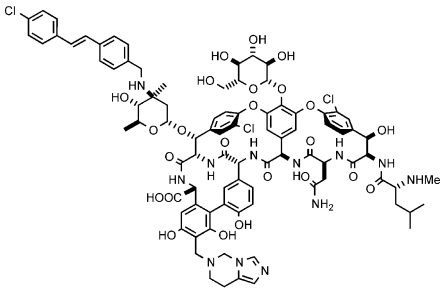
Bioorg. Med. Chem. Lett. 12 (2002) 3027

Novel Semi-Synthetic Glycopeptide Antibiotics Active Against Methicillin-Resistant S*taphylococcus aureus* (MRSA) and Vancomycin-Resistant Enterococci (VRE): Doubly-Modified Water-Soluble Derivatives of Chloroorienticin B

Osamu Yoshida,[a] Tatsuro Yasukata,[a,*] Yukihito Sumino,[a] Tadashi Munekage,[b] Yukitoshi Narukawa[a] and Yasuhiro Nishitani[a]

[a]*Discovery Research Laboratories, Shionogi & Co., Ltd., Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan*
[b]*Discovery Research Laboratories, Shionogi & Co., Ltd., Futaba-cho 3-1-1, Toyonaka, Osaka 561-0825, Japan*

Doubly-modified derivatives of chloroorienticin B exhibited potent antibacterial activities against MRSA and VRE along with considerable water-solubility.



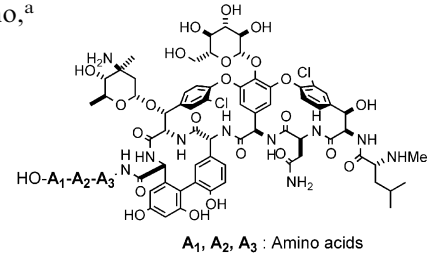
Bioorg. Med. Chem. Lett. 12 (2002) 3033

An Efficient and Practical Method for Solid-Phase Synthesis of Tripeptide-Bearing Glycopeptide Antibiotics: Combinatorial Parallel Synthesis of Carboxamide Derivatives of Chloroorienticin B

Tatsuro Yasukata,[a,*] Hirohisa Shindo,[a] Osamu Yoshida,[a] Yukihito Sumino,[a] Tadashi Munekage,[b] Yukitoshi Narukawa[a] and Yasuhiro Nishitani[a]

[a]*Discovery Research Laboratories, Shionogi & Co., Ltd., Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan*
[b]*Discovery Research Laboratories, Shionogi & Co., Ltd., Futaba-cho 3-1-1, Toyonaka, Osaka 561-0825, Japan*

A series of tripeptide-bearing derivatives of chloroorienticin B were prepared using solid-phase parallel synthesis. Among them, compounds having both tryptophan and tyrosine residues were found to possess potent antibacterial activities against VRE.

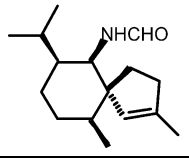


Bioorg. Med. Chem. Lett. 12 (2002) 3037

Exiguamide, a New Spirocyclic Sesquiterpene from the Marine Sponge *Geodia exigua* that Inhibits Cell Fate Specification During Sea Urchin Embryogenesis

Mylene M. Uy,[a] Shinji Ohta,[b,*] Mihoko Yanai,[b] Emi Ohta,[b] Toshifumi Hirata[a] and Susumu Ikegami[c,*]

[a]*Department of Mathematical and Life Sciences, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan*
[b]*Instrument Center for Chemical Analysis, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan*
[c]*Department of Applied Biochemistry, Hiroshima University, 1-4-4 Kagamiyama, Higashi-Hiroshima 739-8528, Japan*



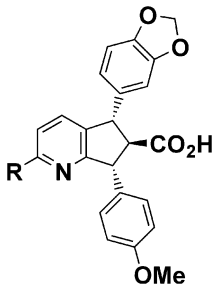
Bioorg. Med. Chem. Lett. 12 (2002) 3041

Structure–Activity Relationships of 2-Substituted 5,7-Diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic Acids as a Novel Class of Endothelin Receptor Antagonists

Kenji Niiyama,* Hirobumi Takahashi, Toshio Nagase, Hisaki Kojima, Yuka Amano, Kasumi Katsuki, Takeru Yamakawa, Satoshi Ozaki, Masaki Ihara, Mitsuo Yano, Takahiro Fukuroda, Masaru Nishikibe and Kiyofumi Ishikawa

Tsukuba Research Institute, Banyu Pharmaceutical Co. Ltd., 3 Okubo, Tsukuba, Ibaraki 300-2611, Japan

2-Substituted 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acids were efficiently synthesized by a versatile method we developed. The substituent at the 2-position of the skeleton affected the binding affinity to ET_A receptors as well as ET_B receptors and highly potent TE_A selective and ET_A/ET_B mixed antagonists were identified through the derivatization.



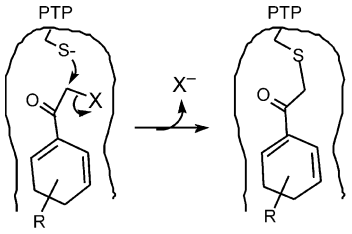
Bioorg. Med. Chem. Lett. 12 (2002) 3047

α-Bromoacetophenone Derivatives as Neutral Protein Tyrosine Phosphatase Inhibitors: Structure–Activity Relationship

Gulnur Arabaci, Tian Yi, Hua Fu, Mary E. Porter, Kirk D. Beebe and Dehua Pei*

Department of Chemistry and Ohio State Biochemistry Program, The Ohio State University, 100 West 18th Avenue, Columbus, OH 43210, USA

A series of α-haloacetophenone derivatives was tested against SHP-1 and PTB1B to define the SAR.

