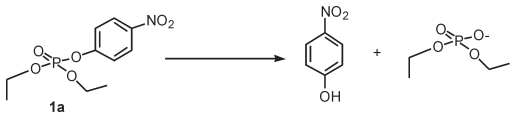
Bioorg. Med. Chem. Lett. 13 (2003) 1623

Structure–Activity Relationship on Human Serum Paraoxonase (PON1) Using Substrate Analogues and Inhibitors

Rakesh S. Bargota,[a] Mahmoud Akhtar,[a] Keith Biggadike,[b] David Gani[a] and and Rudolf K. Allemann[a,*]

[a]*School of Chemical Sciences, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*
[b]*GlaxoSmithKline, Medicine Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK*

Paraoxonase hydrolyses the potent neurotoxin paraoxon **1a** into *p*-nitrophenol and diethyl phosphate. Substrate analogues of **1a** were tested on PON1 in an effort to explore the active site of the enzyme.



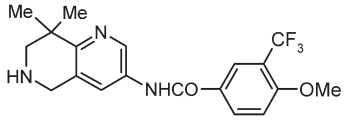
Bioorg. Med. Chem. Lett. 13 (2003) 1627

The Design of 8,8-Dimethyl[1,6]naphthyridines as Potential Anticonvulsant Agents

Nigel E. Austin, Michael S. Hadley, John D. Harling, Frank P. Harrington, Gregor J. Macdonald, Darren J. Mitchell, Graham J. Riley, Tania O. Stean, Geoffrey Stemp, Sharon C. Stratton, Mervyn Thompson* and Neil Upton

Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Research & Development Limited, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

SAR studies on naphthyridines acting at the [^{3}H] SB-204269 binding site have provided anticonvulsants (e.g., **12**) with excellent pharmacokinetic parameters.



12

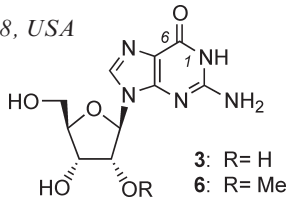
Bioorg. Med. Chem. Lett. 13 (2003) 1631

Novel Synthesis of 2′-*O*-Methylguanosine

Suetying Chow,[a] Ke Wen,[a] Yogesh S. Sanghvi[b] and Emmanuel A. Theodorakis[a,*]

[a]*Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0358, USA*
[b]*ISIS Pharmaceuticals, Inc., Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, CA 92008, USA*

An efficient and chemoselective synthesis of of 2′-*O*-methylguanosine (**6**) has been accomplished in three steps and 61% overall yield from guanosine (**3**) without the need for protection of the nucleobase.



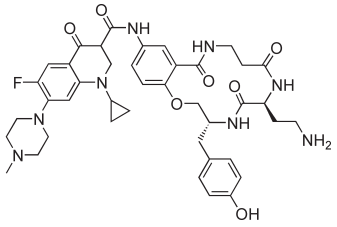
Bioorg. Med. Chem. Lett. 13 (2003) 1635

Antibacterial Activity of Quinolone–Macrocycle Conjugates

Elizabeth A. Jefferson,* Eric E. Swayze, Stephen A. Osgood, Alycia Miyaji, Lisa M. Risen and Lawrence B. Blyn

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

Novel quinolone–macrocycle conjugates displayed low to submicromolar MIC activity against *Escherichia coli* and *Staphylococcus aureus* bacterial strains.

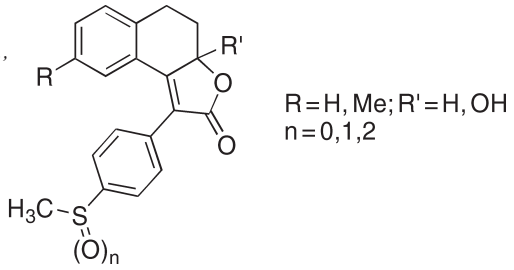


Bioorg. Med. Chem. Lett. 13 (2003) 1639

Conformationally Restricted 3,4-Diarylfuranones (2,3a,4,5-Tetrahydronaphthofuranones) as Selective Cyclooxygenase-2 Inhibitors

Manojit Pal,[a,*] Venugopal Rao Veeramaneni,[a] Murali Nagabelli,[a] Srinivas Rao Kalleda,[a] Parimal Misra,[b] Seshagiri Rao Casturi[b] and Koteswar Rao Yeleswarapu[a,*]

[a]*Department of Chemistry, Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500050, India*
[b]*Department of Biology, Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500050, India*

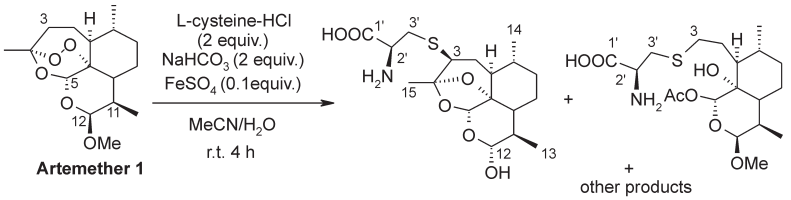


Bioorg. Med. Chem. Lett. 13 (2003) 1645

Study on the Mechanism of Action of Artemether against Schistosomes: The Identification of Cysteine Adducts of Both Carbon-Centred Free Radicals Derived from Artemether

Wen-Min Wu,[a] Yan-Li Chen,[a] Zili Zhai,[b] Shu-Hua Xiao[b] and Yu-Lin Wu[a,*]

[a]*State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Institute of Parasitic Diseases, Chinese Center for Diseases Control and Prevention, Shanghai 200025, China*



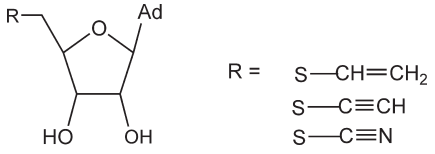
Bioorg. Med. Chem. Lett. 13 (2003) 1649

Inactivation of *S*-Adenosyl-L-Homocysteine Hydrolase with Novel 5′-Thioadenosine Derivatives. Antiviral Effects

Georges Guillerm,[a,*] Danielle Guillerm,[a] Corinne Vandenplas-Vitkowski,[a] Cédric Glapski[a] and Erick De Clercq[b]

[a]*Laboratoire de Chimie Bioorganique, UMR 6519, UFR Sciences, B.P. 1039, 51687 Reims cedex 2, France*
[b]*Rega Institute for Medicinal Research, Katolieke Universiteit of Leuven, Belgium*

A series of 5′-thioadenosine derivatives has been synthesised and their interaction with AdoHcy hydrolase examined. They were evaluated for their inhibititory activity against a variety of viruses.



