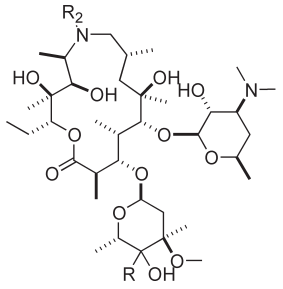
Bioorg. Med. Chem. Lett. 13 (2003) 1955

Synthesis, Stereochemical Assignment and Biological Activity of a Novel Series of C-4″ Modified Aza-Macrolides

Brian S. Bronk,* Michael A. Letavic,* Camilla D. Bertsche, David M. George, Shigeru F. Hayashi, Barbara J. Kamicker, Nicole L. Kolosko, Laura J. Norcia, Margaret A. Rushing, Sheryl L. Santoro and Bingwei V. Yang

Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA

Novel C-4″ modified macrocyclic antibiotics with potent in vitro activity against *Pasteurella multocida* and *Escherichia coli* strains of bacteria are described.



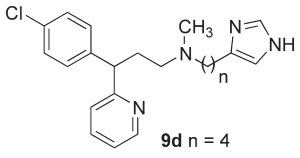
Bioorg. Med. Chem. Lett. 13 (2003) 1959

Identification of a Dual Histamine H_1/H_3 Receptor Ligand Based on the H_1 Antagonist Chlorpheniramine

Robert Aslanian,* Mwangi wa Mutahi, Neng-Yang Shih, John J. Piwinski, Robert West, Shirley M. Williams, Susan She, Ren-Long Wu and John A. Hey

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

The identification of the dual H_1/H_3 ligand, **9d**, is reported.



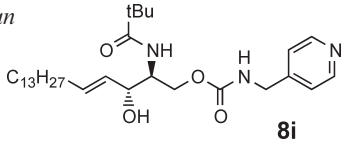
Bioorg. Med. Chem. Lett. 13 (2003) 1963

Sphingomyelin Analogues as Inhibitors of Sphingomyelinase

Minoru Taguchi,[a,*] Kikuo Sugimoto,[b] Ken-ichi Goda,[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*

The synthesis and evaluation of neutral sphingomyelinase inhibitor **8i** is reported.



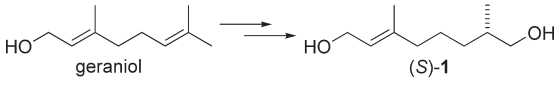
Bioorg. Med. Chem. Lett. 13 (2003) 1967

Chemoenzymatic Synthesis of (*E*)-3,7-Dimethyl-2-octene-1,8-diol Isolated from the Hairpencils of Male *Danaus chrysippus* (African Monarch)

Kunihiko Takabe,* Nobuyuki Mase, Hiroya Hashimoto, Atsushi Tsuchiya, Takashi Ohbayashi and Hidemi Yoda

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

Total synthesis afforded (*S*)-**1** in 12 steps and 26% overall yield from readily available geraniol.



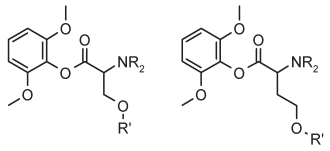
Bioorg. Med. Chem. Lett. 13 (2003) 1971

Novel Water Soluble 2,6-Dimethoxyphenyl Ester Derivatives with Intravenous Anaesthetic Activity

D. Jonathan Bennett,* Alison Anderson, Kirsteen Buchanan, Alan Byford, Andrew Cooke, David K. Gemmell, Niall M. Hamilton, Maurice S. Maidment, Petula McPhail, Donald F. M. Stevenson, Hardy Sundaram and Peter Vijn

Departments of Medicinal Chemistry and Pharmacology, Organon Laboratories Ltd., Newhouse, Motherwell ML1 5SH, Scotland, UK

A number of water soluble 2,6-dimethoxyphenyl ester derivatives were prepared and found to exhibit potent anaesthetic activity after intravenous administration.

