Peptidyl Aldehyde Inhibitors of Calpain Incorporating P_2-Proline Mimetics

Bioorg. Med. Chem. Lett. 13 (2003) 783

Isaac O. Donkor,[a,*] Rajani Korukonda,[a] Tien L. Huang[b] and Louis LeCour, Jr.[b]

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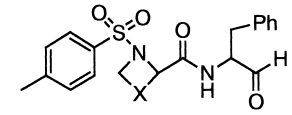
[b]*College of Pharmacy, Xavier University of Louisiana, New Orleans, LA 70125, USA*

Sythesis and selectivity of calpain inhibitors with P_2-proline mimetics is reported.



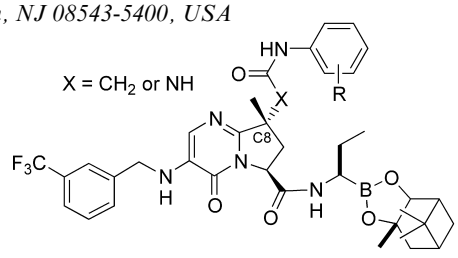
Design and Synthesis of Bicyclic Pyrimidinone-Based HCV NS3 Protease Inhibitors

Bioorg. Med. Chem. Lett. 13 (2003) 785

Peter W. Glunz,* Brent D. Douty and Carl P. Decicco

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543-5400, USA

A series of bicyclic pyrimidinone-based HCV NS3 protease inhibitors was synthesized via selective C8 position functionalization. Substituted phenylamides and phenylureas were preferred in the S2 binding pocket.



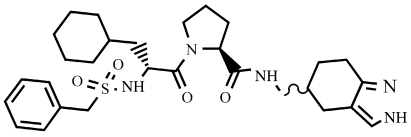
Novel Thrombin Inhibitors Incorporating Non-basic Partially Saturated Heterobicyclic P_1-Arginine Mimetics

Bioorg. Med. Chem. Lett. 13 (2003) 789

Lucija Peterlin-Mašič,[a] Gregor Mlinšek,[b] Tomaž Šolmajer,[b,c] Alenka Trampuš-Bakija,[d] Mojca Stegnar[d] and Danijel Kikelj[a,*]

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

The design, synthesis and biological activity of thrombin inhibitors incorporating novel non-basic partially saturated, heterobicyclic P_1-arginine side-chain mimetics is described.



23, K_i (thrombin) = 140 nM
K_i (trypsin) = > 68.3 μM

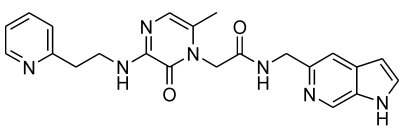
Azaindoles: Moderately Basic P1 Groups for Enhancing the Selectivity of Thrombin Inhibitors

Bioorg. Med. Chem. Lett. 13 (2003) 795

Philip E. J. Sanderson,[a,*] Matthew G. Stanton,[a] Bruce D. Dorsey,[a] Terry A. Lyle,[a] Colleen McDonough,[a] William M. Sanders,[a] Kelly L. Savage,[a] Adel M. Naylor-Olsen,[b] Julie A. Krueger,[c] S. Dale Lewis,[c] Bobby J. Lucas,[c] Joseph J. Lynch[d] and Youwei Yan[e]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Molecular Systems, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*

We describe the development of highly selective pyrazinone acetamide thrombin inhibitors containing azaindole P1 groups.



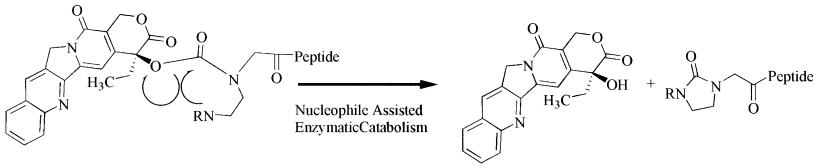
thrombin K_i = 1.2 nM; trypsin K_i = 200,000 nM

Bioorg. Med. Chem. Lett. 13 (2003) 799

An Adjustable Release Rate Linking Strategy for Cytotoxin-Peptide Conjugates

Joseph A. Fuselier,* Lichun Sun, S. Nathaniel Woltering, William A. Murphy, Natalya Vasilevich and David H. Coy

Peptide Research Laboratories, Department of Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana 70112, USA