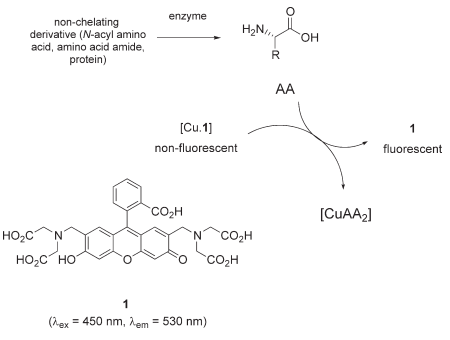
Bioorg. Med. Chem. Lett. 13 (2003) 1653

A Green Fluorescent Chemosensor for Amino Acids Provides a Versatile High-throughput Screening (HTS) Assay for Proteases

Kathryn E. S. Dean, Gérard Klein, Olivier Renaudet and Jean-Louis Reymond*

Department of Chemistry & Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland

A practical and versatile assay for proteases is demonstrated based on the green fluorescent fluorescin derivative **1** (calcein) as a copper(II) complex.



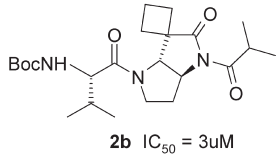
Bioorg. Med. Chem. Lett. 13 (2003) 1657

Design and Synthesis of Spiro-cyclopentenyl and Spiro-[1,3]-dithiolanyl Substituted Pyrrolidine-5,5-*trans*-lactams as Inhibitors of Hepatitis C Virus NS3/4A Protease

David M. Andrews,* Paul S. Jones, Gail Mills, S. Lucy Hind, Martin J. Slater, Naimisha Trivedi and Katrina J. Wareing

GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK

The synthesis of the mechanism-based inhibitor of hepatitis C NS3/4A protease, compound **2b** (replicon $IC_{50} = 3\ \mu M$) is reported.



2b IC_{50} = 3uM

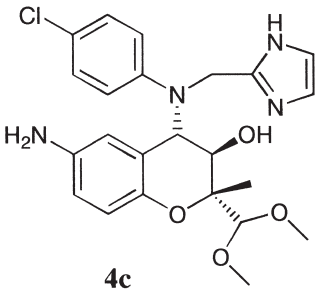
Bioorg. Med. Chem. Lett. 13 (2003) 1661

Identification of a Novel Antiangiogenic Agent; 4-(*N*-Imidazol-2-ylmethyl)amino Benzopyran Analogues

Nakjeong Kim,[b] Sunkyung Lee,[a] Kyu Yang Yi,[a,*] Sung-eun Yoo,[a] Guncheol Kim,[b] Chong Ock Lee,[a] Sung Hee Park[a] and Byung Ho Lee[a]

[a]*Medicinal Science Division, Korea Research Institute of Chemical Technology, 100 Jang-dong, Yoosung-gu, Taejon 305-600, South Korea*
[b]*Department of Chemistry, Chungnam National University, Taejon 305-764, South Korea*

The synthesis, antiangiogenic and antitumor activity of the compound **4c** are reported.



4c

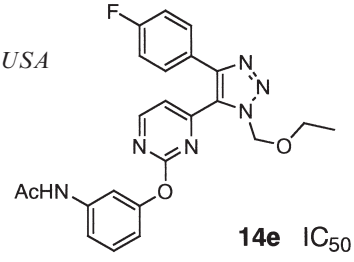
Bioorg. Med. Chem. Lett. 13 (2003) 1665

The Development of New Triazole Based Inhibitors of Tumor Necrosis Factor-α (TNF-α) Production

Joshua S. Tullis,[a] John C. VanRens, Michael G. Natchus,[b] Michael P. Clark,[c,*] Biswanath De, Lily C. Hsieh and Michael J. Janusz

[a]*Array Biopharma, 3200 Walnut Street, Boulder, CO 80301, USA*
[b]*Xemplar BioSciences, 1201 West Peachtree Street, Suite 800, Atlanta, GA 30309, USA*
[c]*Procter and Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Rd, Mason, OH 45040, USA*

The synthesis of potent vicinal aryl/pyridin (pyrimidin)-4-yl triazole TNF-α inhibitors is reported.



14e IC_{50} = 8 nM

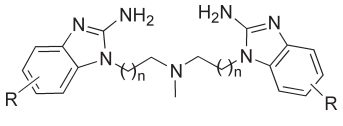
Bioorg. Med. Chem. Lett. 13 (2003) 1669

Identification of 2-Aminobenzimidazole Dimers as Antibacterial Agents

Punit P. Seth,* Elizabeth A. Jefferson, Lisa M. Risen and Stephen A. Osgood

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

The synthesis and evaluation of 2-aminobenzimidazole dimers as antibacterial agents is described.

