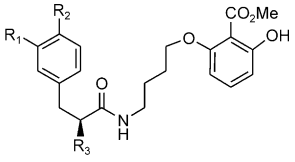
Bioorg. Med. Chem. Lett. 13 (2003) 3129

Discovery and SAR of Novel, Potent and Selective Protein Tyrosine Phosphatase 1B Inhibitors

Zhonghua Pei,[a,*] Xiaofeng Li,[a] Gang Liu,[a] Cele Abad-Zapatero,[b] Tom Lubben,[a] Tianyuan Zhang,[a] Stephen J. Ballaron,[a] Charles W. Hutchins,[b] James M. Trevillyan[a] and Michael R. Jirousek[a]

[a]*Metabolic Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, USA*
[b]*Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, USA*

A salicylate second site binder was linked to three classes of phosphotyrosine mimetics to produce potent protein tyrosine phosphatase 1B (PTP1B) inhibitors which exhibit significant selectivity against other phosphatases including the most homologous member, TCPTP.



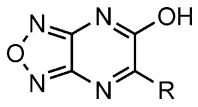
Bioorg. Med. Chem. Lett. 13 (2003) 3133

Synthesis and SAR Evaluation of Oxadiazolopyrazines as Selective *Haemophilus influenzae* Antibacterial Agents

Xenia Beebe,* Angela M. Nilius, Philip J. Merta, Niru B. Soni, Mai H. Bui, Rolf Wagner and Bruce A. Beutel

Infectious Disease Research, Abbott Laboratories, Abbott Park, IL 60064, USA

5-Hydroxy[1,2,5]oxadiazolo[3,4-*b*]pyrazines were synthesized by condensing diaminofurazan with α-keto acids to give a variety of aryl substituted analogues. Halogenated phenyl groups at C-6 give rise to the greatest *Haemophilus influenzae* antibacterial activity.



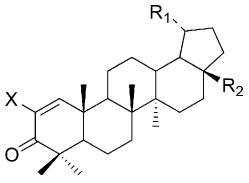
Bioorg. Med. Chem. Lett. 13 (2003) 3137

Synthesis and Cytotoxic Activity of A-ring Modified Betulinic Acid Derivatives

Young-Jae You, Yong Kim, Nguyen-Hai Nam and Byung-Zun Ahn*

College of Pharmacy, Chungnam National University, Taejon 305-764, South Korea

New A-ring modified betulinic acid derivatives having small steric hindrance were prepared and tested for cytotoxic activity on 3 cancer cell lines: 10 compounds showed strong cytotoxic activity than betulinic acid. Especially, the compounds bearing 1-ene-3-oxo with electron withdrawing group at C2 showed strong cytotoxicity.



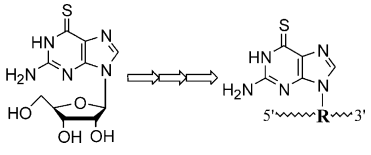
Bioorg. Med. Chem. Lett. 13 (2003) 3141

Synthesis of S^6-(2,4-Dinitrophenyl)-6-thioguanosine Phosphoramidite and Its Incorporation into Oligoribonucleotides

Qinguo Zheng,* Yang Wang and Eric Lattmann

School of Life & Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, UK

The preparation of N^2-phenoxylacetyl-S^6-(2,4-dinitrophenyl)-6-thioguanosine phosphoramidite and its incorporation into oligoribonucleotides is described.



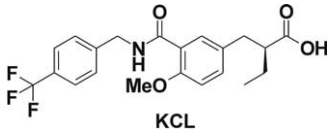
Bioorg. Med. Chem. Lett. 13 (2003) 3145

Analysis of the Critical Structural Determinant(s) of Species-Selective Peroxisome Proliferator-Activated Receptor Alpha (PPARα)-Activation by Phenylpropanoic Acid-Type PPARα Agonists

Hiroyuki Miyachi* and Hideharu Uchiki

Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., 2399-1 Mitarai, Nogi-machi, Shimotsuga-gun, Tochigi 329-0114, Japan

In order to identify the critical structural feature(s) of phenylpropanoic acid-type PPARα agonists, such as KCL, which exhibit human PPARα-selective activation, transient transactivation assay of KCL and related derivatives was performed with PPARα containing wild-type and point-mutated (I272F or T279M) ligand-binding domain.



KCL

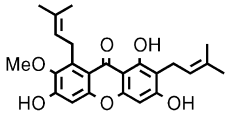
Bioorg. Med. Chem. Lett. 13 (2003) 3151

Biological Activities of α-Mangostin Derivatives against Acidic Sphingomyelinase

Motoko Hamada,[a] Kazuhiko Iikubo,[a] Yuichi Ishikawa,[a] Aya Ikeda,[b] Kazuo Umezawa[b] and Shigeru Nishiyama[a,*]

[a]*Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan*
[b]*Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan*

The prenyl and the diaryl ether moieties of α-mangostin were modified.



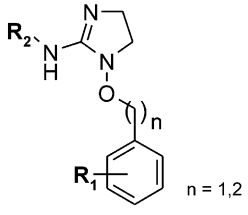
Bioorg. Med. Chem. Lett. 13 (2003) 3155

1-Benzyloxy-4,5-dihydro-*1H*-imidazol-2-yl-amines, a Novel Class of NR1/2B Subtype Selective NMDA Receptor Antagonists

Alexander Alanine,[a,*] Anne Bourson,[b] Bernd Büttelmann,[a] 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 1-alkyloxy-4,5-dihydro-1*H*-imidazol-2-yl-amines were prepared and evaluated as NR1/2B subtype selective NMDA receptor antagonists. 1-Benzyl(or phenethyl)oxy and 2-aminopentyl substitution combine high affinity and selectivity (vs α-adrenergic receptors) with in vivo activity.