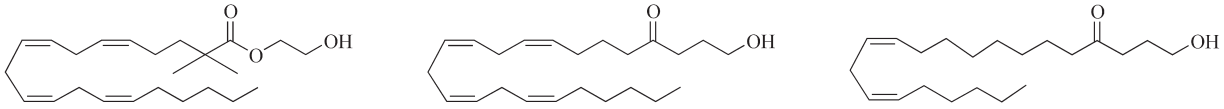


Bioorg. Med. Chem. Lett. 13 (2003) 1977

Hemisynthesis and Preliminary Evaluation of Novel Endocannabinoid Analogues

Siham El Fangour,[a] Laurence Balas,[a,*] Jean-Claude Rossi,[a] Andrey Fedenyuk,[b] Natalia Gretskaya,[b] Mikhail Bobrov,[b] Vladimir Bezuglov,[b] Cecilia J. Hillard[c] and Thierry Durand[a]

[a]*UMR CNRS 5074, Faculté de Pharmacie, 15 av. C. Flahault, BP 14491, F-34093 Montpellier Cedex 5, France*
[b]*Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, 16/10 Miklukho-Maklaya str., 117437 Moscow, Russia*
[c]*Department of Pharmacology and Toxicology, Medicinal College of Wisconsin, Milwaukee, WI 53226, USA*



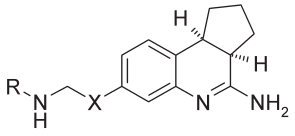
Bioorg. Med. Chem. Lett. 13 (2003) 1981

Dihydroquinolines with Amine-Containing Side Chains as Potent n-NOS Inhibitors

Stefan Jaroch,[a,*] Peter Hölscher,[a] Hartmut Rehwinkel,[a] Detlev Sülzle,[b] Gerardine Burton,[c] Margrit Hillmann[c] and Fiona M. McDonald[c]

[a]*Department of Medicinal Chemistry, Research Center Europe, Corporate Research, Schering AG, D-13342-Berlin, Germany*
[b]*Department of Computational Chemistry, Research Center Europe, Corporate Research, Schering AG, D-13342-Berlin, Germany*
[c]*Department of CNS-Research, Research Center Europe, Corporate Research, Schering AG, D-13342-Berlin, Germany*

Dihydroquinolines with aminoalkyl side chains have been synthesized and have been shown to be potent n-NOS inhibitors. A marked selectivity versus e-NOS of up to approximately 300-fold was observed, whereas i-NOS was moderately inhibited.



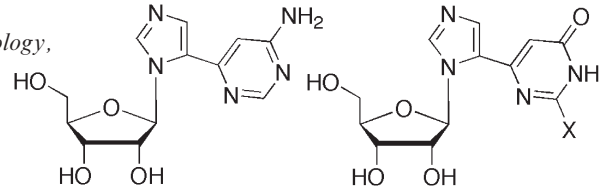
Bioorg. Med. Chem. Lett. 13 (2003) 1985

Unexpected Inhibition of *S*-Adenosyl-L-homocysteine Hydrolase by a Guanosine Nucleoside

Katherine L. Seley,[a,*] Stephen Quirk,[b] Samer Salim,[a] Liang Zhang[a] and Asmerom Hagos[a]

[a]*School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332-0400, USA*
[b]*Kimberly-Clark Corporation, 1400 Holcomb Bridge Rd., Roswell, GA 30076-2199, USA*

A series of shape-modified flexible nucleosides ('fleximers', **1**, **2**, and **3**) was modeled, synthesized, and assayed against SAHase. Moderate inhibitory activity was observed by guanosine fleximer **3**.