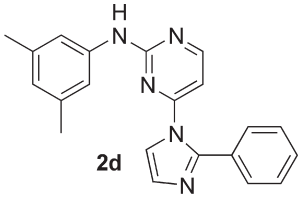


Bioorg. Med. Chem. Lett. 13 (2003) 1673

2,4-Disubstituted Pyrimidines: A Novel Class of KDR Kinase Inhibitors

Peter J. Manley,* Adrienne E. Balitza, Mark T. Bilodeau, Kathleen E. Coll, George D. Hartman, Rosemary C. McFall, Keith W. Rickert, Leonard D. Rodman and Kenneth A. Thomas

Departments of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA



2d

KDR IC_{50} = 6 nM

Cell IC_{50} = 19 nM

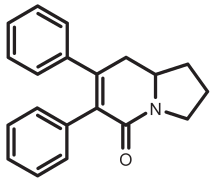
Bioorg. Med. Chem. Lett. 13 (2003) 1679

Novel 6,7-diphenyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one Analogues as Cytotoxic Agents

Vedula M. Sharma,[a,*] K. V. Adi Seshu,[a] C. Vamsee Krishna,[a] P. Prasanna,[a] V. Chandra Sekhar,[a] A. Venkateswarlu,[a] Sriram Rajagopal,[b] R. Ajaykumar,[b] Dhanvanthri S. Deevi,[b] N. V. S. Rao Mamidi[c] and R. Rajagopalan[b]

[a]*Discovery Chemistry, Dr. Reddy's Laboratories, Discovery Research, Miyapur, Hyderabad, 500 050, India*
[b]*Discovery Biology, Dr. Reddy's Laboratories, Discovery Research, Miyapur, Hyderabad, 500 050, India*
[c]*Drug Metabolism and Pharmacokinetics, Dr. Reddy's Laboratories, Discovery Research, Miyapur, Hyderabad, 500 050, India*

A novel series of 6,7-diphenylindolizidinones were synthesized and tested for in vitro anticancer activity in various human cancer cell lines. Active compounds were further tested in the hollow fibre assay to assess their in vivo efficacy.

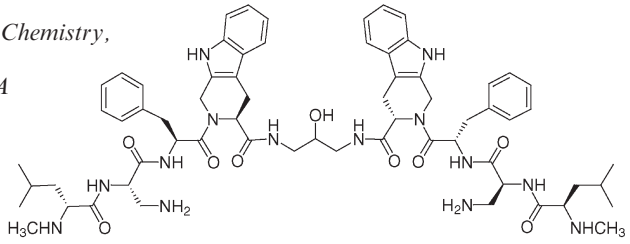


Bioorg. Med. Chem. Lett. 13 (2003) 1683

Identification of Potent and Broad-Spectrum Antibiotics from SAR Studies of a Synthetic Vancomycin Analogue

Kateri A. Ahrendt,[a] Jacob A. Olsen,[a] Masahiro Wakao,[a] Joaquim Trias[b] and Jonathan A. Ellman[a,*]

[a]*Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, CA 94720, USA*
[b]*Versicor Inc., 34790 Ardentech Court, Fremont, CA 94555, USA*



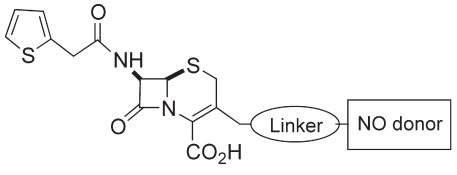
Bioorg. Med. Chem. Lett. 13 (2003) 1687

Synthesis of Beta-Lactamase Activated Nitric Oxide Donors

Xiaoping Tang, Tingwei Cai and Peng George Wang*

Department of Chemistry, Wayne State University, Detroit, MI 48202, USA

The synthesis of beta-lactamase activated nitric oxide donors is reported.



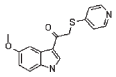
Bioorg. Med. Chem. Lett. 13 (2003) 1691

Discovery of Novel Low Molecular Weight Inhibitors of IMPDH Via Virtual Needle Screening

Stephen D. Pickett,* Bradley S. Sherborne, Trevor Wilkinson, James Bennett, Neera Borkakoti, Michael Broadhurst, David Hurst, Ian Kilford, Murray McKinnell and Philip S. Jones

Roche Discovery Welwyn, Broadwater Road, Welwyn Garden City, Herts AL7 3AY, UK

Novel, low molecular weight inhibitors of IMPDH have been discovered through the application of a validated virtual screening protocol. Application of this procedure to the selection of compounds for screening from an in-house database resulted in a 50-fold reduction in the size of the screening set (3425 to 74 compounds) and gave a hit-rate of 10% on biological evaluation.

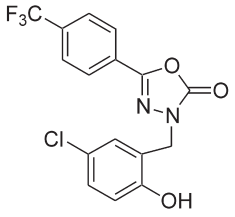
Structure	IC_{50}, μM	Structure	IC_{50}, μM
	31		88
	32		99
	32		168
	54		620

Bioorg. Med. Chem. Lett. 13 (2003) 1695

Synthesis of Water-Soluble Prodrugs of BMS-191011: A Maxi-K Channel Opener Targeted for Post-stroke Neuroprotection

Piyasena Hewawasam,[a,*] Min Ding,[a] Nathan Chen,[a] Dalton King,[a] Jay Knipe,[c] Lorraine Pajor,[c] Astrid Ortiz,[b] Valentin K. Gribkoff[b] and John Starrett[a]

[a]*Department of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[b]*Department of Neuroscience/Genitourinary Drug Discovery, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[c]*Department of Metabolism and Pharmacokinetics, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*

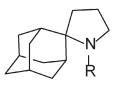


Bioorg. Med. Chem. Lett. 13 (2003) 1699

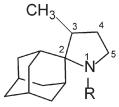
Spiro[pyrrolidine-2,2′-adamantanes]: Synthesis, Anti-Influenza Virus Activity and Conformational Properties

Ioannis Stylianakis,[a] Antonios Kolocouris,[a,*] Nicolas Kolocouris,[a] George Fytas,[a] George B. Foscolos,[a] Elizaveta Padalko,[b] Johan Neyts[b] and Erik De Clercq[b]

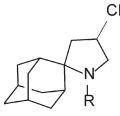
The biologically active 3-, 4- and 5-methylspiro[pyrrolidine-2,2′-adamantanes] **11**, **15**, **12**, **16**, **18**, **20**, were synthesized. These compounds possess a lipophilic part, that is the substituted pyrrolidine ring, in addition to adamantane that can interact with influenza A M2 protein. 5-Me Substitution was optimal for H_2N_2 strain activity. Experimental observation using NMR spectroscopy and molecular mechanics calculations demonstrated only a pair of conformers $\mathbf{A}^+\mathbf{H}$ (*N*-Me(ax), *C*-Me(eq)) and $\mathbf{B}^+\mathbf{H}$ (*N*-Me(ax), *C*-Me(ax)) from the possible four conformers for protonated *C*-Me, *N*-Me derivatives $\mathbf{15}^+\mathbf{H}$, $\mathbf{16}^+\mathbf{H}$ and $\mathbf{20}^+\mathbf{H}$.



