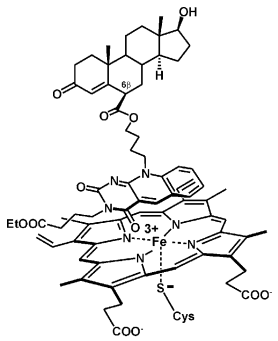
Design and Synthesis of a New Fluorescent Probe for Cytochrome P450 3A4 (CYP 3A4)

Bioorg. Med. Chem. Lett. 13 (2003) 3643

Antoinette Chougnet, Catherine Stoessel and Wolf-D. Woggon*

University of Basel, Department of Chemistry, St Johanns-Ring 19, CH-4056 Basel, Switzerland

Displacement of a fluorescent derivative of testosterone from CYP 3A4 active site by any new drug candidate can be used as a rapid alert for potential drug–drug interactions at the CYP 3A4 level.



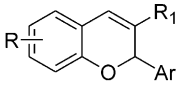
Novel Chromene Derivatives as TNF-α Inhibitors

Bioorg. Med. Chem. Lett. 13 (2003) 3647

Jie-Fei Cheng,[a,*] Akira Ishikawa,[a,b] Yoshinori Ono,[a,b] Thomas Arrhenius[a] and Alex Nadzan[a]

[a]*Department of Chemistry, Chugai Pharma USA, 6275 Nancy Ridge Dr, San Diego, CA 92121, USA*
[b]*Department of Chemistry, Chugai Pharmaceuticals, Ltd., Japan*

A series of chromene-based compounds have been synthesized and SAR studies were performed.



4

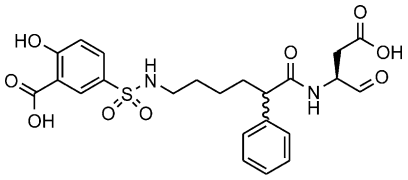
Identification of Potent and Novel Small-Molecule Inhibitors of Caspase-3

Bioorg. Med. Chem. Lett. 13 (2003) 3651

Darin A. Allen,* Phuongly Pham, Ingrid C. Choong, Bruce Fahr, Matthew T. Burdett, Willard Lew, Warren L. DeLano, Eric M. Gordon, Joni W. Lam, Tom O'Brien and Dennis Lee

Sunesis Pharmaceuticals, Inc., 341 Oyster Point Boulevard, South San Francisco, CA 94080, USA

The design and synthesis of a series of novel, reversible, small molecule inhibitors of caspase-3 are described.



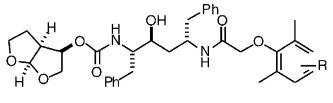
Synthesis and SAR Studies of Potent HIV Protease Inhibitors Containing Novel Dimethylphenoxyl Acetates as P_2 Ligands

Bioorg. Med. Chem. Lett. 13 (2003) 3657

Xiaoqi Chen,* Dale J. Kempf, Lin Li, Hing L. Sham, Sudthida Vasavanonda, Norman E. Wideburg, Ayda Saldivar, Kennan C. Marsh, Edith McDonald and Daniel W. Norbeck

Pharmaceutical Products Division, Abbott Laboratories, D-47D, AP52, 100 Abbott Park Road, Abbott Park, IL 60064, USA

A new series of potent HIV protease inhibitors based on pseudo-C_2-symmetric core diamine of ritonavir has been identified. The antiviral activity of inhibitors showed 10–20-fold improvement over ritonavir.



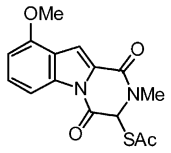
Bioorg. Med. Chem. Lett. 13 (2003) 3661

Pyrazino[1,2-*a*]indole-1,4-diones, Simple Analogues of Gliotoxin, as Selective Inhibitors of Geranylgeranyltransferase I

David M. Vigushin,[a,*] Greg Brooke,[a] David Willows,[b] R. Charles Coombes[b] and Christopher J. Moody[b,*]

[a]*Department of Cancer Medicine, 6th Floor MRC Cyclotron Building, Imperial College of Science, Technology and Medicine, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK*
[b]*Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK*

Some pyrazino[1,2-*a*]indole-1,4-diones, structurally simplified analogues of the natural mycotoxin gliotoxin, have been synthesised and investigated as inhibitors of prenyltransferases.

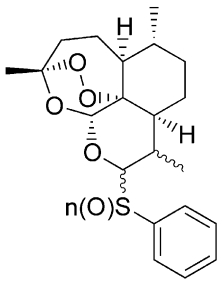


Bioorg. Med. Chem. Lett. 13 (2003) 3665

Growth Inhibition Activity of Thioacetal Artemisinin Derivatives against Human Umbilical Vein Endothelial Cells

Sangtae Oh,[a] In Howa Jeong,[a] Woon-Seob Shin[b,*] and Seokjoon Lee[c,*]

[a]*Department of Chemistry, Yonsei University, Wonju 220-710, South Korea*
[b]*Department of Microbiology, Kwandong University College of Medicine, Gangneung 210-701, South Korea*
[c]*Department of Premedical Science, Kwandong University College of Medicine, Gangneung 210-701, South Korea*



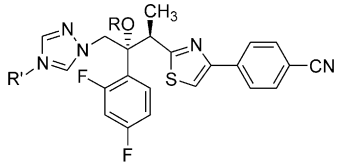
Bioorg. Med. Chem. Lett. 13 (2003) 3669

Phosphonooxymethyl Prodrugs of the Broad Spectrum Antifungal Azole, Ravuconazole: Synthesis and Biological Properties

Yasutsugu Ueda,[a,*] John D. Matiskella,[a] Jerzy Golik,[a] Timothy P. Connolly,[a] Thomas W. Hudyma,[a] Srini Venkatesh,[a] Mandar Dali,[b] Shin-Hong Kang,[a] Nancy Barbour,[b] Ravi Tejwani,[b] Sailesh Varia,[b] Jay Knipe,[a] Ming Zheng,[a] Marina Mathew,[a] Kathy Mosure,[a] Junius Clark,[a] Lucinda Lamb,[a] Ivette Medin,[a] Qi Gao,[a] Stella Huang,[a] Chung-Pin Chen[a] and Joanne J. Bronson[a]

[a]*Bristol-Myers Squibb Company, Pharmaceutical Research Institute, Wallingford, CT 06492-7660, USA*
[b]*Bristol-Myers Squibb Company, Pharmaceutical Research Institute, New Brunswick, NJ 08903-0191, USA*

The synthesis, pharmaceutical and biological properties of two phosphonooxymethyl derivatives (BMS-379224 and BMS-315801) of ravuconazole are described.