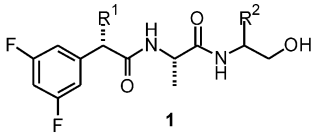


Bioorg. Med. Chem. Lett. 12 (2002) 3051

A Series of C-Terminal Amino Alcohol Dipeptide Aβ Inhibitors

Albert W. Garofalo,[a,*] David W. G. Wone,[a] Angela Phuc,[a] James E. Audia,[b] Cheryl A. Bales,[a] Harry F. Dovey,[a] Darren B. Dressen,[a] Beverly Folmer,[a] Erich G. Goldbach,[a] Ashley C. Guinn,[a] Lee H. Latimer,[a] Thomas E. Mabry,[b] Jeffrey S. Nissen,[b] Michael A. Pleiss,[a] Stephen Sohn,[a] Eugene D. Thorsett,[a] Jay S. Tung[a] and Jing Wu[a]

[a]*Elan, 800 Gateway Blvd, South San Francisco, CA 94080, USA*
[b]*Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA*



1

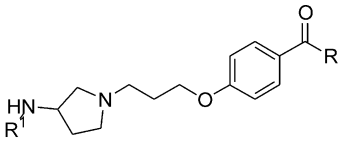
Bioorg. Med. Chem. Lett. 12 (2002) 3055

Synthesis and Evaluation of Potent Pyrrolidine H_3 Antagonists

Anil Vasudevan,* Scott E. Conner, Robert G. Gentles, Ramin Faghih, Huaqing Liu, Wesley Dwight, Lynne Ireland, Chae Hee Kang, Timothy A. Esbenshade, Youssef L. Bennani and Arthur A. Hancock

Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60031, USA

The synthesis of potent pyrrolidine containing H_3 antagonists is reported.



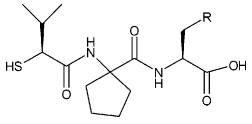
Bioorg. Med. Chem. Lett. 12 (2002) 3059

Synthesis and Biological Activity of Potent Heterocyclic Thiol-Based Inhibitors of Endothelin-Converting Enzyme-1

Fariborz Firooznia,* Candido Gude, Kenneth Chan, Jenny Tan, Cynthia A. Fink, Paula Savage, Michael E. Beil, Charles W. Bruseo, Angelo J. Trapani and Arco Y. Jeng

Metabolic and Cardiovascular Diseases, Novartis Institute for Biomedical Research, Summit, NJ 07901, USA

Through directed screening of metalloprotease inhibitors, CGS 30084 (R = *p*-biphenyl) was identified as a potent inhibitor of endothelin-converting enzyme-1. The replacement of the biphenyl region of this molecule with heterocyclic biaryls and biological activities of the resulting compounds will be described.



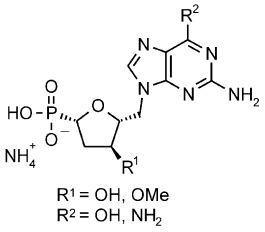
Bioorg. Med. Chem. Lett. 12 (2002) 3063

Novel Nucleotide Phosphonate Analogues with Potent Antitumor Activity

Monica Bubenik,* Rabindra Rej, Nghe Nguyen-Ba, Giorgio Attardo, France Ouellet and Laval Chan

Shire BioChem Inc., 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7

We have identified several nucleotide phosphonates demonstrating in vitro antiproliferative activity in several human cancer cell lines with IC_{50} values in the μM range. The synthesis as well as structure–activity relationship are described.



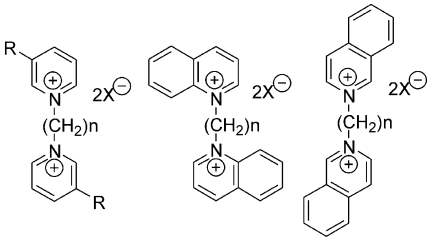
Bioorg. Med. Chem. Lett. 12 (2002) 3067

bis-Azaaromatic Quaternary Ammonium Analogues: Ligands for α4β2* and α7* Subtypes of Neuronal Nicotinic Receptors

Joshua T. Ayers, Linda P. Dwoskin, A. Gabriela Deaciuc, Vladimir P. Grinevich, Jun Zhu and Peter A. Crooks*

Division of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536-0082, USA

A series of *N,N′-n*-alkanediyl-bis-azaaromatic quaternary ammonium halides was prepared and evaluated for binding to α4β2* and α7* nicotinic receptors using rat brain membrane preparations. Variation of *N-n*-alkyl chain together with structural modification of the azaaromatic moiety afforded ligands with good affinity and selectivity for the above receptor subtypes.



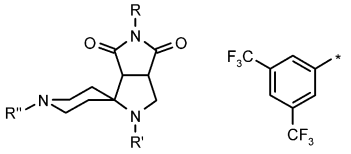
Bioorg. Med. Chem. Lett. 12 (2002) 3073

Parallel Solution- and Solid-Phase Synthesis of Spiropyrrolo-Pyrroles as Novel Neurokinin Receptor Ligands

Konrad H. Bleicher,* Yves Wüthrich, Geo Adam, Torsten Hoffmann and Andrew J. Sleight

F. Hoffmann-La Roche AG, Pharma Research, CH-4070 Basel, Switzerland

The generation of a compound library consisting of a spiropyrrolo-pyrrole as a privileged GPCR scaffold and the 3,5-bis(trifluoromethyl)phenyl motive as a neurokinin-1 specific needle is described. A series of nanomolar activities are disclosed.



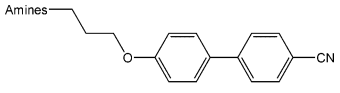
Bioorg. Med. Chem. Lett. 12 (2002) 3077

Aminoalkoxybiphenylnitriles as Histamine-3 Receptor Ligands

Ramin Faghih,* Wesley Dwight, Anil Vasudevan, Jurgen Dinges, Scott E. Conner, Timothy A. Esbenshade, Youssef L. Bennani and Arthur A. Hancock

Neuroscience-Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6123, USA

Series of biaryl nitrile amines ligands of histamine H_3 is described.