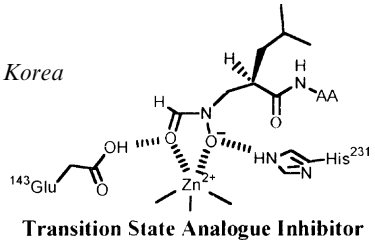


Bioorg. Med. Chem. Lett. 13 (2003) 3161

Reversed Hydroxamate-Bearing Thermolysin Inhibitors Mimic a High-Energy Intermediate Along the Enzyme-Catalyzed Proteolytic Reaction Pathway

Jung Dae Park and Dong H. Kim*

Center for Integrated Molecular Systems, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, South Korea



Transition State Analogue Inhibitor

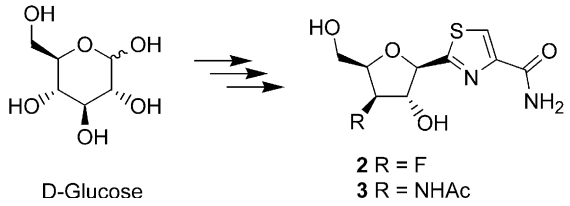
Bioorg. Med. Chem. Lett. 13 (2003) 3167

De Novo Synthesis of Two New Cytotoxic Tiazofurin Analogues with Modified Sugar Moieties

Mirjana Popsavin,[a,*] Ljilja Torović,[a] Vesna Kojić,[b] Gordana Bogdanović,[b] Saša Spaić[a] and Velimir Popsavin[a]

[a]*Department of Chemistry, Faculty of Sciences, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia and Montenegro, Yugoslavia*
[b]*Institute of Oncology Sremska Kamenica, Institutski put 4, 21204 Sremska Kamenica, Serbia & Montenegro, Yugoslavia*

A multistep divergent synthesis of two new cytotoxic tiazofurin analogues **2** and **3** has been achieved starting from D-glucose.



D-Glucose

2 R = F
3 R = NHAc

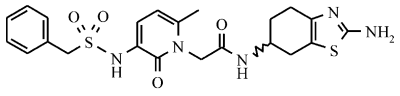
Bioorg. Med. Chem. Lett. 13 (2003) 3171

Selective 3-Amino-2-pyridinone Acetamide Thrombin Inhibitors Incorporating Weakly Basic Partially Saturated Heterobicyclic P_1-Arginine Mimetics

Lucija Peterlin-Mašič,[a] Andreja Kranjc,[a] Petra Marinko,[a] Gregor Mlinšek,[b] Tomaž Šolmajer,[b,c] Mojca Stegnar[d] and Danijel Kikelj[a,*]

[a]*Faculty of Pharmacy, University of Ljubljana, Aškerèeva 7, 1000 Ljubljana, Slovenia*
[b]*National Institute of Chemistry, Hajdrihova 19, 1115 Ljubljana, Slovenia*
[c]*Lek Pharmaceuticals d.d., Drug Discovery, Verovškova 57, 1526 Ljubljana, Slovenia*
[d]*University Medical Centre, Department of Angiology, Riharjeva 24, 1000 Ljubljana, Slovenia*

The design, synthesis, biological activity, and the binding modes of novel and selective thrombin inhibitors combing the 3-benzylsulfonylamino-2-pyridinone acetamide P_2–P_3 surrogate with weakly basic partially saturated heterobicyclic P_1-arginine mimetics is described.



14, K_i (thrombin) = 120 nM
K_i (trypsin) = 260000 nM

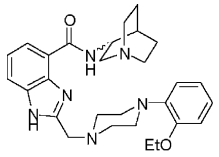
Bioorg. Med. Chem. Lett. 13 (2003) 3177

Design and Synthesis of New Benzimidazole-Arylpiperazine Derivatives Acting as Mixed 5-HT_{1A}/5-HT_3 Ligands

María L. López-Rodríguez,[a,*] Bellinda Benhamú,[a] Mª José Morcillo,[b] Ignacio Tejada,[a] David Avila,[a] Isabel Marco,[a] Lucio Schiapparelli,[c] Diana Frechilla[c] and Joaquín Del Río[c]

[a]*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain*
[b]*Sección de Química, Facultad de Ciencias, Universidad Nacional de Educación a Distancia, E-28040 Madrid, Spain*
[c]*Departamento de Farmacología, Facultad de Medicina, Universidad de Navarra, E-31008 Pamplona, Spain*

Compound **IIIc** was identified as a novel mixed 5-HT_{1A}/5-HT_3 ligand (K_i = 18.0 and 27.2 nM) improving cognitive dysfunction.



IIIc

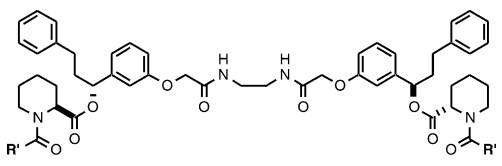
Bioorg. Med. Chem. Lett. 13 (2003) 3181

Regulation of Gene Expression by Synthetic Dimerizers with Novel Specificity

Wu Yang,* Terence P. Keenan, Leonard W. Rozamus, Xiurong Wang, Victor M. Rivera, Carl T. Rollins, Tim Clackson* and Dennis A. Holt

ARIAD Gene Therapeutics, Inc., 26 Landsdowne Street, Cambridge, MA 02139-4234, USA

New synthetic chemical inducers of dimerization (CIDs), comprising homodimeric FKBP ligands with engineered specificity for the designed point mutant F36V, have been evaluated for inducing targeted gene expression in mammalian cells.

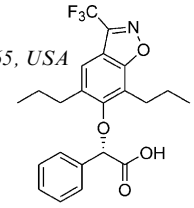


Bioorg. Med. Chem. Lett. 13 (2003) 3185

O-Arylmandelic Acids as Highly Selective Human PPAR α/γ Agonists

Alan D. Adams,[a,*] Zao Hu,[a] Derek von Langen,[a] Adonis Dadiz,[a] Alex Elbrecht,[b] Karen L. MacNaul,[b] Joel P. Berger,[b] Gaochao Zhou,[b] Thomas W. Doebber,[b] Roger Meurer,[c] Michael J. Forrest,[c] David E. Moller[b] and A. Brian Jones[d]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co. Inc., PO Box 2000 Rahway, NJ 07065, USA*
[b]*Department of Molecular Endocrinology, Merck Research Laboratories, Merck & Co. Inc., PO Box 2000 Rahway, NJ 07065, USA*
[c]*Department of Animal Pharmacology, Merck Research Laboratories, Merck & Co. Inc., PO Box 2000 Rahway, NJ 07065, USA*
[d]*Merck Neuroscience Research Center, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*



(S) **10** PPARα K_i 12 nM

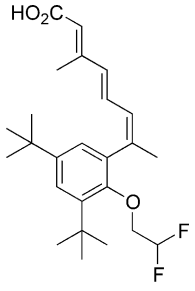
The synthesis and characterization of a new class of PPAR mediated insulin sensitizers is described.