1, Ravuconazole, R = H, NR' = N
2, BMS-379224, R = -$CH_2OP(O)(OH)_2$, NR' = N
3, BMS-315801, R = H, NR' = $N^+CH_2OP(O)(OH)(O^-)$

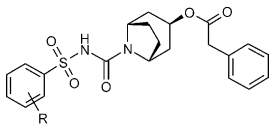
Bioorg. Med. Chem. Lett. 13 (2003) 3673

Nortropinyl-Arylsulfonylureas as Novel, Reversible Inhibitors of Human Steroid Sulfatase

Peter Nussbaumer,[a,*] Dieter Geyl,[b] Amarylla Horvath,[a] Philipp Lehr,[a] Barbara Wolff[a] and Andreas Billich[a]

[a]*Novartis Research Institute Vienna, Brunnerstrasse 59, A-1235 Vienna, Austria*
[b]*Novartis Institutes for Biomedical Research, Basel, Switzerland*

First structure–activity relationships and mechanistic investigations for this novel class of STS inhibitors are presented.



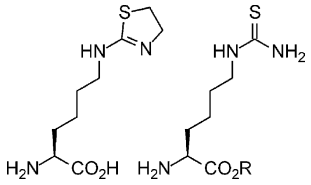
Bioorg. Med. Chem. Lett. 13 (2003) 3679

Time-Dependence and Preliminary SAR Studies in Inhibition of Nitric Oxide Synthase Isoforms by Homologues of Thiocitrulline

Claire L. M. Goodyer,[a] Edwin C. Chinje,[b] Mohammed Jaffar,[b] Ian J. Stratford[b] and Michael D. Threadgill[a,*]

[a]*Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK*
[b]*School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PL, UK*

Compounds inhibit NOS activity; the methyl ester (R = Me) shows time-dependence in inhibition of rat nNOS.



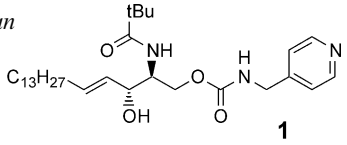
Bioorg. Med. Chem. Lett. 13 (2003) 3681

Biological Evaluation of Sphingomyelin Analogues as Inhibitors of Sphingomyelinase

Minoru Taguchi,[a,*] Ken-ichi Goda,[b] Kikuo Sugimoto,[b] Tomoko Akama,[a] Kyoko Yamamoto,[a] Taizo Suzuki,[a] Yasumitsu Tomishima,[a] Mariko Nishiguchi,[a] Koshi Arai,[a] Kenzo Takahashi[a] and Takeo Kobori[b]

[a]*Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Kita-ku, Saitama-shi, Saitama 331-9530, Japan*
[b]*Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase-shi, Kanagawa 252-1193, Japan*

An evaluation of neutral sphingomyelinase inhibitor **1** is reported.



1

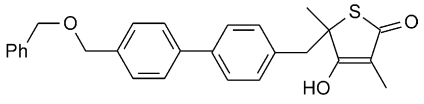
Bioorg. Med. Chem. Lett. 13 (2003) 3685

Biphenyl-Based Analogues of Thiolactomycin, Active against *Mycobacterium tuberculosis* mtFabH Fatty Acid Condensing Enzyme

Suzanne J. Senior,[a,b] Petr A. Illarionov,[a] Sudagar S. Gurcha,[a] Ian B. Campbell,[c] Merrill L. Schaeffer,[d] David E. Minnikin[a] and Gurdyal S. Besra[a,*]

[a]*School of Biosciences, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*
[b]*Department of Microbiology & Immunology, University of Newcastle, Newcastle upon Tyne NE2 4HH, UK*
[c]*GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK*
[d]*GlaxoSmithKline, Collegeville, Pennsylvania, PA 19426, USA*

Analogues of the natural antibiotic thiolactomycin, with biphenyl-based side chains, have significantly enhanced activity against cloned mtFabH condensing enzyme.



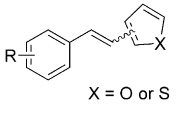
Bioorg. Med. Chem. Lett. 13 (2003) 3689

Styrylheterocycles: A Novel Class of Inhibitors on Lipopolysaccharide-Induced Nitric Oxide Production

Sang Kook Lee,[a] Hye Young Min,[a] Sun Kyung Huh,[a] Eun-Young Kim,[b] Eunjung Lee,[b] Soyoung Song[b] and Sanghee Kim[b,*]

[a]*College of Pharmacy, Ewha Womans University, 11-1 Daehyun, Seodaemun, Seoul 120-750, South Korea*
[b]*Natural Products Research Institute, College of Pharmacy, Seoul National University, 28 Yungun, Jongro, Seoul 110-460, South Korea*

A series of styrylheterocycles was prepared and their inhibitory activities against NO production were evaluated in a cell culture system. Several compounds have shown potent inhibitory activity towards the LPS-induced NO production.



X = O or S

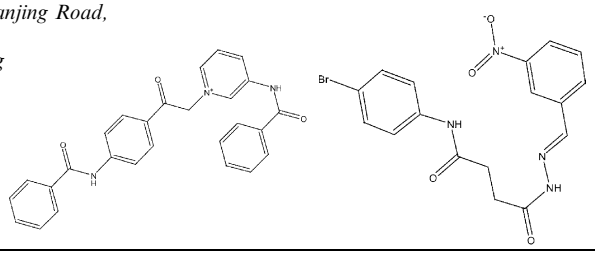
Bioorg. Med. Chem. Lett. 13 (2003) 3693

Identification of Novel Inhibitors of BCR-ABL Tyrosine Kinase via Virtual Screening

Hui Peng,[a] Niu Huang,[a] Jing Qi,[a] Ping Xie,[b] Chen Xu,[a] Jianxiang Wang[a] and Chunzheng Yang[a,*]

[a]*State Key Laboratory of Experimental Hematology, Institute of Hematology, Chinese Academy of Medical Sciences, Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, PR China*
[b]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, PR China*

Novel small molecule inhibitors targeting the catalytic domain of BCR-ABL tyrosine kinase have been discovered via a virtual screening study. Two selected compounds showed promising activity in cell-based assay of the inhibition of ABL tyrosine kinase phosphorylation, and therefore, were identified as lead compounds for further design and optimization.



