of kinases and phosphatases. The crucial roles played by phosphatases have led to considerable interest in designing inhibitors. Phosphonic acids have formed the basis for a number of non-hydrolyzeable phosphate ester substrate mimics. The substitution of a sulfur atom for one of the nonbridging oxygen atoms in a phosphonic acid, yielding a phosphonothioic acid, reduces their pKa to values similar to those of phosphate esters. The resulting compounds are also mimics of phosphate esters, are nonhydrolyzable under physiological conditions. We have synthesized a several such compounds and evaluated their inhibitory properties toward a number of phosphatases. A method for the convenient synthesis of thiophosphonates, or phosphonothioic acids, is presented as well.

303.

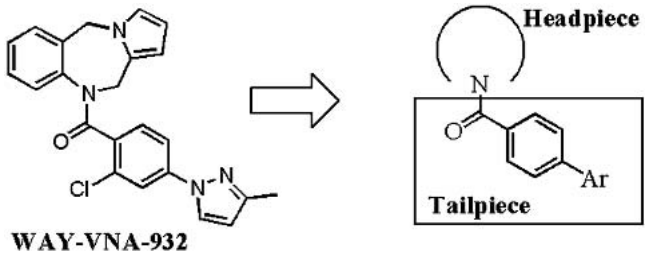
OXYTOCIN AGONIST ACTIVITY OF NON-PEPTIDIC PIPERAZINE UREAS. ***Andrzej R. Batt***[1], *Doreen M. Ashworth*[2], *Andrew J. Baxter*[1], *Robert M. Haigh*[2], *Peter Hudson*[3], *Céline Laurent*[1], *Andrew Penson*[1], *Gary R. W. Pitt*[1], *Peter A. Robson*[2], *David P. Rooker*[1], *André L. Tartar*[4], *Chris M. Yea*[2], *and Michael B. Roe*[1]. *(1) Department of Medicinal Chemistry, Ferring Research Ltd, Chilworth Science Park, Southampton SO16 7NP, United Kingdom, andrzej.batt@ferring-research.co.uk, (2) Department of Biochemistry, Ferring Research Ltd, (3) Investigational Analytical Chemistry, Ferring Pharmaceuticals A/S, (4) Laboratoire de chimie organique, Faculté des sciences pharmaceutiques et biologiques*

Oxytocin (OT) is a cyclic nonapeptide hormone that acts at the OT G-protein coupled receptor. It is localised in a number of different organs including the uterus where it is involved in the onset and progress of labour and the paraventricular nucleus where it is involved in the regulation of male and female sexual response. The range of physiological roles of OT has not been fully elaborated and there exists a need for mimics of OT that may be used as pharmacological tools as well as potential drugs. In particular, there are no orally available OT agonists currently in development. New non-peptidic compounds based on a piperazine urea will be presented. Their SAR will be discussed, leading to compounds with EC_{50} < 30nM. These compounds may have utility where OT function is compromised, in particular as novel and orally available treatments for sexual disorders such as male erectile dysfunction.

304.

VASOPRESSIN RECEPTOR LIGANDS: SAR EXPANSION VIA PARALLEL SYNTHESIS. ***William J. Moore****, Amedeo A. Failli, Jay S. Shumsky, Thomas J. Caggiano, and Eugene J. Trybulski, Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, Fax: 484-865-9398, moorew2@wyeth.com*

Our group has previously reported on the discovery of selective, non-peptidic, orally active vasopressin V_2-receptor ligands, exemplified by the clinical candidates WAY-VPA-985 (Lixivaptan©, V_2-antagonist) and WAY-VNA-932 (V_2-agonist). This communication will report on the application of parallel synthesis to expand the SAR of an in-house biphenyl series. This series was designed to answer some fundamental questions about the structural requirements for non-peptidic vasopressin and oxytocin receptor ligands. In addition to probing the biphenyl moiety as an isosteric extension of the heterocycle-aromatic tailpiece of WAY-VNA-932, a diverse group of headpieces were also investigated resulting in an array of 250 unique compounds.



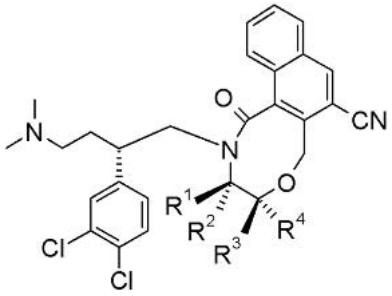
WAY-VNA-932

305.

IDENTIFICATION OF RIGIDIFIED CNS-ACTIVE NK1 RECEPTOR ANTAGONISTS AND DEVELOPMENT OF A DETAILED PHARMACOPHORE MODEL. ***Jeffrey S. Albert***[1], *Cyrus J. Ohnmacht*[1], *Peter R. Bernstein*[1], *William L. Rumsey*[1], *David Aharony*[2], *Daniel J. Russell*[3], *Lihong Shen*[1], *Robert F. Dedinas*[1], *and Keith Russell*[1]. *(1) CNS Discovery Research, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437, jeffrey.albert@astrazeneca.com, (2) Medicinal Chemistry, AstraZeneca Pharmaceuticals, (3) EST, AstraZeneca*

We have previously described a series of antagonists that showed high CNS potency and selectivity at the NK1 receptor. These compounds contained a napthylamide group which was necessary for activity, but also caused the compounds to exist in multiple, slowly interconverting conformational isomers (atropisomers). To address this, we have developed rigidified, highly preorganized cyclic antagonists. Guided by structural and modeling studies, several ring systems were explored and optimized. This has led to the identification of a novel series of CNS active NK1 antagonists that exist in a single predominant

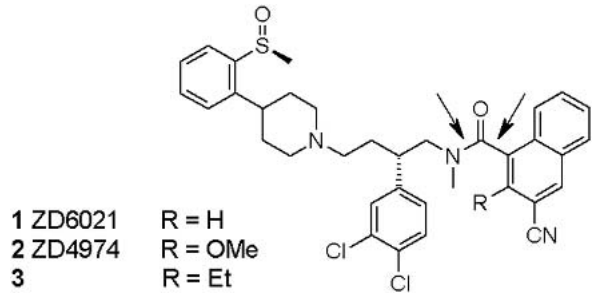
conformational form. Structural analysis of these compounds has enabled the development of a detailed NK1 pharmacophore model.



306.

STRUCTURAL ANALYSIS AND OPTIMIZATION OF NK1 RECEPTOR ANTAGONISTS THROUGH MODULATION OF ATROPISOMER INTERCONVERSION PROPERTIES. ***Jeffrey S. Albert***[1], *Cyrus J. Ohnmacht*[1], *Peter R. Bernstein*[1], *William L. Rumsey*[1], *David Aharony*[1], *Yun Alelyunas*[1], *Daniel J. Russell*[2], *William Potts*[1], *Scott A. Sherwood*[1], *Robert F. Dedinas*[1], *William E. Palmer*[1], *Brian Abbott*[1], *and Keith Russell*[1]. *(1) CNS Discovery Research, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437, jeffrey.albert@astrazeneca.com, (2) EST, AstraZeneca*

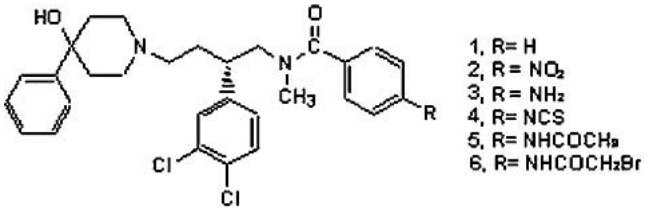
In prior work we identified a series of NK1 receptor antagonists with high potency and selectivity. However, these compounds also had the undesirable property of existing as a mixture of interconverting rotational isomers (atropisomers). We have now found that alteration of the 2-napthyl substituent can modulate the rate of isomer exchange. Comparisons of the NK1 receptor affinity for the various conformational forms has facilitated the development of a detailed NK1 pharmacophore model.



307.

DESIGN AND SYNTHESIS OF NON-PEPTIDE NEUROKININ-2 RECEPTOR SELECTIVE PROBES. ***Shih-Chung Huang***[1], *Bradley J. Undem*[2], *and Vijaya L. Korlipara*[1]. *(1) College of Pharmacy, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, (2) Johns Hopkins Asthma and Allergy Center*

The human neurokinin-2 (NK-2) receptor has been identified and validated as a suitable target for development of novel drugs to be used for treatment of a number of diseases in the respiratory, gastrointestinal, and genitourinary tracts. Design and synthesis of NK-2 receptor selective probes will serve useful in gaining a more detailed understanding of its structural and functional characteristics. Here we report the design and synthesis of a series of N-methylbenzamide analogues (1-6) structurally derived from SR 48968, a potent NK-2 receptor antagonist (Ki 0.5 nM). 4-Isothiocyanato-N-methylbenzamide (4) and 4-bromoacetamido-N-methylbenzamide (6) have been designed to serve as potential electrophilic affinity labels. 4-Amino-N-methylbenzamide (3) and 4-Acetamido-N-methylbenzamide (5) will serve as the nonelectrophilic controls for these ligands. Preliminary functional assay results using guinea pig trachea indicate that the N-methylbenzamide analogues exhibit potent NK-2 receptor antagonist activity.



308.

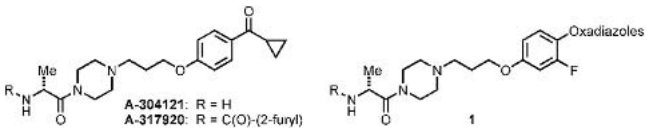
1-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINE-6,7-DIOLS AS A NOVEL AFFINITY AND PHOTOAFFINITY PROBES FOR β-ADRENOCEPTOR SUBTYPES. *Victor I. Nikulin*[1], ***Igor M. Rakov***[1], *Joseph E. De Los Angeles*[1], *Ratna C. Mehta*[2], *LeNe'Sheya Y. Boyd*[3], *Dennis R. Feller*[3], *and Duane D. Miller*[1]. *(1) Department of Pharmaceutical Sciences, University of Tennessee, Memphis, 847 Monroe Ave., Suite 327, Memphis, TN 38163, Fax: 901-448-6828, irakov@utmem.edu, (2) Division of Pharmacology, College of Pharmacy, The Ohio State University, (3) Department of Pharmacology, National Center for Natural Products Research, School of Pharmacy, University of Mississippi*

Affinity and photoaffinity labeled compounds are good tools to determine the exact interaction between a ligand and a specific amino acid(s) in a receptor. In our study of potential agents for the treatment of obesity, we designed and synthesized a series of affinity and photoaffinity labeled analogues of trimetoquinol (TMQ). All of these compounds were full agonists and demonstrated an equal or greater binding affinity and functional activity as compared to TMQ on b1-, b2- and b3-ARs.

309.

ARYLOXADIAZOLEPIPERIDINEAMIDES AS POTENT HUMAN H_3 RECEPTOR ANTAGONISTS. *Gregory A. Gfesser*[1], *Henry Zhang*[2], *Jurgen Dinges*[1], *Timothy A. Esbenshade*[1], *Betty B. Yao*[1], *David Witte*[1], *Thomas R. Miller*[1], *Chae-Hee Kang*[1], *Kathleen M. Krueger*[1], *Youssef L. Bennani*[3], *Arthur A. Hancock*[1], *and* ***Ramin Faghih***[1]. *(1) Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 4MN / AP9A, 100 Abbott Park Road, Abbott Park, IL 60064-6123, Fax: 847-9374143, greg.gfesser@abbott.com, ramin.faghih@abbott.com, (2) Medicinal Chemistry Technologies, Global Pharmaceutical Research and Development, Abbott Laboratories, (3) Athersys, Inc*

The histamine-3 receptor (H_3R) is located presynaptically in the nervous system, where it is proposed to modulate the release of neurotransmitters implicated in a variety of central nervous system activities. H_3R antagonists can increase the levels of these substances, which suggests such agents have potential for the treatment of CNS disorders, including attention-deficit disorder, Alzheimer's disease, and schizophrenia. Our laboratories previously reported non-imidazole H_3R antagonists A-304121 and A-317920, which possessed high affinity for the rat H_3R and displayed in vivo efficacy in animal models of learning, but bound weakly to the human H_3Rs (hH_3R). In order to further improve binding at hH_3R we expanded the SAR and prepared a series of oxadiazoles (1). The synthesis and SAR of these potent hH_3R antagonists will be described.

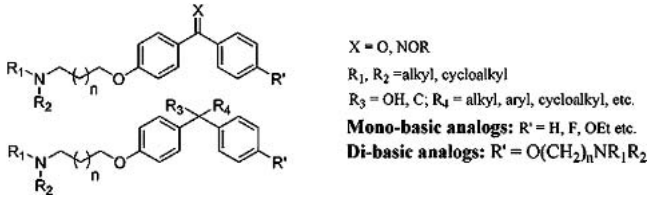


310.

SYNTHESIS AND SAR OF BENZOPHENONE ANALOGS AS A NEW CLASS OF H3 RECEPTOR ANTAGONISTS. ***Meena V. Patel***[1], *Teodozyj Kolasa*[1], *Jeffrey J. Rohde*[1], *Pramila A. Bhatia*[1], *Andrew O. Stewart*[1], *Wesley Dwight*[2], *Ramin Faghin*[1], *Timothy Esbanshade*[1], *Tom Miller*[1], *JiaBao Pan*[1], *Gerard Fox*[1], *Youssef Bennani*[3], *Marlon Cowart*[1], *and Art Hancock*[1]. *(1) Neuroscience Research, Abbott Laboratories, 100, Abbott Park Rd., Abbott Park, IL 60064, Fax: 847-935-5466, meena.v.patel@abbott.com, (2) Neurocrine Biosciences, (3) Athersys Inc*

Since the identification of H3 receptors in 1983, extensive efforts have been made to generate potent and selective H3 ligands in order to better understand the biological functions modulated by the receptor. A role for H3 antagonists has been proposed in the treatment of various neurological diseases, especially

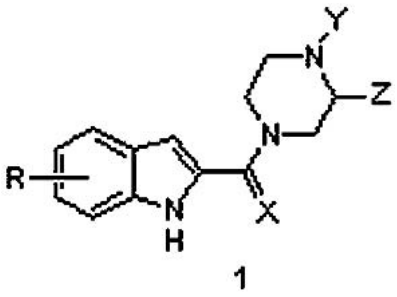
disorders of attention and cognition. Our research efforts led to a series of non-imidazole dibasic and mono-basic benzophenone derivatives, which are potent and selective H3 antagonists. The mono-basic compounds have lownano-molar and sub-nanomolar Kis for the rat H3 and human H3 receptors. The dibasic analogs have H3 Kis in the sub-nanomolar range with >5000x selectivity for H3 over other histaminergic receptors. The synthesis as well as biological activity of these compounds will be described.