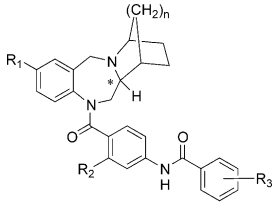


Bioorg. Med. Chem. Lett. 12 (2002) 3081

Bridged Bicyclic Vasopressin Receptor Antagonists with V_2-Selective or Dual V_{1a}/V_2 Activity

Alexey B. Dyatkin,[a,*] William J. Hoekstra,[a] Dennis J. Hlasta,[a] Patricia Andrade-Gordon,[a] Lawrence de Garavilla,[a] Keith T. Demarest,[b] Joseph W. Gunnet,[b] William Hageman,[a] Richard Look[b] and Bruce E. Maryanoff[a,*]

[a]*Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Spring House, PA 19477-0776, USA*
[b]*Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Raritan, NJ 08869-0602, USA*



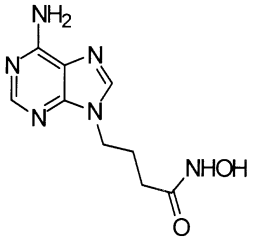
A synthesis, in vitro and in vivo data of novel vasopressin receptor antagonists are reported. Variation of substituents (R_1–R_3), and the configuration of the stereocenter, resulted in potent V_2-selective and balanced dual V_{1a}/V_2 compounds.

Bioorg. Med. Chem. Lett. 12 (2002) 3085

Hydroxamate Based Inhibitors of Adenylyl Cyclase. Part 1: The Effect of Acyclic Linkers on P-site Binding

Daniel E. Levy,* Charles Marlowe, Kim Kane-Maguire, Ming Bao, Diana B. Cherbavaz, James E. Tomlinson, David M. Sedlock and Robert M. Scarborough

Millennium Pharmaceuticals, Inc., 256 East Grand Avenue, South San Francisco, CA 94080, USA



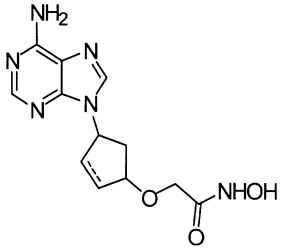
The synthesis of potent acyclic adenylyl cyclase antagonists is reported.

Bioorg. Med. Chem. Lett. 12 (2002) 3089

Hydroxamate Based Inhibitors of Adenylyl Cyclase. Part 2: The Effect of Cyclic Linkers on P-site Binding

Daniel E. Levy,* Ming Bao, James E. Tomlinson and Robert M. Scarborough

Millennium Pharmaceuticals, Inc., 256 East Grand Avenue, South San Francisco, CA 94080, USA



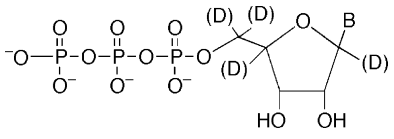
The synthesis of potent cyclic adenylyl cyclase antagonists is reported.

Bioorg. Med. Chem. Lett. 12 (2002) 3093

A General Synthesis of Specifically Deuterated Nucleotides for Studies of DNA and RNA

Bingzi Chen, Elizabeth R. Jamieson and Thomas D. Tullius*

Department of Chemistry, Boston University, Boston, MA 02215, USA



An efficient procedure is described for the preparation of ribonucleotides and deoxyribonucleotides with deuterium incorporated at either the 1′, 4′, or 5′ position of the sugar.

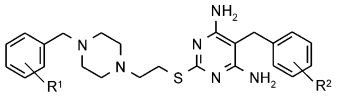
Bioorg. Med. Chem. Lett. 12 (2002) 3097

Synthesis and Evaluation of 5-HT_{2A} and 5-HT_{2C} Receptor Binding Affinities of Novel Pyrimidine Derivatives

Dániel Bózsing,[a,*] Ildikó Simonek,[a] Gyula Simig,[a] Iván Jakóczi,[a] István Gacsályi,[b] György Lévay,[b] Károly Tihanyi[b] and Éva Schmidt[b]

[a]*Chemical Research Department, EGIS Pharmaceuticals Ltd., PO Box 100, 1475 Budapest, Hungary*
[b]*CNS Pharmacology Department, EGIS Pharmaceuticals Ltd., PO Box 100, 1475 Budapest, Hungary*

A series of new pyrimidine derivatives was prepared and the binding affinities for 5-HT_{2A} and 5-HT_{2C} receptors were determined to find potential anxiolytic and/or antipsychotic agents.



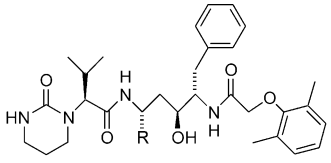
Bioorg. Med. Chem. Lett. 12 (2002) 3101

Novel Lopinavir Analogues Incorporating Non-Aromatic P-1 Side Chains—Synthesis and Structure–Activity Relationships

Hing L. Sham,* Chen Zhao, Leping Li, David A. Betebenner, Ayda Saldivar, Sudthida Vasavanonda, Dale J. Kempf, Jacob J. Plattner and Daniel W. Norbeck

Pharmaceutical Discovery, R47B, Building AP-10, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

Novel analogues of the HIV-1 protease inhibitor lopinavir, incorporating non-aromatic alkyl side chains at P-1 were synthesized and structure–activity relationships explored.



R = benzyl, Lopinavir
R = alkyl, 12b-f

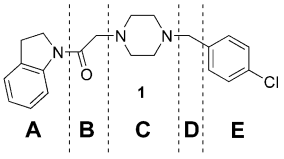
Bioorg. Med. Chem. Lett. 12 (2002) 3105

Indoline and Piperazine Containing Derivatives as a Novel Class of Mixed D_2/D_4 Receptor Antagonists. Part 1: Identification and Structure–Activity Relationships

He Zhao,* Andrew Thurkauf, Xiaoshu He, Kevin Hodgetts, Xiaoyan Zhang, Stanislaw Rachwal, Renata X. Kover, Alan Hutchison, John Peterson, Andrzej Kieltyka, Robbin Brodbeck, Renee Primus and Jan W. F. Wasley

Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, USA

Optimization of the lead compound 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2,3-dihydro-indol-1-yl)-ethanone **1** by systematical SAR studies lead two potent compounds 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **2n** and 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **7b**. Their related synthesis was also reported.