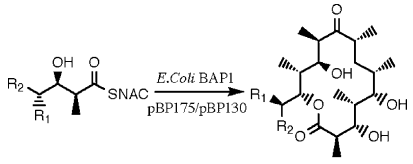
Bioorg. Med. Chem. Lett. 13 (2003) 3701

Precursor-Directed Polyketide Biosynthesis in *Escherichia coli*

Kenji Kinoshita,[a] Blaine A. Pfeifer,[b] Chaitan Khosla[b] and David E. Cane[a,*]

[a]*Department of Chemistry, Box H, Brown University, Providence, RI 02912-9108, USA*
[b]*Departments of Chemical Engineering, Chemistry, and Biochemistry, Stanford University, Stanford, CA 94305-5025, USA*

Precursor-directed polyketide biosynthesis was demonstrated in the heterologous host *Escherichia coli*. Diketide and triketide substrates were fed to a recombinant *E. coli* strain containing a variant form of deoxyerythronolide B synthase (DEBS) from which the first elongation module was deleted resulting in successful macrolactone formation from the diketide, but not the triketide, substrates.



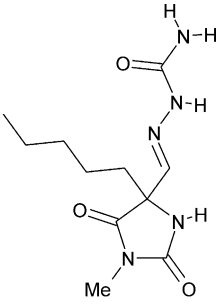
Bioorg. Med. Chem. Lett. 13 (2003) 3705

Identification of a Novel Class of Inhibitor of Human and *Escherichia coli* Thymidine Phosphorylase by In Silico Screening

V. A. McNally, A. Gbaj, K. T. Douglas, I. J. Stratford, M. Jaffar, S. Freeman and R. A. Bryce*

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PL, UK

A new molecular framework that inhibits human and *Escherichia coli* thymidine phosphorylase is reported.



Bioorg. Med. Chem. Lett. 13 (2003) 3711

Low Molecular Mass Peptide Dendrimers that Express Antimicrobial Properties

Jolanta Janiszewska,[a] Joanna Swieton,[a] Andrzej W. Lipkowski[a,b] and Zofia Urbanczyk-Lipkowska[c,*]

[a]*Industrial Chemistry Research Institute, 01-793 Warsaw, Poland*
[b]*Medical Research Centre, Polish Academy of Sciences, 02-106 Warsaw, Poland*
[c]*Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland*

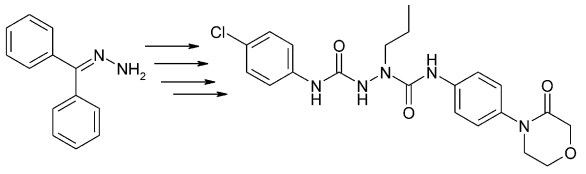
Antimicrobial potency of a series of low molecular mass dendrimeric peptides containing basic (lysine) and aromatic aminoacids is reported.

Bioorg. Med. Chem. Lett. 13 (2003) 3715

A General Synthesis of 1-Aryl Carbamoyl-2-alkyl-4-aryl Substituted Semicarbazides as Nonbasic Factor Xa Inhibitors

Werner W. K. R. Mederski* and Martina Germann

Merck KGaA, Preclinical Pharmaceutical Research, 64271 Darmstadt, Germany



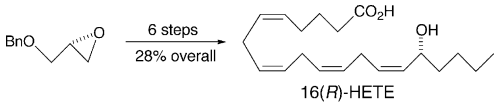
Bioorg. Med. Chem. Lett. 13 (2003) 3719

Practical, Asymmetric Synthesis of 16-Hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic Acid (16-HETE), an Endogenous Inhibitor of Neutrophil Activity

Y. Krishna Reddy,[a] L. Manmohan Reddy,[a] Jorge H. Capdevila[b] and J. R. Falck[a,*]

[a]*Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, USA*
[b]*Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37232, USA*

An asymmetric synthesis of 16-HETE, an endogenous inhibitor of neutrophil activity, was achieved from *R*-(–)-glycidyl benzyl ether.

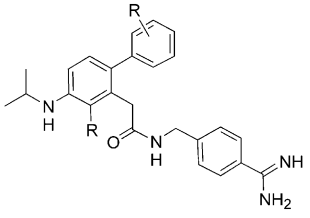


Bioorg. Med. Chem. Lett. 13 (2003) 3721

Synthesis and X-ray Crystal Structures of Substituted Fluorobenzene and Benzoquinone Inhibitors of the Tissue Factor VIIa Complex

John J. Parlow,[a,*] Ravi G. Kurumbail,[b] Roderick A. Stegeman,[b] Anna M. Stevens,[b] William C. Stallings[b] and Michael S. South[a]

[a]*Department of Medicinal and Combinatorial Chemistry, Pharmacia Corporation, 800 North Lindbergh Boulevard, St. Louis, MO 63167, USA*
[b]*Structure and Computational Chemistry, Pharmacia Corporation, 700 Chesterfield Village Parkway, St. Louis, MO 63198, USA*



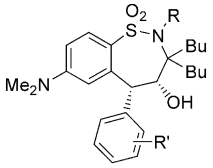
Bioorg. Med. Chem. Lett. 13 (2003) 3727

A Novel Class of Apical Sodium Co-dependent Bile Acid Transporter Inhibitors: The 1,2-Benzothiazepines

Michael B. Tollefson,* Stephen A. Kolodziej, Theresa R. Fletcher, William F. Vernier, Judith A. Beaudry, Bradley T. Keller and David B. Reitz

Pfizer Global Research and Development, 700 Chesterfield Parkway N, Chesterfield, MO 63017, USA

A series of 5-aryl-3,3-dibutyl-7-(dimethylamino)-1,2-benzothiazepin-4-ol 1,1-dioxides were prepared and were found to inhibit the apical sodium co-dependent bile acid transporter (ASBT) for the potential treatment for hyperlipidemia.



Bioorg. Med. Chem. Lett. 13 (2003) 3731

Synthesis of β-Substituted Cationic Porphyrins and Their Interactions with DNA

Bo Chen,[a] Wen Qin,[a] Ping Wang,[a] Tian Tian,[a] Hongjuan Ma,[a] Xiaoping Cao,[c] Xiaojun Wu,[a] Xiang Zhou,[a,*] Xiao-Lian Zhang,[b] Fang Liu,[b] Fang Zheng[b] and Xia Li[b]

[a]*College of Chemistry and Molecular Sciences, Wuhan University, Hubei Wuhan 430072, PR China*
[b]*School of Medicine, Wuhan University, Hubei Wuhan 430072, PR China*
[c]*National Laboratory of Applied Organic Chemistry, Lanzhou Univesity, Gansu, Lanzhou 730000, PR China*

The β-substituted cationic porphyrins have been synthesized and their interactions with plasmid DNA investigated. We found that substituents at the β-position of porphyrins had influenced their interactions with DNA compared with non-β-substituted porphyrins.