1

2, X = H
3, X = NH_2

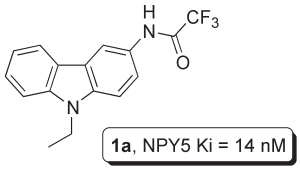
Bioorg. Med. Chem. Lett. 13 (2003) 1989

Structure–Activity Relationships in a Series of NPY Y5 Antagonists: 3-Amido-9-ethylcarbazoles, Core-Modified Analogues and Amide Isosteres

Marlys Hammond,[a,*] Richard L. Elliott,[a] Melissa L. Gillaspy,[a] David C. Hager,[a] Richard F. Hank,[a] Janet A. LaFlamme,[a] Robert M. Oliver,[a] Paul A. DaSilva-Jardine,[a] Ralph W. Stevenson,[a] Christine M. Mack[b] and James V. Cassella[b]

[a]*Department of Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Groton, CT 06340, USA*
[b]*Neurogen Corporation, Branford, CT 06405, USA*

The synthesis and SAR of core-modified analogues and amide isosteres of carbazole-based NPY5 antagonist **1a** are reported.



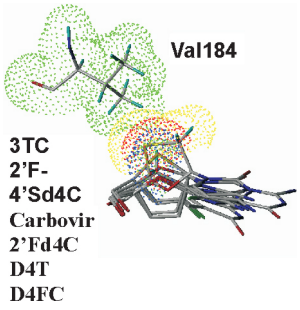
Bioorg. Med. Chem. Lett. 13 (2003) 1993

The Role of 2′,3′-Unsaturation on the Antiviral Activity of Anti-HIV Nucleosides against 3TC-Resistant Mutant (M184V)

Hyunah Choo, Youhoon Chong and Chung K. Chu*

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

The molecular modeling studies of various 2′,3′-unsaturated nucleosides are reported.



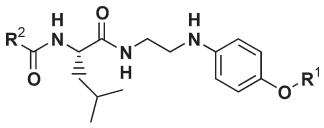
Bioorg. Med. Chem. Lett. 13 (2003) 1997

Arylaminoethyl Amides as Inhibitors of the Cysteine Protease Cathepsin K—Investigating P_1' Substituents

Eva Altmann,[a,*] Jonathan Green[a] and Marina Tintelnot-Blomley[b]

[a]*Arthritis & Bone Metabolism Therapeutic Area, Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Nervous System Therapeutic Area, Novartis Pharma AG, CH-4002 Basel, Switzerland*

Modeling, synthesis and in vitro activities of a series of arylaminoethyl amide based inhibitors of cathepsin K are described. Optimization of P_3/P_1' subunits resulted in highly potent inhibitors of cathepsin K with excellent specificity towards cathepsins L and S.

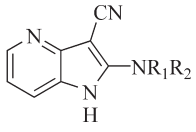


Bioorg. Med. Chem. Lett. 13 (2003) 2003

The Discovery of a New Class of Large-Conductance Ca^{2+}-Activated K^+ Channel Opener Targeted for Overactive Bladder: Synthesis and Structure–Activity Relationships of 2-Amino-4-azaindoles

Sean C. Turner,* William A. Carroll, Tammie K. White, Murali Gopalakrishnan, Michael J. Coghlan, Char-Chang Shieh, Xu-Feng Zhang, Ashutosh S. Parihar, Steven A. Buckner, Ivan Milicic and James P. Sullivan

Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA

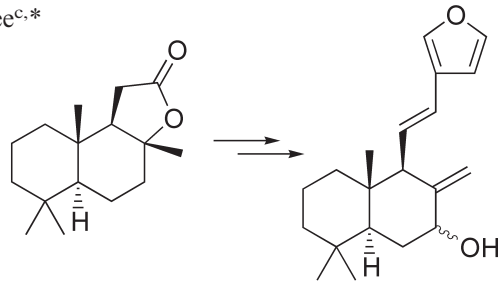


Bioorg. Med. Chem. Lett. 13 (2003) 2009

A Study on the Synthesis of Antiangiogenic (+)-Coronarin A and Congeners from (+)-Sclareolide

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*



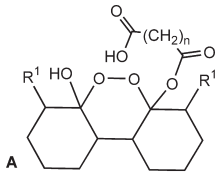
Bioorg. Med. Chem. Lett. 13 (2003) 2013

1,4-Dihydroxy-2,3-dioxatricyclo[8.4.0.0^{4,9}]tetradecane and Derivatives with In Vitro Activity Against *Plasmodium falciparum*, *Trypanasoma b brucei*, *Trypanasoma cruzi*, and *Leishmaniasis infantum*

Joshua Howarth* and Darragh Wilson

School of Chemical Sciences, Dublin City University, Glasnevin, Dublin 9, Ireland

1,4-Dihydroxy-2,3-dioxatricyclo[8.4.0.0^{4,9}]tetradecane and derivatives A have been synthesised and their in vitro activity against several protazoal parasite strains assessed.



