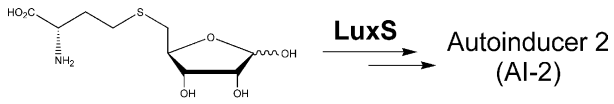
Chemical Synthesis of *S*-Ribosyl-L-homocysteine and Activity Assay as a LuxS Substrate

Bioorg. Med. Chem. Lett. 13 (2003) 3897

Gang Zhao,[a] Wei Wan,[a] Shahrzad Mansouri,[a] Joshua F. Alfaro,[a] Bonnie L. Bassler,[b] Kenneth A. Cornell[c] and Zhaohui Sunny Zhou[a,*]

[a]*Department of Chemistry and School of Molecular Biosciences, Washington State University, Pullman, WA 99164, USA*
[b]*Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA*
[c]*Division of Vascular Surgery, L-456, Oregon Health & Sciences University, Portland, OR 97201, USA*

S-Ribosyl-L-homocysteine (SRH) was synthesized using Mitsunobu coupling. It was confirmed as a LuxS substrate and as an autoinducer 2 (AI-2) precursor. SRH analogues were tested as LuxS inhibitors.



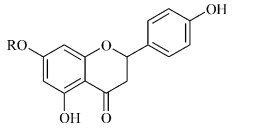
Naringenin Derivatives as Anti-atherogenic Agents

Bioorg. Med. Chem. Lett. 13 (2003) 3901

Sangku Lee,[a] Chul-Ho Lee,[a] Surk-Sik Moon,[b] Eungsoo Kim,[a] Chul-Tae Kim,[a] Bang-Hyun Kim,[a] Song-Hae Bok[a] and Tae-Sook Jeong[a,*]

[a]*Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Daejon 305-333, Republic of Korea*
[b]*Department of Chemistry, Kongju National University, Kongju 314-701, Republic of Korea*

Two classes of naringenin derivatives were evaluated for anti-atherogenic activity. Naringenin 7-*O*-oleic ester (**2**) and naringenin 7-*O*-cetyl ether (**3**) inhibited the formation of aortic atherosclerotic lesions in high cholesterol-fed rabbits.



2 : R = Z-$C_8H_{17}CH{=}CHC_7H_{14}CO$-
3 : R = $C_{16}H_{33}$-

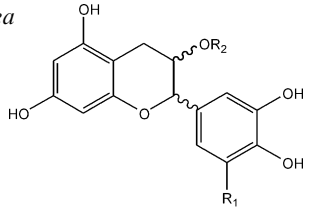
Green Tea Catechins as a BACE1 (β-Secretase) Inhibitor

Bioorg. Med. Chem. Lett. 13 (2003) 3905

So-Young Jeon,[a] KiHwan Bae,[b] Yeon-Hee Seong[c] and Kyung-Sik Song[a,*]

[a]*Division of Applied Biology & Chemistry, College of Agriculture & Life Sciences, Kyungpook National University, 1370, Sankyuk-Dong, Daegu 702-701, South Korea*
[b]*College of Pharmacy, Chungnam National University, Yusung, Daejon 305-764, South Korea*
[c]*College of Veterinary, Chungbuk National University, Cheongju, Chungbuk 361-763, South Korea*

Inhibitory activity of green tea catechins against BACE1, which has been known as one of the most important amyloid precursor protein cleaving enzymes in Alzheimer's disease, is reported. The fundamental structure–activity relationship of catechins is also discussed.



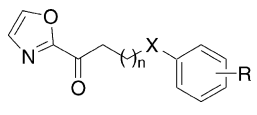
Heterocyclic Ketones as Inhibitors of Histone Deacetylase

Bioorg. Med. Chem. Lett. 13 (2003) 3909

Anil Vasudevan,[a,*] Zhiqin Ji,[b] Robin R. Frey,[b] Carol K. Wada,[b] Douglas Steinman,[b] H. Robin Heyman,[b] Yan Guo,[b] Michael L. Curtin,[b] Jun Guo,[b] Junling Li,[b] Lori Pease,[b] Keith B. Glaser,[b] Patrick A. Marcotte,[b] Jennifer J. Bouska,[b] Steven K. Davidsen[b] and Michael R. Michaelides[b]

[a]*Medicinal Chemistry Technologies, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*
[b]*Cancer Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*

Structure–activity relationships of a novel series of histone deacetylase inhibitors comprising electrophilic ketones are described.

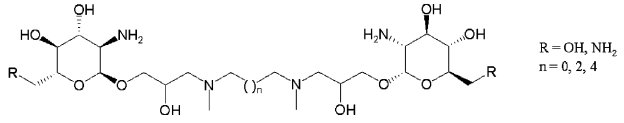


Bioorg. Med. Chem. Lett. 13 (2003) 3915

Synthesis of Linked Carbohydrates and Evaluation of Their Binding for 16S RNA by Mass Spectrometry

Baogen Wu, Jun Yang, Dale Robinson, Steve Hofstadler, Rich Griffey, Eric E. Swayze and Yun He*

Ibis Therapeutics, A Division of Isis Pharmaceuticals, Inc., 2292 Faraday Av., Carlsbad, CA 92008, USA

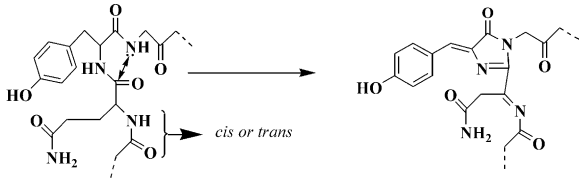


Bioorg. Med. Chem. Lett. 13 (2003) 3919

Structural Analysis of the Immature Form of the GFP Homologue DsRed

M. Shahzad Zaveer and Marc Zimmer*

Chemistry Department, Connecticut College, 270 Mohegan Ave., New London, CT 06320, USA



Immature precyclized DsRed *red mature DsRed*

Bioorg. Med. Chem. Lett. 13 (2003) 3923

Triethylene Tetraamine: A Novel Telomerase Inhibitor

Fei Yin,[a] Jianhui Liu[b,*] and Xiaojun Peng[a]

[a]*State Key Laboratory of Fine Chemicals, Dalian University of Technology, 158 Zhong-shan Road, Dalian 116012, PR China*
[b]*National Key Laboratory of Medical Neurobiology, Shanghai Medical College, Fudan University, 138 Yi-Xue-Yuan Road, Shanghai 200032, PR China*

A small linear molecule, triethylene tetraamine, has been identified as potent telomerase inhibitor. It stabilizes both intra- and inter-molecular G-quadruplexes and shows a good differential between potent telomerase inhibition and acute cytotoxicity.

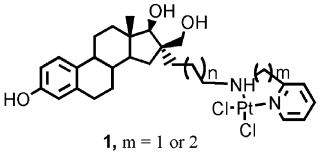
Bioorg. Med. Chem. Lett. 13 (2003) 3927

Synthesis of 17β-Estradiol Platinum(II) Complexes: Biological Evaluation on Breast Cancer Cell Lines

Caroline Descôteaux,[a] Josée Provencher-Mandeville,[a] Isabelle Mathieu,[a] Valérie Perron,[a] Sanat K. Mandal,[b] Éric Asselin[a] and Gervais Bérubé[a,*]

[a]*Département de Chimie-Biologie, Université du Québec à Trois-Rivières, C.P. 500, Trois-Rivières, Québec, Canada G9A 5H7*
[b]*Division of Science & Technology, College of the North Atlantic, Clarenville Campus, Clarenville, Newfoundland, Canada A5A 1V9*

The synthesis of a new class of 17β-estradiol-linked platinum(II) complexes is reported. The derivatives made of a 2-(2′-aminoethyl)pyridine ligand displayed good activity against both ER^+ and ER^- breast cancer cell lines.