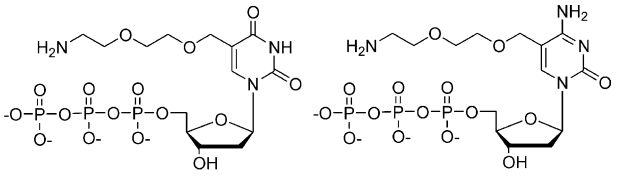
Bioorg. Med. Chem. Lett. 13 (2003) 3735

Substrate Properties of C5-Substituted Pyrimidine 2′-Deoxynucleoside 5′-Triphosphates for Thermostable DNA Polymerases During PCR

Masayasu Kuwahara, Yumi Takahata, Atsushi Shoji, Akiko N. Ozaki, Hiroaki Ozaki and Hiroaki Sawai*

Department of Applied Chemistry, Gunma University, Kiryu, Gunma 376-8515, Japan

Modified analogues of 2′-deoxyuridine triphosphate and 2′-deoxycytidine triphosphate bearing a flexible and hydrophilic 7-amino-2,5-dioxaheptyl linker at a C5 position were designed and synthesized. Both analogues were found to be substrates for thermostable DNA polymerases which belong to an evolutional family B during PCR.



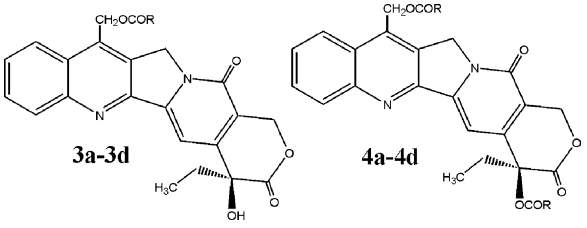
Bioorg. Med. Chem. Lett. 13 (2003) 3739

Regioselective Synthesis and Cytotoxicities of Camptothecin Derivatives Modified at the 7-, 10- and 20-Positions

Xian-dao Pan,[a,*] Rui Han[a] and Piao-yang Sun[b]

[a]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*
[b]*Hengrui Pharmaceutical Co., Ltd., Lianyungang, Jiangsu 222002, China*

A series of 7-acyloxymethylcamptothecin and 20-*O*-acyl-7-acyloxymethylcamptothecin derivatives were regioselectively prepared on different solvents. 7-Acyloxymethylcamptothecin was found more cytotoxic in vitro on several human tumor cell lines than topotecan.



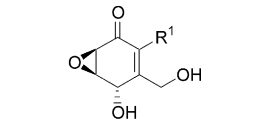
Bioorg. Med. Chem. Lett. 13 (2003) 3743

Novel Non-peptide Inhibitors Targeting Death Receptor-Mediated Apoptosis

Hideaki Kakeya,[a,*] Yasunobu Miyake,[a,c] Mitsuru Shoji,[b] Satoshi Kishida,[b] Yujiro Hayashi,[b] Takao Kataoka[c] and Hiroyuki Osada[a,*]

[a]*Antibiotics Laboratory, RIKEN Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*
[b]*Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*
[c]*Division of Bioinformatics, Center for Biological Resources and Informatics, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan*

Design, synthesis, and biological evaluation of novel non-peptide inhibitors of receptor-mediated apoptosis are reported.



RKTS-33: R^1 = -H
RKTS-34: R^1 = -C(CH_3)=CH-CH_3
(*E*/*Z*=1/1)

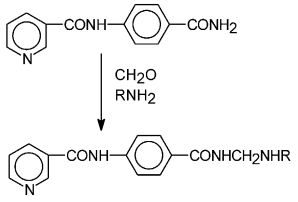
Bioorg. Med. Chem. Lett. 13 (2003) 3741

QSAR Study on Antibacterial Activity of Sulphonamides and Derived Mannich Bases

Sheela Joshi* and Navita Khosla

School of Chemical Sciences, Devi Ahilya Vishwavidyalaya, Takshila campus, Khandwa Road, Indore (M.P.), India

In this comparative study on antibacterial activities of sulphonamides and Mannich bases derived from them, the results have shown that the compounds are quite active against pathogens under study and were non toxic.



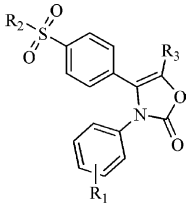
Bioorg. Med. Chem. Lett. 13 (2003) 3753

Exploring Selectivity Requirements for COX-2 versus COX-1 Binding of 3,4-Diaryloxazolones Using E-State Index

Kunal Roy,[a,*] Santanu Chakraborty[a] and Achintya Saha[b]

[a]*Drug Theoretics and Cheminformatics Laboratory, Division of Medicinal and Pharmaceutical Chemistry, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700 032, India*
[b]*Department of Chemical Technology, University of Calcutta, Kolkata 700 009, India*

Considering the importance of developing selective COX-2 inhibitors, the present paper explores selectivity requirements for COX-2 versus COX-1 binding of 3,4-diaryloxazolones using electrotopological state (E-state) index.



1-31

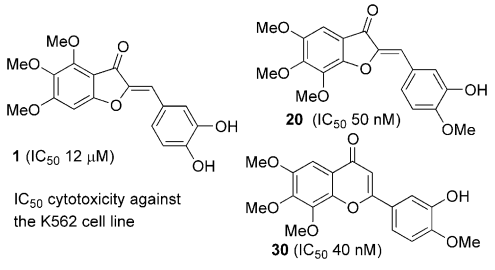
Bioorg. Med. Chem. Lett. 13 (2003) 3759

The Total Synthesis of an Aurone Isolated from *Uvaria hamiltonii*: Aurones and Flavones as Anticancer Agents

Nicholas J. Lawrence,[a,b,*] David Rennison,[b,d] Alan T. McGown[c,d] and John A. Hadfield[c,d]

[a]*Department of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, UK*
[b]*Department of Chemistry, UMIST, PO Box 88, Manchester M60 1QD, UK*
[c]*Centre for Molecular Drug Design, Department of Chemistry, University of Salford, Manchester M5 4WT, UK*
[d]*Cancer Research UK Department of Drug Development, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK*

The naturally occurring aurone **1**, isolated from *Uvaria hamiltonii*, and a series of aurones analogues based structurally on known tubulin binding agents were prepared and evaluated for anticancer activity. Aurone **20** was the most active and caused significant G_2/M cell cycle arrest.