Bioorg. Med. Chem. Lett. 13 (2003) 3191

Design and Synthesis of Fluorinated RXR Modulators

D. L. Gernert,[b,*] R. Ajamie,[d] R. A. Ardecky,[a] M. G. Bell,[b] M. D. Leibowitz,[e] D. A. Mais,[f] C. M. Mapes,[a] P. Y. Michellys,[a] D. Rungta,[f] A. Reifel-Miller,[c] J. S. Tyhonas,[a] N. Yumibe[d] and T. A. Grese[b]

[a]*Department of Medicinal Chemistry, Ligand Pharmaceuticals, Incorporated, San Diego, CA, USA*
[b]*Discovery Chemistry Research, Lilly Research Laboratories, Indianapolis, IN, USA*
[c]*Division of Endocrine Research, Lilly Research Laboratories, Indianapolis, IN, USA*
[d]*ADME, Lilly Research Laboratories, Indianapolis, IN, USA*
[e]*Department of Pharmacology, Ligand Pharmaceuticals, Inc., San Diego, CA, USA*
[f]*Department of New Leads Discovery, Ligand Pharmaceuticals, Inc., San Diego, CA, USA*



1

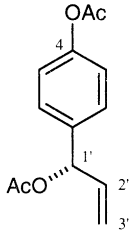
Fluorinated trienoic acid analogues of the RXR selective modulator **1** (LG101506) were synthesized, and tested for their ability to bind RXRα and activate RXR homo and heterodimers.

Bioorg. Med. Chem. Lett. 13 (2003) 3197

Antiallergic Principles from *Alpinia galanga*: Structural Requirements of Phenylpropanoids for Inhibition of Degranulation and Release of TNF-α and IL-4 in RBL-2H3 Cells

Hisashi Matsuda, Toshio Morikawa, Hiromi Managi and Masayuki Yoshikawa*

Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan



1'*S*-1'-acetoxychavicol acetate

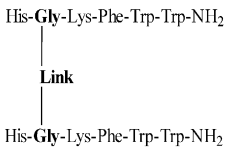
The 80% aqueous acetone extract of the rhizomes of *Alpinia galanga* was found to inhibit release of β-hexosaminidase, as a marker of antigen-IgE-mediated degranulation in RBL-2H3 cells. Nine known phenylpropanoids and *p*-hydroxybenzaldehyde were isolated from the extract. Among them, 1′*S*-1′-acetoxychavicol acetate and 1′*S*-1′-acetoxyeugenol acetate exhibited potent inhibitory activity with IC_{50} values of 15 and 19 μM. From the effects of various related compounds, both the 1′- and 4-acetoxyl groups of 1′*S*-1′-acetoxychavicol acetate and 1′*S*-1′-acetoxyeugenol acetate were essential for their strong activity, and the 2′–3′ double bond enhanced the activity. In addition, 1′*S*-1′-acetoxychavicol acetate and 1′*S*-1′-acetoxyeugenol acetate inhibited ear passive cutaneous anaphylaxis reactions in mice and the antigen-IgE-mediated TNF-α and IL-4 production, both of which participate in the late phase of type I allergic reactions, in RBL-2H3 cells.

Bioorg. Med. Chem. Lett. 13 (2003) 3203

Design and Synthesis of Dimeric HIV-1 Integrase Inhibitory Peptides

Krzysztof Krajewski,[a] Ya-Qiu Long,[b] Christophe Marchand,[c] Yves Pommier[c] and Peter P. Roller[a,*]

[a]*Laboratory of Medicinal Chemistry, CCR, NCI-Frederick, NIH, Frederick, MD 21702, USA*
[b]*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China*
[c]*Laboratory of Molecular Pharmacology, CCR, NCI, NIH, Bethesda, MD 20892, USA*



The synthesis and the inhibitory activity of dimeric hexapeptides with disulphide and thioether links ($-CH_2SCH_2-$, $-CH_2SSCH_2-$, $-C_2H_4SCH_2-$, $-C_2H_4SC_2H_4-$, and $-CH_2SCH_2SCH_2-$) are reported.

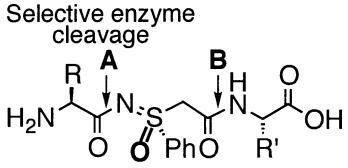
Bioorg. Med. Chem. Lett. 13 (2003) 3207

The Stability of Pseudopeptides Bearing Sulfoximines as Chiral Backbone Modifying Element towards Proteinase K

Carsten Bolm,* Dirk Müller, Christian Dalhoff, Christian P. R. Hackenberger and Elmar Weinhold*

Institut für Organische Chemie, RWTH Aachen, Prof.-Pirlet-Str. 1, D-52056 Aachen, Germany

Incorporation of sulfoximines as backbone modifying element results in two new pseudopeptide bonds **A** and **B** which differ significantly in their reactivity towards hydrolysis by Proteinase K.



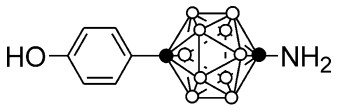
Bioorg. Med. Chem. Lett. 13 (2003) 3213

A Convenient Method for the Computer-Aided Molecular Design of Carborane Containing Compounds

Jayaseharan Johnsamuel,[a,*] Youngjoo Byun,[a] Thomas P. Jones,[b] Yasuyuki Endo[c] and Werner Tjarks[a]

[a]*The Ohio State University, College of Pharmacy, 500 W. 12th Avenue, Columbus, OH 43210, USA*
[b]*Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144, USA*
[c]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai 981-8558, Japan*

Computer-aided molecular design (CAMD) of carborane containing molecules has the potential to be an essential component in drug design for boron neutron capture therapy (BNCT). This is the first report of modeling and docking of carborane containing molecules with the readily available software packages HyperChem, SYBYL and FlexX.



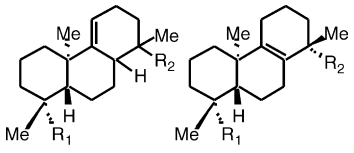
Bioorg. Med. Chem. Lett. 13 (2003) 3217

Synthesis of a Novel Family of Diterpenes and Their Evaluation as Anti-Inflammatory Agents

Thanh Lam,[a] Taotao Ling,[a] Chinmay Chowdhury,[a] Ta-Hsiang Chao,[b] F. R. Bahjat,[b] G. K. Lloyd,[b] Lyle L. Moldawer,[c] Michael A. Palladino[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]*Nereus Pharmaceuticals, Inc, 10480 Wateridge Circle, San Diego, CA 92121, USA*
[c]*Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610, USA*

The synthesis and TNF-α inhibitory profile of a new family of diterpenes, represented by structures **2** and **3**, is presented.