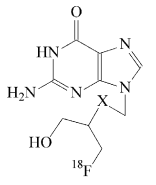
1, m = 1 or 2
n = 2, 4, 6 or 8

Bioorg. Med. Chem. Lett. 13 (2003) 3933

Novel Radiosynthesis of PET HSV-tk Gene Reporter Probes [^{18}F]FHPG and [^{18}F]FHBG Employing Dual Sep-Pak SPE Techniques

Ji-Quan Wang, Qi-Huang Zheng,* Xiangshu Fei, Bruce H. Mock and Gary D. Hutchins

Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L-3 Room 202, Indianapolis, IN 46202-2111, USA



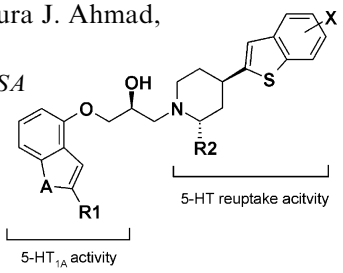
Bioorg. Med. Chem. Lett. 13 (2003) 3939

Advances Toward New Antidepressants Beyond SSRIs: 1-Aryloxy-3-piperidinylpropan-2-ols with Dual 5-HT$_{1A}$ Receptor Antagonism/SSRI Activities. Part 3

Kumiko Takeuchi,* Todd J. Kohn, Nicholas A. Honigschmidt, Vincent P. Rocco, Patrick G. Spinazze, Steven T. Atkinson, Larry W. Hertel, David L. Nelson, D. Bradley Wainscott, Laura J. Ahmad, Janice Shaw, Penny G. Threlkeld and David T. Wong

Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA

A series of 1-aryloxy-3-piperidinylpropan-2-ols possessing potent dual 5-HT$_{1A}$ receptor antagonism and serotonin reuptake inhibition was discovered. Modification of potential metabolic sites of 1-(1*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols further improved the in vitro binding affinities and functional antagonism.



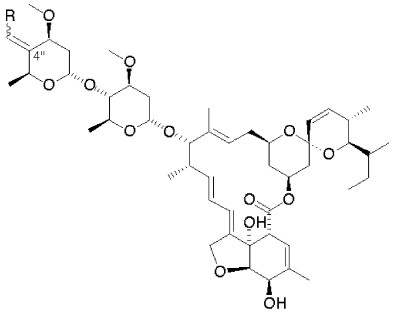
Bioorg. Med. Chem. Lett. 13 (2003) 3943

Synthesis and Biological Activities of Novel 4″-Alkylidene Avermectin Derivatives

Kenichiro Nagai,[a] Toshiaki Sunazuka,[a] Kazuro Shiomi,[a] Achim Harder,[b] Andreas Turberg[b] and Satoshi Ōmura[a,*]

[a]*Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University and The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[b]*Business Group Animal Health Agrocultural Center, Bayer AG, D-51368 Monheim, Germany*

Horner–Emmons reaction of 4″-dehydro-5-*O*-TBDMS-avermectin B$_{1a}$ with a variety of phosphorus ylides using LHMDS gave novel 4″-alkylidene avermectin derivatives in high yields.



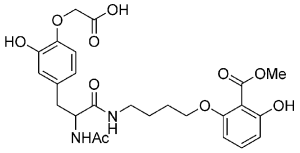
Bioorg. Med. Chem. Lett. 13 (2003) 3947

Identification of a Monoacid-Based, Cell Permeable, Selective Inhibitor of Protein Tyrosine Phosphatase 1B

Zhili Xin,[a,*] Gang Liu,[a] Cele Abad-Zapatero,[b] Zhonghua Pei,[a] Bruce G. Szczepankiewicz,[a] Xiaofeng Li,[a] Tianyuan Zhang,[a] Charles W. Hutchins,[b] Philip J. Hajduk,[b] Stephen J. Ballaron,[a] Michael A. Stashko,[a] Thomas H. Lubben,[a] James M. Trevillyan[a] and Michael R. Jirousek[a]

[a]*Metabolic Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6098, USA*
[b]*Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6098, USA*

The discovery of monoacid-based, cell permeable PTP1B inhibitor **20** with selectivity over TCPTP is reported.



20

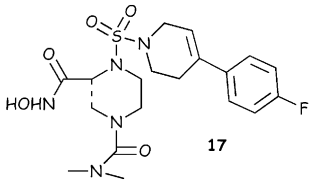
Bioorg. Med. Chem. Lett. 13 (2003) 3951

Design and Synthesis of Orally Active Inhibitors of TNF Synthesis as Anti-rheumatoid Arthritis Drugs

Jian Jeffrey Chen,* Nolan Dewdney, Xiaohong Lin, Robert L. Martin, Keith A. M. Walker, Jane Huang, Frances Chu, Elsie Eugui, Anna Mirkovich, Yong Kim, Keshab Sarma, Humberto Arzeno and Harold E. Van Wart

Roche Bioscience, 3401Hillview Ave., Palo Alto, CA 94304, USA

The synthesis and in vitro and in vivo data for TACE inhibitor **17** are reported.

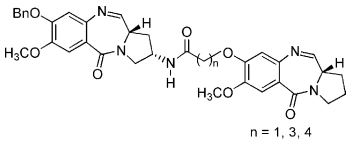


Bioorg. Med. Chem. Lett. 13 (2003) 3955

Synthesis and DNA-Binding Affinity of *A*-C8/*C*-C2 Alkoxyamido-Linked Pyrrolo[2,1-*c*][1,4]benzodiazepine Dimers

Ahmed Kamal,* P. Ramulu, O. Srinivas and G. Ramesh

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

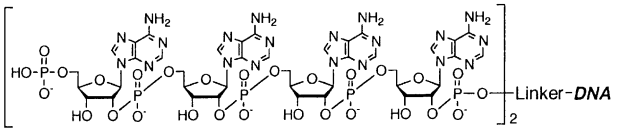


Bioorg. Med. Chem. Lett. 13 (2003) 3959

Synthesis of Double-Headed 2-5A-Antisense Chimeras and Their Ability to Activate Human RNase L

Yoshihito Ueno, Shusaku Okatani, Yuuki Yamada and Yukio Kitade*

Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan



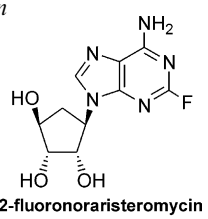
Bioorg. Med. Chem. Lett. 13 (2003) 3963

Synthesis of 2-Fluorononaristeromycin and Its Inhibitory Activity against *Plasmodium falciparum S*-Adenosyl-L-homocysteine Hydrolase

Yukio Kitade,[a,*] Hiroharu Kojima,[a] Fazila Zulfiqur,[a] Hye-Sook Kim[b] and Yusuke Wataya[b]

[a]*Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*
[b]*Faculty of Pharmaceutical Sciences, Okayama University, Tsushimanaka 1-1-1, Okayama 700-8530, Japan*

The synthesis of 2-fluorononaristeromycin and its inhibitory activity against SAH hydrolase is reported.