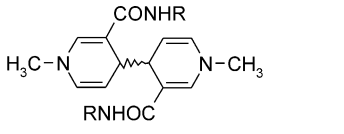


Bioorg. Med. Chem. Lett. 13 (2003) 3765

Synthesis and Biological Evaluation of GABA Derivatives Able to Cross the Blood–Brain Barrier in Rats

Vincenzo Carelli,[a,*] Felice Liberatore,[a] Luigi Scipione,[a] Gianfabio Giorgioni,[b] Antonio Di Stefano,[b] Mariannina Impicciatore,[c] Vigilio Ballabeni,[c] Francesco Calcina,[c] Francesca Magnanini[c] and Elisabetta Barocelli[c]

[a]*Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università 'La Sapienza', P.le A. Moro 5, 00185 Rome, Italy*
[b]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy*
[c]*Dipartimento di Scienze Farmacologiche, Biologiche e Chimiche Applicate, Università di Parma, Parco Area delle Scienze 27/A, 43100 Parma, Italy*



R = $(CH_2)_3COONa$ or $(CH_2)_3COOCH_2C_6H_5$

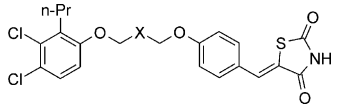
Bioorg. Med. Chem. Lett. 13 (2003) 3771

New Benzylidenethiazolidinediones as Antibacterial Agents

Dirk A. Heerding,[a,*] Lisa T. Christmann,[a] Tammy J. Clark,[a] David J. Holmes,[b] Stephen F. Rittenhouse,[b] Dennis T. Takata[a] and Joseph W. Venslavsky[a]

[a]*Medicinal Chemistry Department, Microbial, Musculoskeletal and Proliferative Diseases, GlaxoSmithKline Pharmaceuticals, 1250 S. Collegeville Road, Collegeville, PA 19426, USA*
[b]*Microbial Genetics and Biochemistry Department, Microbial, Musculoskeletal and Proliferative Diseases, GlaxoSmithKline Pharmaceuticals, 1250 S. Collegeville Road, Collegeville, PA 19426, USA*

A novel benzylidenethiazolidinedione has been discovered with antimicrobial activity. Here, we present the results of a structure–activity study on this compound with respect to its antimicrobial activity.

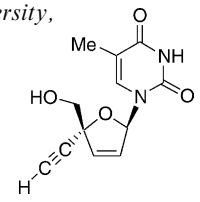


Bioorg. Med. Chem. Lett. 13 (2003) 3775

Synthesis of a Highly Active New Anti-HIV Agent 2′,3′-Didehydro-3′-deoxy-4′-ethynylthymidine

Kazuhiro Haraguchi,[a] Shingo Takeda,[a] Hiromichi Tanaka,[a,*] Takao Nitanda,[b] Masanori Baba,[b] G. E. Dutschman[c] and Yung-Chi Cheng[c]

[a]*School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan*
[b]*Center for Chronic Viral Diseases, Division of Human Retroviruses, Faculty of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan*
[c]*Department of Pharmacology, School of Medicine, Yale University, 333 Cedar street, New Haven, CT 06520, USA*

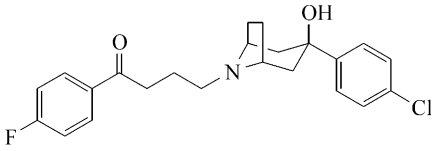


Bioorg. Med. Chem. Lett. 13 (2003) 3779

The Acute EPS of Haloperidol May Be Unrelated to Its Metabolic Transformation to BCPP$^+$

Donald M. N. Sikazwe, Shouming Li, Margaret Lyles-Eggleston and Seth Y. Ablordeppey*

College of Pharmacy & Pharmaceutical Sciences, Florida A & M University, Tallahassee, FL 32307, USA



DS-27 (**2**)

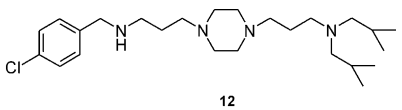
Bioorg. Med. Chem. Lett. 13 (2003) 3783

Synthesis and Antimalarial Evaluation of New 1,4-Bis(3-aminopropyl)piperazine Derivatives

Adina Ryckebusch,[a] Rébecca Deprez-Poulain,[a] Marie-Ange Debreu-Fontaine,[a] Richard Vandaele,[a] Elisabeth Mouray,[b] Philippe Grellier[b] and Christian Sergheraert[a,*]

[a]*Institut de Biologie et Institut Pasteur de Lille, UMR 8525 CNRS, Université de Lille II, 1 rue du Professeur Calmette, B.P. 447, 59021 Lille, France*
[b]*USM 0504 'Biologie fonctionnelle des protozoaires' Département 'Régulations, Développement, Diversité Chimique', Muséum National d'Histoire Naturelle, 61 rue Buffon, 75005 Paris, France*

The synthesis of a new family of 1,4-bis(3-aminopropyl)piperazine derivatives, and evaluation of their activity against a chloroquine-resistant strain of *Plasmodium falciparum*, and as inhibitors of β-hematin formation, are reported. Compound **12** displayed an activity 3-fold better than chloroquine for a comparable selectivity index upon MRC-5 cells.



12

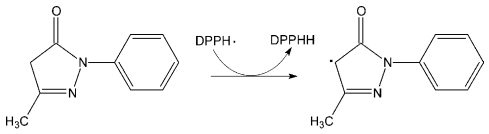
Bioorg. Med. Chem. Lett. 13 (2003) 3789

A Theoretical Investigation on DPPH Radical-Scavenging Mechanism of Edaravone

Lan-Fen Wang[a,b] and Hong-Yu Zhang[a,*]

[a]*Laboratory for Computational Biology, Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Shandong University of Technology, Zibo 255049, PR China*
[b]*Department of Chemistry, Shandong Teachers' University, Jinan 250014, PR China*

The DPPH radical-scavenging mechanism of edaravone was clarified by density functional theory (DFT) calculations.



