Bioorg. Med. Chem. Lett. 13 (2003) 993

Inhibition of Bacterial IF2 Binding to FMet-tRNA$^{(fMet)}$ by Aminoglycosides

J. M. Evans,[a] B. A. Turner,[a] S. Bowen,[b] A. M. Ho,[c] R. W. Sarver,[c] E. Benson[b] and C. N. Parker[a,*]

[a]*Global High Throughput Screening, Pharmacia Corp., Kalamazoo, MI 49007, USA*
[b]*Infectious Diseases Biology, Pharmacia Corp., Kalamazoo, MI 49007, USA*
[c]*Structural & Medicinal Chemistry, Pharmacia Corp., Kalamazoo, MI 49007, USA*

The inhibition of bacterial Initation Factor 2 binding to N-formyl-methionine transfer RNA by aminoglycosides such as amikacin, IC_{50} 1μM, is reported.

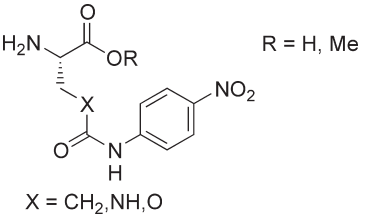
Bioorg. Med. Chem. Lett. 13 (2003) 997

Synthesis of Aza and Oxaglutamyl-*p*-nitroanilide Derivatives and Their Kinetic Studies with γ-Glutamyltranspeptidase

Christian Lherbet, Mylène Morin, Roselyne Castonguay and Jeffrey W. Keillor*

Département de chimie, Université de Montréal, C.P. 6128, Succursale centre-ville, Montréal, Québec, Canada H3C 3J7

The synthesis and kinetic studies of L-γ-glutamic acid *para*-nitroanilide analogues with rat kidney γ-glutamyl transpeptidase (GGT) are reported.

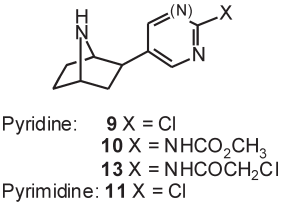


Bioorg. Med. Chem. Lett. 13 (2003) 1001

Syntheses and Biological Properties of Cysteine-Reactive Epibatidine Derivatives

Christian Che,[a] Grégory Petit,[a] Florence Kotzyba-Hibert,[a] Sonia Bertrand,[b] Daniel Bertrand,[b] Thomas Grutter[c] and Maurice Goeldner[a,*]

[a]*Laboratoire de Chimie Bioorganique, UMR 7514 CNRS, Faculté de Pharmacie, Université Louis Pasteur Strasbourg BP 24, 67401 Illkirch, cedex France*
[b]*Laboratoire de Physiologie C.M.U., Faculté de Médecine, CH 1211 Geneva, Switzerland*
[c]*'Récepteurs et Cognition', Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex, France*

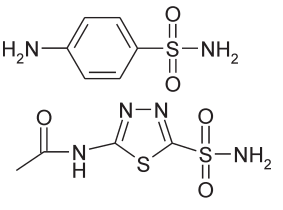


Bioorg. Med. Chem. Lett. 13 (2003) 1005

Carbonic Anhydrase Inhibitors: Inhibition of the Tumor-Associated Isozyme IX with Aromatic and Heterocyclic Sulfonamides

Daniela Vullo,[a] Marco Franchi,[b] Enzo Gallori,[b] Jaromir Pastorek,[c] Andrea Scozzafava,[a] Silvia Pastorekova[c] and Claudiu T. Supuran[a,*]

[a]*Università degli Studi di Firenze, Laboratorio di Chimica Bioinorganica, Rm. 188, Via della Lastruccia 3, I-50019 Sesto Fiorentino (Firenze), Italy*
[b]*Università degli Studi di Firenze, Dipartimento di Biologia Animale e Genetica, Via Romana 17-19, 50122 Firenze, Italy*
[c]*Institute of Virology, Slovak Academy of Sciences, Dubravska cesta 9, 842 45 Bratislava, Slovak Republic*



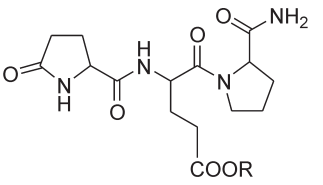
Bioorg. Med. Chem. Lett. 13 (2003) 1011

Prodrugs to Enhance Central Nervous System Effects of the TRH-like Peptide pGlu-Glu-Pro-NH_2

Katalin Prokai-Tatrai,[a] Vien Nguyen,[b] Alevtina D. Zharikova,[b] April C. Braddy,[b] Stanley M. Stevens, Jr.[b] and Laszlo Prokai[b,c,*]

[a]*Center for Neurobiology of Aging, College of Medicine, Gainesville, FL 32610-0485, USA*
[b]*Department of Medicinal Chemistry, College of Pharmacy, Gainesville, FL 32610-0485, USA*
[c]*The McKnight Brain Institute, University of Florida, Gainesville, FL 32610-0485, USA*

Synthesis, membrane affinity and analeptic effect of esters of pGlu-Glu-Pro-NH_2 are reported. Esters with long-chain primary alcohols emerged as potentially useful prodrugs to improve CNS activity of the TRH analogue.



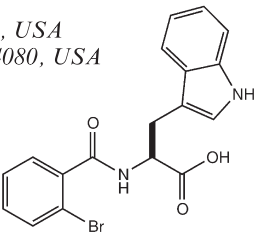
2a-e (R = Me, Hex, cHex, tBu, Bz)

Bioorg. Med. Chem. Lett. 13 (2003) 1015

N-Benzoyl Amino Acids as LFA-1/ICAM Inhibitors 1: Amino Acid Structure–Activity Relationship

Daniel J. Burdick,[a,*] Ken Paris,[a] Kenneth Weese,[a] Mark Stanley,[a] Maureen Beresini,[b] Kevin Clark,[b] Robert S. McDowell,[a] James C. Marsters, Jr.[a] and Thomas R. Gadek[a]

[a]*Department of Bioorganic Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*
[b]*Bioanalytical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*



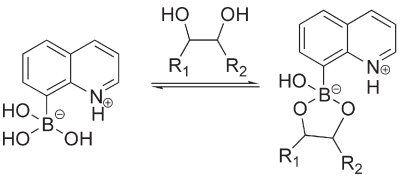
Bioorg. Med. Chem. Lett. 13 (2003) 1019

A Novel Type of Fluorescent Boronic Acid That Shows Large Fluorescence Intensity Changes Upon Binding with a Carbohydrate in Aqueous Solution at Physiological pH

Wenqian Yang, Jun Yan, Greg Springsteen, Susan Deeter and Binghe Wang*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, USA

8-Quinolineboronic acid was found to exhibit up to about 40-fold increases in fluorescence intensity upon binding with various carbohydrates. It shows optimal fluorescence intensity changes at physiological pH making it a great fluorescent reporter compound for carbohydrate synthesis.