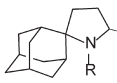
2: R=H
MIC_{50}=1.8 μM, SI>610.5
3: R=CH_3
MIC_{50}=2.9 μM, SI=357



11: R=H
MIC_{50}=3.7 μM, SI>280
15: R=CH_3
MIC_{50}=12.5 μM, SI>60



12: R=H
MIC_{50}=3.3 μM, SI=313.6
16: R=CH_3
MIC_{50}=3.3 μM, SI>226



18: R=H
MIC_{50}=2.5 μM, SI>414
20: R=CH_3
MIC_{50}=2.7 μM, SI=55.3

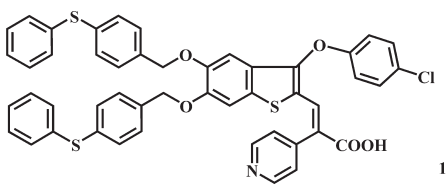
Bioorg. Med. Chem. Lett. 13 (2003) 1705

New Fibrinolytic Agents: Benzothiophene Derivatives as Inhibitors of the t-PA–PAI-1 Complex Formation

Guillaume De Nanteuil,[a,*] Christine Lila-Ambroise,[a] Alain Rupin,[b] Marie-Odile Vallez[b] and Tony J. Verbeuren[b]

[a]*Division D of Medicinal Chemistry, Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*
[b]*Division of Angeiologie, Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*

Benzothiophene derivatives were prepared and evaluated in a t-PA-induced fibrin clot lysis assay. **11** was found to be a potent inhibitor of the t-Pa–PAI-1 complex formation, giving an IC_{50} of 39 nM.



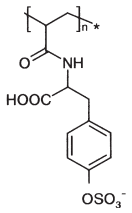
11

Bioorg. Med. Chem. Lett. 13 (2003) 1709

P-Selectin Blocking Potency of Multimeric Tyrosine Sulfates In Vitro and In Vivo

Tatyana V. Pochechueva,[a] Natalia A. Ushakova,[b] Marina E. Preobrazhenskaya,[b] Nikolay E. Nifantiev,[c] Yu. E. Tsvetkov,[c] Marina A. Sablina,[a] Alexander B. Tuzikov,[a] Mike I. Bird,[d] Robert Rieben[e] and Nicolai V. Bovin[a,*]

[a]*Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Miklukho-Maklaya 16/10, 117997 Moscow, Russia*
[b]*Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, Moscow, Russia*
[c]*Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia*
[d]*Gene Expression & Protein Biochemistry Department, GlaxoSmithKline R&D Ltd., Stevenage, SG1 2NY, UK*
[e]*Heart Transplantation Laboratory, Department of Cardiovascular Diseases, University Hospital, CH-3010 Bern, Switzerland*



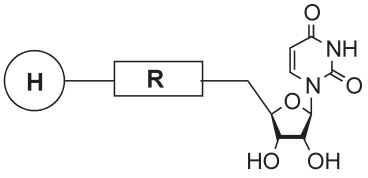
Polymeric *O*-sulfotyrosine is powerful blocker of P-selectin, $IC_{50} = 6$ ng/mL.

Bioorg. Med. Chem. Lett. 13 (2003) 1713

Design, Synthesis and Biological Evaluation of Hetaryl-Nucleoside Derivatives as Inhibitors of Chitin Synthase

Jean-Bernard Behr, Thierry Gourlain, Abdellatif Helimi and Georges Guillerm*

Laboratoire Réactions Sélectives et Applications UMR 6519, UFR Sciences, CNRS BP 1039, 51687 Reims Cedex 2, France



R = malonic, tartaric or carbohydrate moiety
H = hydroxypyridine or quinoline

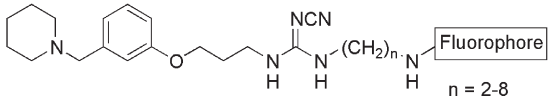
Bioorg. Med. Chem. Lett. 13 (2003) 1717

Synthesis and Pharmacological Activity of Fluorescent Histamine H_2 Receptor Antagonists Related to Potentidine

Liantao Li,[a] Julia Kracht,[b] Shiqi Peng,[a] Günther Bernhardt,[b] Sigurd Elz[b] and Armin Buschauer[b,*]

[a]*College of Pharmaceutical Sciences, Peking University, 100083, Beijing, China*
[b]*Institute of Pharmacy, University of Regensburg, D-93040 Regensburg, Germany*

Fluorescently labeled histamine H_2 receptor antagonists were synthesized from appropriate primary amine intermediates, which were derivatized with, for example, fluorescein, acridine, dansyl, nitrobenzoxadiazole (NBD). On the isolated spontaneously beating guinea pig right atrium the NBD-labeled substances proved to be most potent histamine H_2 receptor antagonists achieving pA_2 values in the range of 7.5–8.0, comparable to the activity of famotidine.



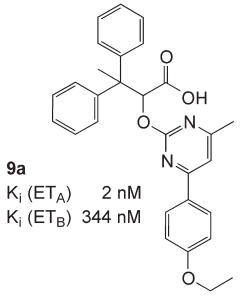
Bioorg. Med. Chem. Lett. 13 (2003) 1721

Solid-Phase Synthesis of Endothelin Receptor Antagonists

Udo E. W. Lange,[a,*] Wilfried M. Braje,[b,*] Willi Amberg[b] and Georg Kettschau[b]

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

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

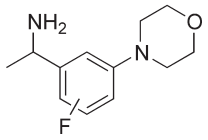


Bioorg. Med. Chem. Lett. 13 (2003) 1725

Synthesis of Fluorinated 1-(3-Morpholin-4-yl-phenyl)-Ethylamines

Yong-Jin Wu,[a,*] Huan He,[a] Li-Qiang Sun,[a] Dedong Wu,[b] Qi Gao[b] and Hui-Yin Li[c]

[a]*Department of Neuroscience Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[b]*Department of Analytical Sciences, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[c]*Chemical Process Research and Development, The Bristol-Myers Squibb Pharmaceutical Research Institute, Deepwater, NJ 08023, USA*



The synthesis of four (±)-fluorinated 1-(3-morpholin-4-yl-phenyl)-ethylamines and an enantioselective approach to these amines through reductive amination are described.