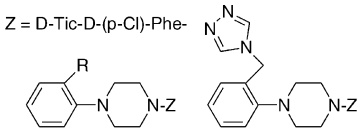
Bioorg. Med. Chem. Lett. 13 (2003) 3793

Aryl Piperazine Melanocortin MC4 Receptor Agonists

Brian Dyck, Jessica Parker, Teresa Phillips, Lee Carter, Brian Murphy, Robin Summers, Julia Hermann, Tracy Baker, Mary Cismowski, John Saunders and Val Goodfellow*

Departments of Medicinal Chemistry, Pharmacology, and Molecular Biology, Neurocrine Biosciences Inc., 10555 Science Center Drive, San Diego, CA, 92121, USA

Incorporation of substituted phenyl piperazine privileged structures into a known MC4 specific dipeptoid consensus sequence resulted in a series of potent (EC_{50} = 24 nm) and selective MC4-R agonists.



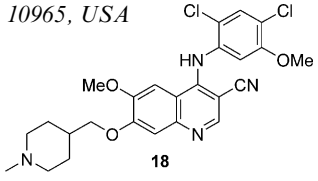
Bioorg. Med. Chem. Lett. 13 (2003) 3797

Investigation of the Effect of Varying the 4-Anilino and 7-Alkoxy Groups of 3-Quinolinecarbonitriles on the Inhibition of Src Kinase Activity

Diane H. Boschelli,[a,*] Fei Ye,[a] Biqi Wu,[a] Yanong D. Wang,[a] Ana Carolina Barrios Sosa,[a] Deanna Yaczko,[a] Dennis Powell,[a] Jennifer M. Golas,[b] Judy Lucas[b] and Frank Boschelli[b]

[a]*Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY, 10965, USA*
[b]*Oncology, Wyeth Research, 401 N. Middletown Road, Pearl River, NY, 10965, USA*

Several 4-anilino-7-alkoxy-3-quinolinecarbonitriles are described as potent Src kinase inhibitors. One of these analogues, **18**, showed in vivo activity.



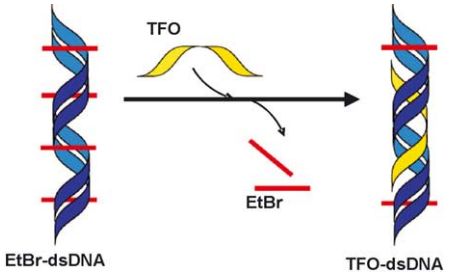
Bioorg. Med. Chem. Lett. 13 (2003) 3801

Determination of Binding Affinities of Triplex Forming Oligonucleotides Using a Fluorescent Intercalator Displacement (FID) Assay

Bryan K. S. Yeung, Winston C. Tse and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

The binding affinities of several triplex forming oligonucleotides were determined using a fluorescent intercalator displacement (FID) assay.



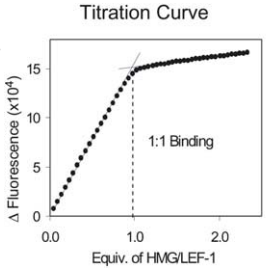
Bioorg. Med. Chem. Lett. 13 (2003) 3805

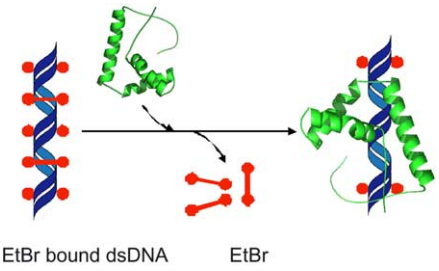
High-Resolution Assessment of Protein DNA Binding Affinity and Selectivity Utilizing a Fluorescent Intercalator Displacement (FID) Assay

Young-Wan Ham, Winston C. Tse and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Protein titration displacement of ethidium bromide bound to hairpin deoxyoligonucleotides containing any sequence of interest provides a well-defined titration curve (measuring the loss of fluorescence derived from the DNA bound ethidium bromide) that provides both absolute binding constants (K_a) and stoichiometry of binding.





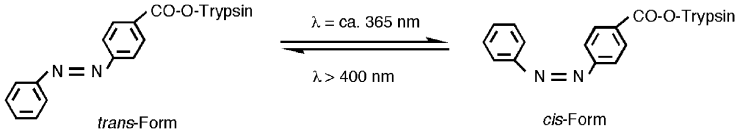
Bioorg. Med. Chem. Lett. 13 (2003) 3809

Photoregulation of Deacylation Rate of Acyl Trypsin Derived from Photoresponsive Inverse Substrate

Haruo Sekizaki,* Asako Kumagai, Kunihiko Itoh, Eiko Toyota, Kiyoshi Horita, Yukari Noguchi and Kazutaka Tanizawa

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

The deacylation rate of *cis*-acyl-trypsin has been shown 18.6 times faster than that of *trans*-acyl-trypsin.



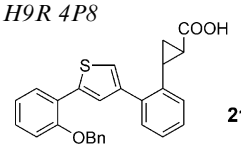
Bioorg. Med. Chem. Lett. 13 (2003) 3813

Structure–Activity Relationship of Triaryl Propionic Acid Analogues on the Human EP_3 Prostanoid Receptor

Michel Gallant,* Michel Belley, Marie-Claude Carrière, Anne Chateauneuf, Danielle Denis, Nicolas Lachance, Sonia Lamontagne, Kathleen M. Metters, Nicole Sawyer, Deborah Slipetz, Jean François Truchon and Marc Labelle

Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe Claire- Dorval, Québec, Canada H9R 4P8

Potent and selective ligands for the human EP_3 prostanoid receptor are described. Triaryl compounds bearing an *ortho* substituted propionic acid moiety were identified as potent EP_3 antagonists based on the SAR described herein. The binding affinities of key compound on all eight human prostanoid receptors is reported.



21

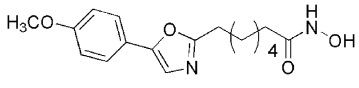
Bioorg. Med. Chem. Lett. 13 (2003) 3817

A Novel Series of Histone Deacetylase Inhibitors Incorporating Hetero Aromatic Ring Systems as Connection Units

Yujia Dai,* Yan Guo, Michael L. Curtin, Junling Li, Lori J. Pease, Jun Guo, Patrick A. Marcotte, Keith B. Glaser, Steven K. Davidsen and Michael R. Michaelides

Cancer Research, Abbott Laboratories, Department R47J, Building AP10, 100 Abbott Park Road, Abbott Park, IL 60031, USA

A series of potent and structurally novel HDAC inhibitors, in which a hetero aromatic ring connects the space with the hydrophobic group, has been designed and synthesized.