Nonfluorescent Fluorescent

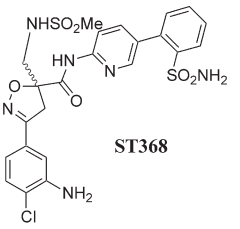
Bioorg. Med. Chem. Lett. 13 (2003) 1023

Nonbenzamidine Isoxazoline Derivatives as Factor Xa Inhibitors

Mimi L. Quan,* Christopher D. Ellis, Ming Y. He, Ann Y. Liauw, Patrick Y. S. Lam, Karen A. Rossi, Robert M. Knabb, Joseph M. Luettgen, Matthew R. Wright, Pancras C. Wong and Ruth R. Wexler

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

A series of nonbenzamidine isoxazoline fXa inhibitors is described. The chloroaniline group was found to be the most potent benzamidine mimic in this series. Chloroaniline **1** (ST368) has a K_i value of 1.2 nM against fXa and is highly selective for fXa relative to thrombin and trypsin.



ST368

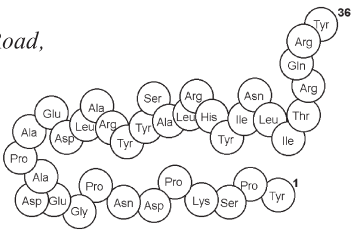
Bioorg. Med. Chem. Lett. 13 (2003) 1029

Synthesis and Binding Affinity of Neuropeptide Y at Opiate Receptors

James J. Kiddle,* Heather J. McCreery and Sonia Soles

Department of Chemistry, University of North Carolina at Wilmington, 601 South College Road, Wilmington, NC 28403, USA

Neuropeptide Y and several fragments were synthesized and shown to bind to non-selective opiate receptors.



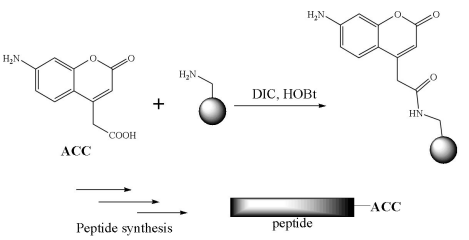
Bioorg. Med. Chem. Lett. 13 (2003) 1033

Facile Synthesis of 7-Amino-4-carbamoylmethylcoumarin (ACC)-Containing Solid Supports and Their Corresponding Fluorogenic Protease Substrates

Qing Zhu,[a] Dong B. Li,[a] Mahesh Uttamchandani[b] and Shao Q. Yao[a,b,*]

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*
[b]*Department of Biological Sciences, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*

The bifunctional fluorophore, 7-amino-4-carbamoylmethylcoumarin (ACC), without the need for any protection groups, was regioselectively attached to different solid supports functionalized with a primary amine. The resulting resins were used to synthesize fluorogenic protease substrates with high yield and purity.



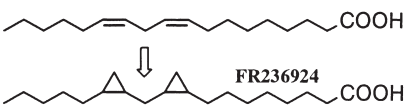
Bioorg. Med. Chem. Lett. 13 (2003) 1037

The Newly Synthesized Linoleic Acid Derivative FR236924 Induces a Long-Lasting Facilitation of Hippocampal Neurotransmission by Targeting Nicotinic Acetylcholine Receptors

Akito Tanaka[a,*] and Tomoyuki Nishizaki[b]

[a]*Molecular Science, Exploratory Res. Lab., Fujisawa Pharmaceutical Co. Ltd., 5-2-3 Tokodai, Tsukuba, Japan*
[b]*Department of Physiology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Japan*

The newly synthesized linoleic acid derivative, FR236924, induces a long-lasting facilitation of hippocampal neurotransmission based on a persistent enhancement in the activity of presynaptic nicotinic ACh receptors via a PKC pathway and the ensuing increase in glutamate release, not only in vitro but in vivo at a low dosage (2 mg/kg, ip), which suggested the possibility of its use as a promising anti-dementia drug.



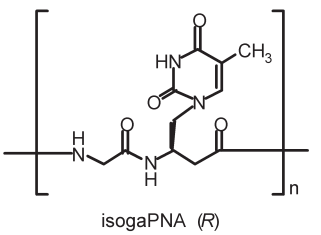
Bioorg. Med. Chem. Lett. 13 (2003) 1041

Synthesis and Hybridization Property of Novel 2′,5′-isoDNA Mimic Chiral Peptide Nucleic Acids

Mohamed Abdel-Aziz, Tetsuo Yamasaki* and Masami Otsuka

Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-Honmachi, Kumamoto 862-0973, Japan

The synthesis and hybridization properties of isogaPNA is reported.



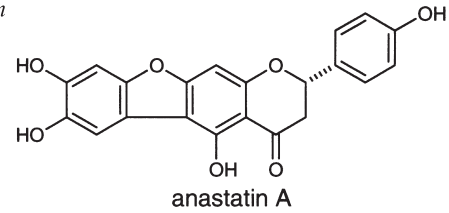
Bioorg. Med. Chem. Lett. 13 (2003) 1045

Anastatins A and B, New Skeletal Flavonoids with Hepatoprotective Activities from the Desert Plant *Anastatica hierochuntica*

Masayuki Yoshikawa,* Fengming Xu, Toshio Morikawa, Kiyofumi Ninomiya and Hisashi Matsuda

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

New skeletal flavonoids, anastatins A and B, were isolated from the methanolic extract of an Egyptian medicinal herb, the whole plants of *Anastatica hierochuntica*. Their flavanone structures having a benzofuran moiety were determined on the basis of chemical and physicochemical evidence. Anastatins A and B were found to show hepatoprotective effects on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes and their activities were stronger than those of related flavonoids and commercial silybin.



anastatin A

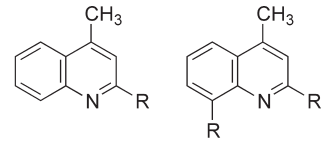
Bioorg. Med. Chem. Lett. 13 (2003) 1051

Substituted 4-Methylquinolines as a New Class of Anti-Tuberculosis Agents

Rahul Jain,* Balasubramanian Vaitilingam, Amit Nayyar and Prakash B. Palde

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India

The synthesis and antimycobacterial activities (*Mycobacterium tuberculosis H37Rv* strain) for a series of ring-substituted 4-methylquinolines are described. The evaluation of cytotoxicity and efficacy against *M. avium* and single-drug-resistant (SDR) strains of *M. tuberculosis* for the most effective compound **3d** ($R = c\text{-}C_5H_9$) are also reported.