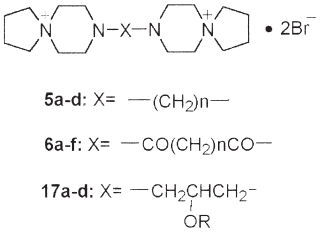
Bioorg. Med. Chem. Lett. 13 (2003) 1729

Unique Spirocyclopiperazinium Salt. Part 2: Synthesis and Structure–Activity Relationship of Dispirocyclopiperazinium Salts as Analgesics

Xin Wang, Feng-Li Gao, Hong-Bin Piao, Tie-Ming Cheng and Run-Tao Li*

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

Unique dispirocyclopiperazinium derivatives **5a–d**, **6a–f** and **17a–d** were prepared. Compounds **5a** ($n=3$), **17a** ($R=$Et) and **17b** ($R=C_6H_{13}$) showed high in vivo analgesic activity.

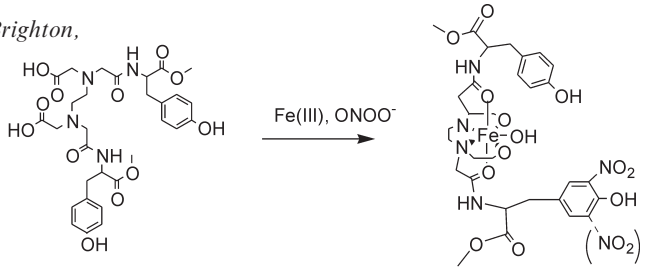


Bioorg. Med. Chem. Lett. 13 (2003) 1733

EDTA Bis-(Methyl Tyrosinate): A Chelating Peptoid Peroxynitrite Scavenger

Anna E. O. Fisher and Declan P. Naughton*

School of Pharmacy and Biomolecular Sciences, University of Brighton, Cockcroft Building, Moulsecoomb, Brighton BN2 4GJ, UK

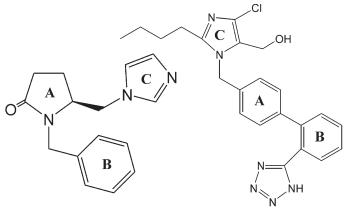


Bioorg. Med. Chem. Lett. 13 (2003) 1737

Design and Synthesis of Novel Antihypertensive Drugs

P. Moutevelis-Minakakis,[a] M. Gianni,[a] H. Stougiannou,[a] P. Zoumpoulakis,[b] A. Zoga,[b] A. D. Vlahakos,[c] E. Iliodromitis[d] and T. Mavromoustakos[b,*]

[a]*University of Athens, Department of Chemistry, Zographou 15771, Athens, Greece*
[b]*Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, Greece*
[c]*Aretaieo University Hospital, Division of Nephrology, Athens University, Medical School, 76 Vas. Sofias, Ave, 11528 Athens, Greece*
[d]*Onassis Cardiac Surgery Center, 356 Sygrou Ave., Athens, Greece*



A novel non-peptide molecule is synthesized, which mimics the His[6]-Pro[7]-Phe[8] part of Ang II and is based on the (*S*)-pyroglutamic acid.

MM1 Losartan

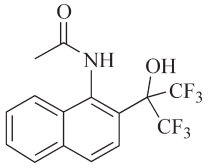
Bioorg. Med. Chem. Lett. 13 (2003) 1741

Structure–Activity Relationship of a Novel Class of Naphthyl Amide K_{ATP} Channel Openers

Sean C. Turner,[a,*] William A. Carroll,[a] Tammie K. White,[a] Michael E. Brune,[a] Steven A. Buckner,[a] Murali Gopalakrishnan,[a] Adebola Fabiyi,[a] Michael J. Coghlan,[a] Victoria E. Scott,[a] Neil A. Castle,[b] Anthony V. Daza,[a] Ivan Milicic[a] and James P. Sullivan[a]

[a]*Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*
[b]*Icagen, Inc., 4222 Emperor Boulevard, Suite 460, Durham, NC 27703, USA*

The discovery of a potent and efficacious potassium channel opener A-151892 (EC_{50} 18 nm) is reported.



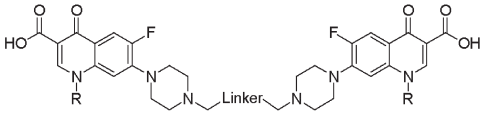
1: A-151892

Bioorg. Med. Chem. Lett. 13 (2003) 1745

Piperazinyl-Linked Fluoroquinolone Dimers Possessing Potent Antibacterial Activity Against Drug-Resistant Strains of *Staphylococcus aureus*

Robert J. Kerns,[a,*] Michael J. Rybak,[b] Glenn W. Kaatz,[c] Flamur Vaka,[d] Raymond Cha,[b] Richard G. Grucz,[b] Veena U. Diwadkar[d] and Tracey D. Ward[d]

[a]*Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, USA*
[b]*Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Detroit, MI 48202, USA*
[c]*John D. Dingell VAMC & Wayne State University School of Medicine, Detroit, MI 48201, USA*
[d]*Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, USA*



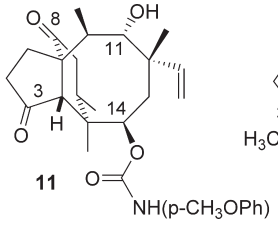
Bioorg. Med. Chem. Lett. 13 (2003) 1751

Synthesis and Activity of a C-8 Keto Pleuromutilin Derivative

Dane M. Springer,[a,*] Margaret E. Sorenson,[a] Stella Huang,[b] Timothy P. Connolly,[a] Joanne J. Bronson,[a] James A. Matson,[c] Ronald L. Hanson,[d] David B. Brzozowski,[d] Thomas L. LaPorte[d] and Ramesh N. Patel[d]

[a]*Department of Anti-infective Chemistry, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA*
[b]*Discovery Analytical Sciences, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA*
[c]*Natural Products Chemistry, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA*
[d]*Process Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, One Squibb Drive, New Brunswick, NJ 08903, USA*

A C-8 keto pleuromutilin derivative (**11**) has been synthesized from the biotransformation product 8-hydroxy mutilin. A key step in the process was the selective oxidation at C-8 of 8-hydroxy mutilin using tetrapropylammonium perruthenate. The presence of the C-8 keto group precipitated interesting intramolecular chemistry to afford a compound (**10**) with a novel pleuromutilin-derived ring system.