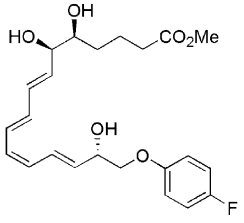
Bioorg. Med. Chem. Lett. 13 (2003) 3223

Synthesis of Methyl (5*S*,6*R*,7*E*,9*E*,11*Z*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-7,9,11,13-hexadecatetraenoate, an Analogue of 15*R*-Lipoxin A_4

Eifion D. Phillips,* Hui-Fang Chang, Christopher R. Holmquist and John P. McCauley

Department of Chemistry, AstraZeneca R&D Wilmington, 1800 Concord Pike, Wilmington, DE 19850, USA

A synthesis of the title compound, an analogue of 15*R*-lipoxin A_4, is described.



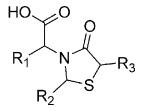
Bioorg. Med. Chem. Lett. 13 (2003) 3227

Novel Inhibitors of an Emerging Target in *Mycobacterium tuberculosis*; Substituted Thiazolidinones as Inhibitors of dTDP-rhamnose Synthesis

Kerim Babaoglu,[a] Mark A. Page,[a] Victoria C. Jones,[b] Michael R. McNeil,[b] Changjiang Dong,[c] James H. Naismith[c] and Richard E. Lee[a,*]

[a]*Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, USA*
[b]*Department of Microbiology, Colorado State University, Fort Collins, CO 80523, USA*
[c]*Centre for Biomolecular Sciences, The University, St. Andrews KY16 9ST, UK*

The structure guided design and synthesis of thiazolidinone inhibitors of *Mycobacterium tuberculosis* dTDP-Rhamnose biosynthesis is described.



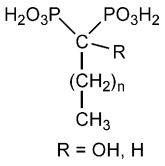
Bioorg. Med. Chem. Lett. 13 (2003) 3231

Bisphosphonates Derived from Fatty Acids are Potent Inhibitors of *Trypanosoma cruzi* Farnesyl Pyrophosphate Synthase

Sergio H. Szajnman,[a] Andrea Montalvetti,[b] Youhong Wang,[b] Roberto Docampo[b] and Juan B. Rodriguez[a,*]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, C1428EHA Buenos Aires, Argentina*
[b]*Laboratory of Molecular Parasitology, Department of Pathobiology and Center for Zoonoses Research, University of Illinois at Urbana-Champaign, 2001 South Lincoln Avenue, Urbana, IL 61802, USA*

Bisphosphonates derived from fatty acid were shown to be potent inhibitors of *Trypanosoma cruzi* farnesylpyrophosphate synthase activity.

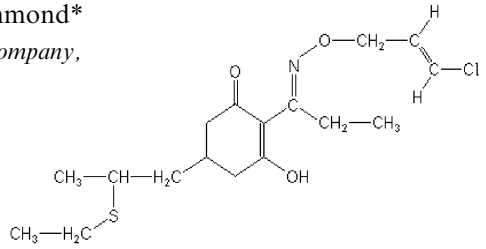


Bioorg. Med. Chem. Lett. 13 (2003) 3237

Cyclohexanedione Herbicides are Inhibitors of Rat Heart Acetyl-CoA Carboxylase

Thomas W. Seng, Tiffanie R. Skillman, Nengyu Yang and Craig Hammond*

Endocrine Research, Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Drop Code 0304, Indianapolis, IN 46285, USA



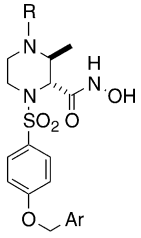
Bioorg. Med. Chem. Lett. 13 (2003) 3243

Synthesis and Biological Activity of Piperazine-Based Dual MMP-13 and TNF-α Converting Enzyme Inhibitors

Michael A. Letavic,* John T. Barberia, Thomas J. Carty, Joel R. Hardink, Jennifer Liras, Lori L. Lopresti-Morrow, Peter G. Mitchell, Mark C. Noe, Lisa M. Reeves, Sheri L. Snow, Ethan J. Stam, Francis J. Sweeney, Marcie L. Vaughn and Chul H. Yu

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

A series of novel piperazine-based hydroxamic acids with potent TACE activity is described.



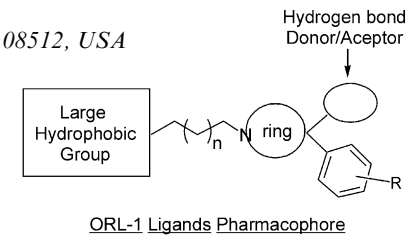
Bioorg. Med. Chem. Lett. 13 (2003) 3247

Design and Parallel Synthesis of Piperidine Libraries Targeting the Nociceptin (N/OFQ) Receptor

Zhengming Chen,[a,*] Wendy S. Miller,[b] Shen Shan[b] and Kenneth J. Valenzano[b]

[a]*Computational, Combinatorial and Medicinal Chemistry, Purdue Pharma L. P., 6 Cedar Brook Drive, Cranbury, NJ 08512, USA*
[b]*Molecular Pharmacology, Purdue Pharma L. P., 6 Cedar Brook Drive, Cranbury, NJ 08512, USA*

Based on literature structures, we proposed a pharmacophore for NOP receptor ligands and used it as a guide for the design of a focused piperidine library and an optimization library. Potent NOP receptor agonists and antagonists were obtained from these libraries as well as a few potent mu selective agonists.