2 **3**

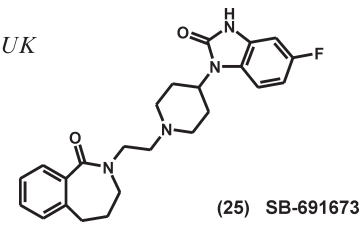
Bioorg. Med. Chem. Lett. 13 (2003) 1055

Identification of a Novel Series of Selective 5-HT$_7$ Receptor Antagonists

Ian T. Forbes,* David G. Cooper, Emma K. Dodds, Sara E. Douglas, Andrew D. Gribble, Robert J. Ife, Andrew P. Lightfoot, Malcolm Meeson, Lorraine P. Campbell, Tanya Coleman, Graham J. Riley and David R. Thomas

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

Novel 5-HT$_7$ receptor antagonists containing the benzocycloheptanone core were identified from high throughput screening. Molecular modelling and SAR studies have converted these intractable hits into a more potent, selective and tractable series, exemplified by compound **25**, SB-691673.



(25) SB-691673

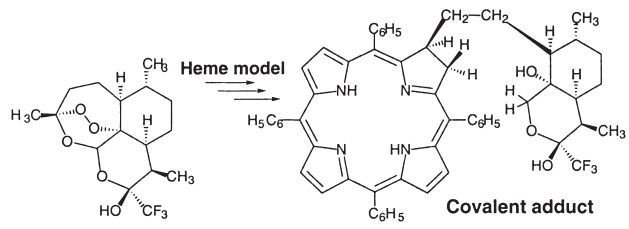
Bioorg. Med. Chem. Lett. 13 (2003) 1059

Alkylation of Manganese(II) Tetraphenylporphyrin by Antimalarial Fluorinated Artemisinin Derivatives

Montserrat Rodriguez,[b] Danièle Bonnet-Delpon,[a] Jean-Pierre Bégué,[a,*] Anne Robert[b] and Bernard Meunier[b,*]

[a]*Molécules Fluorées, BIOCIS-CNRS, Faculté de Pharmacie, rue J.-B. Clément, 92296 Châtenay-Malabry, France*
[b]*Laboratoire de Chimie de Coordination du CNRS, 205, route de Narbonne, 31077 Toulouse Cedex 4, France*

Trifluoromethyl analogues of the antimalarial drug artemisinin are efficient *alkylating agents* toward a heme model, after reductive activation of the peroxide bond. Heme is then both the activator and the target of the peroxide based antimalarials.



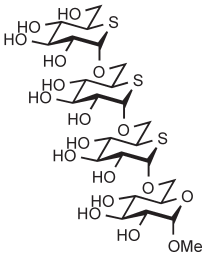
Bioorg. Med. Chem. Lett. 13 (2003) 1063

α-Selective Glycosylation with 5-Thioglucopyranosyl Donors; Synthesis of an Isomaltotetraoside Mimic Composed of 5-Thioglucopyranose Units

Hiroko Matsuda,[b] Keiichiro Ohara,[a] Yasuharu Morii,[a] Masaru Hashimoto,[a,b,*] Kazuo Miyairi[a,b] and Toshikatsu Okuno[a,b]

[a]*Faculty of Agriculture and Life Science, Hirosaki University, Bunkyo-Cho 3, Hirosaki 036-8561, Japan*
[b]*The United Graduate School of Agricultural Sciences, Iwate University, Bunkyo-Cho 3, Hirosaki 036-8561, Japan*

A general method for α-selective glycosylation with 5-thioglucopyranosyl donors followed by efficient deprotection of the resulting products was developed. A isomaltotetraoside analogue was synthesized as the application.



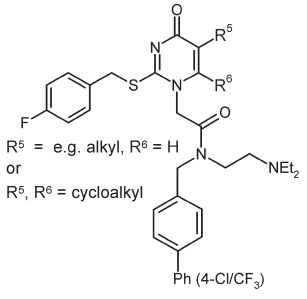
Bioorg. Med. Chem. Lett. 13 (2003) 1067

The Identification of Clinical Candidate SB-480848: A Potent Inhibitor of Lipoprotein-Associated Phospholipase A_2

Josie A. Blackie, Jackie C. Bloomer, Murray J. B. Brown, Hung-Yuan Cheng, Beverley Hammond, Deirdre M. B. Hickey, Robert J. Ife, Colin A. Leach, V. Ann Lewis, Colin H. Macphee, Kevin J. Milliner, Kitty E. Moores, Ivan L. Pinto, Stephen A. Smith,* Ian G. Stansfield, Steven J. Stanway, Maxine A. Taylor and Colin J. Theobald

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

Modification of clinical candidate SB-435495 has given sub-nanomolar inhibitors of recombinant lipoprotein-associated phospholipase A_2. Cyclopentyl fused derivative **21**, SB-480848, showed an enhanced in vitro and in vivo profile versus SB-435495 and has been selected for progression to man.



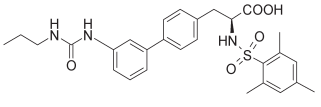
Bioorg. Med. Chem. Lett. 13 (2003) 1071

Biphenyls as Potent Vitronectin Receptor Antagonists. Part 2: Biphenylalanine Ureas

Klaus Urbahns,[a,*] Michael Härter,[a] Andrea Vaupel,[a] Markus Albers,[b] Delf Schmidt,[c] Ulf Brüggemeier,[c] Beatrix Stelte-Ludwig,[d] Christoph Gerdes[d] and Hideki Tsujishita,[e]

[a]*Institute of Medicinal Chemistry, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*
[b]*Combinatorial Chemistry Group, Central Research, Bayer AG, D-51368 Leverkusen, Germany*
[c]*Institute of Molecular Screening Technologies, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*
[d]*Institute of Cardiovascular Research, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*
[e]*Department of Chemistry, Research Center Kyoto, Bayer Yakuhin, J-619-0126 Kyoto, Japan*

Identified from a combinatorial library based on a biphenyl motif, **21** is a subnanomolar vitronectin receptor ($\alpha_V\beta_3$) antagonist. The SAR of these biphenylalanine ureas can be rationalised by computational docking studies using the X-ray structure of $\alpha_V\beta_3$.