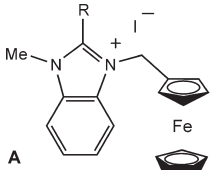
Bioorg. Med. Chem. Lett. 13 (2003) 2017

N-Ferrocenylmethyl, *N*′-Methyl-2-substituted Benzimidazolium Iodide Salts with In Vitro Activity Against the *Leishmania infantum* Parasite Strain L1

Joshua Howarth* and Keith Hanlon

School of Chemical Sciences, Dublin City University, Glasnevin, Dublin 9, Ireland

Our research uncovered a class of benzimidazolium compounds **A** active against the *Leishmania infantum* parasite strain L1.



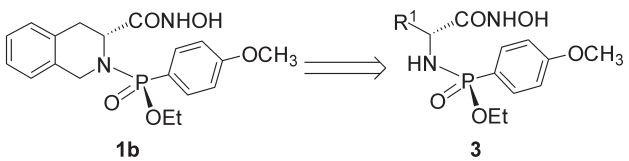
Bioorg. Med. Chem. Lett. 13 (2003) 2021

Discovery of Selective Phosphonamide-Based Inhibitors of Tumor Necrosis Factor-α Converting Enzyme (TACE)

Masaaki Sawa,[a,*] Kiriko Kurokawa,[a] Yoshimasa Inoue,[b] Hirosato Kondo and Kohichiro Yoshino[a]

[a]*Department of Chemistry, R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan*
[b]*Department of Molecular Biology, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan*

The synthesis and biological data for a series of novel acyclic phosphonamide-based inhibitors of TACE is reported.



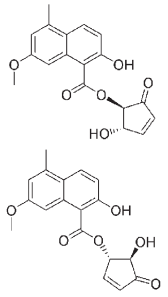
1b **3**

Bioorg. Med. Chem. Lett. 13 (2003) 2025

Chemical Synthesis and Cytotoxicity of Dihydroxylated Cyclopentenone Analogues of Neocarzinostatin Chromophore

Michael D. Urbaniak,[a] Lisa M. Frost,[a] John P. Bingham,[b] Lloyd R. Kelland,[c] John A. Hartley,[b] Derek N. Woolfson[d] and Stephen Caddick[a,*]

[a]*Center for Biomolecular Design and Drug Development, School of Chemistry, University of Sussex, Falmer, Brighton BN1 9QJ, UK*
[b]*Cancer Research UK Drug-DNA Interactions Research Group, Department of Oncology, University College London, London W1W 7BS, UK*
[c]*Department of Bioscience, St. Georges Hospital Medical School, Cranmer Terrace, London, SW17 0QS, UK*
[d]*Center for Biomolecular Design and Drug Development, School of Biological Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, UK*



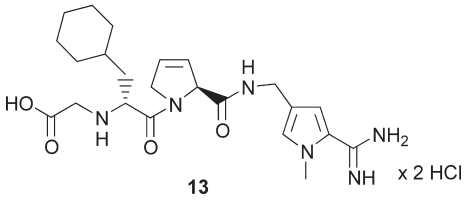
2-Cyclopentenone derivatives containing the naphthoate moiety of Neocarzinostatin chromophore or 2-hydroxy-naphthoate have been synthesized and show in vitro cytotoxic activity.