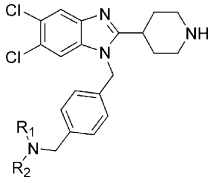


Bioorg. Med. Chem. Lett. 13 (2003) 3253

2-Piperidin-4-yl-benzimidazoles with Broad Spectrum Antibacterial Activities

Yun He,* Baogen Wu, Jun Yang, Dale Robinson, Lisa Risen, Ray Ranken, Lawrence Blyn, Suzie Sheng and Eric E. Swayze

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



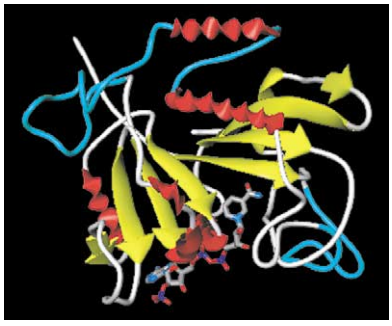
Bioorg. Med. Chem. Lett. 13 (2003) 3257

Structure of *Plasmodium vivax* Dihydrofolate Reductase Determined by Homology Modeling and Molecular Dynamics Refinement

Giulio Rastelli,* Sara Pacchioni and Marco Daniele Parenti

Dipartimento di Scienze Farmaceutiche, Università di Modena e Reggio Emilia. Via Campi 183, 41100 Modena, Italy

The structure of *Plasmodium vivax* dihydrofolate reductase, a potential target for antimalarial therapy, is described.



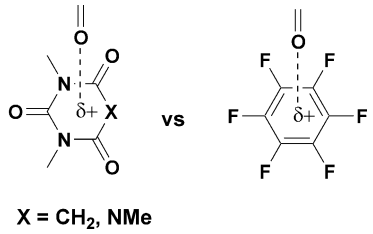
Bioorg. Med. Chem. Lett. 13 (2003) 3261

Electrostatic Interaction of π-Acidic Amides with Hydrogen-Bond Acceptors

Yi Li,[a,*] Lawrence B. Snyder[b] and David R. Langley[a]

[a]*Computer-Assisted Drug Design, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[b]*Department of Discovery Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*

Computational studies of interactions between *N*-methylacetamide and uracil, isocyanurate and barbituric acid are reported, suggesting that these π-acidic amides may be used to complement a hydrogen bond acceptor in molecular recognition and drug design.



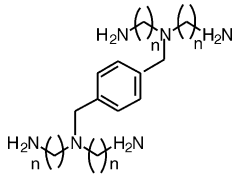
Bioorg. Med. Chem. Lett. 13 (2003) 3267

Xylylated Dimers of Putrescine and Polyamines: Influence of the Polyamine Backbone on Spermidine Transport Inhibition

Laurence Covassin,[a] Michel Desjardins,[b] Denis Soulet,[b] René Charest-Gaudreault,[c] Marie Audette[d] and Richard Poulin[b,*]

[a]*Faculty of Pharmacy, Faculty of Medicine, Laval University, QC, Canada G1K 7P4*
[b]*Department of Physiology, Faculty of Medicine, Laval University, QC, Canada G1K 7P4*
[c]*Department of Pharmacology, Faculty of Medicine, Laval University, QC, Canada G1K 7P4*
[d]*Department of Medical Biology, Faculty of Medicine, Laval University, QC, Canada G1K 7P4*

Putrescine, spermine, and various triamines dimers crosslinked with a xylyl tether inhibit polyamine transport as a function of the polyamine backbone structure.



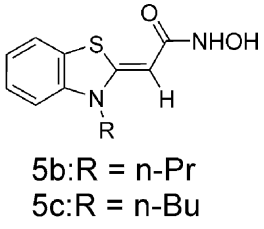
Bioorg. Med. Chem. Lett. 13 (2003) 3273

Synthesis and PDF Inhibitory Activities of Novel Benzothiazolylidenehydroxamic Acid Derivatives

Wataru Takayama,* Yoshihisa Shirasaki, Yusuke Sakai, Emi Nakajima, Shuhei Fujita, Kanako Sakamoto-Mizutani and Jun Inoue

Research Laboratories, Senju Pharmaceutical Co., Ltd.,1-5-4 Murotani, Nishi-Ku, Kobe, Hyogo 651-2241, Japan

A novel series of benzothiazolylidenehydroxamic acid derivatives exhibited micromolar order PDF inhibitory activity and antibacterial activity.



5b:R = n-Pr
5c:R = n-Bu

Bioorg. Med. Chem. Lett. 13 (2003) 3277

Bicyclo[2.2.1]heptanes as Novel Triple Re-uptake Inhibitors for the Treatment of Depression

Lorraine Axford,[a] John R. Boot,[a] Terrence M. Hotten,[a] Martine Keenan,[a] Fionna M. Martin,[a,*] Sandra Milutinovic,[a] Nick A. Moore,[a] Michael F. O'Neill,[a] Ian A. Pullar,[a] David E. Tupper,[a] Kristel R. Van Belle[b] and Vincent Vivien[a]

[a]*Lilly Research Centre, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, UK*
[b]*Lilly Development Centre S.A, Parc Scientifique de Louvain-la-Neuve, Rue Granbonpre, 11-B-1348 Mont Saint-Guibert, Belgium*

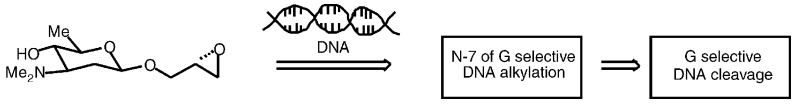
The synthesis and SAR of a series of naphthyl containing chiral [2.2.1]bicycloalkanes as triple re-uptake inhibitors.

Bioorg. Med. Chem. Lett. 13 (2003) 3281

Glycidol-carbohydrate Hybrids: a New Family of DNA Alkylating Agents

Kazunobu Toshima,* Yukiko Okuno and Shuichi Matsumura

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan



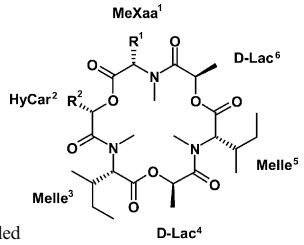
Bioorg. Med. Chem. Lett. 13 (2003) 3285

Synthesis and Anthelmintic Activity of Cyclohexadepsipeptides with (*S*,*S*,*S*,*R*,*S*,*R*)-Configuration

Peter Jeschke,[a,*] Jordi Benet-Buchholz,[b] Achim Harder,[c] Winfried Etzel,[a] Michael Schindler[a] and Gerhard Thielking[a]

[a]*Bayer CropScience AG, Research Monheim, Global Chemistry Insecticides, Building Q 18, D-51368 Leverkusen, Germany*
[b]*Bayer Industry Services, Analytics X-ray Laboratory, Building Q18, D-51368 Leverkusen, Germany*
[c]*Bayer HealthCare, Animal Health Business Group, Research & Development, Parasiticides, Alfred-Nobel-Str 50, D-40789 Monheim, Germany*

The synthesis of novel (*S*,*S*,*S*,*R*,*S*,*R*)-configurated cyclohexadepsipeptides (CHDPs) **5** and **6** with strong in vivo activity against the parasitic nematode *Haemonchus contortus* Rudolphi in sheep is described. 2D NMR spectroscopic analysis revealed for the major conformation the asymmetric conformer, containing a *cis*-amide bond between C_α protons of neighbouring 2-hydroxy-(*S*)-carboxylic acid (HyCar[2]) and *N*-methyl-(*S*)-amino acid (MeXaa[1]). The absolute configuration of **5** was determined by X-ray crystallography. A correlation between the major conformer and its anthelmintic activity was found.