311.

DISCOVERY OF THE FIRST POTENT AND SELECTIVE NON-IMIDAZOLE HUMAN HISTAMINE H_4 RECEPTOR ANTAGONISTS. ***Jill A. Jablonowski***[1], *Cheryl A. Grice*[2], *Wenying Chai*[1], *Curt A. Dvorak*[1], *Jennifer D. Kreisberg*[2], *Annette K. Kwok*[1], *Kiev S. Ly*[1], *Jianmei Wei*[2], *Sherry M. Baker*[2], *Pragyna J. Desai*[2], *Wen Jiang*[2], *Sandy J. Wilson*[1], *Robin L. Thurmond*[2], *Lars Karlsson*[2], *James P. Edwards*[2], *Timothy W. Lovenberg*[1], *and Nicholas I. Carruthers*[1]. *(1) Neuroscience, Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, Fax: 858-450-2049, jjablono@prdus.jnj.com, (2) Immunology, Johnson & Johnson Pharmaceutical Research and Development, LLC*

Following the discovery of the human histamine H_4 receptor, we set out to identify potent, selective, non-imidazole histamine H_4 ligands. We began with a high throughput screen of our corporate compound collection, which produced several lead compounds including indolylpiperazines. Based on these leads, a medicinal chemistry program was initiated to evaluate the structure activity relationships (SAR) for the indolylpiperazines **1**. The SAR for this series and the biological evaluation of selected analogs will be discussed.

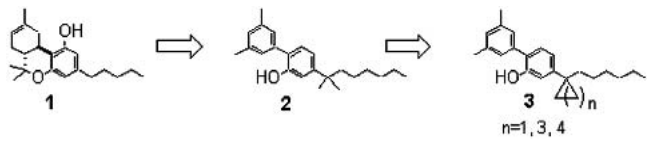


1

312.

NOVEL 1′– AND 1′,1′– CHAIN SUBSTITUTED BIARYL CANNABINOID MIMETICS. ***Karin Worm***[1], *Q. Jean Zhou*[1], *Pamela Seida*[1], *Roland E. Dolle*[1], *Gabriel Stabley*[2], *and Robert N. DeHaven*[2]. *(1) Department of Chemistry, Adolor Corporation, 700 Pennsylvania Drive, Exton, PA 19341-1127, kworm@adolor.com, (2) Department of Pharmacology, Adolor Corporation*

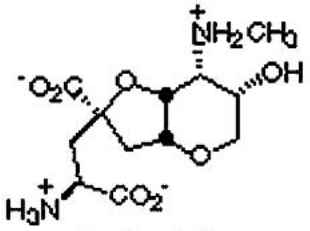
Classical cannabinoids display a wide range of physiological effects including analgesic, antiinflammatory, anticonvulsive and immunosuppressive activity. It was previously shown that substitution of the *n*-pentyl chain of D^8-tetrahydro-cannabinol **1** with a1,1-dimethylheptyl or 1,1-cyclopropylheptyl chain led to enhanced affinity for both cannabinoid receptors. The tricyclic moiety in **1** on the other hand is not essential for binding as demonstrated by the biaryl phenol **2**, a cannabinoid mimetic. We have substituted the 1,1-dimethyl group in **2** with carbocycles of various ring sizes **3** to probe the stereochemical limits of this system. Syntheses, biological data and a molecular modeling study will be presented.



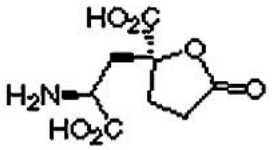
313.

γ, γ-DISUBSTITUTED GLUTAMATES AS GLUTAMATE RECEPTOR PROBES: PROGRESS TOWARD THE TOTAL SYNTHESIS OF (–)-DYSIHERBAINE AND (+)-LYCOPERDIC ACID. ***Jamie L. Cohen****, and A. Richard Chamberlin, Department of Chemistry, University of California, Irvine, Irvine, CA 92612, jlcohen@uci.edu*

Glutamate-containing natural products are among the most potent and selective probes to investigate glutamate mediated neurotransmission in the mammalian CNS. In our continuing efforts to identify selective and powerful agonists or antagonists of glutamate receptors, this presentation will describe recent progress toward the total synthesis of (–)-dysiherbaine, a potent non-NMDA receptor agonist isolated from the Micronesian marine sponge *Dysidea herba-cea*. The synthesis of (S)-(+)-lycoperdic acid, a non-proteinogenic α-amino acid isolated from the mushroom *Lycoperdon perlatum*, will also be presented. This unusual amino acid is the 5-oxo analogue of the tetrahydrofuran core of dysiherbaine. Due to their unique skeletal structure, these naturally occurring γ, γ-disubstituted glutamates are lead compounds for the design of ligands that effectively discriminate between glutamate receptor subtypes.



Dysiherbaine

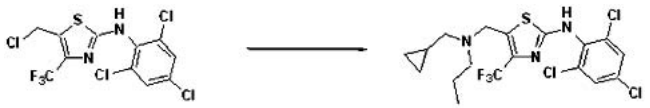


Lycoperdic acid

314.

2-ARYLAMINO-4-TRIFLUOROMETHYL-5-AMINOMETHYLTHIAZOLES ARE HIGH AFFINITY CORTICOTROPIN-RELEASING FACTOR TYPE 1 RECEPTOR ANTAGONISTS: PARALLEL SYNTHESIS, BINDING STUDIES AND BEHAVIORAL EFFICACY. ***Dmitry Zuev****, Jodi A. Michne, Hong Huang, Wendy Schwartz, Paul M. Scola, Clint A. James, Edward H. Ruediger, Sokhom Pin, Kevin D. Burris, Lynn A. Balanda, Qi Gao, Dedong Wu, Lawrence Fung, Tracey Fiedler, Kaitlin E. Browman, Matthew T. Taber, Jie Zhang, and Gene M. Dubowchik, Department of Neuroscience, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, Fax: 203-677-7702, dmitry.zuev@bms.com*

2-Arylamino-4-trifluoromethyl-5-aminomethylthiazoles represent a novel series of high-affinity corticotropin-releasing factor type 1 receptor antagonists. The studied analogs were conveniently prepared in a parallel fashion with high yields from common chloromethyl intermediate 1 by selective monoamination. The binding SAR, pharmacokinetic properties, as well as anxiolytic activity of an exemplary compound (2, Ki=8.6 nM) in a mouse canopy model are discussed herein.



1 **2**

315.

MELANOCORTIN-4 RECEPTOR SELECTIVE SMALL MOLECULES. ***Zhijun Wu****, Ramesh Rajpurohit, Yiqun Shi, and Shubh Sharma, Department of Chemistry, Palatin Technologies, Inc, 4C Cedar Brook Drive, Cranbury, NJ 08512, Fax: 609-495-2204, zwu@palatin.com*

The melanocortin-4 receptor is a drug target for developing therapeutics for various feeding disorders including obesity and cachexia. Various alpha-melanotropin (the endogenous 13 amino acid peptide) based ligands have been shown to modulate feeding behavior of rats under experimental conditions. We have developed a series of tri-substituted oxopiperazine ring compounds [Fig. 1] as MC-4R selective small molecular agents. One of these agents, (2S)-1-(4-Cl-D-Phe)-2-(3-gaunidino-propyl)-3-oxo-4-naphthaleneethyl-piperazine, is an agonist with a Ki of 79 nM. SAR studies of affinity and receptor selectivity with

a series of compounds with different R groups at the 4-position of the oxopiperazine ring will be presented.

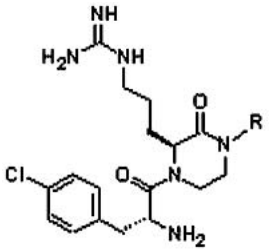


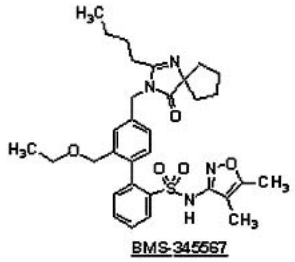
Fig. 1

[R = a substituent moiety]

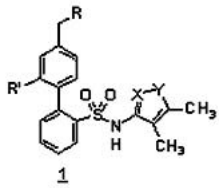
316.

SYNTHESIS AND SAR OF A SERIES OF N-ISOXAZOLYL BIPHENYLSULFONAMIDES AS POTENT DUAL ANGIOTENSIN II AND ENDOTHELIN A RECEPTOR ANTAGONISTS. ***Zhengxiang Gu**, Leena Fadnis, John E. Tellew, Bridgette Kane, Lyndon Cornelius, Rose Ann Baska, Sophie Beyer, Hossain Monshizadegan, Maria Valentine, Saeho Chong, Richard A. Morrison, Kenneth Carlson, William R Ewing, Mark Kowala, John E. Macor, and Natesan Murugesan, Discovery Chemistry and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, Fax: 609-818-3450, zhengxiang.gu@bms.com*

We have previously disclosed a series of biphenylsulfonamide derivatives represented by BMS-346567 as potent and orally active dual antagonists of both AT1 and ETA receptors. We now show that replacement of the imidazolinone heterocycle at the 4′-position with other related AT heterocycles followed by additional optimization of the 2′-substituent led to a series of analogs (1) which show potent binding activity against both receptors. The synthesis and SAR of these dual antagonists will be described.



BMS-345567



1

317.

SOLID-PHASE SYNTHESIS OF ENDOTHELIN RECEPTOR ANTAGONISTS. ***Wilfried M. Braje**[1], Willi Amberg[1], Ralf Bauer[2], Ludwig Fusser[1], Herbert Glesius[1], Ingo Hartlieb[1], Ralf Hogenmüller[2], Georg Kettschau[1], Udo E. W. Lange[1], Margit Lieberknecht[1], Manfred Nebel[1], and Liliane Unger[1]. (1) Abbott GmbH & Co. KG, Ludwigshafen, Germany, wilfried.braje@abbott.com, (2) BASF AG*

A new solid-phase synthesis for ET receptor antagonists suitable for automation is presented. A support bound 2-hydroxybutyric acid derivative was converted to the corresponding ether derivatives using 4-halo-2-methylsulfonylpyrimidines. Subsequent Suzuki coupling with various aryl boronic acids gave the desired antagonists in good yields and purities. Highly potent antagonists with excellent selectivity for ET_A were obtained.

318.

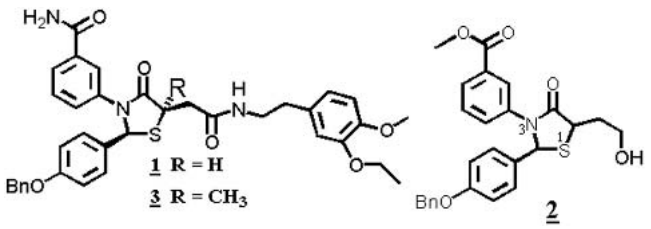
HIGHLY SUBSTITUTED GAMMA LACTAM FOLLICLE STIMULATING HORMONE (FSH) AGONISTS FROM GAMMA LACTONES: A ONE-POT, TWO-STEP STEREOSELECTIVE METHOD INVOLVING WEINREB AMIDATION AND THE MITSUNOBU REACTION. ***Jeffrey C. Pelletier**[1], John Rogers[1], Jay Wrobel[1], Emily Shen[2], and Ed Meade[2]. (1) Department of Chemical and Screening Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, Fax: 484-865-9399, pelletj@wyeth.com, (2) Women's Health Research Institute, Wyeth Research*

Follicle stimulating hormone (FSH) is released into the circulation from the anterior pituitary gland following stimulation with gonadotropin releasing hormone (GnRH). FSH Is responsible for several reproductive functions including gametogenesis in females, spermatogenesis in males and triggering sex hormone synthesis in both genders. Small molecule agonists have potential fertility indications and are, therefore, highly sought after. We will disclose the preparation of highly substituted gamma lactam FSH agonists from gamma lactones. The synthesis methodology involves Weinreb amidation of a diastereomerically pure lactone to an open chain amide that is cyclized in situ to the lactam with triphenylphosphine-DEAD. The Process occurs with inversion of stereochemistry and is highly stereoselective.

319.

SYNTHESIS AND IN VITRO BIOLOGY OF NOVEL 5-ALKYLATED THIAZOLIDINONES AS FSH AGONISTS. ***James Jetter**[1], Wenling kao[2], John rogers[3], Jamin Chi[4], Maria Perez[4], Gi-Chung Chen[4], emily shen[4], and Jay Wrobel[3]. (1) Department of Chemical and Screening Sciences and The Women's Health Research Institute, Wyeth Research, 500 Arcola Rd., Collegeville, PA 19426, Fax: 484-865-9399, jetterj@wyeth.com, (2) department of chemical and screening sciences, (3) department of chemical and screening sciences, Wyeth Research, (4) The Women's Health Research Institute, Wyeth Research*

The pituitary glycoprotein hormone, follicle stimulating hormone (FSH), is considered essential for folliculo-genesis and spermatogenesis. A drug acting as an agonist to FSH or its receptor could be utilized as a fertility agent. In the mid 1990's through an alliance with the Affymax Research Institute, a series of thiazolidinones which had in vitro FSH agonist activity was disclosed (Maclean et. al. J. Combi. Chem. 2003, Submitted). The prototype compound (1) was highly potent in a FSH-R transfected CRE Luciferase assay (EC50=14nM), however, the series suffered synthetic liabilities in that the unwanted trans isomer of (1) predominated over the desired cis isomer. We reasoned that alkylation of intermediate (2) would occur selectively from the bottom face to produce a compound which projected the pharmacophore side chains cis to each other. Further synthetic elaboration of the alkylated intermediate produced (3) the 5-methyl analog of (1), which was equipotent to (1). Synthesis of (3) and related analogs as well as their FSH activity will be presented.