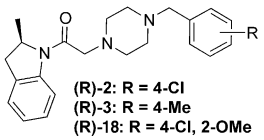
Bioorg. Med. Chem. Lett. 12 (2002) 3111

Indoline and Piperazine Containing Derivatives as a Novel Class of Mixed D_2/D_4 Receptor Antagonists. Part 2: Asymmetric Synthesis and Biological Evaluation

He Zhao,* Xiaoshu He, Andrew Thurkauf, Diane Hoffman, Andrzej Kieltyka, Robbin Brodbeck, Renee Primus and Jan W.F. Wasley

Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, USA

A series of chiral benzylpiperazinyl-1-(2,3-dihydro-indol-1-yl)ethanone derivatives were prepared and examined for their affinity at dopamine D_2 and D_4 receptors. Three compounds having D_2/D_4 affinity ratios approximating that found for the atypical neuroleptic clozapine were further evaluated in behavioral tests of antipsychotic efficacy and motor side effects.



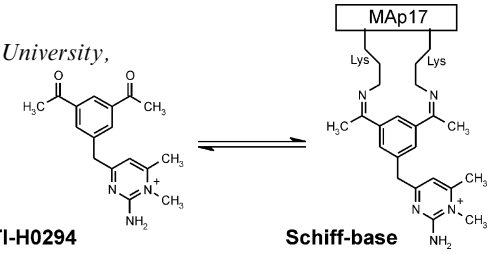
(R)-2: R = 4-Cl
(R)-3: R = 4-Me
(R)-18: R = 4-Cl, 2-OMe

Bioorg. Med. Chem. Lett. 12 (2002) 3117

Inhibition of HIV-1 Nuclear Import via Schiff Base Formation with Arylene Bis(methylketone) Compounds

Yousef Al-Abed,[a,*] Larisa Dubrovsky,[a] Bela Ruzsicska,[a] Mohindra Seepersaud[a] and Michael Bukrinsky[b]

[a]*Laboratory of Medicinal Chemistry, North Shore-LIJ Research Institute, 350 Community Drive, Manhasset, NY 11030, USA*
[b]*Department of Microbiology and Tropical Medicine, The George Washington University, Washington, DC 20037, USA*



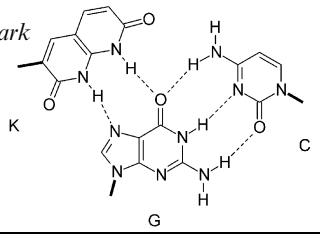
Bioorg. Med. Chem. Lett. 12 (2002) 3121

1,8-Naphthyridin-2,7-(*1,8H*)-dione is an Effective Mimic of Protonated Cytosine in Peptide Nucleic Acid Triplex Recognition Systems

Caspar Christensen,[a,b] Anne B. Eldrup,[a,b] Gerald Haaima[a,b] and Peter E. Nielsen[a,b,*]

[a]*Center for Biomolecular Recognition, Department of Medical Biochemistry and Genetics, The Panum Institute, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark*
[b]*Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark*

A novel bicyclic mimic of protonated cytosine [1,8-naphthyridin-2,7-(*1,8H*)-dione, (K)] for Hogsteen type triplex recognition of guanine has been incorporated into eptide nucleic acids.



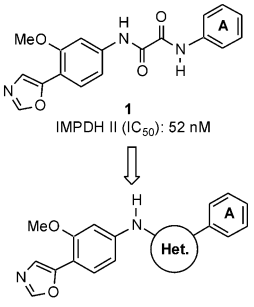
Bioorg. Med. Chem. Lett. 12 (2002) 3125

A Survey of Cyclic Replacements for the Central Diamide Moiety of Inhibitors of Inosine Monophosphate Dehydrogenase

T.G. Murali Dhar,* Chunjian Liu, William J. Pitts, Junquing Guo, Scott H. Watterson, Henry Gu, Catherine A. Fleener, Katherine Rouleau, N.Z. Sherbina, Joel C. Barrish, Diane Hollenbaugh and Edwin J. Iwanowicz

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

The preparation and in vitro biological evaluation of a series of novel heterocyclic small molecule inhibitors of inosine monophosphate dehydrogenase are described.

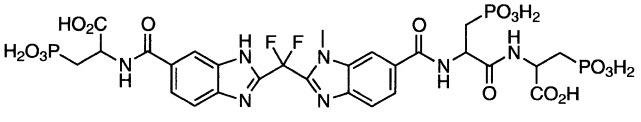


Bioorg. Med. Chem. Lett. 12 (2002) 3129

Highly Potent Non-peptidic Inhibitors of the HCV NS3/NS4A Serine Protease

David Sperandio,[a,*] Anthony R. Gangloff,[a] Joane Litvak,[a] Richard Goldsmith,[a] Jason M. Hataye,[a] Vivian R. Wang,[a] Emma J. Shelton,[a] Kyle Elrod,[a] James W. Janc,[a] James M. Clark,[a] Ken Rice,[a] Steve Weinheimer,[b] Kap-Sun Yeung,[b] Nicholas A. Meanwell,[b] Dennis Hernandez,[b] Andrew J. Staab,[b] Brian L. Venables[b] and Jeffrey R. Spencer[a]

[a]*Celera, 180 Kimball Way, South San Francisco, CA 94080, USA*
[b]*Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA*



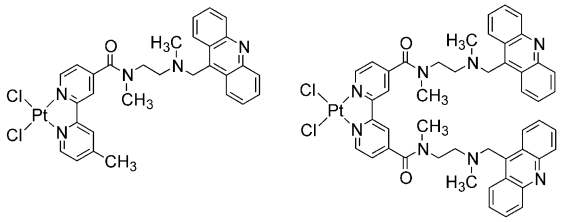
Bioorg. Med. Chem. Lett. 12 (2002) 3135

DNA Interaction and Photonicking Properties of DNA-Targeted Acridine (2,2′-Bipyridine)Platinum(II) Complexes

Lourdes Gude,[a] María-José Fernández,[a] Kathryn B. Grant[b,*] and Antonio Lorente[a,*]

[a]*Departamento de Química Orgánica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain*
[b]*Department of Chemistry, Center for Biotechnology and Drug Design, Georgia State University, University Plaza, Atlanta, GA 30303, USA*

Synthesis and DNA interaction of two acridine (2,2′-bipyridine)platinum(II) complexes are reported.