21, Ki = 4 nM

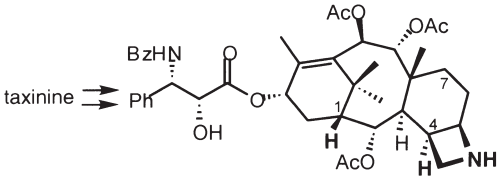
Bioorg. Med. Chem. Lett. 13 (2003) 1075

Synthesis and Biological Evaluation of 4-Deacetoxy-1,7-dideoxy Azetidine Paclitaxel Analogues

Qian Cheng, Hiromasa Kiyota,* Marina Yamaguchi, Tohru Horiguchi and Takayuki Oritani

Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

Three novel 4-deacetoxy-1,7-dideoxy azetidine paclitaxel analogues were synthesized through a convenient route that employed hydroboration-amination and intramolecular S_N2-type substitution reaction from a natural taxoid taxinine. All analogues have been tested for cytotoxicity against three human tumor cell lines. None of them showed remarkable cytotoxicity compared to paclitaxel against tested tumor cell lines.

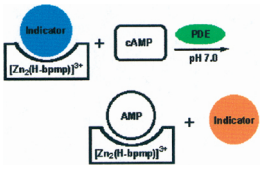


Bioorg. Med. Chem. Lett. 13 (2003) 1079

Visual Detection of AMP and Real-Time Monitoring of Cyclic Nucleotide Phosphodiesterase (PDE) Activity in Neutral Aqueous Solution. Chemosensor-Coupled Assay of PDE and PDE Inhibitors

Min Su Han and Dong H. Kim*

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

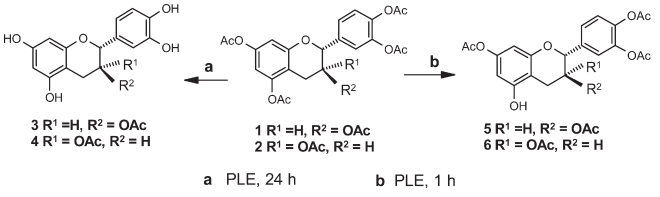


Bioorg. Med. Chem. Lett. 13 (2003) 1083

Regioselective Hydrolysis of Pentaacetyl Catechin and Epicatechin by Porcine Liver Esterase

Amit Basak,* Subrata Mandal and Saibal Bandyopadhyay

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

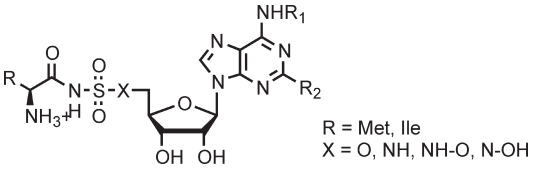


Bioorg. Med. Chem. Lett. 13 (2003) 1087

N-Alkoxysulfamide, *N*-Hydroxysulfamide, and Sulfamate Analogues of Methionyl and Isoleucyl Adenylates as Inhibitors of Methionyl-tRNA and Isoleucyl-tRNA Synthetases

Jeewoo Lee,[a,*] Sung Eun Kim,[a] Ji Young Lee,[a] Su Yeon Kim,[a] Sang Uk Kang,[a] Seung Hwan Seo,[a] Moon Woo Chun,[a] Taehee Kang,[b] Soo Young Choi[b] and Hea Ok Kim[c]

[a]*Laboratory of Medicinal Chemistry, RIPS, College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[b]*Imagene Co., Ltd., #406 Biotechnology Incubating Center, Seoul National University, Seoul, South Korea*
[c]*Division of Chemistry and Molecular Engineering, Seoul National University, Seoul, South Korea*

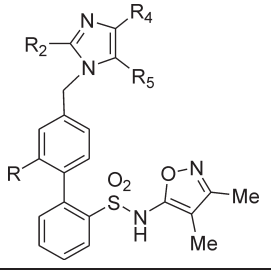


Bioorg. Med. Chem. Lett. 13 (2003) 1097

Discovery of 4′-[(Imidazol-1-yl)methyl]biphenyl-2-sulfonamides as Dual Endothelin/Angiotensin II Receptor Antagonists

John E. Tellew,[a,*] Rose Ann F. Baska,[b] Sophie M. Beyer,[b] Kenneth E. Carlson,[b] Lyndon A. Cornelius,[a] Leena Fadnis,[a] Zhengxiang Gu,[a] Bridgette L. Kunst,[a] Mark C. Kowala,[b] Hossain Monshizadegan,[b] Natesan Murugesan,[a] Carol S. Ryan,[b] Maria T. Valentine,[b] Yifan Yang[b] and John E. Macor[a]

[a]*Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, USA*
[b]*Department of Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, USA*



Bioorg. Med. Chem. Lett. 13 (2003) 1093

Synthesis and Antibacterial Study of 10, 15, 20-Triphenyl-5-{4-hydroxy-3-(trimethylammonium)methyl}phenylporphyrin as Models for Combination of Porphyrin and Alkylating Agent

Jiangye Zhang,[a] Xiaojun Wu,[a] Xiaoping Cao,[c] Fan Yang,[a] Jiangfeng Wang,[a] Xiang Zhou[a,*] and Xiao-Lian Zhang[b,*]

[a]*College of Chemistry and Molecular Sciences, Wuhan University, Hubei Wuhan 430072, PR China*
[b]*School of Medicine, Wuhan University, Hubei Wuhan 430071, PR China*
[c]*National Laboratory of Applied Organic Chemistry, Lanzhou University, Gansu, Lanzhou 730000, PR China*

10, 15, 20-Triphenyl-5-{4-hydroxy-3-(trimethylammonium) methyl}phenylporphyrin **4** and its derivatives have been synthesized. Their antibacterial activities have also been studied. Compound **4** showed stronger inhibition than that of **2** and **6**. It is possible that antibacterial activity of compound **4** involved in photoinducing both *o*-quinone methide intermediate and singlet oxygen formation.