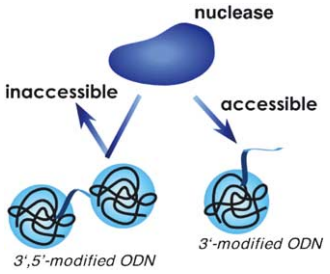
Bioorg. Med. Chem. Lett. 13 (2003) 3967

Novel DNA/Polymer Conjugate for Intelligent Antisense Reagent with Improved Nuclease Resistance

Masaharu Murata,* Wataru Kaku, Takahisa Anada, Yoshikuni Sato, Takeshi Kano, Mizuo Maeda and Yoshiki Katayama

Department of Applied Chemistry, Graduate School of Engineering, Kyushu University, Fukuoka 812-8581, Japan

The ODN–PNIPAAm conjugate could successfully control nuclease resistance property by the conformation change of the polymer chain.



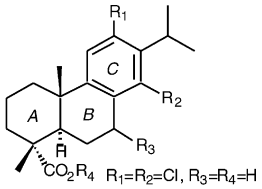
Bioorg. Med. Chem. Lett. 13 (2003) 3971

Dehydroabietic Acid Derivatives as a Novel Scaffold for Large-Conductance Calcium-Activated K^+ Channel Openers

Tomohiko Ohwada,[a,*] Taro Nonomura,[a] Keisuke Maki,[a] Kazuho Sakamoto,[b] Susumu Ohya,[b] Katsuhiko Muraki[b] and Yuji Imaizumi[b]

[a]*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Graduate School of Pharmaceutical Sciences, Nagaya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan*

Dehydroabietic acid structure is a new scaffold for chemical activators of large-conductance calcium-activated K^+ channels (BK channels).



Bioorg. Med. Chem. Lett. 13 (2003) 3975

Synthesis of Novel Fluorescent Probes for the Molecular Chaperone Hsp90

Laura Llauger-Bufi,[a] Sara J. Felts,[b] Henri Huezo,[a] Neal Rosen[a] and Gabriela Chiosis[a,*]

[a]*Program in Cell Biology and Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA*
[b]*Department of Biochemistry and Molecular Biology, Mayo Graduate School, Rochester, MN 55905, USA*

Fluorescent analogues of geldanamycin, a natural product inhibitor of the molecular chaperone Hsp90, have been prepared. These ligands bind Hsp90 with high affinity and are appropriate probes for an Hsp90 fluorescence polarization assay.

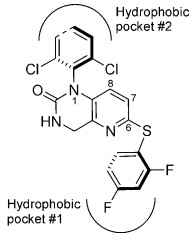
Bioorg. Med. Chem. Lett. 13 (2003) 3979

SAR of 3,4-Dihydropyrido[3,2-*d*]pyrimidone p38 Inhibitors

Luping Liu,[a,*] John E. Stelmach,[a] Swaminathan R. Natarajan,[a] Meng-Hsin Chen,[a] Suresh B. Singh,[a] Cheryl D. Schwartz,[b] Catherine E. Fitzgerald,[b] Stephen J. O'Keefe,[b] Dennis M. Zaller,[b] Dennis M. Schmatz[b] and James B. Doherty[a]

[a]*Departments of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Departments of Inflamation Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

Modification of N-1 aryl and C-6 arylsulfide in 3,4-dihydropyrido(3,2-*d*)pyrimidone analogues for the interaction with the hydrophobic pockets in p38 active site is discussed.



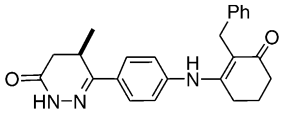
Bioorg. Med. Chem. Lett. 13 (2003) 3983

Benzyl Vinylogous Amide Substituted Aryldihydropyridazinones and Aryldimethylpyrazolones as Potent and Selective PDE3B Inhibitors

Scott D. Edmondson,[a,*] Anthony Mastracchio,[a] Jiafang He,[a] Christine C. Chung,[b] Michael J. Forrest,[c] Scott Hofsess,[c] Euan MacIntyre,[c] Joseph Metzger,[c] Naphtali O'Connor,[a] Kajal Patel,[c] Xinchun Tong,[a] Michael R. Tota,[b] Lex H. T. Van der Ploeg,[b] Jeff P. Varnerin,[b] Michael H. Fisher,[a] Matthew J. Wyvratt,[a] Ann E. Weber[a] and Emma R. Parmee[a]

[a]*Department of Medicinal Chemistry, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Metabolic Disorders, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*

Aryldihydropyridazinones and aryldimethylpyrazolones bearing 2-benzyl vinylogous amides have been identified as potent PDE3B subtype selective inhibitors. Orally bioavailable analogue **8a** was selected for in vivo evaluation.



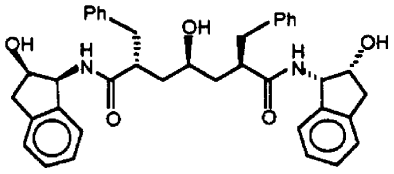
8a
PDE3B IC_{50} = 0.19 nM

Bioorg. Med. Chem. Lett. 13 (2003) 3989

Identifying Inhibitors of the SARS Coronavirus Proteinase

Ekachai Jenwitheesuk and Ram Samudrala*

Computational Genomics Group, Department of Microbiology, University of Washington School of Medicine, Seattle, WA 98195, USA



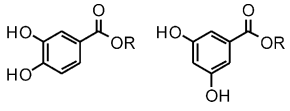
Bioorg. Med. Chem. Lett. 13 (2003) 3993

Rational Design of Antimicrobial Agents: Antifungal Activity of Alk(en)yl Dihydroxybenzoates and Dihydroxyphenyl Alkanoates

Ken-ichi Nihei, Atsuko Nihei and Isao Kubo*

Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720-3112, USA

A homologous series (C_3–C_{14}) of each alkyl 3,4- and 3,5-dihydroxybenzoates, and 3,4- and 3,5-dihydroxyphenyl alkanoates exhibit similar antifungal activity against *Saccharomyces cerevisiae*. Their nonyl derivatives exhibit the most potent antifungal activity against this yeast with the minimum fungicidal concentration (MFC) in the range between 12.5 and 50 μg/mL. In addition, various 3,4-dihydroxybenzoates, possessing different side chains, namely unsaturated, branched and alicyclic were synthesized and their activity was compared.