2b IC_{50} = 2.1 nM

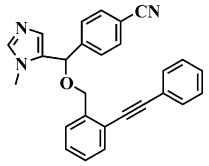
Bioorg. Med. Chem. Lett. 13 (2003) 3821

Synthesis and Biological Evaluation of 4-[(3-Methyl-3*H*-imidazol-4-yl)-(2-phenylethynyl-benzyloxy)-methyl]-benzonitrile as Novel Farnesyltransferase Inhibitor

Nan-Horng Lin,* Le Wang, Jerry Cohen, Wen-Zhen Gu, David Frost, Haiying Zhang, Saul Rosenberg and Hing Sham

Cancer Research, R-47B, Global Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, USA

Analogues of compound **1** were synthesized and tested in vitro for farnesyltransferase inhibition activity.



1

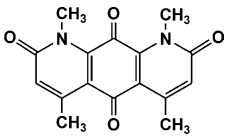
Bioorg. Med. Chem. Lett. 13 (2003) 3827

Structure Elucidation of Sch 538415, a Novel Acyl Carrier Protein Synthase Inhibitor from a Microorganism

Min Chu,* Ronald Mierzwa, Ling Xu, Shu-Wei Yang, Ling He, Mahesh Patel, Jill Stafford, David Macinga, Todd Black, Tze-Ming Chan and Vincent Gullo

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

A new acyl carrier protein synthase (AcpS) inhibitor, Sch 538415 (**1**), was discovered from an unidentified microorganism. The structure of **1** was elucidated by spectroscopic data analyses. Compound **1** showed inhibitory activity with $IC_{50} = 4.19$ μM in the AcpS assay.



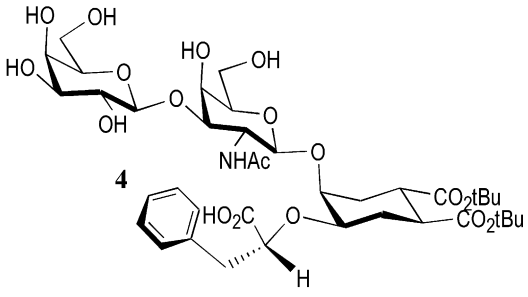
Bioorg. Med. Chem. Lett. 13 (2003) 3831

Ganglioside GM1 Mimics: Lipophilic Substituents Improve Affinity for Cholera Toxin

Daniela Arosio, Sergio Baretti, Stefania Cattaldo, Donatella Potenza and Anna Bernardi*

Dipartimento di Chimica Organica e Industriale, Universita' di Milano, via Venezian 21, 20133 Milan, Italy

The synthesis of the cholera toxin ligand **4** ($K_d = 10$ μM) is reported.



4

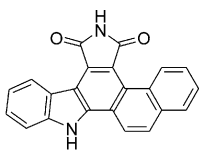
Bioorg. Med. Chem. Lett. 13 (2003) 3835

Aryl[*a*]pyrrolo[3,4-*c*]carbazoles as Selective Cyclin D1-CDK4 Inhibitors

Concha Sanchez-Martinez,[a,*] Chuan Shih,[b] Margaret M. Faul,[b] Guoxin Zhu,[b] Michael Paal,[c] Carmen Somoza,[a] Tiechao Li,[b] Christine A. Kumrich,[b] Leonard L. Winneroski,[b] Zhou Xun,[b] Harold B. Brooks,[d] Bharvin K. R. Patel,[d] Richard M. Schultz,[d] Tammy B. DeHahn,[d] Charles D. Spencer,[d] Scott A. Watkins,[d] Eileen Considine,[d] Jack A. Dempsey,[d] Catherine A. Ogg,[d] Robert M. Campbell,[b] Bryan A. Anderson[b] and Jill Wagner[b]

[a]*DCR&T, Lilly Spain S.A., Avda de la Industria 30, 28108 Alcobendas (Madrid), Spain*
[b]*DCR&T, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*
[c]*DCR&T, Lilly Forschung GmbH, 20253 Hamburg, Germany*
[d]*Cancer Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*

A novel series of aryl[*a*]pyrrolo[3,4-*c*]carbazoles were evaluated as inhibitors of Cyclin D1-CDK4. A potent and selective D1-CDK4 inhibitor, **7a** (D1-CDK4 $IC_{50} = 45$ nM), has been identified.



D1/CDK4 IC_{50} 45nM

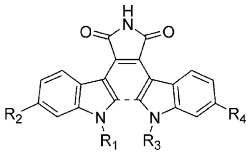
Bioorg. Med. Chem. Lett. 13 (2003) 3841

Studies on Cyclin-Dependent Kinase Inhibitors: Indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazoles versus Bis-indolylmaleimides

Concha Sanchez-Martinez,[a,*] Chuan Shih,[b,*] Guoxin Zhu,[b] Tiechao Li,[b] Harold B. Brooks,[c] Bharvin K. R. Patel,[c] Richard M. Schultz,[c] Tammy B. DeHahn,[c] Charles D. Spencer,[c] Scott A. Watkins,[c] Catherine A. Ogg,[c] Eileen Considine,[c] Jack A. Dempsey[c] and Faming Zhang[b]

[a]*DCRT, Lilly Spain S.A., Avda de la Industria 30, 28108 Alcobendas (Madrid), Spain*
[b]*DCRT, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*
[c]*Cancer Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*

The inhibitory activities of bis-indolyl maleimides and indolocarbazoles towards CDK4 are compared.



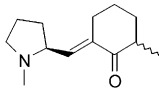
Bioorg. Med. Chem. Lett. 13 (2003) 3847

Rigidified Acetylcholine Mimics: Conformational Requirements for Binding to Neuronal Nicotinic Receptors

Gérald Villeneuve,[a,*] Danielle Cécyre,[b] Hélène Lejeune,[b] Marc Drouin,[a] Ruoxi Lan[a] and Rémi Quirion[b]

[a]*Département de Chimie, Université de Sherbrooke, 2500 boul. de l'Université, Sherbrooke, Québec, Canada, J1K 2R1*
[b]*Centre de Recherche de l'Hôpital Douglas, McGill University, 6857 boul. Lasalle, Verdun, Québec, Canada, H4H 1R3*

Rigidified derivatives have been designed and synthesized assuming the $g+t$ conformer of acetylcholine as active conformation for binding to the cytisine sensitive neuronal nicotinic receptors. The SAR supports the $g+t$ conformer hypothesis. Tertiary amine **3e** has the best affinity and selectivity.