1 R = H

3 R = CH_3

2

320.

PYRAZOLE DERIVATIVES AS NEW LH RECEPTOR AGONISTS. ***Catherine Jorand-Lebrun**[1], Nadia Brugger[2], Hitesh Shroff[2], Sharad Magar[2], Bill Brondyk[3], Weishui Weiser[3], Sean McKenna[3], Robert Murray[2], and Nabil El Tayer[2]. (1) Department of Chemistry, Serono Pharamceutical Research Institute, Plan-Les-Ouates, Geneva, Switzerland, (2) Department of Chemistry, Serono Reproductive Biology Institute, (3) Department of Lead Discovery, Serono Reproductive Biology Institute*

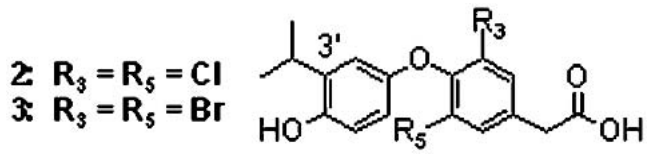
Luteinizing hormone (LH) is a glycoprotein hormone produced by the anterior pituitary gland under the influence of gonadotropin releasing hormone and progesterone. In the female, LH stimulates ovulation and is the major hormone involved in the regulation of progesterone secretion in the corpus luteum. In the male, LH stimulates Leydig cells to secrete androgens, particularly testosterone. The LH receptor belongs to a G-protein coupled receptor subclass that includes receptors for pituitary and placental glycoprotein hormones LH, FSH (follicule-stimulating hormone), TSH (thyrotropin) and hCG (human chorionic gonadotropin). LH receptors are positively coupled to cAMP through the Gs protein and are activated by LH or hCG. LH is a relatively large (28-38 kDa) heterodimeric glycoprotein and is currently utilized in conjunction with FSH to treat infertility and spermatogenesis disorders. We herein report a new series of substituted pyrazole compounds which we have found to be potent activators of the LH receptor and that could be utilized for triggering ovulation in fertility treatment

and to increase testosterone levels in aging male. SAR for this family of compounds along with the biological profile for one of these compounds in our in vitro and in vivo models for LH-related disorders will be presented as well as a new synthetic route enabling the production of this compound on gram scale.

321.

THYROMIMETICS WITH IMPROVED SELECTIVITY FOR THE THYROID HORMONE RECEPTOR BETA. ***Jon J. Hangeland***[1], *Tamara Dejneka*[1], *Todd J. Friends*[1], *Pratik Devasthale*[1], *Karin Mellström*[2], *Johnny Sandberg*[2], *Marlena Grynfarb*[2], *Cheryl Sheppard*[3], *Johan Malm*[2], *and Denis E. Ryono*[1]. *(1) Hopewell Discovery Chemistry, Bristol-Myers Squibb, P.O. Box 5400, Princeton, NJ 08543, Fax: 609-818-3450, jon.hangeland@bms.com, (2) Karo Bio AB, (3) Cardinal Health PTS, Inc*

A set of thyromimetics having improved selectivity for the beta isoform of the thyroid hormone receptor (TR) were prepared by replacing the 3′-isopropyl group of 2 and 3 with substituents having increased steric bulk. Three series were investigated: 3′-phenyls and related heterocycles derived from 2 and 3′-amides and 3′-phenoxys derived from 3. From this SAR study, the most potent and selective compounds identified were derived from 2 and contained a 3′-phenyl moiety bearing small hydrophobic groups meta to the biphenyl link. This study also suggests the portion of the TR receptor binding pocket interacting with the 3′-moiety to be flexible while still permitting the receptor to adopt an agonist conformation.



322.

EVALUATION OF MOLECULAR WEIGHT DISTRIBUTION OF POLY-DISPERSED INSULIN OLIGOMER CONJUGATE (HIM2 POLY-DISPERSED). ***Diti Sangal***, *Monica Puskas, and B. Radha Krishnan, Chemistry Development and Manufacturing, Nobex, 617 Davis Drive, Suite 100, Durham, NC 27713, Fax: 919-474-9407, dsangal@nobexcorp.com*

The purpose of this study was to isolate and identify polyethylene glycol (PEG) molecular weight distribution pattern in the poly-dispersed amphiphilic oligomer conjugated at B29-Lys of insulin, HIM2 (poly-dispersed). The conjugate was analyzed by reverse phase HPLC for evaluation of PEG distribution pattern. A semi-preparative reverse phase HPLC method provided separation of individual molecular weight forms from the polymeric HIM2 (poly-dispersed). These discreet molecular weights were characterized by MALDI (TOF) and will be studied by subcutaneous mouse glucose assay. The PEG distribution of HIM2 (poly-dispersed) ranged from PEG4 to PEG12 with PEG7, PEG8 and PEG9 accounting for approximately 70% of HIM2 (poly-dispersed) composition. Reverse phase HPLC (poly-dispersed) method using high concentration of TFA allowed separation of discreet PEG molecular weights of HIM2 (poly-dispersed). As previously mentioned, the biological potency of these discreet separated PEG molecular weights of HIM2 (poly-dispersed) will be studied using a subcutaneous mouse glucose assay.

323.

INTRAOPERATIVE PARATHYROID EVALUATION AS A DIAGNOSTIC AID FOR PARATHYROID SURGERY. ***Iren Horkayne-Szakaly***[1], *Emmanuel Fadeyi*[1], *Jayashree Krishnan*[1], *Ann Chappie*[1], *Ferenc Horkay*[2], *and Lisa Boyle*[3]. *(1) Department of Pathology, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010, Iren.Horkayne-Szakaly@Medstar.net, (2) Laboratory of Integrative and Medical Biophysics, National Institutes of Health, NICHD, (3) Department of Surgery, Washington Hospital Center*

Primary hyperparathyroidism is a relatively common endocrine disorder, affecting approximately 3 in 100,000 individuals annually. The challenging nature of parathyroid surgery as well as a desire to avoid extensive neck and chest exploration have led to substantial efforts to improve preoperative localization of parathyroid adenomas and to use new intraoperative laboratory procedures (Parathyroid Hormone (PTH) assays). The focus of this presentation is the application of intraoperative laboratory measurements of intact parathyroid hormone (PTH) designed as a point-of-care test at the Washington Hospital Center. Seventy-seven parathyroid surgeries were performed from July 2001 to November 2002 using "IMMULITE Turbo Intact PTH assay". The results indicate that a greater than 70% decrease in the blood PTH level within 5 minutes of resection from preincision baseline, rapidly determine the success of surgery, reduce the overall operative costs more than 50%, and significantly decrease the length of hospital stay.

324.

CARBOHYDRATE-DERIVED N-HYDROXYUREAS AS NEW NITRIC OXIDE DONORS. ***Zhou Zou***, *Dennis A. Parrish, and S. Bruce King, Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109, Fax: 336-758-4656*

Hydroxyurea is a new approved treatment for sickle cell disease. Oxidation of N-hydroxyurea produces nitric oxide(NO), an important biological messenger molecule. Recent experiments also indicate that hydroxyurea acts as an NO donor in vivo and suggest that the biological effects of N-hydroxyurea may be mediated by NO.Our previous results indicate that heme containing proteins and enzymes including hemoglobin and horseradish peroxidase oxidize N-hydroxyurea with NO release. Based upon these introductory results, we began to prepare carbohydrate-derived N-hydroxyureas as potential NO donors. The preparation of these N-hydroxyureas from various glucosamines using a newly developed coupling methodology will be described as well as the results regarding the ability of these compounds to release NO by oxidation with chemical agents and hemoglobin.

325.

METABOLISM OF NO-DONATING ASPIRIN BY RAT LIVER AND COLON AND HUMAN COLON CANCER CELLS: THE EFFECT OF POSITIONAL ISOMERISM. ***Jianjun Gao***[1], *Khosrow Kashfi*[2], *and Basil Rigas*[1]. *(1) American Health Foundation Cancer Center, Institute for Cancer Prevention, Valhalla, NY 10595, 1 Dana road, Valhalla, NY 10595, Fax: 914-592-6317, jgao@ifcp.us, (2) Department of Physiology and Pharmacology, City University of New York Medical School*

NO-donating aspirin [aspirin plus (nitroxymethyl)phenol (NMP)], is effective in colon cancer chemoprevention. We investigated the metabolism of its three positional isomers, which have different potency in inhibiting cancer cell growth, using rat liver and colon cytosol, microsomes and mitochondria. Liver rapidly deacetylates m- and p-, further converting them into salicylic acid. After its release, m-NMP gradually conjugates with glutathione, but no free p-NMP is detectable, as it conjugates rapidly with glutathione. The o- has a fate similar to p-, except that NMP release is slower. We elucidated the structure of glutathione conjugates based on their mass and UV spectra. Colon cytosol metabolized these isomers similar to liver, but slower. In HT-29 human colon cancer cells, all isomers formed the glutathione conjugate, but to a different degree (o- > p- > m-), corresponding to their growth-inhibition potency. We propose a comprehensive metabolic pathway for these compounds and discuss its pharmacological implications.

326.

SYNTHESIS OF A NOVEL CLASS OF I-NOS INHIBITORS. ***Sharon Jackson***[1], *Sukhveen Sahni*[1], *Lan Lee*[1], *Yongyi Luo*[1], *Sam Rebello*[1], *Thaddeus Nieduzak*[1], *Guyan Liang*[1], *Yulin Chiang*[1], *Abdelazize Laoui*[1], *Jean Merrill*[1], *Wei He*[1], *Ray Boffey*[2], *Peter Crackett*[2], *Bryan Rees*[2], *and Melanie Wong*[2]. *(1) Drug Innovation and Approval, Aventis Pharmaceuticals, Bridgewater, NJ 08807, (2) Argenta Discovery Ltd., Harlow, Essex UK*

High throughput screening identified RPR24890 as a weak inhibitor (IC50=18 μM) of the inducible form of nitric oxide synthase (i-NOS). Inhibitors of i-NOS have potential utility for the treatment of diseases such as stroke and multiple sclerosis. The synthesis, SAR, and biological activity of this novel class of compounds will be presented.

327.

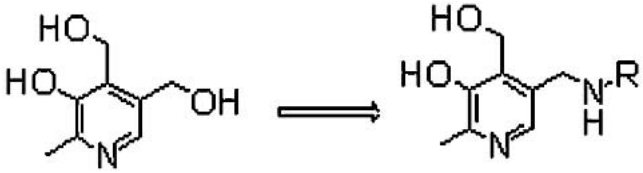
CARDIAC MOLECULAR MARKERS: DETECTION AND IDENTIFICATION OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH DIABETES AND CARDIOVASCULAR DISEASE BY SELDI PROTEINCHIP ARRAYS. ***Bishambar Dayal***[1], *Norman H. Ertel*[2], *Rajeev Narayan*[2], *Faisal Siddiqi*[2], *Bhavin Patel*[3], *Robert Donnelly*[4], *and Sami Haq*[2]. *(1) Medicine, VANJ Health Care System, East Orange, NJ 07018; *UMDNJ, NJ Medical School, Newark, NJ 07103, 385-Tremont Av, East Orange, NJ 07018, Fax: 973-395-7096, bishambar.dayal@med.va.gov, (2) Medicine, VANJ Healthcare System and UMDNJ-New Jersey Medical School, (3) Drew University, (4) Pathology Department, UMDNJ-New Jersey Medical School*

Recently we described a ProteinChip method for the identification and measurement of high-density lipoproteins apoA-1 and apoA-II and their glycosylated products in patients with diabetes and cardiovascular disease (J Proteome Res. 1: 375-380- 2002). The present studies describe a method using Surface-enhanced Laser Desorption Ionization (SELDI) ProteinChip Arrays for the identification and quantification of high sensitivity C-Reactive Protein (hs-CRP) profiles in patients with diabetes who have cardiovascular disease. Expression levels of hs-CRP, specifically the monoisomeric form of this protein (MW@23 kD), were elucidated using Strong Anionic Exchanger surface (SAX2) and preactivated surface (PS1) chips. Using the two ProteinChip Arrays and Surface Enhanced Laser Desorption Ionization Mass Spectrometry, sharp protein peaks were obtained for hs-CRP at 23 kD which did not overlap with the human serum albumin peaks. We were able to show that the SAX2 chip is superior for quantitative purposes due to the increased differentiation capability of the chemically defined surface. These results were independently verified using matrix-assisted laser desorption ionization mass spectrometry. It is suggested that these studies will facilitate clinical trials for a large number of patients in assessing the role of hs-CRP in cardiovascular disease.

328.

PYRIDOXINE AS A TEMPLATE FOR THE DESIGN OF NOVEL ANTI-PLATELET AGENTS. ***James Diakur***[1], *Wenlian Zhang*[1], *John Yao*[1], *Vinh Pham*[1], *Tara Whitney*[1], *Albert D. Friesen*[2], *Wasim Haque*[1], *Linda Stang*[3], *Chen Xu*[4], *and Ashfaq Shuaib*[4]. *(1) Chemistry, Canam Bioresearch Inc, 6-1200 Waverley Street, Winnipeg, MB R3T 0P4, Canada, Fax: 204-488-9823, jdiakur@canambioresearch.com, (2) Medicure Inc, (3) Special Coagulation Laboratory, University of Alberta, Hospital, (4) Department of Medicine, University of Alberta*

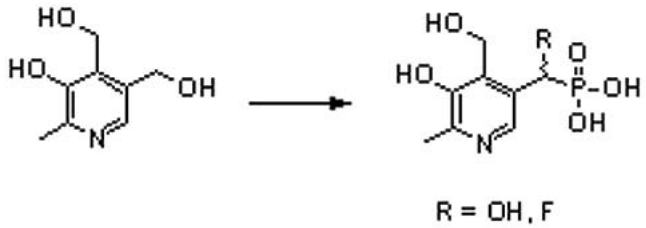
Pyridoxal 5-phosphate (P5P) has been shown to display beneficial therapeutic effects in cardiovascular related disorders. The application of this natural product (MC-1) has recently been reported in the MEND-1 clinical study for reducing ischemic damage in high-risk patients undergoing percutaneous coronary intervention. The design of novel anti-platelet agents using pyridoxine as a template has led to the discovery of a class of novel cardio- and cerebro-protective agents. Synthesis, anti-platelet activity and data on the reduction in infarct-size induced by ischemia/reperfusion injury in the rat model of coronary artery ligation and rat model of focal cerebral ischemia will be presented.