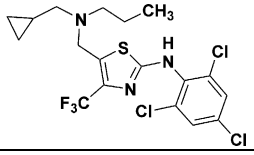


Bioorg. Med. Chem. Lett. 13 (2003) 3997

2-Arylaminothiazoles as High-Affinity Corticotropin-Releasing Factor 1 Receptor (CRF_1R) Antagonists: Synthesis, Binding Studies and Behavioral Efficacy

Gene M. Dubowchik,* Jodi A. Michne,[a] Dmitry Zuev,[a] Wendy Schwartz,[a] Paul M. Scola,[a] Clint A. James,[b] Edward H. Ruediger,[b] Sokhom S. Pin,[a] Kevin D. Burris,[a] Lynn A. Balanda,[a] Qi Gao,[a] Dedong Wu,[a] Lawrence Fung,[a] Tracey Fiedler,[a] Kaitlin E. Browman,[a] Matthew T. Taber[a] and Jie Zhang[a]

[a]*Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5100, Wallingford, CT 06492-7660, USA*
[b]*Bristol-Myers Squibb Pharmaceutical Research Institute, Candiac, Quebec, Canada J5R 1J1*



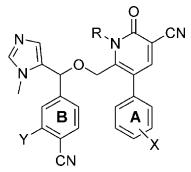
Bioorg. Med. Chem. Lett. 13 (2003) 4001

Pyridone-Containing Farnesyltransferase Inhibitors: Synthesis and Biological Evaluation

Lisa A. Hasvold,* Weibo Wang, Stephen L. Gwaltney, II, Todd W. Rockway, Lissa T. J. Nelson, Robert A. Mantei, Stephen A. Fakhoury, Gerard M. Sullivan, Qun Li, Nan-Horng Lin, Le Wang, Haiying Zhang, Jerome Cohen, Wen-Zhen Gu, Kennan Marsh, Joy Bauch, Saul Rosenberg and Hing L. Sham

Pharmaceutical Discovery, R-47B, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6101, USA

The synthesis, SAR and biological properties of a series of pyridone-containing farnesyltransferase inhibitors (FTIs) are presented.



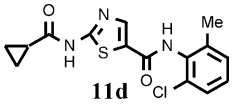
Bioorg. Med. Chem. Lett. 13 (2003) 4007

Discovery and Initial SAR of 2-Amino-5-carboxamidothiazoles as Inhibitors of the Src-family Kinase p56^{Lck}

John Wityak,[a,*] Jagabandhu Das,[a,*] Robert V. Moquin,[a] Zhongqi Shen,[a] James Lin,[a] Ping Chen,[a] Arthur M. Doweyko,[b] Sidney Pitt,[c] Suhong Pang,[c] Ding Ren Shen,[c] Qiong Fang,[c] Henry F. de Fex,[c] Gary L. Schieven,[c] Steven B. Kanner[c] and Joel C. Barrish[a]

[a]*Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA*
[b]*Department of Macromolecular Structure, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA*
[c]*Department of Immunology, Inflammation, and Pulmonary Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA*

A novel series of 2-amino-5-carboxamidothiazoles were identified as inhibitors of Lck. Structure–activity studies demonstrate the structural requirements for potent Lck activity. Cyclopropylamide **11d** is a potent Lck inhibitor having sub-micromolar activity in a PBL proliferation assay.



11d

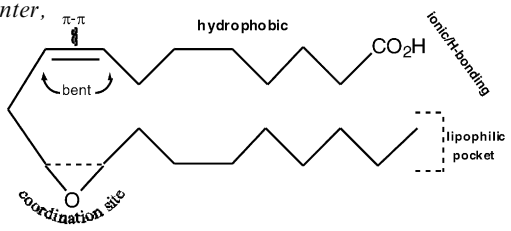
Bioorg. Med. Chem. Lett. 13 (2003) 4011

11,12-Epoxyeicosatrienoic Acid (11,12-EET): Structural Determinants for Inhibition of TNF-α-Induced VCAM-1 Expression

J. R. Falck,[a,*] L. Manmohan Reddy,[a] Y. Krishna Reddy,[a] Muralidhar Bondlela,[a] U. Murali Krishna,[a] Yu Ji,[a] Jianxin Sun[b] and James K. Liao[b,*]

[a]*Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, USA*
[b]*Vascular Medicine and Atherosclerosis Unit, Cardiovascular Division, Brigham & Women's Hospital and Harvard Medical School, Cambridge, MA 02139, USA*

A series of 11,12-EET analogues were synthesized and compared using a human endothelial cell based TNF-α-induced VCAM-1 expression assay. The resulting data were used to map a putative recognition/binding domain for 11,12-EET.



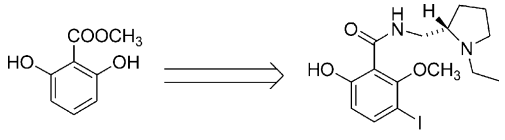
Bioorg. Med. Chem. Lett. 13 (2003) 4015

Synthesis and Affinity of a Possible Byproduct of Electrophilic Radiolabeling of [^{123}I]IBZM

Ronald M. Baldwin,[a] Xing Fu,[a] Nora S. Kula,[b] Ross J. Baldessarini,[b] Louis Amici,[a] Robert B. Innis[a] and Gilles D. Tamagnan[a,*]

[a]*Department of Psychiatry, Yale University and VA CT/HCS, West Haven, CT 06516, USA*
[b]*Department of Psychiatry and Neuroscience Program, Harvard Medical School and Laboratories for Psychiatric Research, McLean Research Center, McLean Division of Massachusetts General Hospital, Belmont, MA 02478-9106, USA*

The iodobenzamide neuroleptic analogue (*S*)-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-5-iodo-6-methoxybenzamide was synthesized stereospecifically and found to have 100-fold lower D_2 receptor affinity than the 3-iodo isomer (IBZM).



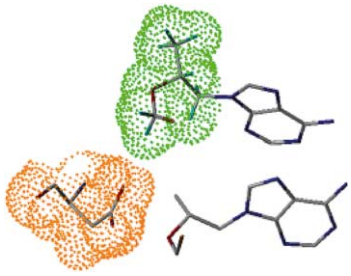
Bioorg. Med. Chem. Lett. 13 (2003) 4019

Studies of Molecular Mechanism of Tenofovir against 3TC- and AZT-Resistance Mutant HIV-1 Reverse Transcriptase

Youhoon Chong, Nagaraju Akula and Chung K. Chu*

Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, GA 30602, USA

The molecular mechanisms of tenofovir against drug-resistant RTs are studied by molecular modeling studies.



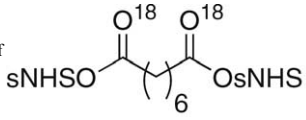
Bioorg. Med. Chem. Lett. 13 (2003) 4023

Isotopically Labeled Crosslinking Reagents: Resolution of Mass Degeneracy in the Identification of Crosslinked Peptides

Christopher J. Collins,[a] Birgit Schilling,[a] Malin Young,[c] Gavin Dollinger[d] and R. Kiplin Guy[a,b,*]

[a]*Department of Pharmaceutical Chemistry, University of California at San Francisco, San Francisco, CA 94143, USA*
[b]*Department of Cellular and Molecular Pharmacology, University of California at San Francisco, San Francisco, CA 94143, USA*
[c]*Biosystems Research Department, Sandia National Laboratories, Livermore, CA 94551-0969, USA*
[d]*Small Molecule Drug Discovery, Chiron Corporation, Emeryville, CA 94608, USA*

Mass spectrometry in three dimensions (MS3D) is a newly developed method for the determination of protein structures involving intramolecular chemical crosslinking of proteins, proteolytic digestion of the resulting adducts, identification of crosslinks by mass spectrometry (MS), peak assignment using theoretical mass lists, and computational reduction of crosslinks to a structure by distance geometry methods. To facilitate the unambiguous identification of crosslinked peptides from proteolytic digestion mixtures of crosslinked proteins by MS, we introduced double ^{18}O isotopic labels into the crosslinking reagent to provide the crosslinked peptides with a characteristic isotope pattern. The presence of doublets separated by 4 Da in the mass spectra of these materials allowed ready discrimination between crosslinked and modified peptides, and uncrosslinked peptides using automated intelligent data acquisition (IDA) of MS/MS data. This should allow ready automation of the method for application to whole expressible proteomes.