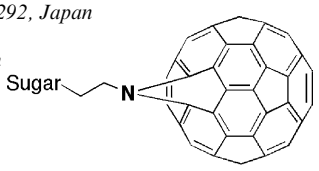
5 R^1 = *s*Bu; R^2 = *n*Bu
6 R^1, R^2 = Me

Bioorg. Med. Chem. Lett. 13 (2003) 3289

Detection of 1270 nm Emission from Singlet Oxygen and Photocytotoxic Property of Sugar-Pendant [60] Fullerenes

Yuji Mikata,[a,*] Satowa Takagi,[b] Maki Tanahashi,[b] Sayoko Ishii,[b] Makoto Obata,[b] Yuichi Miyamoto,[c] Kazuhito Wakita,[c] Tsuyoshi Nishisaka,[c] Toru Hirano,[d] Toshiaki Ito,[e] Mikio Hoshino,[f] Chikara Ohtsuki,[g] Masao Tanihara[g] and Shigenobu Yano[b,*]

[a]*KYOUSEI Science Center, Nara Women's University, Nara 630-8506 Japan*
[b]*Division of Material Science, Nara Women's University, Nara 630-8506, Japan*
[c]*School of Material Science, Japan Advanced Institute of Science and Technology (JAIST), Ishikawa 923-1292, Japan*
[d]*Hamamatsu Photonics KK, Hamakita 434-8601, Japan*
[e]*Photon Medical Research Center, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan*
[f]*The Institute of Physical and Chemical Research, Saitama 352-0198, Japan*
[g]*Nara Institute of Science and Technology (NAIST), Nara 630-0192, Japan*



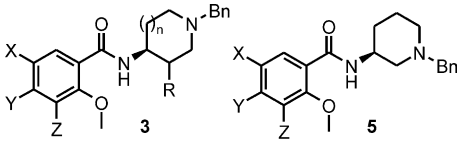
Bioorg. Med. Chem. Lett. 13 (2003) 3293

Stereocontrolled Dopamine Receptor Binding and Subtype Selectivity of Clebopride Analogues Synthesized from Aspartic Acid

Jürgen Einsiedel, Klaus Weber, Christoph Thomas, Thomas Lehmann, Harald Hübner and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstraße 19, D-91052 Erlangen, Germany

Starting from aspartic acid, chiral benzamides of type **3** and **5** have been synthesized and investigated for stereospecific dopamine receptor binding profiles.



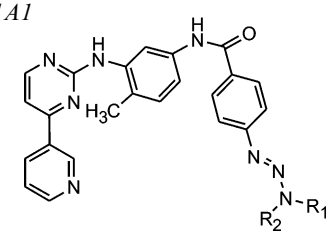
Bioorg. Med. Chem. Lett. 13 (2003) 3297

Synthesis of Pyrimidinopyridine–Triazene Conjugates Targeted to abl Tyrosine Kinase

Zakaria Rachid, Athanasia Katsoulas, Fouad Brahimi and Bertrand Jacques Jean-Claude*

Cancer Drug Research Laboratory, Division of Medical Oncology, Department of Medicine, McGill University/ Royal Victoria Hospital, 687 Pine Avenue West Rm M-719, Montreal, Québec, Canada H3A 1A1

The synthesis and abl tyrosine kinase inhibitory activities of alkyltriazenes conjugated to phenylaminopyrimidines are described. Significant abl inhibitory activities were observed only when a benzamido spacer was inserted between the 1,2,3-triazene chain and the 2-phenyaminopyridopyrimidine moiety.



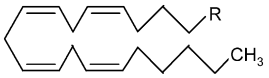
Bioorg. Med. Chem. Lett. 13 (2003) 3301

Arachidonylsulfonyl Derivatives as Cannabinoid CB1 Receptor and Fatty Acid Amide Hydrolase Inhibitors

Yoffi Segall, Gary B. Quistad, Daniel K. Nomura and John E. Casida*

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

Arachidonylsulfonyl fluoride (**3**) inhibits mouse brain fatty acid amide hydrolase and a CB1 agonist site with IC_{50} values of 0.11 and 304 nM, respectively. The corresponding *N*-(2-hydroxyethyl) sulfonamide (**4**) is at least 2500-fold less active than its analogue anandamide (**1**) at the CB1 agonist site.



1 R=C(O)NHCH$_2$CH$_2$OH
3 R=CH$_2$SO$_2$F
4 R=CH$_2$SO$_2$NHCH$_2$CH$_2$OH

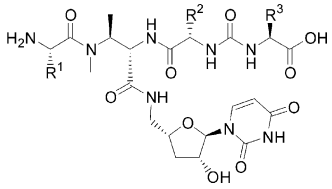
Bioorg. Med. Chem. Lett. 13 (2003) 3305

Synthetic Dihydropacidamycin Antibiotics: A Modified Spectrum of Activity for the Pacidamycin Class

Constantine G. Boojamra,* Rémy C. Lemoine, Johanne Blais, Nicole G. Vernier, Karin A. Stein, Angela Magon, Suzanne Chamberland, Scott J. Hecker and Ving J. Lee

Essential Therapeutics, Inc. (formerly Microcide Pharmaceuticals, Inc.), 850 Maude Avenue, Mountain View, CA 94043, USA

Dihydropacidamycins having an antibacterial spectrum modified from that of the natural product pacidamycins and mureidomycins have been synthesized. Synthetic dihydropacidamycins with noteworthy antibacterial activity against wild-type and resistant *Escherichia coli* have been identified (MIC = 4–8 μg/mL). Some dihydropacidamycins are shown to have activity against multi-resistant clinical strains of *Mycobacterium tuberculosis*. Compounds of this class are inhibitors of the cell-wall biosynthetic enzyme, MraY.