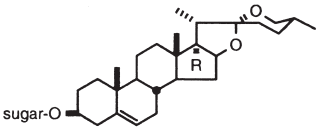
Bioorg. Med. Chem. Lett. 13 (2003) 1101

Protective Effects of Steroid Saponins from *Paris polyphylla* var. *yunnanensis* on Ethanol- or Indomethacin-Induced Gastric Mucosal Lesions in Rats: Structural Requirement for Activity and Mode of Action

Hisashi Matsuda, Yutana Pongpiriyadacha, Toshio Morikawa, Akinobu Kishi, Shinya Kataoka and Masayuki Yoshikawa*

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

The methanolic extract from the rhizomes of *Paris polyphylla* var. *yunnanensis* was found to potently inhibit ethanol-induced gastric lesions in rats. Through bioassay-guided separation, four known spirostanol-type steroid saponins, pennogenin and diosgenin 3-*O*-glycosides, and a new furostanol-type steroid saponin named parisaponin I together with two known furostanol-type steroid saponins were isolated from the active fraction. Some structural requirements of steroid saponins for the protective activity and mode of action against ethanol-induced gastric lesions were discussed.



pennogenin 3-*O*-glycosides: R=OH
diosgenin 3-*O*-glycosides: R=H

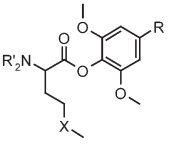
Bioorg. Med. Chem. Lett. 13 (2003) 1107

Novel α-Amino-Acid Phenolic Ester Derivatives with Intravenous Anaesthetic Activity

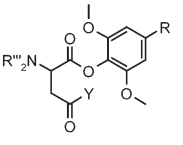
Andrew Cooke,* Alison Anderson, Jonathan Bennett, Kirsteen Buchanan, David Gemmell, Niall Hamilton, Maurice Maidment, Petula McPhail, Donald Stevenson and Hardy Sundaram

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

A novel series of α-amino-acid phenolic ester derivatives containing sulphide, sulphoxide, sulphone, ester and amide side-chains were prepared and shown to display potent intravenous anaesthetic activity.



X = S, SO, SO_2



Y = N"R_2, OMe

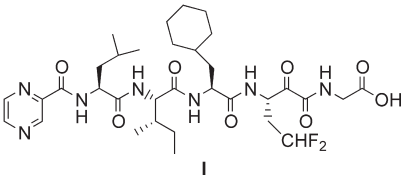
Bioorg. Med. Chem. Lett. 13 (2003) 1111

Glycine α-Ketoamides as HCV NS3 Protease Inhibitors

Wei Han,* Zilun Hu, Xiangjun Jiang, Zelda R. Wasserman and Carl P. Decicco

Department of Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, PO Box 5400, Princeton, NJ 08543, USA

A series of tetrapeptide-based α-ketoamides was designed, synthesized, and evaluated as HCV NS3 protease inhibitors. Glycine α-ketoamide **I** was identified as a potent inhibitor with an IC_{50} of 0.060 μM.



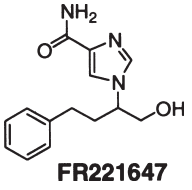
I

Bioorg. Med. Chem. Lett. 13 (2003) 1115

Structure-Based De Novo Design of Non-nucleoside Adenosine Deaminase Inhibitors

Tadashi Terasaka,[a,*] Isao Nakanishi,[b,*] Katsuya Nakamura,[a] Yoshiteru Eikyu,[b] Takayoshi Kinoshita,[b] Nobuya Nishio,[b] Akihiro Sato,[c] Masako Kuno,[d] Nobuo Seki[b] and Kazuo Sakane[a]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 5-2-3 Tokodai, Tsukuba, Ibaraki 300-2698, Japan*
[c]*Analytical Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[d]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*



FR221647

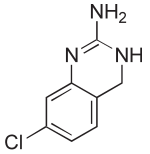
Structure-based de novo design of non-nucleoside adenosine deaminase inhibitors is reported.

Bioorg. Med. Chem. Lett. 13 (2003) 1119

Conformationally-Restricted Analogues and Partition Coefficients of the 5-HT_3 Serotonin Receptor Ligands *meta*-Chlorophenylbiguanide (*m*CPBG) and *meta*-Chlorophenylguanidine (*m*CPG)

Ashraf A. Rahman,[a] Maha Khalifa Daoud,[a] Małgorzata Dukat,[a] Katharine Herrick-Davis,[b] Anil Purohit,[b] Milt Teitler,[b] Antonia Taveres do Amaral,[c] Alberto Malvezzi[c] and Richard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*
[b]*Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA*
[c]*Instituto de Quimica, Universidade de São Paulo, São Paulo, Brazil*



14

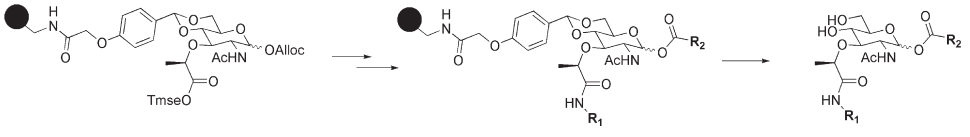
Compound **14** (5-HT_3 $K_i = 34$ nM) might reflect an important conformational contributor for the binding of arylguanidines at 5-HT_3 receptors. Also, several arylguanidines were found to possess lower lipophilicities than their corresponding arylbiguanides.

Bioorg. Med. Chem. Lett. 13 (2003) 1125

Preparation of Potential Inhibitors of the Mur-Pathway Enzymes on Solid Support Using an Acetal Linker

Milana Maletic,* Jelena Antonic, Aaron Leeman, Gina Santorelli and Sherman Waddell

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA



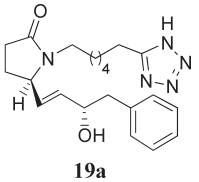
Bioorg. Med. Chem. Lett. 13 (2003) 1129

Discovery of a Potent and Selective Agonist of the Prostaglandin EP_4 Receptor

Xavier Billot, Anne Chateauneuf, Nathalie Chauret, Danielle Denis, Gillian Greig, Marie-Claude Mathieu, Kathleen M. Metters, Deborah M. Slipetz and Robert N. Young

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

Analogues of PGE_2 wherein the hydroxycyclopentanone ring has been replaced by a lactam have been prepared and evaluated as ligands for the EP_4 receptor. An optimized compound (**19a**) shows high potency and agonist efficacy at the EP_4 receptor and is highly selective over the other seven known prostaglandin receptors.