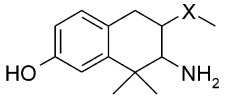
Bioorg. Med. Chem. Lett. 12 (2002) 3141

Synthesis and Structure–Activity Relationship of Novel Aminotetralin Derivatives with High μ Selective Opioid Affinity

Caroline Roy,[a,*] Ticheao Li, Pavel Krasik,[a] Marie-Josée Gilbert,[a] Christine Pelletier,[a] Diane Gagnon,[a] Ed Robert,[b] Julie Ducharme,[b] Richard Storer[a] and Jean-François Lavallée[a]

[a]*Shire Biochem, 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7*
[b]*Astra Research Center Montreal, 7171 Frederick Banting, Ville St-Laurent, Québec, Canada H4S 1Z9*

Several novel racemic aminotetralin derivatives have been prepared using a stereoselective aziridine ring opening reactions and were evaluated for their μ-opioid receptor binding affinity. Selectivity index towards other opioid receptors and antinociceptive activity in mice have been evaluated for the most potent derivatives.



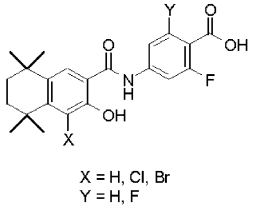
Bioorg. Med. Chem. Lett. 12 (2002) 3145

Synthesis and Biological Activity of Retinoic Acid Receptor-α Specific Amides

Richard L. Beard,[a,*] Tien T. Duong,[a] Min Teng,[a] Elliott S. Klein,[b] Andrew M. Standevan[b] and Roshantha A. S. Chandraratna[a,b,*]

[a]*Retinoid Research, Department of Chemistry, Allergan Inc., Irvine, CA 92623-9534, USA*
[b]*Retinoid Research, Department of Biology, Allergan Inc., Irvine, CA 92623-9534, USA*

A new series of retinoic acid receptor-α specific amides is described.



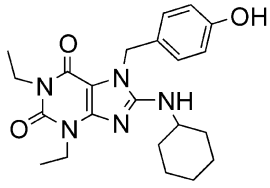
Bioorg. Med. Chem. Lett. 12 (2002) 3149

Design and Synthesis of Xanthine Analogues as Potent and Selective PDE5 Inhibitors

Yuguang Wang,* Samuel Chackalamannil, Zhiyong Hu, Craig D. Boyle, Claire M. Lankin, Yan Xia, Ruo Xu, Theodros Asberom, Dmitri Pissarnitski, Andrew W. Stamford, William J. Greenlee, Jeffrey Skell, Stanley Kurowski, Subbarao Vemulapalli, Jairam Palamanda, Madhu Chintala, Ping Wu, Joyce Myers and Peng Wang

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

We have discovered potent and selective xanthine PDE5 inhibitors. Compound **25** (PDE5 $IC_{50} = 0.6$ nM, PDE6/PDE5 = 101) demonstrated similar functional efficacy and PK profile to Sildenafil (PDE5 $IC_{50} = 3.5$ nM, PDE6/PDE5 = 7).



25

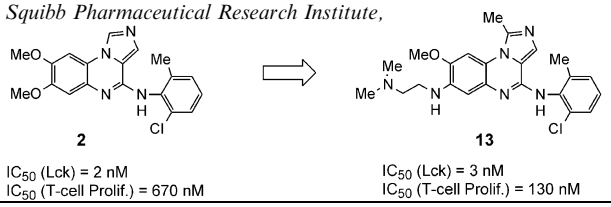
Bioorg. Med. Chem. Lett. 12 (2002) 3153

Synthesis and SAR of Novel Imidazoquinoxaline-based Lck Inhibitors: Improvement of Cell Potency

Ping Chen,[a,*] Edwin J. Iwanowicz,[a,*] Derek Norris,[a] Henry H. Gu,[a] James Lin,[a] Robert V. Moquin,[a] Jagabandhu Das,[a] John Wityak,[a] Steven H. Spergel,[a] Henry de Fex,[b] Suhong Pang,[b] Sydney Pitt,[b] Ding Ren Shen,[b] Gary L. Schieven[b] and Joel C. Barrish[a]

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

A series of anilino(imidazoquinoxaline) analogues bearing solubilizing side chains at the 6- and 7-positions of the fused phenyl ring has been prepared and evaluated for inhibition against Lck enzyme and of T-cell proliferation. Significant improvement of the cellular activity against T cell proliferation was achieved over the initial lead, compound **2**.



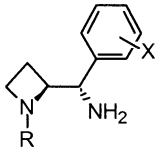
Bioorg. Med. Chem. Lett. 12 (2002) 3157

Synthesis and Structure–Activity Relationships of Aminoalkylazetidines as ORL1 Receptor Ligands

Wen-Lian Wu,* Mary Ann Caplen, Martin S. Domalski, Hongtao Zhang, Ahmad Fawzi and Duane A. Burnett*

Schering Plough Research Institute, 2015 Galloping Hill Road, MS 2800, Kenilworth, NJ 07033-0539, USA

A series of aminoalkylazetidines has been discovered as novel ORL1 receptor ligands. Structure–activity relationships have been investigated at the azetidine N and the alkyl side chain sites. Several potent and selective analogues have been identified.



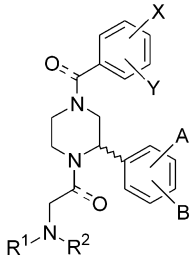
Bioorg. Med. Chem. Lett. 12 (2002) 3161

Synthesis and NK_1/NK_2 Binding Activities of a Series of Diacyl-Substituted 2-Arylpiperazines

David J. Blythin,[a,*] Xiao Chen,[a] John J. Piwinski,[a] Neng-Yang Shih,[a] Ho-Jane Shue,[a] John C. Anthes[b] and Andrew T. McPhail[c]

[a]*Chemical Research Department, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Department of Allergy and Immunology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[c]*Paul M. Gross Chemical Laboratory, Duke University, Durham, NC 27708, USA*

The synthesis and binding affinity for hNK_1 and hNK_2 receptors of a series of diacyl substituted 2-aryl piperazines are described.