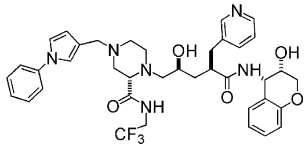
Bioorg. Med. Chem. Lett. 13 (2003) 4027

Novel HIV-1 Protease Inhibitors Active against Multiple PI-resistant Viral Strains: Coadministration with Indinavir

Nancy J. Kevin,[a] Joseph L. Duffy,[a,*] Brian A. Kirk,[a] Kevin T. Chapman,[a] William A. Schleif,[b] David B. Olsen,[c] Mark Stahlhut,[c] Carrie A. Rutkowski,[c] Lawrence C. Kuo,[d] Lixia Jin,[e] Jiunn H. Lin,[e] Emilio A. Emini[b] and James R. Tata[a]

[a]*Department of Basic Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

N-Arylpyrrole substituents in the P_3 position of HIV-1 protease inhibitors afforded excellent antiviral potency and substantially improved aqueous solubility over previously reported variants. Oral coadministration with indinavir was investigated to hinder the metabolism of the compounds by the cyctochrome P450 3A4 isozyme, and allow for in vivo PK assessment.



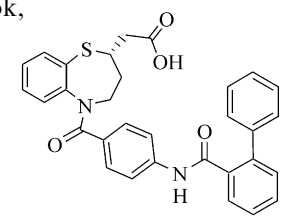
Bioorg. Med. Chem. Lett. 13 (2003) 4031

2,5-Disubstituted 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazepines as Potent and Selective V_2 Arginine Vasopressin Receptor Antagonists

Maud J. Urbanski,* Robert H. Chen, Keith T. Demarest, Joseph Gunnet, Richard Look, Eric Ericson, William V. Murray, Philip J. Rybczynski and Xiaoyan Zhang

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development L.L.C., 1000 Route 202, Raritan, NJ 08869-0602, USA

A number of 2,5-disubstituted benzothiazepines were synthesized and evaluated in vitro as arginine vasopressin antagonists. The SAR showed a preference for an acidic unit appended from the benzothiazepine scaffold. This substitution pattern provided compound **4**, a potent and selective V_2 antagonist with oral activity in vivo.



4

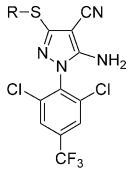
Bioorg. Med. Chem. Lett. 13 (2003) 4035

5-Amino-1-(2,6-dichloro-4-trifluoromethyl-phenyl)-3-[$^3H_3$]-methylsulfanyl-1*H*-pyrazole-4-carbonitrile (*CTOM*): Synthesis and Characterization of a Novel and Selective Insect GABA Receptor Radioligand

Sanath K. Meegalla,[a,*] Dario Doller,[a] Gary M. Silver,[b] Nancy Wisnewski,[b] Richard M. Soll[a] and Dale Dhanoa[a]

[a]*3-Dimensional Pharmaceuticals, Inc., 665 Stockton Drive, Suite 104, Exton, PA 19341, USA*
[b]*Heska Corporation, 1613 Prospect Parkway, Fort Collins, CO 80525, USA*

Synthesis and characterization of novel insect GABA receptor radioligand is described.



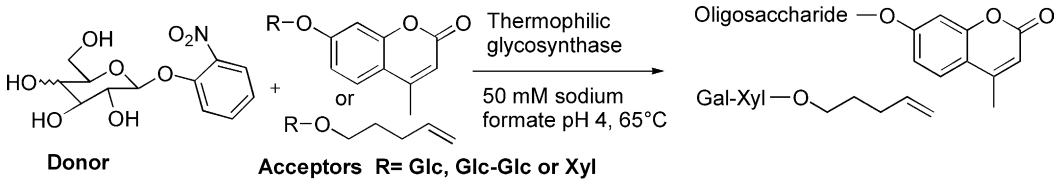
R = CH_3
R = [$^3H_3$]-CH_3

Bioorg. Med. Chem. Lett. 13 (2003) 4039

Glycosynthase-Catalysed Syntheses at pH below Neutrality

Antonio Trincone,[a,*] Assunta Giordano,[a] Giuseppe Perugino,[b] Mosè Rossi[b] and Marco Moracci[b]

[a]*Istituto di Chimica Biomolecolare C.N.R., Via Campi Flegrei 34, 80072 Pozzuoli, Napoli, Italy*
[b]*Institute of Protein Biochemistry C.N.R., Via Pietro Castellino 111, 80131 Napoli, Italy*



Donor

Acceptors R= Glc, Glc-Glc or Xyl

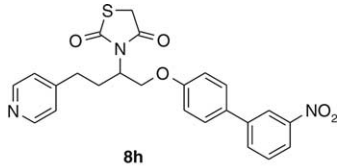
Bioorg. Med. Chem. Lett. 13 (2003) 4043

Novel P2X$_7$ Receptor Antagonists

L. Alcaraz,[a,*] A. Baxter,[a] J. Bent,[a] K. Bowers,[b] M. Braddock,[b] D. Cladingboel,[a] D. Donald,[a] M. Fagura,[b] M. Furber,[a] C. Laurent,[a] M. Lawson,[b] M. Mortimore,[a] M. McCormick,[b] N. Roberts[a] and M. Robertson[b]

[a]*Department of Medicinal Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK*
[b]*Department of Discovery Biosciences, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK*

The synthesis and pharmacological evaluation of a new series of P2X$_7$ receptor antagonists is reported. Compound **8h** displayed the greatest activity of the series.



8h

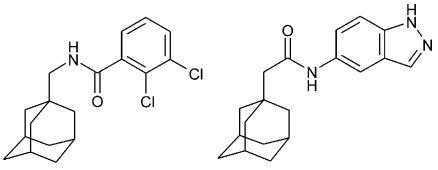
Bioorg. Med. Chem. Lett. 13 (2003) 4047

Hit-to-Lead Studies: The Discovery of Potent Adamantane Amide P2X$_7$ Receptor Antagonists

Andrew Baxter,* Janice Bent, Keith Bowers, Martin Braddock, Steve Brough, Malbinder Fagura, Mandy Lawson, Tom McInally, Mike Mortimore, Mark Robertson, Richard Weaver and Peter Webborn

AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK

A Hit-to-Lead programme was carried out resulting in the discovery of the potent P2X$_7$ antagonists **16** and **31**.