19a

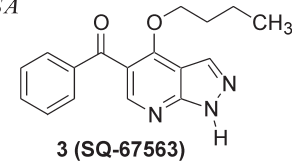
Bioorg. Med. Chem. Lett. 13 (2003) 1133

1*H*-Pyrazolo[3,4-*b*]pyridine Inhibitors of Cyclin-Dependent Kinases

Raj N. Misra,* David B. Rawlins, Hai-yun Xiao, Weifang Shan, Isia Bursuker, Kristin A. Kellar, Janet G. Mulheron, John S. Sack, John S. Tokarski, S. David Kimball and Kevin R. Webster

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

Pyrazolopyridine **3** (SQ-67563) has been identified as a potent, selective inhibitor of CDK1 ($IC_{50}=0.15$ μM) and CDK2 ($IC_{50}=0.11$ μM) in vitro which binds at the ATP site. In cells **3** blocks cell cycle progression.



3 (SQ-67563)

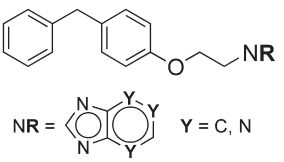
Bioorg. Med. Chem. Lett. 13 (2003) 1137

Synthesis of Imidazopyridines and Purines as Potent Inhibitors of Leukotriene A_4 Hydrolase

Thomas D. Penning,[a,*] Nizal S. Chandrakumar,[a] Bipin N. Desai,[a] Stevan W. Djuric,[a] Alan F. Gasiecki,[a] James W. Malecha,[a] Julie M. Miyashiro,[a] Mark A. Russell,[a] Leslie J. Askonas,[b] James K. Gierse,[b] Elizabeth I. Harding,[b] Maureen K. Highkin,[b] James F. Kachur,[b] Suzanne H. Kim,[b] Doreen Villani-Price,[b] E. Yvonne Pyla,[b] Nayereh S. Ghoreishi-Haack[b] and Walter G. Smith[b]

[a]*Department of Medicinal Chemistry, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*
[b]*Departments of Inflammatory Diseases Research and Molecular Pharmacology, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*

The synthesis and biological evaluation of a series of imidazopyridine and purine LTA_4 hydrolase inhibitors are described.



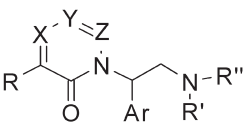
Bioorg. Med. Chem. Lett. 13 (2003) 1141

Synthesis and Biological Activity of Kappa Opioid Receptor Agonists. Part 2: Preparation of 3-Aryl-2-pyridone Analogues Generated by Solution- and Solid-Phase Parallel Synthesis Methods

Graeme Semple,[a,*] Britt-Marie Andersson,[b] Vijay Chhajlani,[b] Jennie Georgsson,[a] Magnus J. Johansson,[a] Åsa Rosenquist[a] and Lars Swanson[a]

[a]*Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, S-431 83, Sweden*
[b]*Department of Biochemistry and Cell Biology, AstraZeneca R&D Mölndal, S-431 83, Sweden*

New analogues of the previously described 3-aryl pyridone KOR agonists have been synthesised by parallel synthetic methods, both in solution- and with solid-phase chemistry, making use of the well known and versatile Mitsunobu, Suzuki and Buchwald reactions. Opioid receptor binding data for the compounds produced is reported.



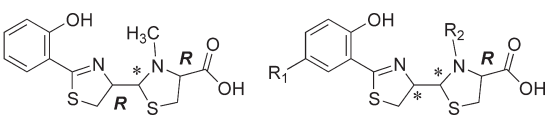
Bioorg. Med. Chem. Lett. 13 (2003) 1147

Bacterial Siderophores: Synthesis and Biological Activities of Novel Pyochelin Analogues

A. Zamri,[a,b] I. J. Schalk,[b] F. Pattus[b] and M. A. Abdallah[b,*]

[a]*Laboratorium Kimia Organik FMIPA-UNRI, Jl Raya Bangkinang Km 12.5, Pekanbaru 28293, Indonesia*
[b]*Département des Récepteurs et Protéines Membranaires, UPR 9050 CNRS, Ecole Supérieure de Biotechnologie de Strasbourg, Boulevard Sébastien Brant, F-67400-Illkirch, France*

The synthesis and biological activities of four pyochelin analogues substituted in different parts of the molecule are reported: 5-NHBoc-pyochelin, 3″*N*-Boc-pyochelin, 3″-nor-*N*H-pyochelin and neopyochelin II, the enantiomer of natural pyochelin. All these compounds complex iron(III) and transport it at different rates into the cells of *Pseudomonas aeruginosa*.



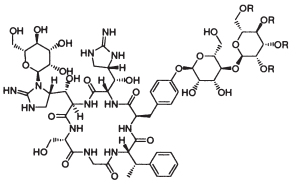
Bioorg. Med. Chem. Lett. 13 (2003) 1151

Novel Ether Derivatives of Mannopeptimycin Glycopeptide Antibiotic

Phaik-Eng Sum,[a,*] David How,[a] Nancy Torres,[a] Peter J. Petersen,[b] Eileen B. Lenoy,[b] William J. Weiss[b] and Tarek S. Mansour[a]

[a]*Department of Chemical Sciences, Wyeth Research, Chemical Sciences Building 222/Room 3147, 401 N. Middleton Road, Pearl River, New York, NY 10965, USA*
[b]*Department of Infectious Disease, Wyeth Research, Pearl River, NY 10965, USA*

Novel ether derivatives of mannopeptimycin glycopeptide were synthesized. Many of these derivatives exhibited potent antibacterial activity against VRE, MRSA, and PRSP.

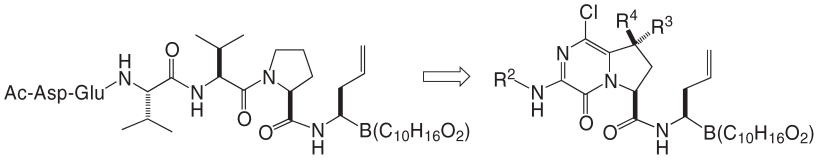


Bioorg. Med. Chem. Lett. 13 (2003) 1157

Design and Synthesis of Potent, Non-peptide Inhibitors of HCV NS3 Protease

Xiaojun Zhang,* Aaron C. Schmitt, Wen Jiang, Zelda Wasserman and Carl P. Decicco

Discovery Chemistry, Bristol-Myers Squibb, Route 141 and Henry Clay Road, Wilmington, DE 19880, USA