329.

PYRIDOXINE AS A TEMPLATE FOR NOVEL PHOSPHONATES AS POTENTIAL ANTI-ISCHEMIC AGENTS. ***Wenlian Zhang***[1], *Vinh Pham*[1], *Vince Chen*[1], *Tara Whitney*[1], *John Yao*[1], *Doug Froese*[1], *Albert D. Friesen*[2], *James Diakur*[1], *and Wasim Haque*[1]. *(1) Chemistry, Canam Bioresearch Inc, 6-1200 Waverley Street, Winnipeg, MB R3T 0P4, Canada, Fax: 204-488-9823, wzhang@canambioresearch.com, (2) Medicure Inc*

Pyridoxal 5-phosphate (P5P) has been reported to possess beneficial cardioprotective properties. The biological degradation and elimination pathways of this natural product and its vitamers are well known. Our objective was to generate active phosphonate mimetics that are potentially less light sensitive and more stable in vivo than P5P. These mimetics were found to reduce infarct size in the rat model of regional myocardial ischemia and reperfusion similar to P5P. In an effort to identify other relevant cardioprotective models in order to potentially define structure activity relationships, two of the novel phosphonates were compared to dichloroacetic acid (DCA) as positive control in the rat working heart model. These two compounds were found to induce a shift towards glucose oxidation. No significant differences in hemodynamic parameters were observed between the test animals and control group, demonstrating that the observed effects on glucose metabolism are not occurring secondarily to changes in contractile function. The preparation and preliminary biological evaluation of these compounds will be presented.



330.

SYNTHESIS AND PHARMACOLOGICAL SCREENING OF SOME CYCLOADDUCTS OF NINHYDRIN WITH N-(N′,N′-DISUBSTITUTED AMINOAKYL)ANILINES. *Jian-Cheng Li, and* ***Ralph A. Stephani****, Pharmaceutical Sciences, St. John's University, College of Pharmacy and Allied Health Professions, 8000 Utopia Parkway, Jamaica, NY 11439, Fax: 718-990-1876, stephanr@stjohns.edu*

Previous work from this laboratory, showed that a series of N′,N′-dialkylaminoalkylbenzo[g][2]benzopyrano[4,3-b]indol-5-[13H]-ones (benzoisochromenoindoles) possessed analgesic activity against PQW-induced writhing in mice. Although they were relatively nontoxic (LD502 g/kg, rats), the aqueous solubility was rather limited (log P~4-5). The study indicated that an alkyl chain of 2-3 carbons in length was the most active. Consequently, we prepared N′N′-dialkylaminoalky-N-alkylisochromenoindoles, i.e. containing 2-3 carbon chains but lacking the benzene ring fused to the indole, in order to reduce log P. We report here the preparation of the m-hydroxy- and m-methoxy- substituted N′,N′-dialkylamino alkylanilines and their reaction products with ninhydrin. The former produced the expected aryl-substituted indeno[1,2-b]indole cycloadducts. However, the latter (m-methoxy) precursors reacted with ninhydrin to give the 2[4-methoxy-2-dialkylaminoalkyl]-2-hydroxyindane-1,3-diones, rather than the cycloadducts. Analgesic activity, in PQW-treated mice, of the products indicated that these adducts were comparable to the previously reported benzoisochromenoindoles. Most active were the cycloadduct bearing the N′,N′-dimethylaminoethyl side chain, ED50 of 8.9 mg/kg and the uncyclized adduct, bearing the N-piperidinoethyl side chain with an ED50 of 17.5mg/kg.

331.

STEREOCHEMISTRY OF THE GASTROINTESTINAL ANTISECRETORY DRUG ESOMEPRAZOLE. A THEORETICAL STUDY. ***Hava Caner***[1], *James R. Cheeseman*[2], *and Israel Agranat*[1]. *(1) Department of Organic Chemistry, The Hebrew University of Jerusalem, Philadelphia Building 201/205, Jerusalem 91904, Israel, Fax: 972-2-6511907, canerh@chem.ch.huji.ac.il, (2) Gaussian, Inc*

Esomeprazole Magnesium (NexiumTM) is the chiral switch, first launched in 2000, of the racemic blockbuster gastric antisecretory proton-pump inhibitor Omeprazole. Esomeprazole is the (S)-(-)-enantiomer of omeprazole. In 2001-2002 aaiPharma, Inc. obtained several US patents claiming the 5-methoxy and 6-methoxy tautomers of (S)- and (R)-omeprazole. The patents also include discussions on the stereochemistry of these systems stemming from the overcrowding of the substituents at the pyridine moiety. The results of a theoretical study of the stereochemistry of Esomeprazole, using ab initio methods, will be reported. Special emphasis is given to the stereogenic sulfur and the chiral axis due to the spatial orientation of the 4-methoxy-3,5-dimethyl pyridine moiety leading to the (R,M)/(S,P) and (S,M)/(R,P) pairs of enantiomers. A comparison between the stereoisomers of the 5-methoxy and the 6-methoxy tautomers will also be considered.

332.

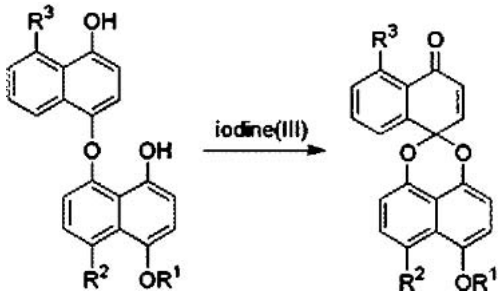
DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL ANTI SPERMATOGENIC AGENTS. ***Ramappa Chakrasali***[1], *Sudhakar R. Jakkaraj*[1], *Apurba Datta*[1], *Joseph, S. Tash*[2], *and Gunda I. Georg*[1]. *(1) Department of Medicinal Chemistry, University of kansas, 1251 Wescoe Hall Drive, Malott Hall, Room 4005, Lawrence, KS 66045, Fax: 785-864-5836, chakrasa@ku.edu, (2) Department of Molecular and Integrative Physiology, University of Kansas Medical Center*

Lonidamine is a substituted indazole carboxylic acid with anti tumor and anti spermatogenic properties. In vitro studies using testicular germinal cells indicate that lonidamine affects energy metabolism causing a decrease in cellular oxygen consumption mediated by a specific effect on mitochondrial function. It also acts by direct interference with the spermatogenic process by 1) blocking meiotic and post-meiotic cell maturation and 2) terminating support of post-meiotic spermatogenic cells by Sertoli cells. In our ongoing efforts to synthesize non steroidal and non hormonal anti spermatogenic agents, various structurally novel analogs of lonidamine have been prepared. The syntheses and the in vivo evaluations of those compounds in sexually mature male rats will be described.

333.

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PALMARUMYCIN ANALOGUES AS INHIBITORS OF THE THIOREDOXIN-THIOREDOXIN REDUCTASE REDOX SYSTEM. *Peter Wipf*[1], ***Stephen M. Lynch***[1], *and Garth Powis*[2]. *(1) Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, PA 15260, pwipf+@pitt.edu, sml19@pitt.edu, (2) Arizona Cancer Center, University of Arizona*

The cytosolic protein thioredoxin-1 (Trx-1) acts on the cellular level as a non-specific disulfide reductase. This implicates Trx-1 as a critical component in redox regulation, cell signaling, prevention of oxidative stress and control of growth and apoptosis. Preliminary screening of natural products possessing the naphthoquinone spiroketal moiety has lead to the identification of members of the palmarumycin family of fungal metabolites as potent inhibitors of the thioredoxin-thioredoxin reductase system. The most active compound in this series, palmarumycin CP_1, was found to inhibit thioredoxin-1 with an IC_{50} of 0.35 μM. The synthesis and biological evaluation of a series of new spironaphthoquinone spiroketal containing analogues derived from this lead structure will be described.



334.

DESIGN AND SYNTHESIS OF TRIPEPTIDYL AZA-PEPTIDE EPOXIDE INHIBITORS TARGETING *SCHISTOSOMA MANSONI* LEGUMAIN. ***Marion G. Götz***[1], *Karen E. James*[1], *Conor Caffrey*[2], *James H. McKerrow*[2], *and James C. Powers*[1]. *(1) Department of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, gte733r@prism.gatech.edu, (2) Department of Pathology, UCSF*

Legumain, along with caspases, clostripains and gingipains, is a clan CD cysteine protease, which selectively hydrolyzes asparaginyl peptide bonds. Legumains were first identified in leguminous plants and later in the parasitic blood fluke *Schistosoma mansoni* and also mammalian tissues. The mammalian enzyme plays a key role in bone resorption and in the processing of bacterial antigen for the MHC class II system. The parasitic legumain is involved in the metabolic pathway of hemoglobin degradation in the mammalian host. *Schistosoma mansoni* legumain therefore presents an attractive target for the remote inhibition of hemoglobin degradation. Herein we report the design and synthesis of a series of potent and stable tripeptidyl aza-peptide epoxide inhibitors of *Schistosoma mansoni* legumain.

335.

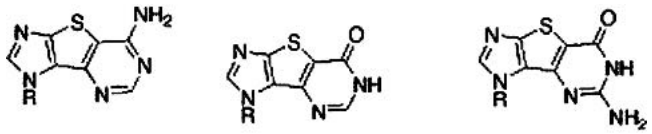
POLYAMINE ANALOGUES WITH ANTITRYPANOSOMAL AND ANTIMICROSPORIDIAL ACTIVITY SELECTIVELY INHIBIT TRYPANOTHIONE REDUCTASE. *Tracey Ward*[1], ***Christina Lopez***[1], *Cyrus J. Bacchi*[2], *and Patrick M. Woster*[1]. *(1) Department of Pharmaceutical Sciences, Wayne State University, 3132 Applebaum Hall, 259 Mack Ave, Detroit, MI 48202, Fax: 313-577-2033, tward@wizard.pharm.wayne.edu, pwoster@wayne.edu, (2) Haskins Laboratories and Department of Biology, Pace University*

Human African trypanosomiasis is caused by the parasitic protozoon Trypanosoma brucei. While reduced glutathione protects cells from oxidative stress in normal mammalian cells, typanosomes require the de novo synthesis of polyamines and the formation of trypanothione for protection against oxidative stress and free radicals. Trypanothione reductase is an enzyme that is only found in patients inflicted with T. brucei. It does not reduce oxidized GSSG, making it an ideal target in designing inhibitors. Trypanosomes only recognize trypanothione as a substrate, so inhibiting the synthesis of trypanothione will lead to the death of this parasite. A series of symmetrically- and unsymmetrically substituted alkylpolyamine derivatives were synthesized and evaluated for antitrypanosomal activity against 4 strains of T. brucei. The four most effective analogues tested (N1, N8-bis(3,3diphenylpropane)spermidine, N1,N12-bis(3,3 diphenylpropane)spermine, N1,N11-bis(3,3 diphenylpropane)-4,8-diazanondecane and N1,N15-bis(3,3diphenylpropane)-4,12-diazatridecane) were highly selective trypanothione reductase inhibitors, with percent inhibitions ranging from 64 to 76 percent at 20μM. In addition, these and other analogues were effective against the microsporidial parasite Encephalozoon cuniculi. The synthesis and biological evaluation of these analogues will be discussed.

336.

TRICYCLIC PURINE ANALOGUES AS ANTIPARASITIC AGENTS. ***Asmerom M. Hagos***[1], *Liang Zhang*[1], *Julia Sponaugle*[1], *Harry de Koning*[2], *and Katherine L. Seley*[3]. *(1) School of Chemistry and Biochemistry, Georgia Institute of Technology, 770 State Street, Atlanta, GA 30332, Asmeromh2000@yahoo.com, (2) Institute of Biomedical and Life Sciences, University of Glagow, (3) Department of Chemistry and Biochemistry, University of Maryland Baltimore County*

Use of modified purine nucleosides and nucleobases have long been considered an important strategy for the treatment of cancer and infectious diseases, including parasitic ailments. In that regard, energy-dependent membrane transporters exist which allow nucleoside and nucleobase analogues to specifically accumulate to high levels within the parasite. This is of great clinical interest, as drugs to treat late stage tripanosomiasis and leishmaniasis must cross the blood brain barrier and target parasites that are present in the brain if the patient is to survive. We have designed and synthesized a series of expanded nucleosides and their corresponding nucleobases employing a thiophene spacer ring to separate the imidazole and the pyrimidine moieties. These tricyclic analogues retain the necessary hydrogen bonding functionalities found in the normal purine nucleosides and nucleobases, but have the advantage of an extended pi system. Both hydrogen bonding and pi interactions are critical for recognition by the transporters. Their synthesis and biological activity will be presented.



R = H
R = β-D-ribofuranose

337.

INHIBITORS OF BACTERIAL NAD SYNTHETASE: TETHERED DIMERS CONTAINING SUBSTITUTED ARYL GROUPS. *Wayne J. Brouillette,* ***Sadanandan E. Velu****, Christie G. Brouillette, Chi-Hao Luan, and Lawrence J. DeLucas, Center for Biophysical Sciences and Engineering, The University of Alabama at Birmingham, 1530 3rd Ave S, Birmingham, AL 35294-4400*

NAD synthetase catalyzes the transformation of nicotinic acid adenine dinucleotide to the amide product NAD via a two-step process. NAD is a coenzyme that

plays an important role in numerous biochemical transformations such as DNA repair and energy production. The protein crystal structure of *Bacillus subtilis* NAD synthetase provided a potential target for the structure-based design of compounds that are new antibacterial agents. Earlier combinatorial synthesis and high throughput screening identified a group of tethered dimers as lead inhibitors with antibacterial activity against gram positives. The lead compounds contained an aryl group at one end and a positively charged trimethylammonium group at the other end of an eight carbon polymethylene linker. A small library was designed to modify the aryl end of these lead compounds by incorporating substituents. More potent inhibitors were identified from this series. The design, synthesis and biological data will be presented.