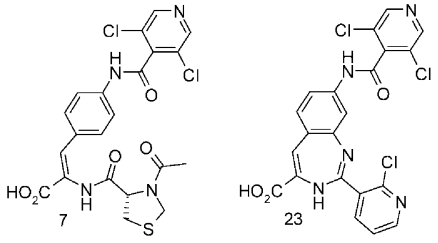
Bioorg. Med. Chem. Lett. 13 (2003) 805

Dehydrophenylalanine Derivatives as VLA-4 Integrin Antagonists

John R. Porter,* Sarah C. Archibald, Julien A. Brown, Kirstie Childs, David Critchley, John C. Head, Ted A. H. Parton, Martyn K. Robinson, Anthony Shock, Richard J. Taylor and Graham J. Warrellow

Department of Medicinal Chemistry, Celltech R&D Ltd, 216 Bath Road, Slough SL1 4EN, UK

The potencies and clearance properties of a series of *Z* and *E* dehdrophenylalanine derivatives such as **7** are described. These configurationally constrained molecules led to the design of a novel class of benzodiazepine VLA-4 antagonists, **23**.



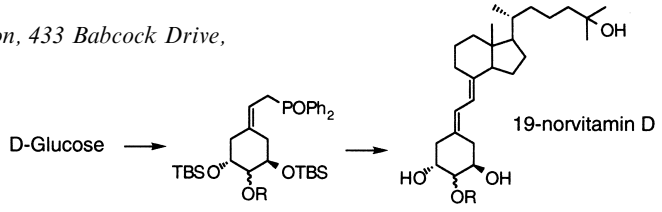
Bioorg. Med. Chem. Lett. 13 (2003) 809

Novel Synthesis of 2-Substituted 19-Norvitamin D A-Ring Phosphine Oxide from D-Glucose as a Building Block

Masato Shimizu,[a,*] Yukiko Iwasaki,[a] Yoshinori Shibamoto,[a] Miki Sato,[a] H. F. DeLuca[b] and Sachiko Yamada[a,*]

[a]*Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan*
[b]*Department of Biochemistry, University of Wisconsin-Madison, 433 Babcock Drive, Madison, WI 53706-1544, USA*

19-Norvitamin D A-ring phosphine oxide was synthesized by a new sequence mode starting from D-glucose as a chiral template.



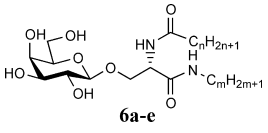
Bioorg. Med. Chem. Lett. 13 (2003) 813

Design, Synthesis, and Evaluation of β-Galactosylceramide Mimics Promoting β-Glucocerebrosidase Activity in Keratinocytes

Kyoko Fukunaga,[a,b,*] Masahiro Yoshida,[b] Fumio Nakajima,[b,c] Rie Uematsu,[b] Mariko Hara,[a] Shintaro Inoue,[a] Hirosato Kondo[c] and Shin-Ichiro Nishimura[d]

[a]*Basic Research Laboratory, Kanebo Ltd., 3-28, 5-chome Kotobuki-cho, Odawara-shi, Kanagawa-ken 250-0002, Japan*
[b]*Sapporo Laboratory for Glycocluster Project, Japan Bioindustry Association, Hokkaido University, Sapporo 060-0810, Japan*
[c]*Department of Chemistry, Nippon Organon Ltd., 5-90, 1-chome Tomobuchi-cho, Miyakojima-ku, Osaka, Japan*
[d]*Laboratory of Bio-Macromolecular Chemistry, Division of Biological Sciences, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan*

The mimic study of β-galactosylceramide having an increasing activity of β-glucocerebrosidase is reported.



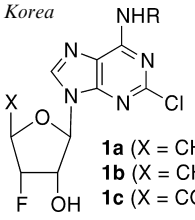
Bioorg. Med. Chem. Lett. 13 (2003) 817

Design, Synthesis and Binding Affinity of 3′-Fluoro Analogues of Cl-IB-MECA as Adenosine A_3 Receptor Ligands

Moo Hong Lim,[a] Hea Ok Kim,[b] Hyung Ryong Moon,[c] Seung Jin Lee,[c] Moon Woo Chun,[a,*] Zhan-Guo Gao,[d] Neli Melman,[d] Kenneth A. Jacobson,[d] Joong Hyup Kim[e] and Lak Shin Jeong[c,*]

[a]*College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[b]*Division of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, South Korea*
[c]*Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, South Korea*
[d]*Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Disease, National Institutes of Health, Bethesda, MA 20892, USA*
[e]*Korea Institute of Science and Technology, Seoul 136-791, South Korea*

Synthesis of novel 3′-fluoro-N^6-subsituted adenosines and their binding affinities to adenosine receptors are described.