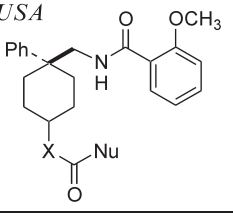
Bioorg. Med. Chem. Lett. 13 (2003) 1161

Benzamide Derivatives as Blockers of Kv1.3 Ion Channel

Shouwu Miao,[a,*] Jianming Bao,[a,*] Maria L. Garcia,[b] Joung L. Goulet,[a] Xingfang J. Hong,[a] Gregory J. Kaczorowski,[b] Frank Kayser,[a] Gloria C. Koo,[c] Andrew Kotliar,[a] William A. Schmalhofer,[b] Kashmira Shah,[c] Peter J. Sinclair,[a] Robert S. Slaughter,[b] Marty S. Springer,[c] Mary Jo Staruch,[c] Nancy N. Tsou,[a] Frederick Wong,[a] William H. Parsons[a] and Kathleen M. Rupprecht[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Ion Channels, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Immunology Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

SAR of a benzamide class of Kv1.3 channel blockers in two functional assays, Rb_Kv and T-cell (anti-CD3), is presented. The *trans* isomers display moderate selectivity to Kv1.3 over other Kv1.x channels in human brain.



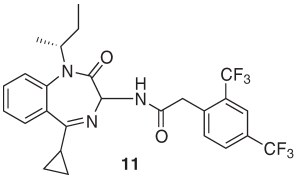
Bioorg. Med. Chem. Lett. 13 (2003) 1165

Novel 5-Cyclopropyl-1,4-benzodiazepin-2-ones as Potent and Selective I_{Ks}-Blocking Class III Antiarrhythmic Agents

John W. Butcher,[a,*] Nigel J. Liverton,[a] David A. Claremon,[a] Roger M. Freidinger,[a] Nancy K. Jurkiewicz,[b] Joseph J. Lynch,[b] Joseph J. Salata,[b] Jixin Wang,[b] Christine M. Dieckhaus,[c] Donald E. Slaughter[c] and Kamlesh Vyas[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

Novel 5-cyclopropyl-1,4-benzodiazepin-2-ones having various N-l substituents were identified as potent and selective blockers of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}). Compound **11** is the most potent I_{Ks} channel blocker reported to date.



11

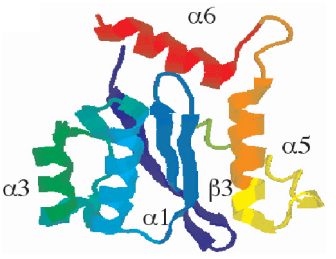
Bioorg. Med. Chem. Lett. 13 (2003) 1175

Interfacial Peptide Inhibitors of HIV-1 Integrase Activity and Dimerization

Lei Zhao, Mary K. O'Reilly, Michael D. Shultz and Jean Chmielewski*

Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

Low micromolar inhibitors of HIV-1 integrase are reported based on peptides from the enzyme's dimerization interface.



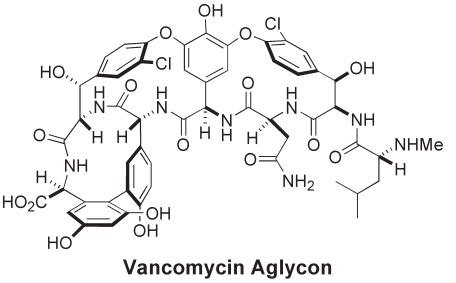
Bioorg. Med. Chem. Lett. 13 (2003) 1169

A New and Improved Method for Deglycosidation of Glycopeptide Antibiotics Exemplified with Vancomycin, Ristocetin, and Ramoplanin

Jutta Wanner, Datong Tang, Casey C. McComas, Brendan M. Crowley, Wanlong Jiang, Jason Moss and Dale L. Boger*

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

A general method for the deglycosidation of glycopeptide antibiotics has been developed. Using this procedure, the aglycons of vancomycin, ristocetin, and ramoplanin are prepared in high yield without chromatographic purification.



Vancomycin Aglycon

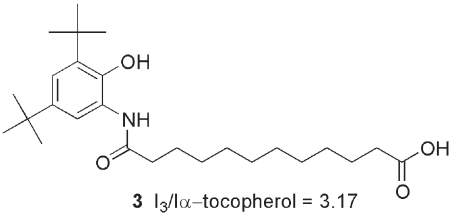
Bioorg. Med. Chem. Lett. 13 (2003) 1179

Synthesis and Properties of 11-(3,5-Di-*tert*-butyl-2-hydroxyphenylcarbamoyl)undecanoic Acid, a New Amphiphilic Antioxidant

Vladimir I. Lodyato,[a] Irina L. Yurkova,[a] Viktor L. Sorokin,[a] Oleg I. Shadyro,[a] Vladimir I. Dolgopalets[b] and Mikhail A. Kisel[b,*]

[a]*Department of Chemistry of the Belarusian State University, Skaryna av., 4, 220050 Minsk, Belarus*
[b]*Institute of Bioorganic Chemistry of the Belarus National Academy of Sciences, Kuprevich st., 5/2, 220141 Minsk, Belarus*

Synthesis and LPO-inhibiting properties ($I_3/I_{\alpha\text{-tocopherol}} = 3.17$) of a new efficient antioxidant **3** and its analogues are reported.



3 $I_3/I\alpha$–tocopherol = 3.17

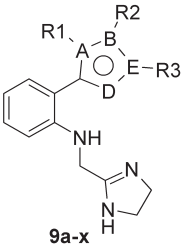
Bioorg. Med. Chem. Lett. 13 (2003) 1183

2-(Anilinomethyl)imidazolines as α_1 Adrenergic Receptor Agonists: α_{1a} Subtype Selective 2′-Heteroaryl Compounds

Jason D. Speake,* Frank Navas, III, Michael J. Bishop, Deanna T. Garrison, Eric C. Bigham, Stephen J. Hodson, David L. Saussy, Jim A. Liacos, Paul E. Irving and Bryan W. Sherman

GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA

The structure–activity relationship of 2′-pyrrole, pyrazole and triazole substituted 2-(anilinomethyl)imidazolines as α_1 adrenergic agonists was investigated. The size and orientation of substituents, as well as the position of the heteroatoms were found to have a profound effect on the potency and selectivity of the molecules. Potent α_{1A} subtype selective agonists have been identified.