338.

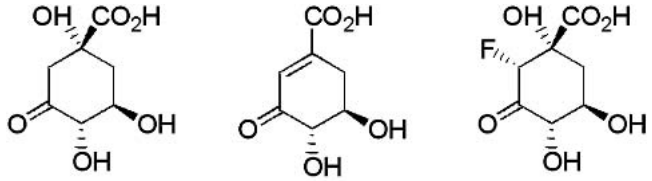
SYNTHESIS AND EVALUATION OF HYDROXYBENZOATE ESTERS AS MALATE SYNTHASE INHIBITORS. ***Anne T. Kotchevar***[1], *Jin Lisa Hung*[2], *and Laurence Sekansky*[2]. *(1) Department of Chemistry and Biochemistry, California State University, Hayward, 25800 Carlos Bee Boulevard, Hayward, CA 94542-3089, akotchev@csuhayward.edu, (2) Department of Chemistry and Biochemistry, Long Island University, Brooklyn*

Persistent infection by Mycobacterium tuberculosis has been shown to require the glyoxylate pathway. Malate synthase, which converts glyoxylate and acetyl Coenzyme A to malate and Coenzyme A, is one of the key enzymes in this pathway. A series of aminoethyl hydroxybenzoates has been prepared and evaluated as inhibitors against malate synthase. Structure-activity relationships for enzyme binding and inhibition are presented.

339.

SYNTHESIS OF SHIKIMATE PATHWAY INHIBITORS AS POTENTIAL ANTIMICROBIAL AGENTS. ***Mary A. Gower***, *Christine Le Sann, and Andrew D. Abell, Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch, New Zealand*

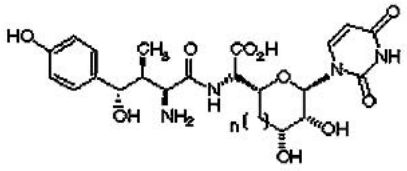
The shikimate pathway makes a desirable target for the design of herbicides and antimicobials due to its presence in plants and microorganisms but absence in mammals. The third enzyme of the shikimate pathway, dehydroquinase, makes an intriguing target for the design of inhibitors as it has two structurally and mechanistically distinct forms. Types I and II dehydroquinase catalyze the dehydration of 3-dehydroquinic acid (1) to 3-dehydroshikimic acid (2) with opposite stereochemistry at C2. (2R)-2-Fluoro-3-dehydroquinic acid (3) is a known inhibitor of type I dehydroquinase and substrate for type II dehydroquinase. This poster describes the convenient synthesis of the epimer (2S)-2-fluoro-3-dehydroquinic acid and the result of assays against representative species of both types I and II dehydroquinase. The facile synthesis of the substrate 3-dehydroquinic acid will also be described.



340.

TOTAL SYNTHESIS OF A NOVEL PYRANOSYL ANALOG OF THE ANTIFUNGAL ANTIBIOTIC NIKKOMYCIN B. ***Christina S. Stauffer***, *Pushpal Bhaket, and Apurba Datta, Department of Medicinal Chemistry, University of Kansas, 4062 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, KS 66045, Fax: 785-864-5326, christie_kansas@hotmail.com*

Nikkomycins are a naturally occurring family of complex peptidyl nucleoside antibiotics. As selective inhibitors of chitin synthase, these compounds show strong and selective antifungal activity, while being non-toxic to plants, fish, and animals. This class of compounds shows promise as useful models towards the development of novel, non-toxic antifungal agents, especially for the treatment of Candida albicans in humans. The need for new antifungal agents has been emphasized with the emergence of resistance to current antifungal drugs, as well as the larger population of immunocompromised individuals, such as AIDS victims or organ transplant recipients, who contract opportunistic fungal infections. As part of a program on structure-activity relationship studies of this nikkomycin class of compounds, we are investigating the effect of carbohydrate ring size of these nucleosides on biological activity. A stereoselective synthesis of a novel pyranosyl nucleoside analog of nikkomycin has thus been undertaken. Details of the synthesis will be presented.



n = 0; Nikkomycin B

n = 1; proposed pyranosyl analog

Figure. Natural Nikkomycin B and the proposed pyranosyl analog

341.

SYNTHETIC AND BIOLOGICAL STUDIES OF 1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANES: POTENTIAL INHIBITORS OF THE UL30-UL42 PROTEIN-PROTEIN INTERACTION IN HERPES SIMPLEX VIRUS. ***Wenchun Xie***, *Steven M. Firestine, and Cynthia Schmid, Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, Fax: 412-396-5599, xiewenchun@hotmail.com*

Herpes Simplex Virus (HSV)is one of the most difficult viruses to control. The widely used drugs for HSV target only the DNA polymerase (UL30).Our research focuses on investigating alternative targets to treat HSV. Previous studies have found that disruption of the interaction between UL30 and UL42, UL30's processivity subunit, results in a virus which is unable to synthesize long chain DNA and is thus unable to replicate. Recently, a crystal structure of the interaction between UL30 and UL42 has been published. Utilizing this information, we have designed a scaffold, 1-aza-3,7-dioxabicyclo[3.3.0]octane to mimic the UL42-binding region of UL30. A homogeneous library of 66 different octanes has been made and analyzed on their ability to inhibit the UL30-UL42 interaction. Further study on the synthesis of heterogeneous library is undergoing. This poster will outline the synthesis and biological study of these agents.

342.

ASYMMETRIC SYNTHESES OF 3,4-DISUBSTITUTED TETRAHYDROFURANES AND 1,3,4-TRISUBSTITUTED PYRROLIDINES VIA N-HYDROXY-A-METHYLBENZYLAMINE INDUCED INTRAMOLECULAR NITRONE CYCLOADDITION REACTIONS. ***Hui-Yin Harry Li***, *Nan Zhou, and Philip Ma, Wilmington PharmaTech Company, One Innovation Way, Suite 302, Newark, DE 19711, Fax: 302-234-4829, Harry@wilmingtonpharmatech.com*

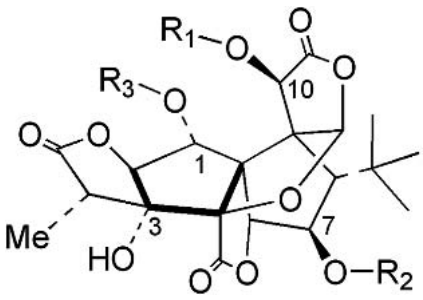
Asymmetric syntheses of 3,4-disubstituted tetrahydrofuranes and 1,3,4-trisubstituted pyrrolidines via an intramolecular cycloaddition reaction of nitrones derived from alkenals and chiral hydroxylamines are described. This synthesis consists of a three-step process. Alkylation of substituted allyllic acohols or allyllic amines with ethyl bromoacetate, reduction ester functionality to aldehyde, treatment of this in-situ gnerated alkenal with (R)-(+)-N-hydroxy- α -methylbenzylamine oxalate or (S)-(-)-N-hydroxy- α -methylbenzylamine oxalate produced 3,4-disubstituted tetrahydrofuranes or 1,3,4-trisubstituted pyrrolidines in high diastrereoselectivity. A practical larger scale process for the preparation of both (R) and (S)-N-hydroxy- α -methylbenzylamines were also developed and both enantiomers now can be prepared at multi-kilogram scale.

343.

COMBINATORIAL SYNTHESIS AND BIOLOGICAL EVALUATION OF GINKGOLIDE DERIVATIVES. ***Stanislav Jaracz***[1], *Kristian Stromgaard*[2], *Anders A. Jensen*[2], *and Koji Nakanishi*[1]. *(1) Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, Fax: 212-932-8273, sj246@columbia.edu, (2) Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences*

Ginkgolides are diterpenoid constituents of the Ginkgo biloba tree that has been used for thousands of years as a herbal medicine. Ginkgolides are well known as potent antagonists of the platelet activating factor receptor. Recently, it was found that ginkgolides function also as antagonists of glycine receptors. We report the design and parallel combinatorial synthesis of a small ginkgolide

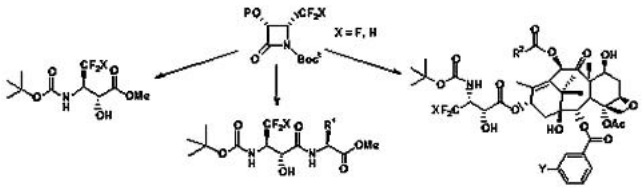
library from ginkgolide C and application of the new derivatives in SAR study of glycine receptors. Initially, a solid-phase methodology was considered. Various linkage strategies were investigated e.g., silicon linker, sulfonyl linker, etc. Selective derivatizations were studied on both solid-phase and in solution. Interestingly, transformations in solution were very selective without the need of exhaustive protection of other functional groups. On the other hand, solid-phase methodology resulted in lower selectivity. The library was therefore generated by the solution method. Translactonization and migration mechanisms of the selective derivatizations have also been investigated.



344.

TRIFLUOROMETHYL- AND DIFLUOROMETHYL-β-LACTAMS AS USEFUL INTERMEDIATES FOR THE SYNTHESIS OF FLUORINATED AMINO ACIDS, DIPEPTIDES, AND FLUORO-TAXOIDS. ***Larissa Kuznetsova****, Ioana M. Ungureanu, Antonella Pepe, and Iwao Ojima, Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, lkuznets@ic.sunysb.edu*

Special properties of fluorine make fluorine-containing biologically active compounds unique in medicinal chemistry. It has been shown that fluoroamino acids, their peptides, and peptidomimetics play significant roles in drug design and development. We report here the efficient synthesis of enantiomerically pure 4-trifluoromethyl and 4-difluoromethyl-β-lactams which serve as building blocks for fluoroamino acids and their dipeptides. Synthesis and biological activities of 3′-trifluoromethyl- or 3′-difluoromethyl-taxoids will also be discussed.



345.

FAST ANALOG FORMATION USING SILICA-SUPPORTED SULFONYL CHLORIDES – PART II. *J. Liu, and* ***O. Mneimne****, Biotage, INC., A Dyax Corp Company, PO Box 8006, Charlottesville, VA 22906, Jliu@biotage.com, OMneimne@biotage.com*

Sulfonyl chlorides react with oxygen nucleophiles in the presence of an amine base to form reactive sulfonates. Various sulfur, oxygen, and nitrogen nucleophiles were then used to form the corresponding substitution products. This paper illustrates the potential use of silica-supported sulfonyl chlorides in the synthesis of small compound libraries. Due to its porosity, rigidity, thermal stability, and high-surface area, silica-supported reagents are reactive without swelling and therefore are compatible with all organic solvents. All reactions were performed in pre-formatted Syntage chemistry cartridges, which conveniently fit into the top of a FLASH+ purification cartridge. It is found that the cartridge-based technique has many advantages over traditional solid-phase methods. In addition to fast analoging, cartridge-based synthesis dramatically simplifies compound purification. The methodology developed in this study has general applicability for fast compound generation in drug discovery.

346.

FLOW-THROUGH HETEROGENEOUS OXIDATION OF ALCOHOLS. ***J. Liu****, and O. Mneimne, Biotage, INC., A Dyax Corp Company, PO Box 8006, Charlottesville, VA 22906, JLiu@biotage.com*

This paper focuses on the utility of solid-supported potassium permanganate as an oxidant in organic synthesis. Potassium permanganate is typically used as an aqueous oxidant that commonly results in solvent and substrate incompatibilities and lengthy extractive workups. A number of solid-supported reagents where permanganate oxidations play a major role have drawn attention in both solution-phase and solid-phase synthesis. We present results on the use of silica-supported potassium permanganate to prepare carbonyl compounds in a flow-through system. The flow of substrate into the reagent bed was regulated such that the dynamics and extent of the oxidation can be controlled. A variety of primary and secondary alcohols were oxidized using this technique resulting in quick, high yielding, and extraction-free reactions.

347.

RAPID SYNTHESIS AND CLEAN –UP OF AN ARRAY OF AMINES USING PRE-PACKED SILICA SUPPORTED THIOL CARTRIDGES. ***Shahnaz Ghassemi****, Biotage, Inc, Charlottesville, VA 22906, Fax: 434-979-4743, SGhassemi@biotage.com, and P. C. Rahn, R & D, Biotage, Inc*

We describe a new method for the rapid clean up of an array of tertiary amines formed by N-alkylation of cyclic amines with alkyl halides in solution phase parallel synthesis. Excess electophiles (alkyl halides) are used to drive the reaction to completion. After completion, the reaction mixture is transferred onto KP-PrSH (propyl thiol silica) cartridge to scavenge the unreacted alkyl halides

348.

UNDERSTANDING THE IMPORTANCE OF TLC IN FLASH METHOD DEVELOPMENT ACCURACY. ***J. Robert Bickler****, Biotage, Inc., a Dyax Corp. Co, PO Box 8006, Charlottesville, VA 22906-8006, Fax: 434-979-4743, bbickler@biotage.com*

FLASH chromatography is commonly used to purify synthetic organic products. Prepacked disposable cartridges and automated gradient elution flash systems have made this purification methodology routine. It is as easy as load your sample on a column and run a method - almost. Method development with Thin-layer chromatography (TLC) is still required to determine which solvents in what concentration provide the best separation of their sample. Theory says TLC data provide elution conditions, elution order, and sample loading data. However, differences between TLC silica and flash silica often provide inaccurate data, which lead to poorer than expected purity and yield. In this poster we show the importance of using TLC plates and flash cartridges with matching silica using organic chemical mixtures.

349.