Bioorg. Med. Chem. Lett. 13 (2003) 2029

D-Phe-Pro-Arg Type Thrombin Inhibitors: Unexpected Selectivity by Modification of the P1 Moiety

Udo E. W. Lange,[a,*] Dorit Baucke,[a] Wilfried Hornberger,[b] Helmut Mack,[b] Werner Seitz[a] and H. Wolfgang Höffken[a]

[a]*BASF AG, D-67056 Ludwigshafen, Germany*
[b]*Abbott GmbH & Co. KG, D-67061 Ludwigshafen, Germany*



13

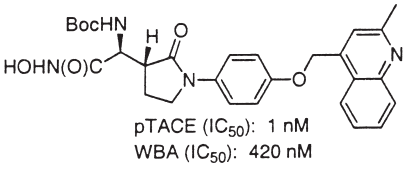
The synthesis of thrombin inhibitors and the X-ray structures of their complexes with human thrombin are reported. These inhibitors were designed to enhance selectivity versus trypsin. The selectivity observed is explained by differences in backbone flexibility at Gly219. The increased flexibility in thrombin is attributed to an insertion of three amino acids in the adjacent loop 184 to 188, which allows for an induced fit of the inhibitor in the S1 binding pocket. This change in enzyme structure could not be predicted with today's molecular modeling tools.

Bioorg. Med. Chem. Lett. 13 (2003) 2035

Discovery of *N*-Hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamides as Potent and Selective Inhibitors of Tumor Necrosis Factor-α Converting Enzyme (TACE)

James J.-W. Duan,* Zhonghui Lu, Chu-Biao Xue, Xiaohua He, Jennifer L. Seng, John J. Roderick, Zelda R. Wasserman, Rui-Qin Liu, Maryanne B. Covington, Ronald L. Magolda, Robert C. Newton, James M. Trzaskos and Carl P. Decicco

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA

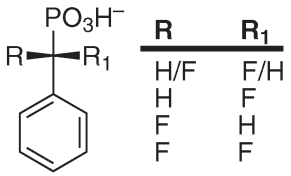


Bioorg. Med. Chem. Lett. 13 (2003) 2041

Inhibition of Mandelate Racemase by α-Fluorobenzylphosphonates

Martin St. Maurice,[a] Stephen L. Bearne,[a,*] Wallach Lu[b] and Scott D. Taylor[b]

[a]*Department of Biochemistry and Molecular Biology, Dalhousie University, Halifax, Nova Scotia, Canada B3H 1X5*
[b]*Department of Chemistry and Biochemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1*



R	R1
H/F	F/H
H	F
F	H
F	F

Mandelate racemase catalyzes the interconversion of the enantiomers of mandelic acid. The enzyme binds the intermediate analogues (*R*)- and (*S*)-α-fluorobenzylphosphonate, and α,α-difluorobenzyl-phosphonate with 100–2500 times less affinity than it exhibits for (*R*,*S*)-α-hydroxybenzylphosphonate at pH 7.5. This apparent low affinity, relative to that of α-hydroxybenzylphosphonate, arises from the altered pK_a values of the α-fluorobenzylphosphonates. For example, (*S*)-α-fluorobenzylphosphonate is bound with the same affinity as the substrate at pH 7.5, but this affinity is increased ~6-fold at pH 6.3.

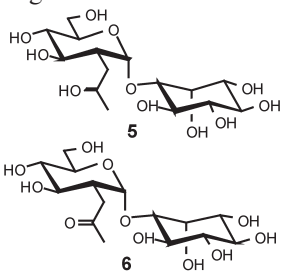
Bioorg. Med. Chem. Lett. 13 (2003) 2045

Synthesis of 2-Deoxy-2-C-Alkylglucosides of *myo*-Inositol as Possible Inhibitors of a *N*-Deacetylase Enzyme in the Biosynthesis of Mycothiol

David W. Gammon,[a,*] Roger Hunter,[a] Daniel J. Steenkamp[b] and Theophilus T. Mudzunga[a]

[a]*Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*
[b]*Division of Chemical Pathology, Department of Laboratory Medicine, University of Cape Town, Observatory, 7925, South Africa*

The preparation is described of two new analogues **5** and **6** of 1-D-1-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol, a biosynthetic intermediate in the production of Mycothiol in the *Mycobacteria*. **5** and **6** inhibit uptake of [^{3}H]Inositol by whole cells of *M. smegmatis*.