1a (X = CH_2OH, R = 3-iodobenzyl)
1b (X = CH_2OH, R = CH_3)
1c (X = CONHMe, R = 3-iodobenzyl)

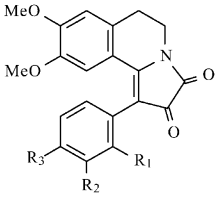
Bioorg. Med. Chem. Lett. 13 (2003) 821

Antiplatelet Activity of Synthetic Pyrrolo-Benzylisoquinolines

Reen-Yen Kuo,[a] Chin-Chung Wu,[a] Fang-Rong Chang,[a] Jwu-Lai Yeh,[b] Ing-Jun Chen[b] and Yang-Chang Wu[a,*]

[a]*Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan*
[b]*Department of Pharmacology, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

Pyrrolo-benzylisoquinolines **1d**–**9d** were prepared and their antiplatelet aggregation activity, adreno-receptor affinity (β_1 and β_2), and cytotoxicity were screened. Compounds **1d**–**9d** showed specific inhibition of platelet aggregation induced by arachidonic acid and collagen.



	R_1	R_2	R_3
1d	**Cl**	**H**	**H**
2d	**H**	**Cl**	**H**
3d	**H**	**H**	**Cl**
4d	**Br**	**H**	**H**
5d	**H**	**Br**	**H**
6d	**H**	**H**	**Br**
7d	**OMe**	**H**	**H**
8d	**H**	**OMe**	**H**
9d	**H**	**H**	**OMe**

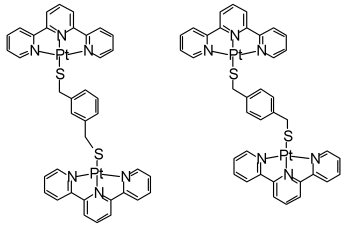
Bioorg. Med. Chem. Lett. 13 (2003) 825

Interaction of Binuclear Xylylthiolato(2,2′,2″-terpyridine)platinum(II) Complexes with DNA

Hiromasa Kurosaki, Naoki Yamakawa, Masamitsu Sumimoto, Kana Kimura and Masafumi Goto*

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi 5-1, Kumamoto 862-0973, Japan

Two binuclear platinum(II) complexes, **5** and **6**, were synthesized and their DNA binding affinity was investigated. Complex **5** has found to strongly intercalate with calf thymus DNA than **6**.



5 **6**

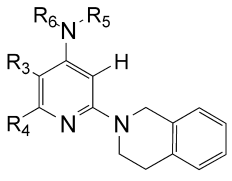
Bioorg. Med. Chem. Lett. 13 (2003) 829

2-(3,4-Dihydro-1*H*-isoquinolin-2yl)-pyridines as a Novel Class of NR1/2B Subtype Selective NMDA Receptor Antagonists

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

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

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



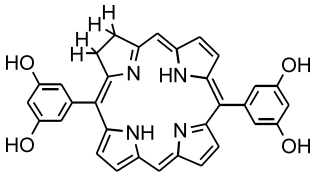
Bioorg. Med. Chem. Lett. 13 (2003) 833

Hydroporphyrins as Tumour Photosensitizers: Synthesis and Photophysical Studies of 2,3-Dihydro-5,15-di(3,5-dihydroxyphenyl) Porphyrin

Yann Ferrand,[a] Ludovic Bourré,[b] Gérard Simonneaux,[a,*] Sonia Thibaut,[b] Fabrice Odobel,[c] Y. Lajat[b] and Thierry Patrice[b,*]

[a]*Laboratoire de Chimie Organométallique et Biologique, UMR CNRS 6509, Université de Rennes 1, 35042 Rennes cedex, France*
[b]*Département Laser, Neurochirurgie, CHU Nantes, 44480 Nantes, France*
[c]*Laboratoire de Synthèse Organique, UMR CNRS 6513, Université de Nantes, 44322 Nantes cedex 3, France*

The synthesis and some properties of the new photosensitizer **5** is reported.