SIMPLIFIED INDAZOLE SYNTHESIS BY MICROWAVE ENHANCED NITRENE CHEMISTRY. ***Ajay K. Bose****, Maghar S. Manhas, Deepu J. Varughese, Arun Mandadi, and Sochan Rumthao, Department of Chemistry and Chemical Biology, Stevens Insitute of Technology, Castle Point on Hudson, Hoboken, NJ 07030, Fax: 201-216-8240, abose@stevens.edu*

Indazoles are of growing interest to medicinal chemists as potential anti-tumor, anti-HIV, anti-inflammatory drugs. The classical Cadogan reaction for indazoles involves a 2 h. Schiff base (1) synthesis followed by reflux with excess triethylphosphite (2) in an inert atmosphere for 8 h: nitrene formation by the deoxygenation of the nitro-group leads to cyclization with the formation of an indazole (3). We have prepared N-phenylindazole by two methods: (a)Compound(1) was prepared under microwave irradiation for 2 min in a solventless reaction; next,the reaction of (1) with 3 moles of (2) was carried out under microwave irradiation for 6 to 8 min. (b) This synthesis was also conducted in a one pot reaction in a microwave oven in 10 min. We used our MORE chemistry techniques (Bose, A. K., et al. Synthesis 2002, 1578 - 1591) but without an inert atmosphere. We removed the excess of (2) by oxidative conversion to water-soluble triethylphosphate using 3 % H2O2 instead of dis-tillation. Yield and purity of (3)obtained by these pro-cedures were comparable to those reported in the literature [Cadogan, J.I.G., Org. Synth.Coll.Vol.5, 941].

350.

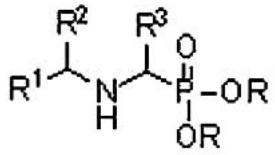
SOLID PHASE LIBRARY SYNTHESIS OF TETRAHYDRO-1,4-BENZODIAZEPINE-2-ONE DERIVATIVES. ***Isak Im**, Kwanyoung Jeong, and Yongchul Kim, Life Science, Kwangju Institute of Science and Technology, 1 Oryong-dong, Buk-gu, Kwangju 500-712, South Korea, Fax: 62-970-2484, imisak@kjist.ac.kr*

Benzodiazepine classes have been served as not only the important pharmacophores of CNS drugs but also one of the nonpeptide β-turn mimic scaffolds in academia and pharmaceutical industry. We have developed a new efficient solid phase library synthesis of 7-substituted 1,4 benzodiazepin-2-one derivatives as privileged peptidomimetics. Three points of diversity in the scaffold were introduced including carbon 7 position. Each point of functional variation is corresponding to Cα atom of β-turn. The scaffold itself was synthesized in solution phase with various R1 group, and loaded to the PL-FDMP resin with reductive amination in high yields. Two substitution reactions, alkylations or acylations of 7-hydroxyl and N-alkylation of 1-amide nitrogen were accomplished in solid phase using Miniblock parallel synthesizer. TFA cleavages and subsequent purification using Biotage parallel column chromatography system resulted in the 192 members of peptidomimetic library with 85-95% average purity.

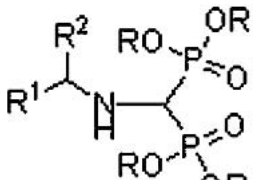
351.

SYNTHESIS OF NOVEL AMINO PHOSPHONATES AND AMINO BISPHOSPHONATES. *Nicos A. Petasis, and **Wei Huang**, Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, 837 West 37th Street, Los Angeles, CA 90089-1661, Fax: 213-740-6684, petasis@usc.edu, weihuang@usc.edu*

Amino phosphonates (**1**) and amino bisphosphonates (**2**)have been used in a number of applications in drug discovery. For example, compounds of type **1** having R2=COOH or CONHR4, have been used as inhibitors of several enzymes, including: neutral endopeptidase (NEP), endothelin converting enzyme (ECE) and matrix metalloproteinases (MMP). Also, compounds of type **2** have been used as diphosphate mimics for the treatment of bone resorption diseases and as antiparasitic agents. Herein we present a new approach to molecules of type **1** and type **2** that allows the introduction of a wide range of substituents in a highly convergent manner.



1



2

352.

MODELING OF ACTIVITY FOR BIOLOGICAL SAMPLES USING ARTIFICIAL NEURAL NETWORK. *S. Sardari, Department of Biomedical Sciences, University of Rhode Island, Kingston, RI 02881-0809, sardari7@yahoo.com, and **K. Parang**, Department of Biomedical Sciences, Assistant Professor, University of Rhode Island, 41 Lower College Road, Fogarty Hall, Kingston, RI 02881, Fax: 401-874-5048, kayparang@uri.edu*

Purpose: The applicability of artificial neural network (ANN) modeling to bioactivity determination of a group of natural product samples based on bioinformatic descriptors, laboratory data and database indexing terms is studied. Method: The system of analyzing large amounts of indexing term from CA database, using ANN is presented. The architecture was optimized to prevent memorization while maximizing the efficiency. The group of selected descriptors applied into the optimized ANN included designated taxonomic position of the sources, DNA-C values, chemical, ecological and bioactivity notions. The predictability of the model was tested on members of the training and test groups. Results: The average error of 0.049 for a target of 0.05 after 63 cycles was obtained. The relative importance for descriptor data was pooled. The top three were biological activity, DNA values and chemical notion. Predictability of the model was %95.00. The applicability of database terms in such modeling has been discussed.

353.

NOVEL RELEASABLE LINKER TECHNOLOGIES FOR TARGETED DRUG DELIVERY. *Franciscus M.H. de Groot[1], Laetitia Devy[2], Agnes Noel[2], Jean-Michel Foidart[2], **Patrick H. Beusker**[1], and Hans W. Scheeren[3]. (1) Syntarga B.V, Toernooiveld, 6525 ED Nijmegen, Netherlands, fmhdegroot@syntarga.com, fmhdegroot@syntarga.com, (2) Laboratory of Tumor and Developmental Biology, Department of Pathology, University of Liege, (3) Department of Organic Chemistry, University of Nijmegen*

Most chemotherapeutic agents have a small therapeutic window and cause severe side effects. Prodrug therapy can increase the therapeutic window of cytotoxic agents. Linkage of a peptide specifier, which is a substrate for a tumor-specific enzyme, to a cytotoxic drug may yield a non-toxic and selectively activatible prodrug. A number of releasable linker technologies have been developed, which can be used to connect a specifier to a parent drug. One linker type concerns elongated spacers that position the specifier at sufficient distance from the parent drug. Both in vitro and in vivo, the plasmin-activated doxorubicin prodrug ST-9905, containing one of the novel linkers, has been demonstrated to possess superior drug release kinetics and antitumor efficacy when compared at equimolar and equitoxic dose with both Dox and ST-9802, which contains a conventional linker, without showing discernible side effects. Besides novel elongated linkers, other newly developed linker technology will be presented.

354.

QSAR MODEL FOR CYP2D6 INHIBITION IN THE ARYLOXYPROPANOLAMINE SERIES. ***Ashvinikumar V. Gavai**, Roy J. Vaz, Kenneth Santone, Gamini Chandrasena, and Akbar Nayeem, Bristol-Myers Squibb Pharmaceutical Research Institute, P. O. Box 4000, Princeton, NJ 08543, Fax: 609-252-6601, ashvinikumar.gavai@bms.com*

Cytochrome P450 2D6 has been reported as one of the primary metabolizing enzymes for compounds containing a basic amine. CYP2D6 is absent in 5-9% of the Caucasian population, resulting in deficiencies in oxidation of drugs that are metabolized primarily by this enzyme. Due to the issues related with drug-drug interactions as well as pharmacogenomic variability, small molecule drug optimization process involves optimizing compounds such that activity towards this and other CYP enzymes is decreased. Besides the basic nitrogen, the substrates and inhibitors for CYP2D6 also include a hydrophobic group which is near the site of oxidation. Aryloxypropanolamines represent an important class of biologically active compounds that show potent inhibition of CYP2D6. This presentation will describe a 3D-QSAR model for CYP2D6 inhibition for a series of analogues of propranolol. Strategies to design new analogues with reduced CYP2D6 inhibition will be discussed.

355.

SYNTHESES AND STRUCTURE VERIFICATION OF 4-BROMOFLAVONE METABOLITES. ***Simonida Grubjesic**[1], Yongmei Li[2], Jerome W. Kosmeder II[3], Richard B. van Breemen[2], John M. Pezzuto[4], and Robert M. Moriarty[1]. (1) Department of Chemistry, College of Liberal Arts and Sciences, University of Illinois at Chicago, 845 W. Taylor St., Chicago, IL 60607, Fax: 312-996-0431, sgrubj2@uic.edu, (2) Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, (3) Discovery Partners International, ChemRx Division, (4) School of Pharmacy, Purdue University*

Quinone reductase (QR) is a phase II detoxifying enzyme, which plays an important role in the area of cancer chemoprevention. 4-Bromoflavone was found to be a potent inducer of QR. This compound was further identified to be a highly effective cancer chemopreventive agent in both in vitro and in vivo studies. As part of the comprehensive evaluation of this agent, metabolite studies with rat and human hepatocytes were performed. Four monohydroxylated derivatives of 4-bromoflavone were found as metabolites using tandem mass spectrometry (MS). Syntheses were then performed in order to prove the proposed structures of isolated metabolites. The synthetic compounds corresponded to the metabolites detected in the MS. Short and efficient syntheses of these metabolites will be presented.

356.

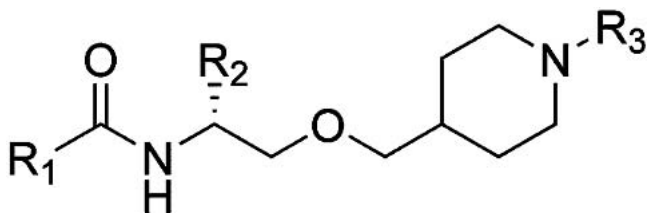
DISCOVERING POTENT AND SELECTIVE REVERSIBLE INHIBITORS OF ENZYMES IN COMPLEX PROTEOMES. ***Donmienne Leung***[1], *Christophe Hardouin*[2], *Dale L. Boger*[2], *and Benjamin F. Cravatt*[3]. *(1) Department of Chemistry and Cell Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, dleung@scripps.edu, (2) Department of Chemistry, The Scripps Research Institute, (3) Departments of Chemistry and Cell Biology, The Scripps Research Institute*

Advances in combinatorial synthesis have provided unprecedented access to large compound libraries of considerable diversity, shifting the bottleneck in drug discovery to the development of efficient screens for protein targets. Inhibitor screening typically requires extensive target-specific work, including protein expression, purification, as well as the development of substrate assays. Here, we report a proteomic method for the discovery of enzyme inhibitors that is free of these restrictions. We show that competitive profiling of a library of candidate serine hydrolase inhibitors with activity-based chemical probes simultaneously identifies nanomolar inhibitors for several enzymes in complex proteomes; including fatty acid amide hydrolase, triacylglycerol hydrolase, an uncharacterized membrane-associated hydrolase and others. Importantly, because this strategy tests inhibitors against numerous enzymes in parallel, it assigns both potency and selectivity to each agent. In this way, promiscuous inhibitors were readily triaged in favor of compounds of equivalent potency that displayed greater selectivity for their respective targets.

357.

1,2-AMINOETHANOL-DERIVED NON-COVALENT FACTOR XA INHIBITORS. ***Scott M. Sheehan***[1], *Brian M. Watson*[1], *Michael R. Wiley*[1], *J.W Liebeschuetz*[2], *Daniel J. Sall*[1], *Jeffry B. Franciskovich*[1], *Jothirajah Marimuthu*[1], *Jeffrey K. Smallwood*[1], *Ronald S. Foster*[1], *Larry L. Froelich*[1], *Donetta Gifford-Moore*[1], *David W. Snyder*[1], *Michael L. Chouinard*[1], *Marsha K. Chastain*[1], *Lea M. Johnson*[1], *Philip R. Sipes*[1], *John P. Tluczek*[1], *N. Y. Chirgadze*[1], *Mark W. Farmen*[1], *R. D. Towner*[1], *Trelia J. Craft*[1], *and Gerald F. Smith*[1]. *(1) Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-433-0715, sheehan_scott@lilly.com, (2) Computational Chemistry, Tularik Ltd*

During the course of our research efforts focused on the identification of novel non-covalent inhibitors of the serine protease factor Xa (fXa), we have discovered a series of substituted 1,2-aminoethanol derived inhibitors that feature an ether linkage to the S4 binding element (Figure 1). The factor Xa inhibitory activity and functional activity of these compounds will be presented. Comparisons to amine-, amide-, and carbon-based replacements of the ether linkage will be made to elucidate the effects of S4-linker modification on functional activity, species profile, and rat oral absorption. Figure 1:



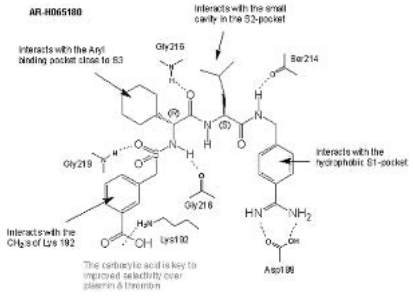
358.

DIPEPTIDE SULPHONAMIDE INHIBITORS OF SERINE PROTEASES IN THE COAGULATION CASCADE - AN INITIAL STRUGGLE FOR FVIIA SELECTIVITY AND POTENCY. ***Kenneth L. Granberg***[1], *Fredrik R. Johansson*[1], *Ulf E. Fahlander*[1], *Jens Petersen*[2], *Andy Stocker*[3], *Pete Caulkette*[3], *Harji Rakesh*[3], *Roger James*[3], *John Preston*[3], *Frederico Nardi*[2], *Kristina Nilsson*[1], *Susanne Alenfalk*[1], *and Johanna Deinum*[4]. *(1) Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, 43183 Mölndal, Sweden, Fax: +46317763710, kenneth.granberg@astrazeneca.com, (2) Department of Structural Chemistry, AstraZeneca R&D Mölndal, (3) Department of Cardiovascular, Gastro-Intestinal, AstraZeneca R&D Alderley Park, (4) Department of Cell Biology and Biochemistry, AstraZeneca R&D Mölndal*

Cardio- and cerebrovascular diseases constitute a leading cause of death in the world and there is large unmet need for an oral, effective and safe anticoagulant therapy. Coagulation factor VIIa (FVIIa) is central to the *initiation* of events leading to thrombus formation.