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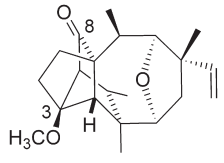

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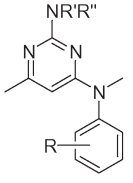
Bioorg. Med. Chem. Lett. 13 (2003) 1755

Anilinopyrimidines as Novel Antituberculosis Agents

Jody Morgan,[a] Rachada Haritakul[b] and Paul A. Keller[a,*]

[a]*Department of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia*
[b]*National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), 113 Phaholyothin Rd., Klong 1, Klong Luang, Pathumthani 12120, Thailand*

The structure and activity of new antituberculosis compounds is reported.



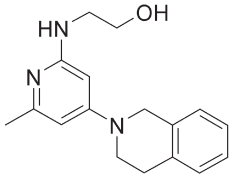
Bioorg. Med. Chem. Lett. 13 (2003) 1759

4-(3,4-Dihydro-1*H*-isoquinolin-2yl)-pyridines and 4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-quinolines as Potent NR1/2B Subtype Selective NMDA Receptor Antagonists

Bernd Büttelmann,[a,*] Alexander Alanine,[a] Anne Bourson,[b] Ramanjit Gill,[b] Marie-Paule Heitz,[a] Vincent Mutel,[b] Emmanuel Pinard,[a] Gerhard Trube[b] and René Wyler[a]

[a]*Pharma Division, Discovery Chemistry, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland*
[b]*Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland*

A series of 4-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridines and analogous quinolines was prepared and evaluated as NR1/2B subtype selective NMDA receptor antagonists. 2-Hydroxyalkylamino substitution combines high affinity with selectivity (vs α1 and M1 receptors) and activity in vivo.

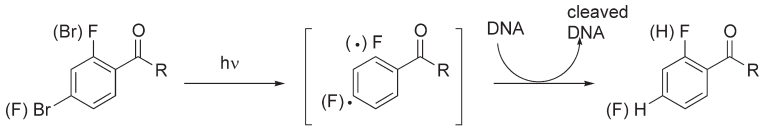


Bioorg. Med. Chem. Lett. 13 (2003) 1763

Photoinduced Cleavage of DNA by Bromofluoroacetophenone–Pyrrolecarboxamide Conjugates

Paul A. Wender[a] and Raok Jeon[b,*]

[a]*Department of Chemistry, Stanford University, Stanford, CA 94305, USA*
[b]*College of Pharmacy, Sookmyung Women's University, Chungpa-Dong 2-Ka, Yongsan-Ku, Seoul 140-742, South Korea*



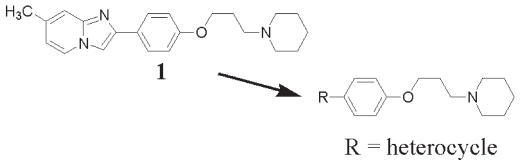
Bioorg. Med. Chem. Lett. 13 (2003) 1767

Non-imidazole Heterocyclic Histamine H_3 Receptor Antagonists

Wenying Chai,* J. Guy Breitenbucher, Annette Kwok, Xiaobing Li, Victoria Wong, Nicholas I. Carruthers, Timothy W. Lovenberg, Curt Mazur, Sandy J. Wilson, Frank U. Axe and Todd K. Jones

Johnson & Johnson Pharmaceutical Research and Development L. L. C., 3210 Merryfield Row, San Diego, CA 92121, USA

Continued exploration of the SAR around the lead imidazopyridine histamine H_3 antagonist **1** has led to the discovery of several related series of heterocyclic histamine H_3 antagonists. The synthesis and SAR of indolizine, indole and pyrazolopyridine based compounds are now described.



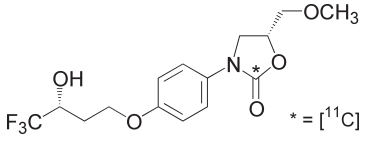
Bioorg. Med. Chem. Lett. 13 (2003) 1771

Synthesis and In Vivo Imaging Properties of [^{11}C]Befloxatone: A Novel Highly Potent Positron Emission Tomography Ligand for Mono-Amine Oxidase-A

Frédéric Dolle,[a,*] Héric Valette,[a] Yann Bramoulle,[a] Ilonka Guenther,[a] Chantal Fuseau,[a] Christine Coulon,[a] Carole Lartizien,[a] Samir Jegham,[b] Pascal George,[b] Olivier Curet,[b] Jean-Louis Pinquier[b] and Michel Bottlaender[a]

[a]*Service Hospitalier Frédéric Joliot, Département de Recherche Médicale, CEA/DSV, 4 place du Général Leclerc, F-91406 Orsay, France*
[b]*Synthélabo Recherche, 31 Avenue Paul Vaillant Couturier, F-92200 Bagneux, France*

[^{11}C]Befloxatone appears as an excellent tool for the assessment of MAO-A binding sites using positron emission tomography, a high-resolution, sensitive, non-invasive and quantitative imaging technique.