9a-x

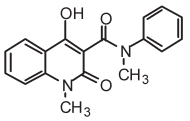
Bioorg. Med. Chem. Lett. 13 (2003) 1187

Structure–Activity Relationships Studies of the Anti-Angiogenic Activities of Linomide

Jiandong Shi,[a] Zili Xiao,[a] Michael A. Ihnat,[b] Chandrashekhar Kamat,[b] Bulbul Pandit,[a] Zhigen Hu[a] and Pui-Kai Li[a,*]

[a]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*
[b]*The University of Oklahoma, School of Medicine, Oklahoma City, OK 73104, USA*

The synthesis and antiangiogenic activities of linomide and its analogues are reported. Three of the analogues are 3.3–69 times more potent than linomide at inhibiting blood vessel formation in the CAM angiogenesis assay. These compounds possessed considerable anti-proliferative activity against isolated HUVEC cells with no activity against epithelial-derived prostate tumor cells.



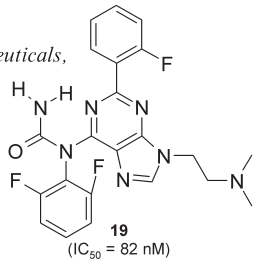
Linomide

Bioorg. Med. Chem. Lett. 13 (2003) 1191

N-Phenyl-*N*-purin-6-yl Ureas: The Design and Synthesis of P38α MAP Kinase Inhibitors

Zehong Wan,[a,*] Jeffrey C. Boehm,[a] Michael J. Bower,[b] Shouki Kassis,[c] John C. Lee,[d] Baoguang Zhao[c] and Jerry L. Adams[e]

[a]*Department of Medicinal Chemistry, Respiratory and Inflammation CEDD, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406, USA*
[b]*Department of Computational, Analytical and Structural Science, Discovery Research, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406, USA*
[c]*Department of Discovery Biology, Discovery Research, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406, USA*
[d]*Department of High Throughput Biology, Discovery Research, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406, USA*
[e]*Department of Medicinal Chemistry, Microbial, Musculoskeletal and Proliferative Diseases CEDD, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406, USA*



19
(IC_{50} = 82 nM)

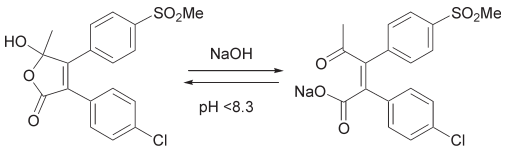
Bioorg. Med. Chem. Lett. 13 (2003) 1195

3,4-Diaryl-5-hydroxyfuranones: Highly Selective Inhibitors of Cyclooxygenase-2 with Aqueous Solubility

W. Cameron Black,* Christine Brideau, Chi-Chung Chan, Stella Charleson, Wanda Cromlish, Robert Gordon, Erich L. Grimm, Gregory Hughes, Serge Leger, Chun-Sing Li, Denis Riendeau, Michel Thérien, Zhaoyin Wang, Li-Jing Xu and Petpiboon Prasit

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

Diaryl hydroxyfuranones are highly selective, water-soluble COX-2 inhibitors.



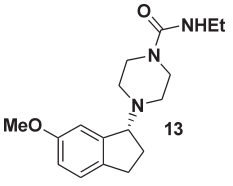
Bioorg. Med. Chem. Lett. 13 (2003) 1199

Indanyl Piperazines as Melatonergic MT_2 Selective Agents

Ronald J. Mattson,[a,*] John D. Catt,[a] Daniel Keavy,[a] Charles P. Sloan,[a] James Epperson,[a] Qi Gao,[a] Donald B. Hodges,[a] Lawrence Iben,[a] Cathy D. Mahle,[b] Elaine Ryan[a] and Frank D. Yocca[a]

[a]*Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT 06492-7660, USA*
[b]*Bayer Pharmaceutical Research Center, West Haven, CT, USA*

(*R*)-4-(2,3-Dihydro-6-methoxy-1*H*-inden-1-yl)-*N*-ethyl-1-piperazine-carboxamide fumarate (**13**) is a water soluble, selective MT_2 agonist, which produces advances in circadian phase in rats at doses of 1–56 mg/kg that are no different from those of melatonin at 1 mg/kg. Unlike melatonin, **13** produced only weak contractile effects in rat tail artery.



13

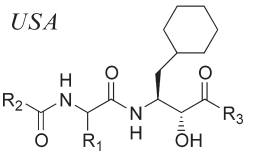
Bioorg. Med. Chem. Lett. 13 (2003) 1203

Inhibitors of Aβ Production: Solid-Phase Synthesis and SAR of α-Hydroxycarbonyl Derivatives

Owen B. Wallace,* David W. Smith, Milind S. Deshpande, Craig Polson and Kevin M. Felsenstein

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

Following the identification of a 5 μM inhibitor of amyloid-β protein (Aβ) production in a high-throughput screen, two series of α-hydroxy esters and α-hydroxy ketones were prepared using solid-phase chemistry. The most potent compound identified is a 160 nM inhibitor of Aβ production.



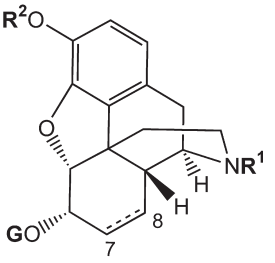
Bioorg. Med. Chem. Lett. 13 (2003) 1207

Structure–Activity Relationships of Some Opiate Glycosides

Andrew V. Stachulski,[a,*] Feodor Scheinmann,[a] John R. Ferguson,[a] Jayne L. Law,[a] Keith W. Lumbard,[a] Peter Hopkins,[a] Naina Patel,[b] Simon Clarke,[b] Anna Gloyne[b] and Simon P. Joel[b]

[a]*Ultrafine UFC Ltd., Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, UK*
[b]*Barry Reed Oncology Laboratory, Department of Medical Oncology, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK*

The μ-receptor binding and in vivo antinociceptive activity of a series of analogues of morphine-6-glucuronide are described. Variations in the glycoside residue, *N*- and *O*(3)-substituents and 7,8-double bond are encompassed.



Bioorg. Med. Chem. Lett. 13 (2003) 1215

Azido-Containing Aryl β-Diketo Acid HIV-1 Integrase Inhibitors

Xuechun Zhang,[a] Godwin C. G. Pais,[a] Evguenia S. Svarovskaia,[b] Christophe Marchand,[c] Allison A. Johnson,[c] Rajeshri G. Karki,[a] Marc C. Nicklaus,[a] Vinay K. Pathak,[b] Yves Pommier[c] and Terrence R. Burke, Jr.[a,*]

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[b]*HIV Drug Resistance Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, MD, USA*
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