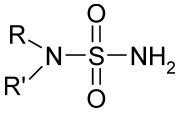
5

Bioorg. Med. Chem. Lett. 13 (2003) 837

Carbonic Anhydrase Inhibitors: Inhibition of Cytosolic Isozymes I and II with Sulfamide Derivatives

Angela Casini,[a] Jean-Yves Winum,[b] Jean-Louis Montero,[b] Andrea Scozzafava[a] and Claudiu T. Supuran[a,*]

[a]*Università degli Studi di Firenze, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Rm. 188, Via della Lastruccia 3, I-50019 Sesto Fiorentino (Firenze), Italy*
[b]*Université Montpellier II, Laboratoire de Chimie Biomoléculaire, UMR 5032, Ecole Nationale Supérieure de Chimie de Montpellier, 8 rue de l'Ecole Normale, 34296 Montpellier Cedex, France*

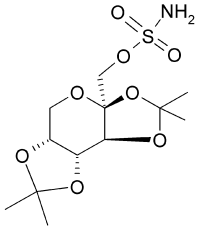


Bioorg. Med. Chem. Lett. 13 (2003) 841

Carbonic Anhydrase Inhibitors: SAR and X-ray Crystallographic Study for the Interaction of Sugar Sulfamates/Sulfamides with Isozymes I, II and IV

Angela Casini,[a] Jochen Antel,[b,*] Francesco Abbate,[a] Andrea Scozzafava,[a] Samuel David,[b] Harald Waldeck,[b] Siegfried Schäfer[b] and Claudiu T. Supuran[a,*]

[a]*Dipartimento di Chimica, Università degli Studi di Firenze, Via della Lastruccia 3, Rm. 188, I-50019 Sesto Fiorentino (Firenze), Italy*
[b]*Solvay Pharmaceuticals GmbH, Hans Böckler-Allee 20, D-30173 Hannover, Germany*

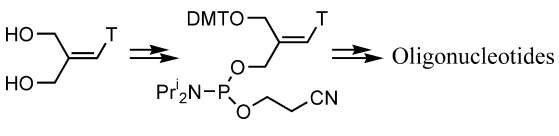


Bioorg. Med. Chem. Lett. 13 (2003) 847

Oligonucleotides Containing a New Type of Acyclic, Achiral Nucleoside Analogue: 1-[3-Hydroxy-2-(hydroxymethyl)prop-1-enyl]thymine

Thomas Boesen, Daniel Sejer Pedersen, Brian M. Nielsen, Asger B. Petersen, Ulla Henriksen, Britta M. Dahl and Otto Dahl*

Department of Chemistry, University of Copenhagen, The H. C. Ørsted Institute, Universitetsparken 5, DK-2100 Copenhagen, Denmark



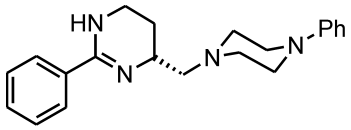
Bioorg. Med. Chem. Lett. 13 (2003) 851

Cyclic Amidines as Benzamide Bioisosteres: EPC Synthesis and SAR Studies Leading to the Selective Dopamine D4 Receptor Agonist FAUC 312

Jürgen Einsiedel, Harald Hübner and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstraße19, D-91052 Erlangen, Germany

The chiral phenyltetrahydropyrimidine derivative **ent2a** (FAUC 312) proved strong and highly selective dopamine D4 receptor binding ($K_{i_{high}} = 1.5$ nM). Mitogenesis experiments clearly indicated agonist properties.



ent2a

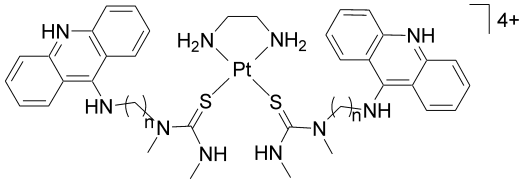
Bioorg. Med. Chem. Lett. 13 (2003) 855

Bis(acridinylthiourea)platinum(II) Complexes: Synthesis, DNA Affinity, and Biological Activity in Glioblastoma Cells

Todd M. Augustus,[a] Joel Anderson,[b] Suzanne M. Hess[b] and Ulrich Bierbach[a,*]

[a]*Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109, USA*
[b]*Department of Radiation Oncology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*

When the chloro leaving groups in $[PtCl_2(en)]$ (en = ethane-1,2-diamine) are replaced with acridinylthiourea, a new type of bisintercalating agent, **3**, is generated that binds strongly to DNA and exerts a pronounced cytotoxic effect in brain cancer cells.