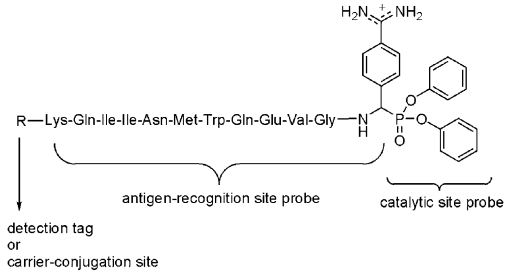


Bioorg. Med. Chem. Lett. 12 (2002) 3167

A Mechanism-Based Probe for gp120-Hydrolyzing Antibodies

Hiroaki Taguchi, Gary Burr, Sangeeta Karle, Stephanie Planque, Yong-Xin Zhou, Sudhir Paul* and Yasuhiro Nishiyama*

Chemical Immunology and Therapeutics Research Center, Department of Pathology and Laboratory Medicine, University of Texas—Houston Medical School, 6431 Fannin, Houston, TX 77030, USA

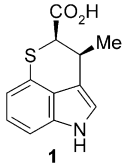


Bioorg. Med. Chem. Lett. 12 (2002) 3171

The Antimicrobial Natural Product Chuangxinmycin and Some Synthetic Analogues are Potent and Selective Inhibitors of Bacterial Tryptophanyl tRNA Synthetase

Murray J. Brown, Paul S. Carter, Ashley E. Fenwick, Andrew P. Fosberry, Dieter W. Hamprecht, Martin J. Hibbs, Richard L. Jarvest,* Lucy Mensah, Peter H. Milner, Peter J. O'Hanlon, Andrew J. Pope, Christine M. Richardson, Andrew West and David R. Witty

GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK



1

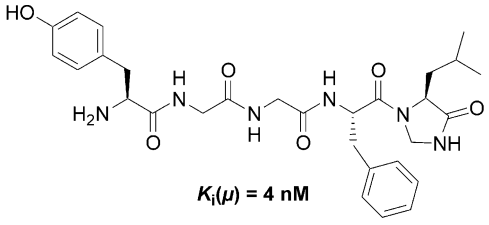
The antimicrobial natural product chuangxinmycin (**1**) has been found to be a potent and selective inhibitor of bacterial tryptophanyl tRNA synthetase (WRS). A number of analogues have been synthesised. The interaction with WRS appears to be highly constrained, as only sterically smaller analogues afforded significant inhibition. The only analogue to show inhibition comparable to chuangxinmycin also had antibacterial activity. WRS inhibition may contribute to the antibacterial action of chuangxinmycin.

Bioorg. Med. Chem. Lett. 12 (2002) 3175

Opioid Activity of 4-Imidazolidinone Positional Analogues of Leu-Enkephalin

Markéta Rinnová, Adel Nefzi and Richard A. Houghten*

Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, CA 92121, USA

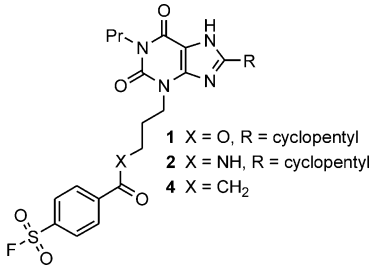


Bioorg. Med. Chem. Lett. 12 (2002) 3179

New Irreversible Adenosine A_1 Antagonists Based on FSCPX

Anthony R. Beauglehole,[a] Stephen P. Baker[b] and Peter J. Scammells[a,*]

[a]*Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia*
[b]*Department of Pharmacology and Therapeutics, University of Florida, PO Box 100267, Gainesville, FL 32610, USA*



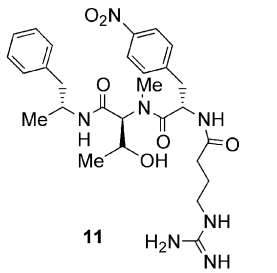
FSCPX (**1**) and its amide analogue (**2**) have been reported to exhibit potent and selective irreversible antagonism of the A_1 adenosine receptor (A_1AR) when used in in vitro biological preparations. In order to obtain an irreversible A_1AR antagonist with improved in vivo stability, analogues of FSCPX incorporating the chemoreactive 4-(fluorosulfonyl)phenyl moiety separated from the xanthine pharmacophore by a ketone linkage were explored. Compound **4** (R = cyclopentyl, cyclohexyl and 2*S-endo* norborn-2-yl) exhibited high affinity for the A_1AR and concentration-dependent irreversible binding to the A_1AR.

Bioorg. Med. Chem. Lett. 12 (2002) 3183

Retro-Binding Thrombin Active Site Inhibitors: Identification of an Orally Active Inhibitor of Thrombin Catalytic Activity

Edwin J. Iwanowicz,* S. David Kimball, James Lin, Wan F. Lau, W.-C. Han, Tammy C. Wang, Daniel G. M. Roberts, W. A. Schumacher, Martin L. Ogletree and Steven M. Seiler

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



11

α-Thrombin Inhibition IC_{50} 0.030 μM

A series of inhibitors of human α-thrombin was prepared to elucidate the structure–activity relationships (SARs) for this retro-binding chemotype. Studies were focused on reducing unnecessary functionality that was found to be a metabolic liability. Compound **11** was identified as a potent, selective and orally active inhibitor of thrombin catalytic activity.

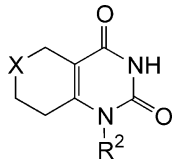
Bioorg. Med. Chem. Lett. 12 (2002) 3187

Substituted Uracil Derivatives as Potent Inhibitors of Poly(ADP-ribose)polymerase-1 (PARP-1)

Henning Steinhagen,[a,*] Michael Gerisch,[a] Joachim Mittendorf,[a] Karl-Heinz Schlemmer[b] and Barbara Albrecht[c]

[a]*Institute of Medicinal Chemistry, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*
[b]*Institute of Pharmacokinetics, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*
[c]*Institute of Cardiovascular Research, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*

A new class of PARP-1 inhibitors, namely substituted fused uracil derivatives were synthesised. The chemical optimisation program led to compounds with an $IC_{50} < 20$ nM. Additionally, physicochemical and pharmacokinetic properties were optimised. Compounds bearing a piperazine or phenyl substituted βAla-Gly side chain R^2 exhibited the best overall profile.