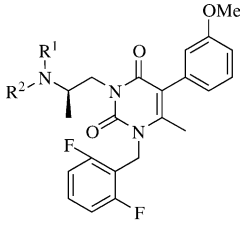
Bioorg. Med. Chem. Lett. 13 (2003) 3311

Synthesis and Structure–Activity Relationships of 1-Arylmethyl-3-(2-aminopropyl)-5-aryl-6-methyluracils as Potent GnRH Receptor Antagonists

Zhiqiang Guo,[a,*] Yun-Fei Zhu,[a] Fabio C. Tucci,[a] Yinghong Gao,[a] R. Scott Struthers,[b] John Saunders,[a] Timothy D. Gross,[a] Qiu Xie,[b] Greg J. Reinhart[b] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*
[b]*Department of Exploratory Discovery, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*

The novel synthesis and SAR studies of 6-methyluracils as human GnRH receptor antagonists are discussed. Introduction of a methyl substituent at the β-position from N3 of the uracil improved the GnRH binding potency by 5- to 10-fold.



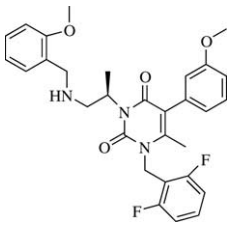
Bioorg. Med. Chem. Lett. 13 (2003) 3317

Synthesis and Structure–Activity Relationships of 1-Arylmethyl-3-(1-methyl-2-amino)ethyl-5-aryl-6-methyluracils as Antagonists of the Human GnRH Receptor

Fabio C. Tucci,[a,*] Yun-Fei Zhu,[a] Zhiqiang Guo,[a] Timothy D. Gross,[a] Patrick J. Connors, Jr.,[a] R. Scott Struthers,[b] Greg J. Reinhart,[b] John Saunders[a] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*
[b]*Department of Exploratory Discovery, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*

The design and synthesis of this novel class of GnRH receptor antagonists are described. The best compound of this series showed $K_i = 20$ nM.



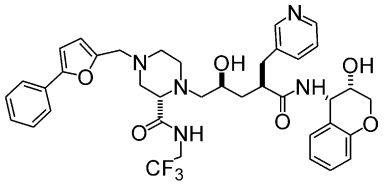
Bioorg. Med. Chem. Lett. 13 (2003) 3323

HIV-1 Protease Inhibitors with Picomolar Potency against PI-Resistant HIV-1 by Modification of the P_1' Substituent

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

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

Transposition of the pyridyl nitrogen from the P_3 substituent to the P_1' substituent in HIV-1 protease inhibitors affords compounds with superior potency and an improved inhibitory profile against multiple P450 isoforms.



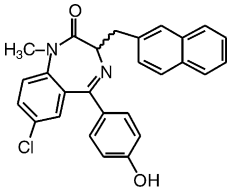
Bioorg. Med. Chem. Lett. 13 (2003) 3327

Structure Activity Studies of a Novel Cytotoxic Benzodiazepine

Anthony Boitano,[a] Cory D. Emal,[a] Francesco Leonetti,[b] Neal B. Blatt,[a] Thomas A. Dineen,[a] Jonathan A. Ellman,[b] William R. Roush,[a] Anthony W. Opipari[a,*] and Gary D. Glick[a,*]

[a]*Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109-1055, USA*
[b]*University of California—Berkeley, 724 Latimer Hall, Berkeley, CA 94720-1460, USA*

Analogues of Bz-423, a pro-apoptotic 1,4-benzodiazepine active in animal models of lupus and rheumatoid arthritis, have been designed, synthesized, and evaluated in cell culture assays. These experiments have defined the structural elements of this new cytotoxic agent required for activity.



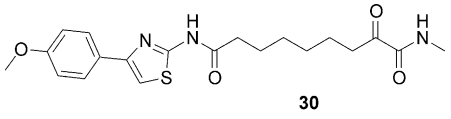
Bioorg. Med. Chem. Lett. 13 (2003) 3331

α-Keto Amides as Inhibitors of Histone Deacetylase

Carol K. Wada,* Robin R. Frey, Zhiqin Ji, Michael L. Curtin, Robert B. Garland, James H. Holms, Junling Li, Lori J. Pease, Jun Guo, Keith B. Glaser, Patrick A. Marcotte, Paul L. Richardson, Shannon S. Murphy, Jennifer J. Bouska, Paul Tapang, Terrance J. Magoc, Daniel H. Albert, Steven K. Davidsen and Michael R. Michaelides

Cancer Research, Abbott Laboratories, Department R47J, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064, USA

α-Keto ester and amides were found to be potent inhibitors of histone deacetylase. Nanomolar inhibitors against the isolated enzyme and sub-micromolar inhibitors of cellular proliferation were obtained. The alpha-keto amide **30** also exhibited significant anti-tumor effects in an in vivo tumor model.



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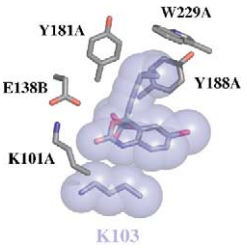
Bioorg. Med. Chem. Lett. 13 (2003) 3337

Activity Predictions for Efavirenz Analogues with the K103N Mutant of HIV Reverse Transcriptase

Marina Udier-Blagović, Edward K. Watkins, Julian Tirado-Rives and William L. Jorgensen*

Department of Chemistry, Yale University, New Haven, CT 06520-8107, USA

Monte Carlo-extended linear response (MC/ELR) calculations are used to examine the binding of efavirenz analogues with the K103N mutant of HIV-1 reverse transcriptase (HIVRT). A regression equation previously reported for the wild type (WT) enzyme is shown to predict 47 experimental activities for the K103N mutant with a $q^2 = 0.55$ and avg error of only 0.46 kcal/mol. Further analysis identifies the key features for binding to the K103N mutant: ligand flexibility, burial of hydrophobic surface area, and protein–ligand van der Waals interactions.



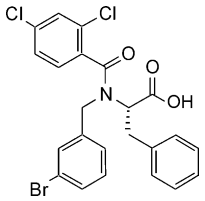
Bioorg. Med. Chem. Lett. 13 (2003) 3341

Further SAR Studies on Novel Small Molecule Inhibitors of the Hepatitis C (HCV) NS5B Polymerase

T. Jagadeeswar Reddy,* Laval Chan, Nathalie Turcotte, Melanie Proulx, Oswy Z. Pereira, Sanjoy K. Das, Arshad Siddiqui, Wuyi Wang, Carl Poisson, Constantin G. Yannopoulos, Darius Bilimoria, Lucille L'Heureux, Hicham M. A. Alaoui and Nghe Nguyen-Ba

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

The structure–activity relationship (SAR) of NS5B polymerase inhibitor (**1**) with an IC_{50} of 3.5 μM is reported.