3a (n = 2), **3b** (n = 3)

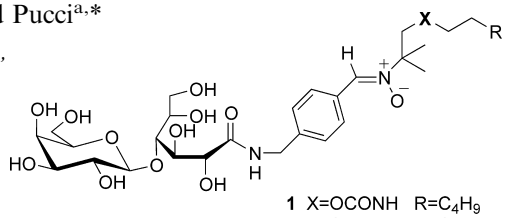
Bioorg. Med. Chem. Lett. 13 (2003) 859

Synthesis of a New Family of Glycolipidic Nitrones as Potential Antioxidant Drugs for Neurodegenerative Disorders

Grégory Durand,[a] Ange Polidori,[a,*] Jean-Pierre Salles[b] and Bernard Pucci[a,*]

[a]*Laboratoire de Chimie BioOrganique et des Systèmes Moléculaire Vectoriels, Faculté des Sciences, 33 rue Louis Pasteur, 84000 Avignon, France*
[b]*Targeting System Pharma, 830 chemin de vergon, 13510 Eguilles, France*

The synthesis of a novel series of amphiphilic glycosylated spin-traps derived from α-phenyl-*N*-*tert*-butyl nitrone (PBN) is reported.



1 X=OCONH R=C_4H_9
2 X=S R=C_6H_{13}
3 X=S R=C_6F_{13}
4 X=NHCO R=C_5H_{11}
5 X=NHCO R=C_6H_{13}

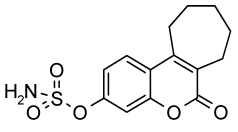
Bioorg. Med. Chem. Lett. 13 (2003) 863

Docking Studies of Sulphamate Inhibitors of Estrone Sulphatase in Human Carbonic Anhydrase II

Nigel Vicker,[a] Yaikat Ho,[b] James Robinson,[a] Lawrence L. W. Woo,[a] Atul Purohit,[b] Michael J. Reed[b] and Barry V. L. Potter[a,*]

[a]*Medicinal Chemistry, Department of Pharmacy and Pharmacology and Sterix Ltd, University of Bath, Bath BA2 7AY, UK*
[b]*Endocrinology and Metabolic Medicine and Sterix Ltd., Imperial Faculty School of Medicine, St Mary's Hospital, London W2 1NY, UK*

The docking of selected steroidal and non-steroidal estrone sulphatase inhibitors, including the Phase I clinical trial candidate 667COUMATE (**6**), into the active site of human carbonic anhydrase II (hCA II).



6 IC_{50} = 17 nM

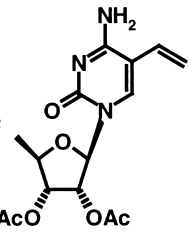
Bioorg. Med. Chem. Lett. 13 (2003) 867

Design and Synthesis of the Tumor-Activated Prodrug of Dihydropyrimidine Dehydrogenase (DPD) Inhibitor, RO0094889 for Combination Therapy with Capecitabine

Kazuo Hattori,[a] Yasunori Kohchi,[a] Nobuhiro Oikawa,[a] Hitomi Suda,[a] Masako Ura,[b] Tohru Ishikawa,[b] Masanori Miwa,[b] Mika Endoh,[b] Hiroyuki Eda,[b] Hiromi Tanimura,[b] Akira Kawashima,[c] Ikuo Horii,[c] Hideo Ishitsuka[b] and Nobuo Shimma[a,*]

[a]*Department of Chemistry, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*
[b]*Department of Oncology, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*
[c]*Department of Preclinical Science, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*

A series of tumor-activated prodrugs of the inhibitors of DPD, an enzyme catabolizing 5-fluorouracil (5-FU), has been designed and synthesized. RO0094889 (**11c**) is a prodrug of 5-vinyluracil (**4c**), a known DPD inhibitor, and was designed to generate **4c** selectively in tumor tissues by sequential conversion of **11c** by three enzymes: esterase, cytidine deaminase and thymidinephosphorylase, the latter two of which are known to be highly expressed in various tumor tissues.



RO0094889 (11c)

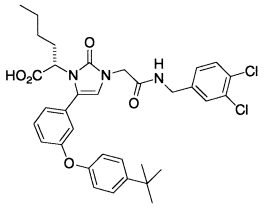
Bioorg. Med. Chem. Lett. 13 (2003) 873

Discovery of the First Antibacterial Small Molecule Inhibitors of MurB

Joanne J. Bronson, Kenneth L. DenBleyker, Paul J. Falk, Robert A. Mate, Hsu-Tso Ho, Michael J. Pucci and Lawrence B. Snyder*

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

A series of imidazolinone analogues were synthesized and shown to possess potent MurB inhibitory as well as good antibacterial activity.