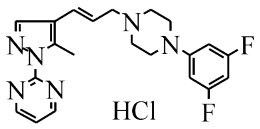
Bioorg. Med. Chem. Lett. 12 (2002) 3191

Synthesis and Mechanism of Action of Novel Pyrimidinyl Pyrazole Derivatives Possessing Antiproliferative Activity

Hitoshi Ohki,[a,*] Kenji Hirotani,[b] Hiroyuki Naito,[a] Satoru Ohsuki,[a] Megumi Minami,[b] Akio Ejima,[a] Yukiko Koiso[c] and Yuichi Hashimoto[c]

[a]*Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co. Ltd., 16-13, Kita-kasai 1-chome, Edogawa-ku, Tokyo 134, Japan*
[b]*New Product Research Laboratories III, Daiichi Pharmaceutical Co. Ltd., 16-13, Kita-kasai 1-chome, Edogawa-ku, Tokyo 134, Japan*
[c]*Institute of Molecular and Cellular Biosciences (IMCB), The University of Tokyo, 1-1-1, Yayoi, Bunkyo-ku, Tokyo 113, Japan*

Pyrimidinyl pyrazole derivative **2**, a new scaffold as an antitumor agent, showed an antiproliferative activity against the *p*-glycoprotein-mediated multi-drug-resistant (MDR) cell line PC-12 and inhibited tubulin polymerization.



2

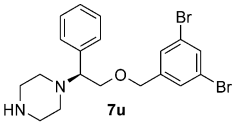
Bioorg. Med. Chem. Lett. 12 (2002) 3195

Dual NK_1 Antagonists—Serotonin Reuptake Inhibitors as Potential Antidepressants. Part 2: SAR and Activity of Benzyloxyphenethyl Piperazine Derivatives

Thomas Ryckmans,[a] Olivier Berton,[b] Renée Grimée,[b] Thierry Kogej,[a] Yves Lamberty,[b] Patrick Pasau,[a] Patrice Talaga[a] and Christophe Genicot[a]

[a]*Chemical Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*
[b]*Preclinical CNS Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*

The synthesis, structure–affinity relationship and activity of benzyloxyphenethyl piperazine derivatives combining NK_1 antagonism and serotonin reuptake inhibition is described. Compound **7u** was shown to be active in animal models of 5-HT reuptake inhibition and central NK_1 receptor blockade, and was demonstrated to be orally active in an integrated model sensitive to both mechanisms. This class of compounds potentially represents a new generation of antidepressants.



7u

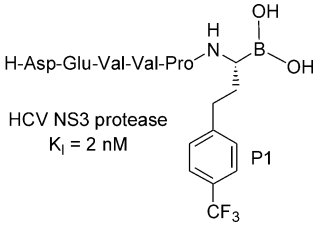
Bioorg. Med. Chem. Lett. 12 (2002) 3199

P1 Phenethyl Peptide Boronic Acid Inhibitors of HCV NS3 Protease

E. Scott Priestley,* Indawati De Lucca, Bahman Ghavimi, Susan Erickson-Viitanen and Carl P. Decicco

Bristol-Myers Squibb Pharmaceutical Research Institute, Experimental Station, Wilmington, DE, 19880-0500, USA

Synthesis and structure–activity relationships for P1 phenethyl peptide boronic acid inhibitors of HCV NS3 protease are reported.



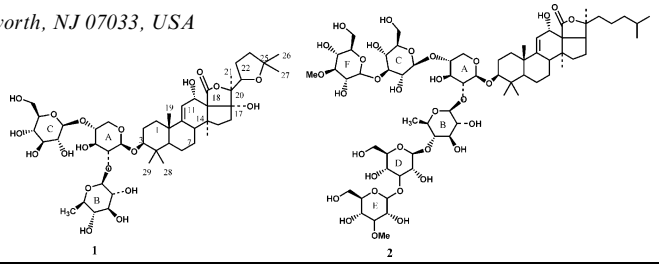
Bioorg. Med. Chem. Lett. 12 (2002) 3203

Two Selective Novel Triterpene Glycosides from Sea Cucumber, *Telenata Ananas*: Inhibitors of Chemokine Receptor-5

Vinod R. Hegde,[a,*] T.-M. Chan,[a] Haiyan Pu,[a] Vincent P. Gullo,[a] Mahesh G. Patel,[a] Pradip Das,[a] Nicole Wagner,[a] P. S. Parameswaran[b] and C. G. Naik[b]

[a]*Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*National Institute of Oceanography, Dona Paula, Goa, India*

The aqueous methanolic extract of a sea cucumber was found to contain two triterpene glycosides **1** and **2**. The structures of **1** and **2** were established based on high resolution NMR studies. Compounds **1** and **2** exhibited inhibitory activity (K_i) of 30 and 5 μM, respectively, in a chemokine receptor subtype 5 (CCR5) assay. Both compounds did not show any significant inhibition in a CXCR2 assay at 50 μM, suggesting their selectivity for the CCR5 receptor.



1 **2**

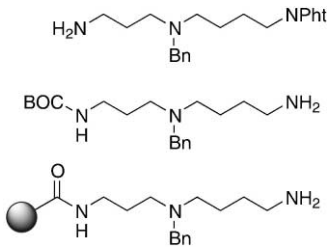
Bioorg. Med. Chem. Lett. 12 (2002) 3207

An Efficient Protocol for Solution- and Solid-Phase End-Group Differentiation of Spermidine

Emerson T. Silva, Andréa S. Cunha and Edson L. S. Lima*

Universidade Federal do Rio de Janeiro, Instituto de Química, Departamento de Química Orgânica, Cidade Universitária, 21945-970, Rio de Janeiro, RJ, Brazil

The short synthesis of a selectively functionalized spermidine and its end-group differentiation in solution, and in solid-phase is reported. The solid-phase sequence was monitored by FT-IR.