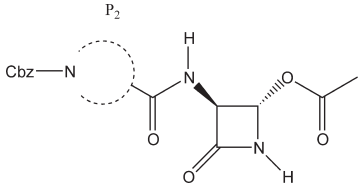
Bioorg. Med. Chem. Lett. 13 (2003) 2051

3,4-Disubstituted Azetidinones as Selective Inhibitors of the Cysteine Protease Cathepsin K. Exploring P2 Elements for Selectivity

Eduardo L. Setti,* Dana Davis, Tobee Chung and John McCarter

Department of Medicinal Chemisty, Celera, 180 Kimball Way, South San Francisco, CA 94080, USA

The importance of cyclic P2 elements for cathepsin K(Cat K) selectivity in 3,4-disubstituted azetidinones has been reported.



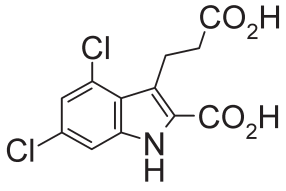
Bioorg. Med. Chem. Lett. 13 (2003) 2055

3-(2-Carboxyethyl)-4,6-dichloro-1*H*-indole-2-carboxylic Acid: An Allosteric Inhibitor of Fructose-1,6-bisphosphatase at the AMP Site

Stephen W. Wright,[a,*] Anthony A. Carlo,[a] Dennis E. Danley,[a] David L. Hageman,[a] George A. Karam,[a] Mahmoud N. Mansour,[a] Lester D. McClure,[a] Jayvardhan Pandit,[a] Gayle K. Schulte,[a] Judith L. Treadway,[a] Ing-Kae Wang[a] and Paul H. Bauer[b]

[a]*Pfizer Central Research, Eastern Point Road, Box 8220-3141, Groton, CT 06340, USA*
[b]*Pfizer Discovery Technology Center, 620 Memorial Drive, Cambridge, MA 02139, USA*

3-(2-Carboxyethyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (MDL-29951), an antagonist of the glycine site of the NMDA receptor, has been found to be an allosteric inhibitor of the enzyme fructose 1,6-bisphosphatase that binds at the AMP regulatory site by X-ray crystallography.



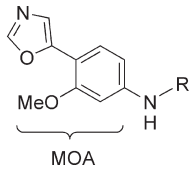
Bioorg. Med. Chem. Lett. 13 (2003) 2059

Inhibitors of Inosine Monophosphate Dehydrogenase: SARs about the *N*-[3-Methoxy-4-(5-oxazolyl)phenyl Moiety

Edwin J. Iwanowicz,* Scott H. Watterson, Junqing Guo, William J. Pitts, T. G. Murali Dhar, Zhongqi Shen, Ping Chen, Henry H. Gu, Catherine A. Fleener, Katherine A. Rouleau, Daniel L. Cheney, Robert M. Townsend and Diane L. Hollenbaugh

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA

The first reported structure–activity relationships (SAR) about the *N*-[3-methoxy-4-(5-oxazolyl)phenyl (MOA) moiety for a series of recently disclosed inosine monophosphate dehydrogenase (IMPDH) inhibitors are described.



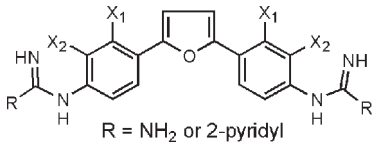
R: represents a series of IMPDH inhibitors

Bioorg. Med. Chem. Lett. 13 (2003) 2065

The Activity of Diguanidino and 'Reversed' Diamidino 2,5-Diarylfurans versus *Trypanosoma cruzi* and *Leishmania donovani*

Chad E. Stephens,[a] Reto Brun,[b] Manar M. Salem,[c] Karl A. Werbovetz,[c] Farial Tanious,[a] W. David Wilson[a] and David W. Boykin[a,*]