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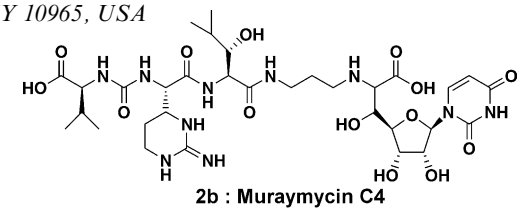
Bioorg. Med. Chem. Lett. 13 (2003) 3345

Muraymycins, Novel Peptidoglycan Biosynthesis Inhibitors: Synthesis and SAR of Their Analogues

Ayako Yamashita,* Emily Norton, Peter J. Petersen, Beth A. Rasmussen, Guy Singh, Youjin Yang, Tarek S. Mansour and Douglas M. Ho

Chemical Sciences and Infectious Diseases, Wyeth Research, Pearl River, NY 10965, USA

A series of muraymycin analogues was synthesized. These analogues showed good antimicrobial activity against gram-positive organisms.



2b : Muraymycin C4

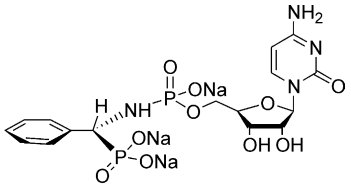
Bioorg. Med. Chem. Lett. 13 (2003) 3351

Stereoselective Synthesis of Phosphoramidate α(2-6)Sialyltransferase Transition-State Analogue Inhibitors

Danielle Skropeta, Ralf Schwörer and Richard R. Schmidt*

Fachbereich Chemie, Universitaet Konstanz, Fach M 725, D-78457 Konstanz, Germany

The asymmetric synthesis of novel, potent phosphoramidate α(2-6)sialyltransferase transition-state analogue inhibitors such as (*R*)-**9** (K_i = 68 μM) is reported.



(*R*)-**9** K_i = 68 μM

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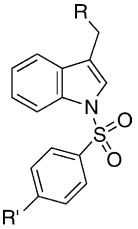
N_1-Benzenesulfonylgramine and N_1-Benzenesulfonylskatole: Novel 5-HT_6 Receptor Ligand Templates

Manik R. Pullagurla,[a] Małgorzata Dukat,[a] Vincent Setola,[b] Bryan Roth[b,c] and Richard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*
[b]*Department of Biochemistry, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA*
[c]*Departments of Psychiatry and Neurosciences, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA*

Compound **10a** [R = $N(CH_3)_2$; R′ = H] and **11b** (R = H, R′ = NH_2), tryptamine-derived compounds with high affinity (K_i = 3.1 and 12 nM, respectively) and antagonist action at human 5-HT_6 receptors, indicate that the tryptamine aminoethyl moiety is not required for binding or antagonist activity.



10a, 11b

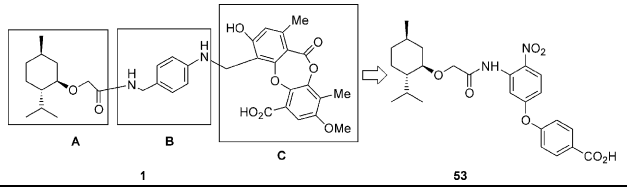
Bioorg. Med. Chem. Lett. 13 (2003) 3361

Synthesis and Biological Evaluation of Menthol-Based Derivatives as Inhibitors of Plasminogen Activator Inhibitor-1 (PAI-1)

Bin Ye,* Shawn Bauer, Brad O. Buckman, Ameen Ghannam, Brian D. Griedel, Seock-Kyu Khim, Wheeseong Lee, Karna L. Sacchi, Kenneth J. Shaw, Amy Liang, Qingyu Wu and Zuchun Zhao*

Discovery Research, Berlex Biosciences, 2600 Hilltop Drive, PO Box 4099, Richmond, CA 94804-0099, USA

Optimization of the B and C-segments of lead **1** found through HTS led to the identification of a more potent PAI-1 inhibitor **53** with a simplified structure.

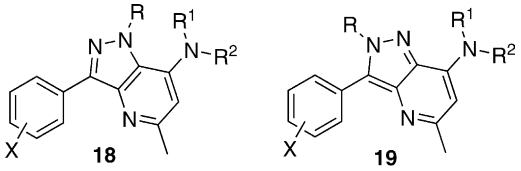


Bioorg. Med. Chem. Lett. 13 (2003) 3367

Synthesis of 3-Phenylpyrazolo[4,3-*b*]pyridines Via a Convenient Synthesis of 4-Amino-3-arylpyrazoles and SAR of Corticotropin-Releasing Factor Receptor Type-1 Antagonists

Keith Wilcoxen, Charles Q. Huang, James R. McCarthy, Dimitri E. Grigoriadis and Chen Chen*

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

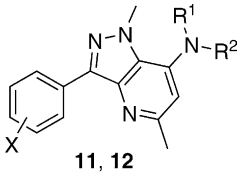


Bioorg. Med. Chem. Lett. 13 (2003) 3371

Synthesis of 1-Methyl-3-phenylpyrazolo[4,3-*b*]pyridines Via a Methylation of 4-Phthalimino-3-phenylpyrazoles and Optimization toward Highly Potent Corticotropin-Releasing Factor Type-1 Antagonists

Charles Q. Huang, Keith Wilcoxen, James R. McCarthy, Mustaph Haddach, Dimitri Grigoriadis and Chen Chen*

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



Bioorg. Med. Chem. Lett. 13 (2003) 3375

Synthesis and SAR of 8-Arylquinolines as Potent Corticotropin-Releasing Factor$_1$ (CRF$_1$) Receptor Antagonists

Charles Q. Huang, Keith Wilcoxen, James R. McCarthy, Mustapha Haddach, Thomas R. Webb, Jian Gu, Yun-Feng Xie, Dimitri E. Grigoriadis and Chen Chen*

Department of Medicinal Chemistry and Department of Pharmacology, Neurocrine Biosciences, Inc., 10555 Science Centre Drive, San Diego, CA 92121, USA