16 $pA_2 = 8.8$ **31** $pA_2 = 7.4$

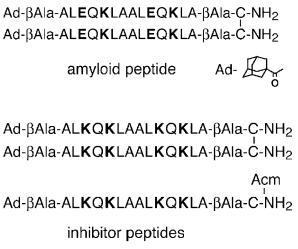
Bioorg. Med. Chem. Lett. 13 (2003) 4051

Inhibition of Peptide Amyloid Formation by Cationic Peptides with Homologous Sequences

Taro Yamashita,[a] Yuta Takahashi,[a] Tsuyoshi Takahashi[a] and Hisakazu Mihara[a,b,*]

[a]*Department of Bioengineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8501, Japan*
[b]*SORST Project, Japan Science and Technology Corporation, Nagatsuta, Midori-ku, Yokohama 226-8501, Japan*

The amyloid fibril formation of a model peptide was successfully inhibited by the peptides with homologous structures.



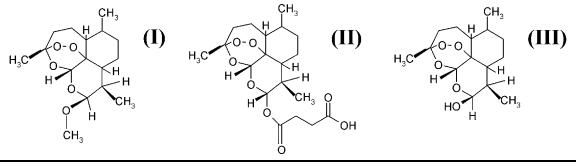
Bioorg. Med. Chem. Lett. 13 (2003) 4055

Spectrophotometric and ESI-MS/HPLC Studies Reveal a Common Mechanism for the Reaction of Various Artemisinin Analogues with Hemin

Luigi Messori,[a,*] Francesca Piccioli,[a] Brigitte Eitler,[b,c] Maria Camilla Bergonzi,[b] Anna Rita Bilia[b] and Franco Francesco Vincieri[b]

[a]*Department of Chemistry, University of Florence, Via della Lastruccia 3, I-50019 Sesto Fiorentino, Florence, Italy*
[b]*Department of Pharmaceutical Sciences, University of Florence, Via Gino Capponi 9, I-50121 Florence, Italy*
[c]*Faculty of Natural Sciences and Mathematics, Institute of Pharmacognosy, Center of Pharmacy, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria*

A common molecular pathway is revealed for the reaction of three antimalarial artemsinin derivatives, artemether (I), artesunate (II) and dihydroartemisinin (III) with hemin, the presumed biomolecular target.



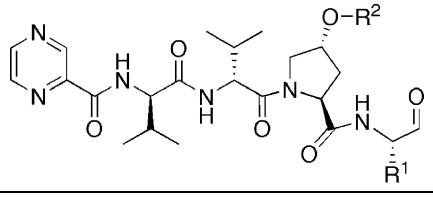
Bioorg. Med. Chem. Lett. 13 (2003) 4059

Inhibitors of Hepatitis C Virus NS3·4A Protease 1. Non-Charged Tetrapeptide Variants

Robert B. Perni,* Shawn D. Britt, John C. Court, Lawrence F. Courtney, David D. Deininger, Luc J. Farmer, Cynthia A. Gates, Scott L. Harbeson, Joseph L. Kim, James A. Landro, Rhonda B. Levin, Yu-Ping Luong, Ethan T. O'Malley, Janos Pitlik, B. Govinda Rao, Wayne C. Schairer, John A. Thomson, Roger D. Tung, John H. Van Drie and Yunyi Wei

Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139, USA

The synthesis and structure–activity relationships of a novel series of reversible covalent inhibitors of the hepatitis C NS3·4A protease are described.



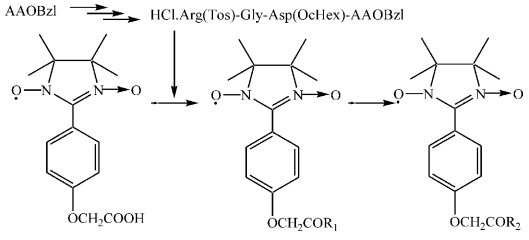
Bioorg. Med. Chem. Lett. 13 (2003) 4065

Synthesis and Bioactivities of Nitronyl Nitroxide and RGD Containing Pseudopeptides

Junling Liu, Ming Zhao, Chao Wang and Shiqi Peng*

College of Pharmaceutical Sciences, Peking University, Beijing 100083, PR China

Wherein R_1 = Arg(Tos)-Gly-Asp(OcHex)-AA-OBzl, R_2 = Arg-Gly-Asp-AA-OH, AA = Ser, Val, or Phe. The present combinations provided a beneficial strategy for simultaneous scavenging NO and anti-thrombosis, and for the use of spin label of RGD peptides in the conformational researches.

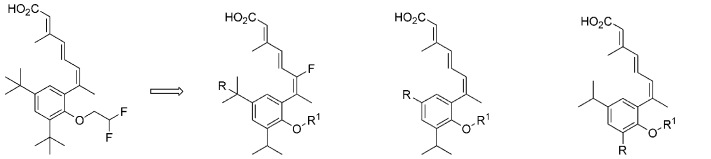


Bioorg. Med. Chem. Lett. 13 (2003) 4071

Design and Synthesis of Novel RXR-Selective Modulators with Improved Pharmacological Profile

Pierre-Yves Michellys,[a,*] Marcus F. Boehm,[a] Jyun-Hung Chen,[a] Timothy A. Grese,[b] Donald S. Karanewsky,[a] Mark D. Leibowitz,[c] Sha Liu,[c] Dale A. Mais,[d] Christopher M. Mapes,[a] Anne Reifel-Miller,[e] Katheen M. Ogilvie,[e] Deepa Rungta,[d] Anthony W. Thompson,[a] John S. Tyhonas,[a] Nathan Yumibe[e] and Robert J. Ardecky[a]

[a]*Department of Medicinal Chemistry, Ligand Pharmaceuticals, Incorporated, 10275 Science Center Drive, San Diego, CA 92121, USA;* [b]*Discovery Chemistry Research, Lilly Research Laboratories, Indianapolis, IN, USA;* [c]*Department of Pharmacology, Ligand Pharmaceuticals, Incorporated, 10275 Science Center Drive, San Diego, CA 92121, USA;* [d]*Department of New Leads Discovery, Ligand Pharmaceuticals, Incorporated, 10275 Science Center Drive, San Diego, CA 92121, USA;* [e]*Division of Endocrine Research, Lilly Research Laboratories, Indianapolis, IN, USA*



3

Ar = 2-fluorophenyl, **34a**
Ar = 3-fluorophenyl, **34b**
Ar = 2-thienyl, **34c**
Ar = 3,5-difluorophenyl, **34d**
Ar = 2-furyl, **34e**
Ar = 4-fluorophenyl, **34f**

R = CF_2CF_3, R^1 = Et, **42a**
R = CF_2CF_3, R^1 = Pr, **42b**
R = CF_2CF_3, R^1 = But, **42c**

R = Phenyl, R^1 = CH_2CHF_2, **56**
R = CF_3CF_2, R^1 = Pr, **57**

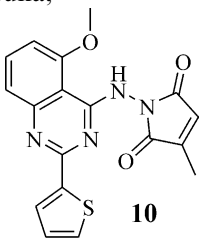
Bioorg. Med. Chem. Lett. 13 (2003) 4077

The Design and Synthesis of Novel Orally Active Inhibitors of AP-1 and NF-κB Mediated Transcriptional Activation. SAR of In Vitro and In Vivo Studies

Moorthy S. S. Palanki,[a,*] Paul E. Erdman,[a] Minghuan Ren,[a] Mark Suto,[a] Brydon L. Bennett,[a] Anthony Manning,[a] Lynn Ransone,[a] Cheryl Spooner,[a] Sonal Desai,[a] Arnie Ow,[a] Ryuichi Totsuka,[b] Peter Tsao[b] and Wataru Toriumi[b]

[a]*Celgene, 4550 Towne Centre Court, San Diego, CA 92121, USA*
[b]*Tanabe Seiyaku Co Ltd., 16-89 Kashima, 3-Chome, Yodogawa-ku, Osaka, 532-8505, Japan*

A novel orally active quinazoline analogue, (1-[2-(2-thienyl)quinazolin-4-ylamino]-3-methyl-3-pyrroline-2,5-dione (**10**)), was developed as inhibitor of AP-1 and NF-κB mediated transcriptional activation. The synthesis, structure–activity relationship, and in vivo activity are described.