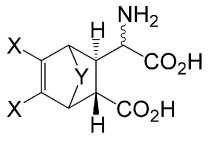
Bioorg. Med. Chem. Lett. 12 (2002) 3209

Synthesis and Preliminary Evaluation of *trans*-3,4-Conformationally-Restricted Glutamate and Pyroglutamate Analogues as Novel EAAT2 Inhibitors

Travis T. Denton,[a] Todd Seib,[b] Richard J. Bridges[b] and Charles M. Thompson[a,b,*]

[a]*Department of Chemistry, The University of Montana, Missoula, MT 59812, USA*
[b]*Department of Pharmaceutical Sciences, COBRE Center for Structural and Functional Neuroscience, The University of Montana, Missoula, MT 59812, USA*

Select glutamate and pyroglutamate analogues (not shown) were found to inhibit the sodium dependent excitatory amino acid transporter EAAT2 with activity comparable to dihydrokaintate.



glutamate analogues
X = H, CH_3
Y = no atom, CH_2, CH_2CH_2

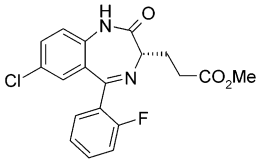
Bioorg. Med. Chem. Lett. 12 (2002) 3215

Identification and Structure–Activity Studies of Novel Ultrashort-Acting Benzodiazepine Receptor Agonists

Jeffrey A. Stafford, Gregory J. Pacofsky, Richard F. Cox, Jill R. Cowan, George F. Dorsey, Jr., Stephen S. Gonzales, David K. Jung, George W. Koszalka, Maggie S. McIntyre, Jeffrey H. Tidwell, Robert P. Wiard and Paul L. Feldman*

GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA

The synthesis and evaluation of novel ultrashort-acting benzodiazepine (USA BZD) agonists are described. A BZD scaffold was modified by incorporation of amino acids and derivatives. The propionate side chain of glutamic acid tethers an enzymatically labile functionality where the metabolite carboxylic acid displays markedly reduced BZD receptor affinity.



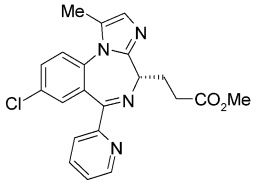
Bioorg. Med. Chem. Lett. 12 (2002) 3219

Relating the Structure, Activity, and Physical Properties of Ultrashort-Acting Benzodiazepine Receptor Agonists

Gregory J. Pacofsky, Jeffrey A. Stafford, Richard F. Cox, Jill R. Cowan, George F. Dorsey, Jr., Stephen S. Gonzales, Istvan Kaldor, George W. Koszalka, George G. Lovell, Maggie S. McIntyre, Jeffrey H. Tidwell, Dan Todd, Graham Whitesell, Robert P. Wiard and Paul L. Feldman*

GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA

The ultrashort-acting benzodiazepine (USA BZD) agonists reported previously have been modified structurally to improve aqueous solubility. Lactam-to-amidine modifications, replacement of the C5-haloaryl ring, and annulation of heterocycles are presented. These analogues retain BZD receptor potency and full agonism profiles.

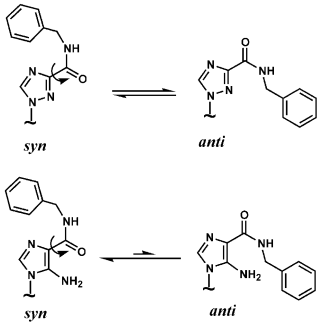


Bioorg. Med. Chem. Lett. 12 (2002) 3223

Conformational Restraint is a Critical Determinant of Unnatural Nucleotide Recognition by Protein Kinases

Scott M. Ulrich,[a] Nathan A. Sallee[b] and Kevan M. Shokat[a,c,*]

[a]*Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94143-0450, USA*
[b]*Program in Chemistry and Chemical Biology, University of California, San Francisco, CA 94143-0450, USA*
[c]*Department of Chemistry, University of California, Berkeley, CA 94720, USA*



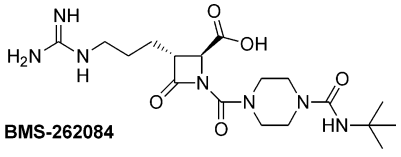
Bioorg. Med. Chem. Lett. 12 (2002) 3229

Synthesis and SAR of 4-Carboxy-2-azetidinone Mechanism-Based Tryptase Inhibitors

James C. Sutton,* Scott A. Bolton, Karen S. Hartl, Ming-Hsing Huang, Glenn Jacobs, Wei Meng, Martin L. Ogletree, Zulan Pi, William A. Schumacher, Steven M. Seiler, William A. Slusarchyk, Uwe Treuner, Robert Zahler, Guohua Zhao and Gregory S. Bisacchi

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

BMS-262084 was identified as a potent and selective tryptase inhibitor that, when dosed intratracheally in ovalbumin-sensitized guinea pigs, reduced allergen-induced bronchoconstriction and inflammatory cell infiltration into the lung.



BMS-262084

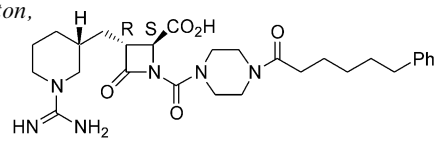
Bioorg. Med. Chem. Lett. 12 (2002) 3235

Synthesis of Potent and Highly Selective Inhibitors of Human Tryptase

William A. Slusarchyk,* Scott A. Bolton, Karen S. Hartl, Ming-Hsing Huang, Glenn Jacobs, Wei Meng, Martin L. Ogletree, Zulan Pi, William A. Schumacher, Steven M. Seiler, James C. Sutton, Uwe Treuner, Robert Zahler, Guohua Zhao and Gregory S. Bisacchi

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

The synthesis and SAR of a series of azetidinones are described resulting in identification of BMS-363131 as a potent inhibitor of human tryptase with high selectivity for tryptase versus related serine proteases including trypsin.



BMS-363131