Synthesis of serine protease inhibitors relied on a blend of solid and solution phase chemistries and gave dipeptide sulphonamides (β1-P3-P2-P1). Modification of β1 gave selectivity for FVIIa over both FIIa and plasmin. Lys192 and Arg174 form an induced pocket, which we denote β1, as shown by X-ray structures of des-Gla-FVIIa/sTF inhibitor complexes. Potent inhibitors of plasmin, trypsin, FXIa and FIIa using the same scaffold were prepared. Replacement for the bensamidine (P1) proved most difficult in FVIIa while some success was experienced with FIIa and FXIa.

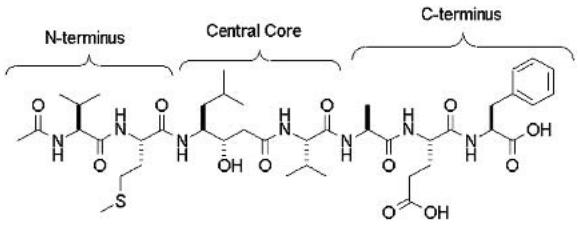
Comparison with other non-peptidic inhibitors in complex with des-Gla-FVIIa/sTF will also be discussed.



359.

DESIGN OF CELL PERMEABLE PEPTIDOMIMETIC INHIBITORS OF BACE. ***Roy K. Hom***, *Larry Y. Fang, Shumeye Mamo, Jay S. Tung, Ashley C. Guinn, Don E. Walker, David L. Davis, Andrea F. Gailunas, Eugene D. Thorsett, Sukanto Sinha, Jeroen E. Knops, Nancy E. Jewett, John P. Anderson, and Varghese John, Chemistry, Elan Pharmaceuticals, 800 Gateway Blvd, South San Francisco, CA 94080*

We describe the development of peptidomimetic inhibitors of human β-secretase (BACE). The conversion of peptide inhibitor 1 into cell-permeable peptidomimetic inhibitors of BACE was achieved through an iterative strategy of conceptually subdividing the polypeptide into three regions: an N-terminal portion, a central core, and a C-terminus. Replacement of the amino acid residues with moieties with less peptidic character was achieved with retention of BACE enzyme inhibitory activity and resulted in inhibitors with significantly reduced molecular weights that showed inhibition of Aβ production in cells.



Ac-Val-Met-[Sta]-Val-Ala-Glu-Phe (**1**)
BACE IC_{50} = 0.3 μM

360.

DESIGNED HELICAL PEPTIDES INHIBIT AN INTRAMEMBRANE PROTEASE. ***Michael S. Wolfe***[1], *Chittaranjan Das*[1], *Oksana Berezovska*[2], *and Bradley T. Hyman*[2]. *(1) Center for Neurologic Diseases, Harvard Medical School and Brigham and Women's Hospital, 77 Avenue Louis Pasteur, H.I.M. 754, Boston, MA 02115, (2) Alzheimer's Disease Research Laboratory, Harvard Medical School and Massachusetts General Hospital*

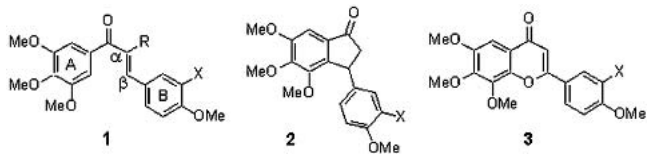
Gamma-secretase cleaves the transmembrane domain of the amyloid precursor protein, a process implicated in the pathogenesis of Alzheimer's disease, and this enzyme is a founding member of an emerging class of intramembrane proteases. Biochemical evidence supports the presence of an initial docking site for substrate on gamma-secretase that is distinct from the active site, a property predicted to be general for intramembrane proteases. Here we show that peptides designed to adopt a helical conformation are inhibitors of gamma-secretase in both cells and enzyme preparations. Modifications that disrupt helicity reduce potency, suggesting that this conformation is critical for effective inhibition. Fluorescence lifetime imaging in cells demonstrate that helical peptides disrupt binding between substrate and protease, whereas an active site-directed inhibitor does not. These findings are consistent with helical

peptides interacting with the initial substrate docking site of gamma-secretase, suggesting a general strategy for designing potent and specific inhibitors of intramembrane proteases.

361.

CONFORMATIONALLY RESTRICTED ANALOGS OF CHALCONES AS POTENT INHIBITORS OF TUBULIN POLYMERISATION. ***Nicholas J. Lawrence**, Department of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, United Kingdom, Fax: 44-29-2087-4030, Lawrencenj1@cardiff.ac.uk, David Rennison, Department of Chemistry, UMIST, and Alan T. McGown, Centre for Molecular Drug Design, University of Salford*

The α-methyl chalcone **1** is a potent inhibitor of tubulin polymerisation, related to colchicine and combretastatin A-4. It inhibits cancer cell growth at low concentrations [IC_{50} (K562) 0.21 nM] and binds to the colchicine-binding site of isolated tubulin more strongly than colchicine itself. We report the design and synthesis of conformationally constrained surrogates of the *s-trans* conformer of chalcone **1**. These surrogates serve as novel tumour vasculature targeting compounds. The first generation analogs are based on linking the β-carbon atom to the A-ring, either directly or *via* a heteroatom as in the indanones **2** and flavones **3**. A structure activity relationship for both series will be presented. The analogs disrupt the cell cycle at the G_2/M stage and bind to tubulin at the colchicine site and possess tumour vasculature targeting properties.



362.

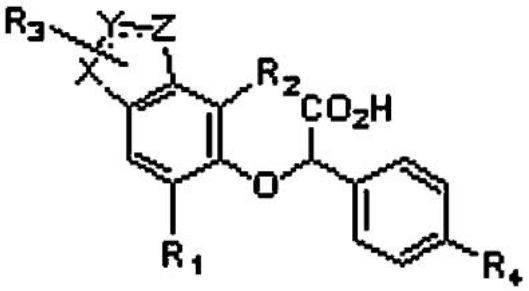
α-ARYLOXY-α-METHYLHYDROCINNAMIC ACIDS: A NOVEL CLASS OF PPARα/γ DUAL AGONISTS. ***Yanping Xu**, Dawn A Brooks, Samuel J. dominianni, Garret Etgen, Sarah B Jones, Raymond F Kauffman, Chahrzad Montrose-Rafizadeh, Christopher J. Rito, Anthony J. Shuker, Allie Tripp, Leonard L. Winneroski Jr., Richard W Zink, and James McCarthy, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, Fax: 317-277-2035, xu_yanping@lilly.com*

Type 2 diabetes, insulin resistant diabetes, can result in hyperglycemia and trigger a range of secondary long-term organ complications, such as neuropathy, nephropathy, retinopathy, and premature atherosclerosis. There are numerous reports on efforts to discover euglycemic agents. PPARγ agonists (e.g., rosiglitazone, pioglitazone) have displayed clinical utility by increasing insulin sensitivity and improving glycemic control in Type 2 diabetes. PPARα agonists (e.g., gemfibrozil, fenofibrate) demonstrate the ability to reduce serum triglycerides and increase HDL cholesterol, and also to reduce serum fibrinogen and PAI-1. The combined profile of a PPARα/γ dual agonist thus appears well suited for the treatment of hyperglycemia along with the prevention of cardiovascular disease in Type 2 diabetes and Syndrome X. Our laboratories have previously disclosed a series of PPARα/γ dual agonist including 2-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid. Herein we report our SAR leading to LY929, a second generation PPARα/γ dual agonist with 10^{-9}M activity at both receptor isoforms.

363.

IDENTIFICATION OF A NOVEL CLASS OF ORALLY ACTIVE PPARƒÑ/ƒ× DUAL AGONISTS FOR TREATMENT OF TYPE-2 DIABETES AND LIPID DISORDERS. ***Guo Q. Shi**[1], Jame F. Dropinski[1], Alan D. Adams[1], karen L. Macnaul[2], Alex Elbrecht[2], Joel P. Berger[2], Gaochao Zhou[2], Thomas W. Doebber[2], Roger Meurer[3], Michael J. Forrest[3], David E. Moller[2], and A. Brian Jones[1]. (1) Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc, PO Box 2000, Rahway, NJ NJ 07065, Fax: 732-594-9556, guoqiang_shi@merck.com, (2) Department of Molecular Endocrinology, Merck Research Laboratories, Merck & Co., Inc, (3) Department of Animal Pharmacology, Merck Research Laboratories, Merck & Co., Inc*

PPARs are nuclear receptors that regulate the expression of genes controlling lipid and glucose metabolism. Using PPARs as molecular targets, three thiazolidinedione insulin sensitizers (PPARƒ× agonists) were marketed for the treatment of type 2 diabetes. As a class, these drugs have modest antidiabetic efficacy when used as monotherapy and are associated with adverse effects such as edema and weight gain. Activation of PPARƒÑƒnis known to be the predominant mechanism by which fibrates lower triglycerides and elevate HDL. The combined profile of a PPARƒÑ/ƒ× dual agonist appears to be a promising treatment for hyperglycemia and dyslipidemia in type 2 diabetes. We have focused our efforts on a novel class of compounds known as ƒÑ-aryloxyphenylacetic acids. These compounds showed a unique in vitro profile and superior in vivo efficacy compared with benchmark compounds in animal models. Their synthesis and SAR development, including in vivo evaluation, will be presented.



364.

NOVEL SMALL MOLECULE AGONISTS OF THE HUMAN CALCITONIN RECEPTOR. ***David J Cowan**[1], Anthony L. Handlon[2], Clifton E Hyman[1], Michael H Rabinowitz[3], Ashok Bhandari[4], Richard F Cox[5], Lawrence A Wolfe[5], Makda Mebrahtu[5], Alan A Payne[6], and Ginger Boncek[7]. (1) Department of Medicinal Chemistry, GlaxoSmithKline Research and Development, 5 Moore Drive, PO Box 13398, Research Triangle Park, NC 27709-3398, Fax: 919-315-0430, david.j.cowan@gsk.com, (2) Medicinal Chemistry, GlaxoSmithKline, (3) Department of Medicinal Chemistry, R.W. Johnson Pharmaceutical Research Institute, (4) Department of Medicinal Chemistry, Affymax, Inc, (5) Discovery Research, GlaxoSmithKline Research and Development, (6) Molecular Pharmacology, GlaxoSmithKline Research and Development, (7) Howard's Associates*

Calcitonin is a 32 amino acid peptide secreted primarily from C-cells within the thyroid gland of mammals, which plays an important role in the maintaining of bone homeostasis. Its receptor has been cloned and shown to be a member of the seven-transmembrane, G protein-coupled receptor family. Calcitonin suppresses resorption of bone by inhibiting the activity of osteoclasts, a cell type that digests the bone matrix and releases calcium and phosphorus into the blood. High-turnover bone loss has recently been shown to be preventable by the administration of salmon calcitonin (s-CT). The most common route currently marketed today is that of intranasal delivery. The side effects associated with this type of administration as well as the wide variation in bioavailability have limited its potential use. We wish to disclose the synthesis and biological evaluation of a class of novel small molecule agonists of the human calcitonin receptor designed to be used as an effective orally bioavailable agent for the treatment of osteoporosis.

365.

PROLINE AND PIPECOLIC ACID-BASED AGONISTS OF THE FOLLICLE-STIMULATING HORMONE RECEPTOR. ***Andreas Goutopoulos**, Adulla Reddy, Yihua Liao, Sharad Magar, Robert Murray, Weishui Weiser, Roustem Nabioullin, Judy Rosenthal, David Buckler, Shirley Cheng, Jane Liu, Sean McKenna, Xiuliang Jiang, David Evans, Mark Tepper, and Nabil El Tayar, Serono Reproductive Biology Institute, One Technology Place, Rocland, MA 02370, Fax: 781-681-2939, andreas.goutopoulos@serono.com*

Follicle stimulating hormone (FSH) is a native glycoprotein hormone that is necessary for follicle growth. This action is mediated via a specific G protein-coupled receptor, the FSH receptor (FSHR), present in the membrane of granulosa cells within the follicles of the ovary. Decreased levels of FSH result in reduced fertility or infertility. In an effort to develop a small-molecule FSH receptor agonist, a series of substituted prolines was found to mimic the action of FSH in cells expressing the FSHR. An SAR around this series was developed and is described herein. A piperidine homolog was found to have a tenfold increased potency than its proline congener. This compound induced cAMP production in CHO cells expressing the FSH receptor, but not in parental cells, or in cells expressing the other two glycoprotein hormone receptors (LHR and

TSHR). In addition, this compound similarly to FSH, induced estradiol release from rat granulosa cells.

366.

DEVELOPMENT OF A HIGHLY POTENT PHOSPHODIESTERASE-4 (PDE4) INHIBITOR : STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDY DIRECTED TOWARDS MINIMIZING HERG POTASSIUM CHANNEL BINDING AFFINITY.