10

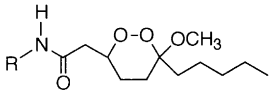
Bioorg. Med. Chem. Lett. 13 (2003) 4081

New Anti-Malarial Peroxides with In Vivo Potency Derived from Spongean Metabolites

Nobutoshi Murakami,[a] Motoyuki Kawanishi,[a] Huq Mohammad Mostaqul,[a] Jie Li,[b] Sawako Itagaki,[b] Toshihiro Horii[b] and Motomasa Kobayashi[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan*
[b]*Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan*

The structure–activity relationship of the anti-malarial substance having a 6-carbomethoxymethyl-3-methoxy-1,2-dioxane structure was studied. The amide analogues robust to mouse serum were disclosed to exhibit in vivo anti-malarial potency.



R = Et or n-Pr

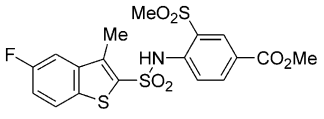
Bioorg. Med. Chem. Lett. 13 (2003) 4085

Structure–Activity Relationship of Benzo[*b*]thiophene-2-sulfonamide Derivatives as Novel Human Chymase Inhibitors

Hidekazu Masaki,[a,*] Yusuke Mizuno,[a] Akira Tatui,[b] Akira Murakami,[b] Yuuki Koide,[a] Shoji Satoh[a] and Atsuo Takahashi[a]

[a]*Drug Research Department, Tokyo Research Laboratories, Toa Eiyo Ltd., 2-293-3 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama 330-0834, Japan*
[b]*Drug Research Department, Fukushima Research Laboratories, Toa Eiyo Ltd., 1 Tanaka, Yuno, Iizaka-cho, Fukushima-shi, Fukushima 960-0280, Japan*

TY-51076 (**7**) showed high potency (IC_{50} = 56 nM) and excellent selectivity for chymase compared to chymotrypsin and cathepsin G (> 400-fold). The synthesis and structure–activity relationship of this class are described.



TY-51076 (7)

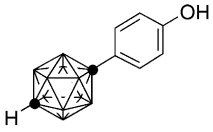
Bioorg. Med. Chem. Lett. 13 (2003) 4089

Utility of Boron Clusters for Drug Design. Relation Between Estrogen Receptor Binding Affinity and Hydrophobicity of Phenols Bearing Various Types of Carboranyl Groups

Yasuyuki Endo,[a,*] Keisuke Yamamoto[b] and Hiroyuki Kagechika[b]

[a]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai 981-8558, Japan*
[b]*Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Quantitative structure–activity relationship analysis based on the values of log*P* and the pK_a of various 4-carboranylphenols showed that the hydrophobicity of these compounds is highly correlated to the estrogen receptor a (ERα)-binding affinity.



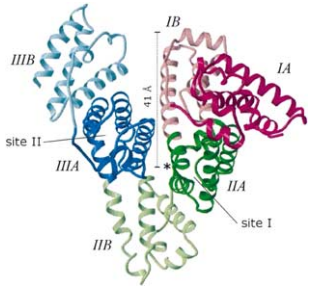
Bioorg. Med. Chem. Lett. 13 (2003) 4093

Interaction of the Disodium Disuccinate Derivative of *meso*-Astaxanthin with Human Serum Albumin: From Chiral Complexation to Self-Assembly

Ferenc Zsila,[a] Miklós Simonyi[a] and Samuel F. Lockwood[b,*]

[a]*Department of Molecular Pharmacology, Institute of Chemistry, Chemical Research Center, PO Box 17, H-1525 Budapest, Hungary*
[b]*Hawaii Biotech, Inc., 99-193 Aiea Heights Drive, Suite 200, Aiea, HI 96701, USA*

Interaction of a novel carotenoid derivative with human serum albumin in vitro.

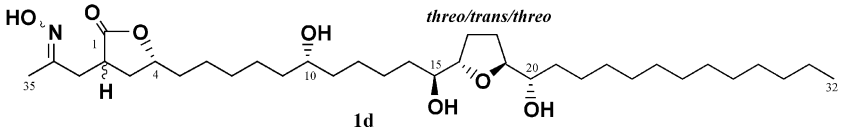


Bioorg. Med. Chem. Lett. 13 (2003) 4101

Inhibitory Effects on Mitochondrial Complex I of Semisynthetic Mono-Tetrahydrofuran Acetogenin Derivatives

José R. Tormo,[a] Teresa Gallardo,[a] Eva Peris,[a] Almudena Bermejo,[a] Nuria Cabedo,[a] Ernesto Estornell,[b] M. Carmen Zafra-Polo[a] and Diego Cortes[a,*]

[a]*Departamento de Farmacología, Laboratorio de Farmacognosia, Facultad de Farmacia, Universidad de Valencia, Avda. Vicent Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain*
[b]*Departamento de Bioquímica y Biología Molecular, Facultad de Farmacia, Universidad de Valencia, Avda. Vicent Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain*



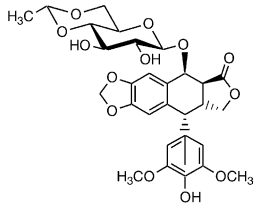
1d

Bioorg. Med. Chem. Lett. 13 (2003) 4107

Synthesis and Antiproliferative Activity of Retroetoposide

Philippe Meresse, Prokopios Magiatis, Emmanuel Bertounesque* and Claude Monneret

Laboratoire de Pharmacochimie, UMR 176 CNRS-Institut Curie, Section Recherche, 26 rue d'Ulm, 75248 Paris cedex 05, France



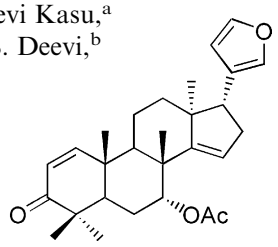
Bioorg. Med. Chem. Lett. 13 (2003) 4111

Biological Investigation and Structure–Activity Relationship Studies on Azadirone from *Azadirachta indica* A. Juss

Srinivas Nanduri,[a,*] Siva Sanjeeva Rao Thunuguntla,[a] Vijay Kumar Nyavanandi,[a] Sridevi Kasu,[a] P. Mahesh Kumar,[a] P. Sai Ram,[a] Sriram Rajagopal,[b] R. Ajaya Kumar,[b] Dhanvanthri S. Deevi,[b] R. Rajagopalan[b] and A. Venkateswarlu[a]

[a]*Discovery Chemistry, Dr. Reddy's Laboratories Ltd., Discovery Research, Bollaram Road, Miyapur, Hyderabad 500 050, India*
[b]*Discovery Biology, Dr. Reddy's Laboratories Ltd., Discovery Research, Bollaram Road, Miyapur, Hyderabad 500 050, India*

Azadirone **1** from *Azadirachta indica* is found to possess potent cytotoxic activity against a panel of human cancer cell lines in our in vitro studies. Structure–activity relationships of **1** and its analogues were derived based on their in vitro cytotoxic activity screening results.