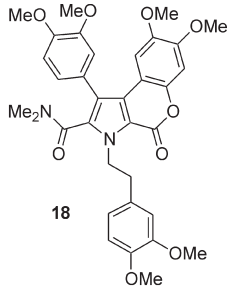
Bioorg. Med. Chem. Lett. 13 (2003) 1777

Multidrug Resistance Reversal Activity of Key Ningalin Analogues

Danielle R. Soenen, Inkyu Hwang, Michael P. Hedrick and Dale L. Boger*

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

Key analogue derivatives of the ningalins, potent multidrug resistance (MDR) reversal compounds, were examined resulting in the discovery of a potent MDR reversal agent that hypersensitizes P-gp resistant tumor cell lines to front-line conventional therapeutic agents.

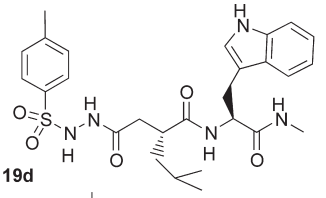


Bioorg. Med. Chem. Lett. 13 (2003) 1783

Improved Gelatinase A Selectivity by Novel Zinc Binding Groups Containing Galardin Derivatives

Franck Augé,[a] William Hornebeck,[b] Martine Decarme[b] and Jean-Yves Laronze[a,*]

[a]*UMR 6013 'Isolement, Structure, Transformation et Synthèse de Produits Naturelles', Faculté de Pharmacie, France*
[b]*FRE 2534 CNRS, Faculté de Médecine, IFR53 Biomolécules, Université de Reims Champagne-Ardenne, 51 Rue Cognacq Jay, 51096 Reims Cedex, France*



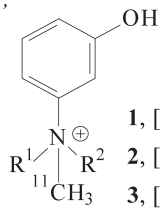
	MMP-1	MMP-2
IC_{50} (nM)	$> 10^4$	30

Bioorg. Med. Chem. Lett. 13 (2003) 1787

Facile Synthesis of [^{11}C]Edrophonium and Its Analogues as New Potential PET Imaging Agents for Heart Acetylcholinesterase

Qi-Huang Zheng,* Xuan Liu, Xiangshu Fei, Ji-Quan Wang, Bruce H. Mock, Barbara E. Glick-Wilson, Michael L. Sullivan and Gary D. Hutchins

Department of Radiology, Indiana University School of Medicine, 975 West Walnut Street, Room 028C, Indianapolis, IN 46202-5121, USA



1, [^{11}C]Edrophonium; R^1=CH_3, R^2=CH_2CH_3
2, [^{11}C]Edrophonium ethyl analog; R^1=R^2=CH_2CH_3
3, [^{11}C]Edrophionium methyl analog; R^1=R^2=CH_3

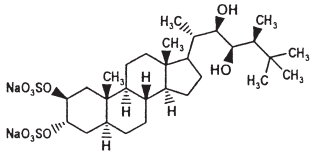
Bioorg. Med. Chem. Lett. 13 (2003) 1791

A New Sterol Sulfate, Sch 572423, from a Marine Sponge, *Topsentia* sp.

Shu-Wei Yang,[a,*] Alexei Buivich,[a] Tze-Ming Chan,[a] Michelle Smith,[a] Jean Lachowicz,[a] Shirley A. Pomponi,[b] Amy E. Wright,[b] Ronald Mierzwa,[a] Mahesh Patel,[a] Vincent Gullo[a] and Min Chu[a]

[a]*Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Harbor Branch Oceanographic Institution, 5600, U.S. 1 North, Fort Pierce, FL 34946, USA*

A new sterol sulfate, Sch 572423, discovered from *Topsentia* sp. exhibited a $P2Y_{12}$ inhibition (IC_{50} 2.2 μM). Its structure was elucidated by spectroscopic data analyses.



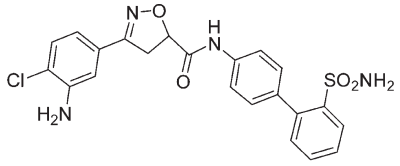
Bioorg. Med. Chem. Lett. 13 (2003) 1795

Discovery of 3-Amino-4-Chlorophenyl P1 as a Novel and Potent Benzamidine Mimic Via Solid-Phase Synthesis of an Isoxazoline Library

Patrick Y. S. Lam,* Jessica J. Adams, Charles G. Clark, W. Jason Calhoun, Joseph M. Luettgen, Robert M. Knabb and Ruth R. Wexler

Bristol-Myers Squibb Co., Experimental Station, PO Box 80500, Wilmington, DE 19880-0500, USA

In an effort to identify orally bioavailable factor Xa inhibitors, two isoxazolines libraries were prepared to scan for novel P1 ligands. From this work, 4-chloro-3-aniline was identified as a novel and potent benzamidine mimic.



11a FXa K_i 0.13 μM

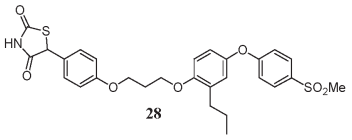
Bioorg. Med. Chem. Lett. 13 (2003) 1801

5-Aryl Thiazolidine-2,4-diones as Selective PPARγ Agonists

Hiroo Koyama,[a,*] Julia K. Boueres,[a] Wei Han,[a] Edward J. Metzger,[a] Jeffrey P. Bergman,[a] Dominick F. Gratale,[a] Daniel J. Miller,[a] Richard L. Tolman,[a] Karen L. MacNaul,[b] Joel P. Berger,[b] Thomas W. Doebber,[b] Kwan Leung,[c] David E. Moller,[b] James V. Heck[a] and Soumya P. Sahoo[a,*]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Department of Metabolic Disorders—Diabetes, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*

Compound **28** exhibited glucose level correction comparable to rosiglitazone in *db*/*db* mice.



28

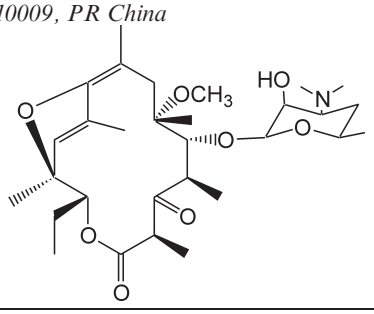
Bioorg. Med. Chem. Lett. 13 (2003) 1805

A Novel Bicyclic Ketolide Derivative

Ying Zhao, Qidong You* and Wenbin Shen

Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, Jiangsu 210009, PR China

A novel derivative of macrolide with a bicyclic structure was synthesized. The structure and stereochemistry of this novel compound were elucidated and established by NMR and X-ray crystallography.