MurB IC_{50} = 15μM
MIC (*S. aureus*) = 4μg/ml

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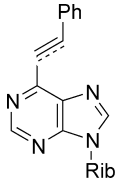
Cytotoxic Activity of 6-Alkynyl- and 6-Alkenylpurines

Anders Bråthe,[a] Lise-Lotte Gundersen,[a,*] Jon Nissen-Meyer,[b] Frode Rise[a] and Bjørn Spilsberg[a]

[a]*Department of Chemistry, University of Oslo, PO Box 1033, Blindern, 0315 Oslo, Norway*
[b]*Department of Biochemistry, University of Oslo, PO Box 1041, Blindern, 0316 Oslo, Norway*



IC_{50} (K-562 cells):

0.1 μg/mL (alkyne)
2.0 μg/mL (*E*-alkene)

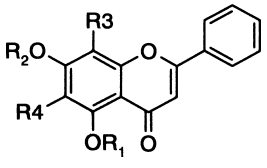
Bioorg. Med. Chem. Lett. 13 (2003) 881

Synthesis and Anticancer Effect of Chrysin Derivatives

Xing Zheng,[a] Wei-Dong Meng,[a] Yang-Yan Xu,[b] Jian-Guo Cao[b] and Feng-Ling Qing[a,*]

[a]*College of Chemistry and Chemical Engineering, Donghua Unversity, 1882 West Yanan Lu, Shanghai 200051, PR China*
[b]*Cancer Research Institute, Nanhua University, Hengyang, Hunan 421001, PR China*

A series of chrysin derivatives were prepared and tested for their in vitro anticancer activities against SGC-7901 and HT-29 cells.



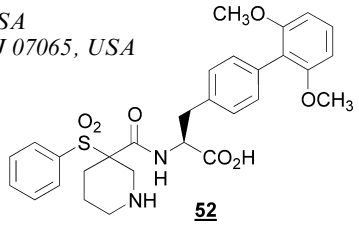
Bioorg. Med. Chem. Lett. 13 (2003) 885

N-(3-Phenylsulfonyl-3-piperidinoyl)-phenylalanine Derivatives as Potent, Selective VLA-4 Antagonists

Clare E. Gutteridge,[a,*] Stephen E. de Laszlo,[a] Theodore M. Kamenecka,[a] Ermengilda McCauley,[b] Gail van Riper,[b] Richard A. Mumford,[b] Usha Kidambi,[c] Linda A. Egger,[c] Sharon Tong[d] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Immunology and Rheumatology, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck Research Laboratories, Rahway, NJ 07065, USA*
[d]*Department of Basic Chemistry Analytical Services, Merck Research Laboratories, Rahway, NJ 07065, USA*

Optimization of a lead from a chemical library afforded the novel VLA-4 antagonist *N*-(α-*p*-fluorophenylsulfonyl-cyclopentanoyl)-2′,6′-dimethoxyphenylalanine (VLA-4 $IC_{50} = 0.07$ nM). Subsequent optimization for selectivity versus the related integrin $\alpha_4\beta_7$ led to discovery of *N*-(3-phenylsulfonyl-3-piperidinoyl)-phenylalanine **52** (VLA-4 $IC_{50} = 0.09$ nM, $\alpha_4\beta_7$ $IC_{50} = 168$ nM).



52

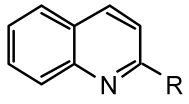
Bioorg. Med. Chem. Lett. 13 (2003) 891

Substituted Quinolines Induce Inhibition of Proliferation of HTLV-1 Infected Cells

Alain Fournet,[a,b] Renaud Mahieux,[c] Mohammed A. Fakhfakh,[a] Xavier Franck,[a] Reynald Hocquemiller[a] and Bruno Figadère[a,*]

[a]*Laboratoire de Pharmacognosie (associé au CNRS-BioCIS) Faculté de Pharmacie, Université de Paris-Sud, rue J. B. Clément, 92296 Châtenay-Malabry, France*
[b]*Institut de Recherche pour le Développement (IRD), 213 rue Lafayette, 75480 Paris, France*
[c]*Unité d'Epidemiologie et Physiopathologie des Virus Oncogènes, 28 rue du Dr. Roux, Institut Pasteur, 75724 Paris, France*

Twenty-nine 2-substituted quinolines were synthesized and evaluated against HTLV-1 transformed cell lines. Several of these showed around 85% inhibition at 10 μM.