Azadirone **1**

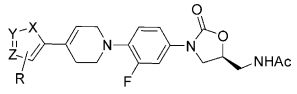
Bioorg. Med. Chem. Lett. 13 (2003) 4117

Synthesis and In Vitro Activity of Novel Isoxazolyl Tetrahydropyridinyl Oxazolidinone Antibacterial Agents

Jae Seok Lee,[a] Yong Seo Cho,[a] Moon Ho Chang,[a] Hun Yeong Koh,[a] Bong Young Chung[b] and Ae Nim Pae[a,*]

[a]*Biochemicals Research Center, Korea Institute of Science and Technology, Cheongryang, Seoul 130-650, South Korea*
[b]*Department of Chemistry, Korea University, 1-Anamdong, Seoul 136-701, South Korea*

A series of isoxazolyl tetrahydropyridinyl oxazolidinones with various substituents at the 3-position of the isoxazole ring have been synthesized and their in vitro antibacterial activities (MIC) were evaluated against several Gram-positive strains including the resistant strains of *Staphyloccus* and *Enterococcus*, such as MRSA and VRE. One of the most potent compounds synthesized, **4f**, showed comparable or better activity against selected bacterial strains than those of linezolid and vancomycin.



X = C or O, Y = N or O, Z = C or N

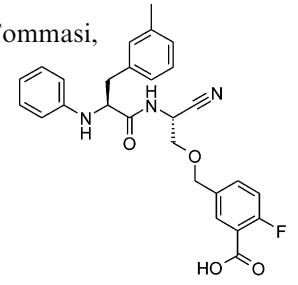
Bioorg. Med. Chem. Lett. 13 (2003) 4121

N-Arylaminonitriles as Bioavailable Peptidomimetic Inhibitors of Cathepsin B

Paul D. Greenspan,* Kirk L. Clark, Scott D. Cowen, Leslie W. McQuire, Ruben A. Tommasi, David L. Farley, Elizabeth Quadros, David E. Coppa, Zengming Du, Zheng Fang, Huanghai Zhou, John Doughty, Karen T. Toscano, Andrew M. Wigg and Siyuan Zhou

Novartis Institute of Biomedical Research, One Health Plaza, East Hanover, NJ 07936, USA

To improve the pharmacokinetics of a previously reported series of dipeptidyl nitrile cathepsin B inhibitors, the P_2–P_3 amide group was replaced with an arylamine. Further optimization of this template resulted in highly potent and selective inhibitors with excellent oral availability.



25

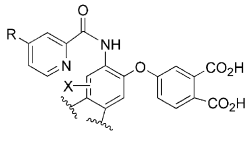
Bioorg. Med. Chem. Lett. 13 (2003) 4125

A New Class of Glycogen Phosphorylase Inhibitors

Zhijian Lu,[a,*] Joann Bohn,[a] Raynald Bergeron,[b] Qiaolin Deng,[a] Kenneth P. Ellsworth,[b] Wayne M. Geissler,[b] Georgianna Harris,[b] Peggy E. McCann,[b] Brian McKeever,[a] Robert W. Myers,[b] Richard Saperstein,[b] Christopher A. Willoughby,[a] Jun Yao[b] and Kevin Chapman[a]

[a]*Department of Basic Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*
[b]*Departments of Biochemistry and Metabolic Disorders, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*

A new class of diacid analogues that binds at the AMP site not only are very potent but have ~10-fold selectivity liver versus muscle glycogen phosphorylase (GP) in the in vitro assay. The synthesis, structure, and in vitro and in vivo biological evaluation of these liver selective glycogen phosphorylase inhibitors are discussed.



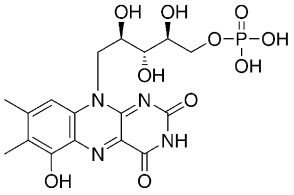
R = NO_2, Cl, OMe, CN, etc.
X = H, F

Bioorg. Med. Chem. Lett. 13 (2003) 4129

A Mechanism for Substrate-Induced Formation of 6-Hydroxyflavin Mononucleotide Catalyzed by C30A Trimethylamine Dehydrogenase

Xingliang Lu,[a] Dejan Nikolic,[b] Deanna J. Mitchell,[a] Richard B. van Breemen,[b] John A. Mersfelder,[c] Russ Hille[c] and Richard B. Silverman[a,*]

[a]*Department of Chemistry and Department of Biochemistry, Molecular Biology, and Cell Biology, Northwestern University, Evanston, IL 60208-3113, USA*
[b]*Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612-7231, USA*
[c]*Department of Molecular and Cellular Biochemistry, Ohio State University, Columbus, OH 43210-1218, USA*



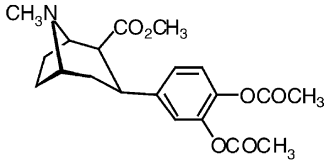
Bioorg. Med. Chem. Lett. 13 (2003) 4133

Synthesis and Biological Activity of 2-Carbomethoxy-3-catechol-8-azabicyclo[3.2.1]octanes

Peter C. Meltzer,[a,*] Mark McPhee[a] and Bertha K. Madras[b]

[a]*Organix Inc., 240 Salem Street, Woburn, MA 01801, USA*
[b]*Harvard Medical School and New England Regional Primate Research Center, Southborough, MA 01772, USA*

3-Catechol tropanes that bind to monoamine uptake systems and that substitute for cocaine in drug discrimination paradigms are reported.

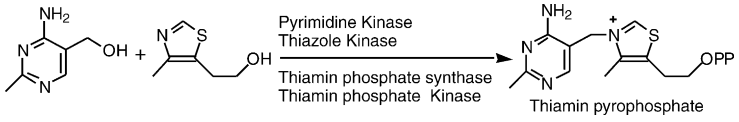


Bioorg. Med. Chem. Lett. 13 (2003) 4139

An Efficient Enzymatic Synthesis of Thiamin Pyrophosphate

Jonathan S. Melnick, K. Ingrid Sprinz, Jason J. Reddick, Cynthia Kinsland and Tadhg P. Begley*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14850, USA



Bioorg. Med. Chem. Lett. 13 (2003) 4143

High Affinity, Bioavailable 3-Amino-1,4-benzodiazepine-Based γ-Secretase Inhibitors

Andrew P. Owens,[a,*] Alan Nadin,[a] Adam C. Talbot,[a] Earl E. Clarke,[b] Timothy Harrison,[a] Huw D. Lewis,[b] Michael Reilly,[a] Jonathan D.J. Wrigley[b] and José L. Castro[a]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Biochemistry and Molecular Biology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

We describe the development of a novel series of high affinity, orally bioavailable 3-amino-1,4-benzodiazepine-based γ-secretase inhibitors for the potential treatment of Alzheimer's disease.