Evelyn O. Martins[1], *Richard G. Ball*[2], *Marc Blouin*[1], *Louise Boulet*[3], *Bernard Côté*[1], *Yves Ducharme*[1], *Richard Frenette*[1], *Rick W. Friesen*[1], *Mario Girard*[1], *Yves Girard*[1], *Daniel Guay*[1], *Zheng Huang*[3], *Thomas R. Jones*[3], *France Laliberté*[3], *Joseph J. Lynch Jr.*[4], *Joseph A. Mancini*[3], *Paul Masson*[3], *Eric Muise*[3], *Douglas J. Pon*[3], *Peter K. S. Siegl*[4], *Angela Styhler*[3], *Nancy N. Tsou*[2], *Mervyn J. Turner*[1], *and Robert N. Young*[1]. *(1) Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, P. O. Box 1005, Pointe Claire-Dorval, QC H9R 4P8, Canada, Fax: 514-428-4900, evelyn_martins@merck.com, (2) Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, (3) Department of Biology, Merck Frosst Center for Therapeutic Research, (4) Department of Pharmacology, Merck and Co., Inc, West Point*

The evaluation of the structure-activity relationship (SAR) study on a tertiary alcohol series of phosphodiesterase-4 (PDE4) inhibitors is described. The inhibitory potency against PDE4 and the LPS-induced production of TNFα in human whole blood was examined. In addition, the binding affinity of these compounds for the hERG potassium channel (an *in vitro* measure for the potential to cause QTc prolongation) was assessed. Through these studies, we identified a highly potent PDE4 inhibitor L-869,298 which exhibits low binding affinity to the hERG potassium channel and a desirable pharmacokinetic profile. L-869,298 also demonstrated good *in vivo* efficacy in several models of pulmonary function with a wide therapeutic index with respect to emesis and prolongation of the QTc interval.

367.

DISCOVERY OF SCH 444877, A POTENT, SELECTIVE AND ORALLY ACTIVE CYCLIC GUANINE PDE5 INHIBITOR.

Yuguang Wang[1], *Samuel Chackalamannil*[1], *Andrew Stamford*[1], *Craig D. Boyle*[1], *Zhiyong Hu*[1], *Claire Lankin*[1], *John Clader*[1], *Ruo Xu*[1], *Theodros Asberom*[1], *Dmitri Pissarnitski*[2], *William Greenlee*[1], *Stanley Kurowski*[3], *Subbarao Vemulapalli*[3], *Jairam Palamanda*[4], *Mahdu Chintala*[3], *Ping Wu*[3], *Joyce Myers*[3], *and Peng Wang*[3]. *(1) CV/CNS Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, Fax: 9087407152, yuguang.wang@spcorp.com, (2) CV & CNS Chemical Research, Schering-Plough Research Institute, (3) Biological Research, Schering-Plough Research Institute, (4) Department of DMPK, Schering-Plough Research Institute*

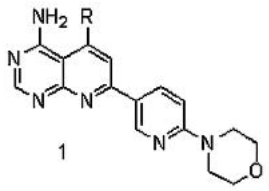
Sch 444877 is a tricyclic guanine derived potent inhibitor of human PDE5 isozyme with an IC50 value of 1.5 nM. Its PDE6/PDE5 selectivity is about 250-fold. In the dog pelvic nerve stimulation model, Sch 444877 dose-dependently increased cavernosal pressure with an ED100 slightly more potent than sildenafil. It also showed a rapid onset and fast clearance PK profile.

368.

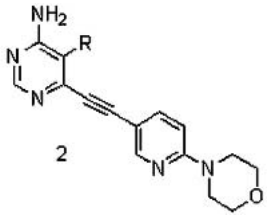
DESIGN AND SYNTHESIS OF NOVEL NONNUCLEOSIDE ADENOSINE KINASE INHIBITORS WITH ANALGESIC AND ANTI-INFLAMMATORY PROPERTIES.

Arthur Gomtsyan, *Stanley Didomenico, Chih-Hung Lee, Jiang Meiqun, Erol Bayburt, Marlon Cowart, Mark Matulenko, Andrew Stewart, Michael Jarvis, and Shripad Bhagwat, Global Pharmaceutical Products Division, Neuroscience Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-937-9195, arthur.r.gomtsyan@abbott.com*

Adenosine kinase (AK) inhibitors significantly increase adenosine concentrations at sites of tissue injury and provide effective antinociceptive and anti-inflammatory activity in animal models. Pyridopyrimidines 1 and alkynylpyrimidines 2 are potent and selective nonnucleoside AK inhibitors. The choice of the substituent R and the point of its attachment to the core structure are important for filling a putative hydrophobic pocket of the protein. "SAR by NMR" technique was employed to identify new high-affinity ligands that after incorporation into the original scaffold served as R substituent or fragment of it. A number of representatives of these AK inhibitors exhibited good efficacy in animal models of neuropathic and inflammatory pain as well as inflammation.



1



2

369.

WITHDRAWN.

370.

DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF A NOVEL CLASS OF POTENT, SELECTIVE, ORALLY ACTIVE OXYTOCIN RECEPTOR ANTAGONISTS.

Matthias K. Schwarz[1], *Anna Quattropani*[1], *Patrick Page*[1], *Russell J. Thomas*[2], *Anthony Baxter*[3], *Jérôme Dorbais*[1], *Vincent Pomel*[1], *Maurizio Maio*[1], *Claudia Mannino*[4], *David Covini*[1], *Pierre-André Pittet*[1], *Catherine Jorand-Lebrun*[1], *Delphine Valognes*[1], *Serge Halazy*[1], *Alexander Scheer*[1], *Marc Missotten*[1], *Guidon Ayala*[1], *Rocco Cirillo*[5], *Enrico Gillio Tos*[5], *Paolo Marinelli*[5], *Claudio Giacchetti*[5], *Claude Barberis*[6], *and André Chollet*[1]. *(1) Department of Chemistry, Serono Pharmaceutical Research Institute, 14, Chemin des Aulx, 1228 Plan-les-Ouates, Switzerland, Fax: +4122-794-6965, matthias.schwarz@serono.com, (2) EvotecOAI, (3) Argenta Discovery, (4) Institut für Chemie, Organische Chemie, Freie Universität Berlin, (5) Istituto di Ricerche Biomediche "A.Marxer", LCG-RBM, (6) INSERM U469*

Premature delivery is the largest cause of perinatal morbidity and mortality, affecting around 10% of all births. Today, pharmacological intervention aimed at preventing preterm labour by maintaining uterine quiescence (tocolysis) remains the cornerstone of pharmaceutical management of preterm birth. Classical tocolytic agents used in the clinic, such as the b2-adrenergic agonist ritodrine, suffer from moderate effectiveness and lack of uterine selectivity, causing important foetal and maternal side effects. The peptide oxytocin receptor antagonist Atosiban combines similar efficacy with a better side-effect profile, but its peptidic nature requiring constant infusion, as well as its poor selectivity towards the closely related vasopressin V1a receptor, limit its use to short-term treatment of the acute phase of preterm labour. We report the discovery of a new class of potent, non-peptide oxytocin receptor antagonists displaying a high degree of selectivity towards vasopressin receptors, as well as oral efficacy in several animal models of preterm labour.

371.

WITHDRAWN.

372.

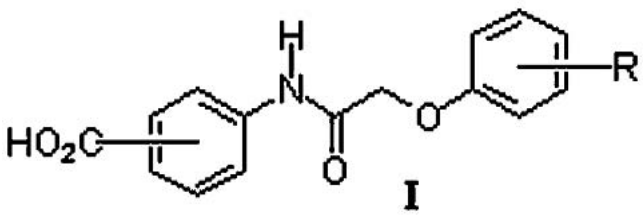
FROM VIRTUAL SCREEN TO A FIRST LIBRARY: THE SEARCH FOR A FATTY ACID SYNTHASE INHIBITOR. ***Kilian Conde-Frieboes***[1], *Henning Thøgersen*[2], *Carsten E. Stidsen*[3], *Jesper M. Nielsen*[3], *Ole H. Olsen*[4], *and Michael K. Bauer*[5]. *(1) Protein and Peptide Chemistry, Novo Nordisk, Novo Nordisk Park, DK-2760 Maaloev, Denmark, Fax: +45-44663450, kcf@novonordisk.com, (2) MedChem Research, Novo Nordisk A/S, (3) Molecular Pharmacology, Novo Nordisk A/S, (4) Med Chem Res IV, Novo Nordisk, (5) Pharmacology Research 5, Novo Nordisk*

While bacterial fatty acid synthesis works via a multi enzyme cascade, mammalian fatty acid synthesis is located on a multifunctional enzyme (fatty acid synthase, FAS). Inhibition of the fatty acid synthesis has long been of interest as target for new antibiotics. Since the discovery of C75 as a FAS inhibitor and its effect on food intake, FAS has been discussed as a possible target for the treatment of obesity by reducing appetite and increasing energy expenditure. Herein we report our results on an study to find a viable lead structure starting from a virtual screen using a homology model of the human FAS, in vitro screen of selected compounds, library design based on a preliminary pharmacophore hypothesis, and finally synthesis and in vitro screen of the library. By this strategy a new class of low micromolar covalent binding inhibitors for the porcine FAS was identified.

373.

SMALL-MOLECULE MODULATION OF READ-THROUGH (SMMRT): DISCOVERY OF 2-PHENOXYACETANILIDES AS IN VIVO PROMOTERS OF DYSTROPHIN SYNTHESIS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY. ***Richard G. Wilde***[1], *Stephen W. Jones*[1], *Hongyu Ren*[1], *Haiqing Hu*[1], *Bryan A. Vining*[1], *Richard L. DePinto*[1], *Neil G. Almstead*[1], *Ellen M. Welch*[1], *Jin Zhuo*[1], *Westley J. Friesen*[1], *Yuki Tomizawa*[1], *Marla L. Weetall*[1], *John Babiak*[1], *Stuart W. Peltz*[1], *H. Lee Sweeney*[2], *and Elisabeth R. Barton*[3]. *(1) PTC Therapeutics Inc, 100 Corporate Court, South Plainfield, NJ 07080, Fax: 908-222-7231, rwilde@ptcbio.com, (2) Department of Physiology, University of Pennsylania, (3) Department of Anatomy and Cell Biology, University of Pennsylvania School of Dental Medicine*

Duchenne muscular dystrophy (DMD) afflicts one of every 3,500 male children, and is characterized by severe muscle wasting. Mutations in the dystrophin gene are the cause of the disease. Approximately 10% of patients harbor a nonsense mutation that results in premature termination of translation and production of a truncated protein. Small molecule agents were sought to suppress the nonsense codon and produce full-length functional dystrophin. High-throughput screening of a compound collection identified a hit series of 2-phenoxyacetanilide benzoic acids (I). The lead compound in the series was demonstrated to promote dystrophin production in an mdx mouse model of muscular dystrophy.



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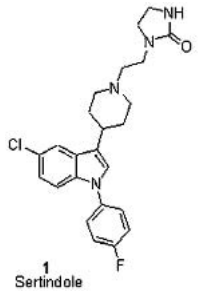
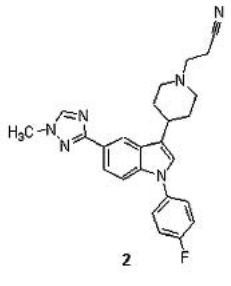
374.

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF A NEW CLASS OF HIGHLY SELECTIVE α_1-ADRENOCEPTOR ANTAGONISTS DERIVED FROM THE ANTIPSYCHOTIC SERTINDOLE. ***Thomas Balle***[1], *Jens Perregaard*[1], *Martha T. Ramirez*[2], *Anna K. Larsen*[2], *Karina K. Søby*[2], *Tommy Liljefors*[3], *and Kim Andersen*[1]. *(1) Medicinal Chemistry Research, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark, Fax: +45-36438237, tb@lundbeck.com, (2) Biological Research, H. Lundbeck A/S, (3) Department of Medicinal Chemistry, The Royal Danish School of Pharmacy*

α_1-adrenoceptor antagonism has remained a joker in antipsychotic drug research for decades. Most of the so-called atypical antipsychotics, including sertindole (**1**), have nanomolar affinity for these receptors in addition to affinity for dopamine D_2 and serotonin 5-HT_2 receptors. Little is known about the importance of the α_1-component of these drugs, primarily due to the lack of truly selective and subtype selective compounds penetrating the blood-brain barrier. This presentation will focus on the synthesis and SAR of a new class of α_1-adrenoceptor antagonists derived from sertindole, finally leading to the highly selective antagonist **2**. The molecular features responsible for $\alpha_1/D_2/5\text{-}HT_2$ affinity will be discussed in relation to previously reported pharmacophore models. Furthermore, a new basic pharmacophore model for α_1-adrenoceptor antagonists will be presented. Finally, the molecular features responsible for selectivity between α_1-adrenoceptor subtypes, α_{1a}, α_{1b}, and α_{1d}, as investigated by 3D-QSAR methodology will be discussed.



1
Sertindole



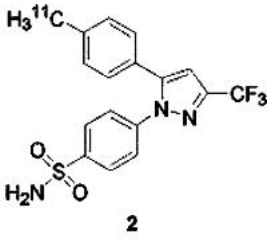
2

375.

SYNTHESIS OF [11C]-CELECOXIB: A POTENTIAL PET TRACER FOR IMAGING COX-2 EXPRESSION. ***J. S. Dileep Kumar***[1], *Jaya Prabhakaran*[1], *Mark D. Underwood*[1], *Ramin V. Parsey*[1], *Victoria Arango*[1], *Vattoly J. Majo*[1], *Norman R. Simpson*[2], *Julie Arcement*[1], *Anna R. Cooper*[1], *Ronald L. Van Heertum*[2], *and J. John Mann*[1]. *(1) Department of Psychiatry & Division of Neuroscience, Columbia University & New York State Psychiatric Institute, 1051 Riverside Drive, Box:42, New York, NY 10032, Fax: 212-543-6017, dk2038@columbia.edu, (2) Department of Radiology, Columbia University*

Elevated expression of COX-2 enzyme contributes to the pathogenesis and development of the growth of certain types of arthritis, cancer, pain sensation, stroke and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. To fully understand the roles of COX-2, it would be great advantageous to quantify in vivo, expression of COX-2 non-invasively and repeatedly over time. Synthesis of [11C]-celecoxib, a COX-2 selective inhibitor and prescription drug for arthritis and pain has been investigated. DMT-protected 4-[5-(4-tributylstannanylphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (1), the precursor molecule for the radiolabeling was synthesized from 4′-bromoacetophenone in five steps with 23% overall yield. Synthesis of [11C]-celecoxib (2) was achieved via a Stille type reaction using [11C]-methyl iodide with 8% yield (decay corrected). The specific activity of [11C]-celecoxib was >1000 Ci/ mmol with a radiochemical purity >99%. The details of the synthesis and preliminary in vivo validations of [11C]-celecoxib will be presented.

1



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