3e IC_{50} = 460 nM

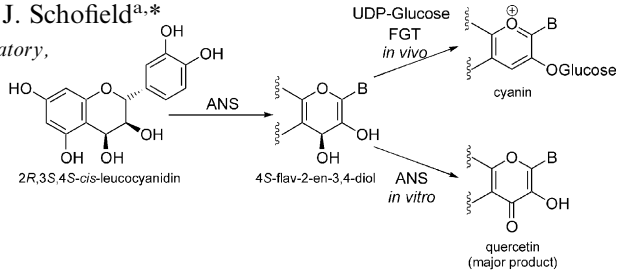
Bioorg. Med. Chem. Lett. 13 (2003) 3853

The C-4 Stereochemistry of Leucocyanidin Substrates for Anthocyanidin Synthase Affects Product Selectivity

Jonathan J. Turnbull,[a] Michael J. Nagle,[b] Jürgen F. Seibel,[a] Richard W.D. Welford,[a] Guy H. Grant[b] and Christopher J. Schofield[a,*]

[a]*The Oxford Centre for Molecular Sciences and The Dyson Perrins Laboratory, The Department of Chemistry, South Parks Road, Oxford OX1 3QY, UK*
[b]*The Physical and Theoretical Chemistry Laboratory, The Department of Chemistry, South Parks Road, Oxford OX1 3QZ, UK*

In vitro studies on anthocyanidin synthase with leucocyanidin substrates show that the C-4 stereochemistry alters product formation. The results suggest that the in vivo product of ANS could be a 4*S*-flav-2-en-3,4-diol.



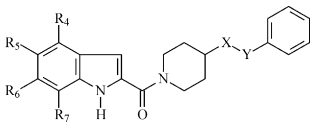
Bioorg. Med. Chem. Lett. 13 (2003) 3859

Indole-2-Carboxamides as Novel NR2B Selective NMDA Receptor Antagonists

István Borza,[a,*] Sándor Kolok,[a] Anikó Gere,[a] Éva Ágai-Csongor,[a] Béla Ágai,[b] Gábor Tárkányi,[a] Csilla Horváth,[a] Gizella Barta-Szalai,[a] Éva Bozó,[a] Csilla Kiss,[a] Attila Bielik,[a] József Nagy,[a] Sándor Farkas[a] and György Domány[a]

[a]*Gedeon Richter Ltd., Budapest 10 POB 27, H-1475, Hungary*
[b]*Budapest University of Technology and Economics, Budapest POB 91, H-1521, Hungary*

A novel series of indole-2-carboxamide derivatives was prepared and identified as NR2B selective NMDA receptor antagonists. The influence of the number and position of OH groups on the indole skeleton as well as the substitution of the piperidine ring on the biological activity of the compounds was studied.



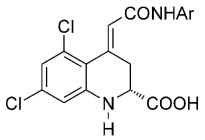
Bioorg. Med. Chem. Lett. 13 (2003) 3863

Enantiomerically Pure Tetrahydroquinoline Derivatives as In Vivo Potent Antagonists of the Glycine Binding Site Associated to the NMDA Receptor

Romano Di Fabio,* Elvira Tranquillini, Barbara Bertani, Giuseppe Alvaro, Fabrizio Micheli, Fabio Sabbatini, Maria Domenica Pizzi, Giorgio Pentassuglia, Alessandra Pasquarello, Tommaso Messeri, Daniele Donati, Emiliangelo Ratti, Roberto Arban, Giovanna Dal Forno, Angelo Reggiani and Robert J. Barnaby

Medicines Research Centre, GlaxoSmithKline S.p.A, Via Fleming 4, 37135 Verona, Italy

The synthesis and the neuroprotective profile of enantiomerically pure THQ derivatives is reported.



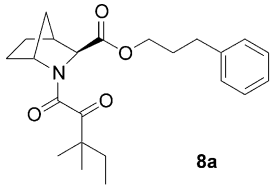
Bioorg. Med. Chem. Lett. 13 (2003) 3867

Synthesis and Evaluation of Chiral Bicyclic Proline FKBP12 Ligands

David C. Limburg, Bert E. Thomas, IV, Jia-He Li, Mike Fuller, Dawn Spicer, Yi Chen, Hongzhi Guo, Joseph P. Steiner, Gregory S. Hamilton and Yong-Qian Wu*

Guilford Pharmaceuticals Inc., Research Department, 6611 Tributary St., Baltimore, MD 21224, USA

As part of our ongoing program to explore novel structural classes of FKBP12 ligands, we herein wish to report a new class of FKBP12 ligands containing chiral bicyclic proline analogues. Details of the synthetic routes, together with preliminary biological activity will be presented.



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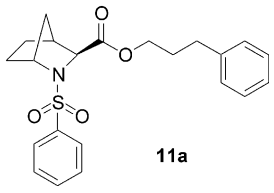

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Bioorg. Med. Chem. Lett. 13 (2003) 3871

X-ray Structures of Two Xanthine Inhibitors Bound to PEPCK and *N*-3 Modifications of Substituted 1,8-Dibenzylxanthines

Louise H. Foley,[a,*] Ping Wang,[a] Pete Dunten,[a] Gwendolyn Ramsey,[b] Mary-Lou Gubler[b] and Stanley J. Wertheimer[b]

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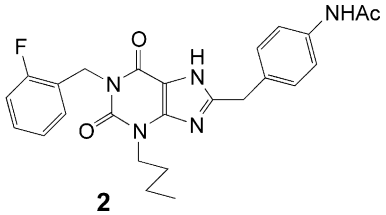
X-ray structures of two xanthine inhibitors bound to PEPCK are presented and compared to the structure of GTP bound to PEPCK. We also describe *N*-3 modifications of compound **2** that resulted in sub-micromolar inhibitors.



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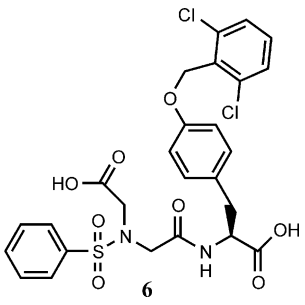
Bioorg. Med. Chem. Lett. 13 (2003) 3875

Sulphonamide-Based Small Molecule VLA-4 Antagonists

Marcin Stasiak, Christopher Mehlin, Erica Boni, Tomas Vaisar, Thomas Little, Hwa-Ok Kim and Maher Qabar*

Molecumetics, 2023 120th Ave. N E., Bellevue, WA 98005, USA

The discovery of a sulphonamide by-product with VLA-4 antagonistic activity led to a series of potent, small molecule VLA-4 antagonists. Synthesis, SAR and *in vitro* evaluation of the selected compound will be represented.



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