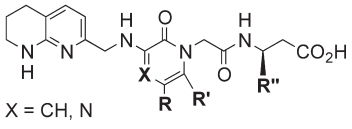
Bioorg. Med. Chem. Lett. 13 (2003) 1809

Non-Peptide $\alpha_v\beta_3$ Antagonists. Part 6: Design and Synthesis of $\alpha_v\beta_3$ Antagonists Containing a Pyridone or Pyrazinone Central Scaffold

Michael J. Breslin,[a,*] Mark E. Duggan,[a] Wasyl Halczenko,[a] Carmen Fernandez-Metzler,[c] Cecilia A. Hunt,[a] Chih-Tai Leu,[b] Kara M. Merkle,[c] Adel M. Naylor-Olsen,[e] Thomayant Prueksaritanont,[c] Gary Stump,[d] Audrey Wallace,[d] Sevgi B. Rodan[b] and John H. Hutchinson[a,*]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*
[b]*Department of Bone Biology and Osteoporosis Research, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*
[d]*Department of Pharmacology, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*
[e]*Department of Molecular Design and Diversity, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*

Two novel series of small-molecule RGD mimetics containing either a substituted pyridone or pyrazinone central constraint were prepared. Modification of the β-alanine 3-substituent produced compounds that are potent and selective $\alpha_v\beta_3$ antagonists and exhibit a range of physicochemical properties.



X = CH, N

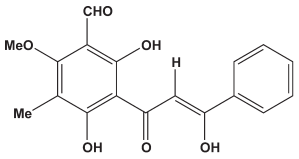
Bioorg. Med. Chem. Lett. 13 (2003) 1813

Anti-AIDS Agents 54. A Potent Anti-HIV Chalcone and Flavonoids from Genus *Desmos*

Jiu-Hong Wu,[a] Xi-Hong Wang,[b] Yang-Hua Yi[c] and Kuo-Hsiung Lee[b,*]

[a]*Department of Pharmacy, 306 Hospital of PLA, Beijing 100101, China*
[b]*Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA*
[c]*School of Pharmacy, Second Military Medical University, Shanghai, 200433, China*

The anti-HIV activities of 2-methoxy-3-methyl-4, 6-dihydroxy-5-(3′-hydroxy) cinnamoylbenzaldehyde (**12**), lawinal (**6**), desmosflavanone II (**10**), and desmethoxyatteucinol (**8**) are reported.



12 TI=489

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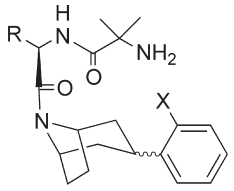
Substituted Bridged Phenyl Piperidines: Orally Active Growth Hormone Secretagogues

Zhijian Lu,[a,*] James R. Tata,[a] Kang Cheng,[b] Liente Wei,[b] Wanda W.-S. Chan,[b] Bridget Butler,[b] Klaus D. Schleim,[b] Thomas M. Jacks,[b] Gerard Hickey[b] and Arthur A. Patchett[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Biochemistry and Physiology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

A new series of growth hormone secretagogues has been discovered. The best compound **26j** shows excellent ability to release growth hormone both in vitro and in vivo. The synthesis and biological activity of these compounds are discussed.



R= Phenylpropyl, alkylindole
X= H, Me, CO_2Et

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Design and Synthesis of Highly Potent HIV Protease Inhibitors with Activity Against Resistant Virus

Zhijian Lu,[a,*] Subharekha Raghavan,[a] Joann Bohn,[a] Mark Charest,[a] Mark W. Stahlhut,[b] Carrie A. Rutkowski,[b] Amy L. Simcoe,[b] David B. Olsen,[b] William A. Schleif,[b] Anthony Carella,[b] Lori Gabryelski,[b] Lixia Jin,[c] Jiunn H. Lin,[c] Emilio Emini,[b] Kevin Chapman[a] and James R. Tata[a]

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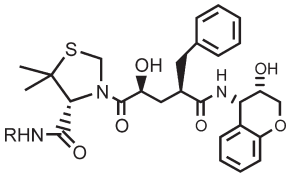
[b]*Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

A series of highly potent HIV protease inhibitors have been designed and synthesized. These compounds are active against various clinical viral isolates as well as wild-type virus. The synthesis and biological activity of these HIV protease inhibitors are discussed.



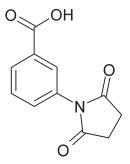
Bioorg. Med. Chem. Lett. 13 (2003) 1825

Synthesis, Anticholinesterase Activity and Structure–Activity Relationships of *m*-Aminobenzoic Acid Derivatives

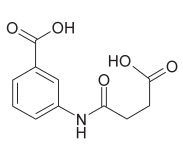
José Trujillo-Ferrara,* Leticia Montoya Cano and Michel Espinoza-Fonseca

Sección de graduados y Departamento de Bioquímica, Escuela Superior de Medicina del Instituto Politécnico Nacional, Apartado Postal 42-161, C.P. 11340, Mexico City, Mexico

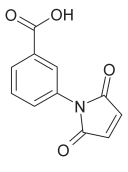
The synthesis, acetylcholinesterase inhibitory capacity and SAR of *m*-Aminobenzoic acid derivatives are reported.



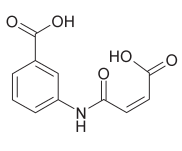
1b (IC50=33.4 nM)



1a (IC50=92.5 nM)



2b (IC50=256nM)



2a (IC50=357nM)

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Characterization of HERG Potassium Channel Inhibition Using CoMSiA 3D QSAR and Homology Modeling Approaches

Robert A. Pearlstein,[a] Roy J. Vaz,[a,*] Jiesheng Kang,[a] Xiao-Liang Chen,[a] Maria Preobrazhenskaya,[b] Andrey E. Shchekotikhin,[b] Alexander M. Korolev,[b] Ludmila N. Lysenkova,[b] Olga V. Miroshnikova,[b] James Hendrix[a] and David Rampe[a]

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