[a]*Department of Chemistry, Georgia State University, Atlanta, GA 30303-3083, USA*
[b]*Antiparasite Chemotherapy, Swiss Tropical Institute, Basel, Switzerland*
[c]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*



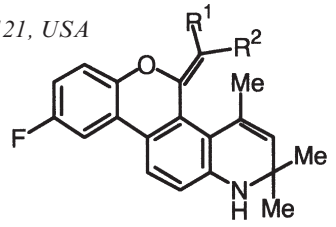
Bioorg. Med. Chem. Lett. 13 (2003) 2071

Synthesis and Biological Activity of 5-Methylidene 1,2-Dihydrochromeno[3,4-*f*]quinoline Derivatives as Progesterone Receptor Modulators

Lin Zhi,* Christopher M. Tegley, Barbara Pio, James P. Edwards, Todd K. Jones, Keith B. Marschke, Dale E. Mais, Boris Risek and William T. Schrader

Discovery Research, Ligand Pharmaceuticals, 10275 Science Center Drive, San Diego, CA 92121, USA

A series of 5-methylidene 1,2-dihydrochromeno[3,4-*f*]quinoline derivitives were synthesized and evaluated as progesterone receptor agonists.



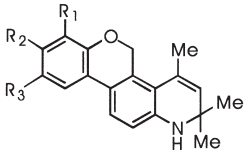
Bioorg. Med. Chem. Lett. 13 (2003) 2075

Development of Progesterone Receptor Antagonists from 1,2-Dihydrochromeno[3,4-*f*]quinoline Agonist Pharmacophore

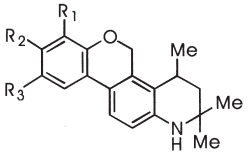
Lin Zhi,* Josef D. Ringgenberg, James P. Edwards, Christopher M. Tegley, Sarah J. West, Barbara Pio, Mehrnouch Motamedi, Todd K. Jones, Keith B. Marschke, Dale E. Mais and William T. Schrader

Discovery Research, Ligand Pharmaceuticals, 10275 Science Center Drive, San Diego, CA 92121, USA

A series of the nonsteroidal progesterone receptor antagonists **11** and **12** were synthesized and evaluated.



11



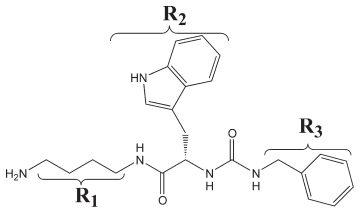
12

Bioorg. Med. Chem. Lett. 13 (2003) 2079

Urea Small Molecule Agonists on Mouse Melanocortin Receptors

Christine G. Joseph, Rayna M. Bauzo, Zhimin Xiang and Carrie Haskell-Luevano*

Department of Medicinal Chemistry, University of Florida, PO Box 100485, Gainesville, FL 32610 USA



1

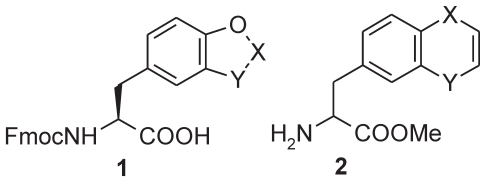
Bioorg. Med. Chem. Lett. 13 (2003) 2083

Design and Synthesis of Phosphotyrosine Mimetics

Zheng Yan,[a] Michael Kahn,[b,c] Maher Qabar,[a] Jan Urban,[a] Hwa-Ok Kim[a] and Mark A. Blaskovich[a,*]

[a]*Molecumetics Ltd., 2023 120th Ave. N.E., Bellevue, WA 98005-2199, USA*
[b]*Department of Pathobiology, University of Washington, Seattle, WA 98195, USA*
[c]*Pacific Northwest Research Institute, 720 Broadway, Seattle, WA 98122, USA*

Several phenylalanine derivatives (**1**, **2**) designed as putative phosphotyrosine mimetics or irreversible active site inhibitors of PTPases were successfully synthesized, then incorporated into a combinatorial library based on a peptidomimetic β-strand template.



1 **2**