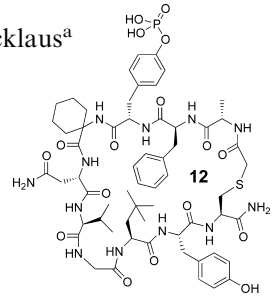
Bioorg. Med. Chem. Lett. 13 (2003) 895

Structure-Based Design of Thioether-Bridged Cyclic Phosphopeptides Binding to Grb2-SH2 Domain

Peng Li,[a] Megan L. Peach,[a] Manchao Zhang,[b] Hongpeng Liu,[b] Dajun Yang,[b] Marc Nicklaus[a] and Peter P. Roller[a,*]

[a]*Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health, Frederick, MD 21702, USA*
[b]*School of Medicine, University of Michigan, Ann Arbor, MI 48109, USA*

A series of phosphotyrosine-containing cyclic peptides was designed and synthesized based upon the phage library derived cyclopeptide **G1**. A highly potent peptide ligand **12** was discovered with an $IC_{50} = 1.68$ nM, which is at least 10^5 more potent than the lead peptide **G1TE**.



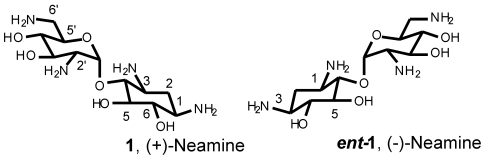
12

Bioorg. Med. Chem. Lett. 13 (2003) 901

Synthesis of (+),(−)-Neamine and Their Positional Isomers as Potential Antibiotics

Do Hyun Ryu, Choon-Hong Tan and Robert R. Rando*

Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 45 Shattuck Street, Boston, MA 02115, USA



1, (+)-Neamine

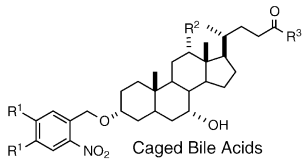
***ent*-1**, (-)-Neamine

Bioorg. Med. Chem. Lett. 13 (2003) 905

Design, Synthesis and Photochemical Properties of Caged Bile Acids

Yuuki Hirayama,[a] Michiko Iwamura[a] and Toshiaki Furuta[a,b,*]

[a]*Department of Biomolecular Science, Toho University, 2-2-1 Miyama, Funabashi, 274-8510, Japan*
[b]*Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Coorporation (JST), 4-1-8 Honcho, Kawaguchi 332-0012, Japan*



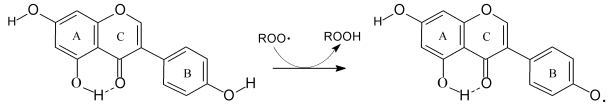
Bioorg. Med. Chem. Lett. 13 (2003) 909

Why B-Ring is the Active Center for Genistein to Scavenge Peroxyl Radical: A DFT Study

Hong-Yu Zhang,[a,*] Lan-Fen Wang[b] and You-Min Sun[c,*]

[a]*Laboratory for Computational Biology, Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Shandong University of Technology, Zibo 255049, PR China*
[b]*Department of Chemistry, Shandong Teachers' University, Jinan 250014, PR China*
[c]*Institute of Theoretical Chemistry, Shandong University, Jinan 250100, PR China*

The structure–activity relationship for genistein to scavenge xperoxyl radical was clarified by density functional theory (DFT) calculations using the B3LYP/6-31G(d,p) method.

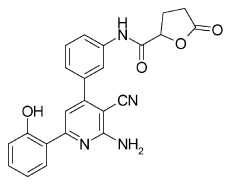


Bioorg. Med. Chem. Lett. 13 (2003) 913

Discovery of Novel and Selective IKK-β Serine-Threonine Protein Kinase Inhibitors. Part 1

Toshiki Murata,[a,*] Mitsuyuki Shimada,[a] Sachiko Sakakibara,[a] Takashi Yoshino,[a] Hiroshi Kadono,[a] Tsutomu Masuda,[a] Makoto Shimazaki,[a] Takuya Shintani,[a] Kinji Fuchikami,[b] Katsuya Sakai,[b] Hisayo Inbe,[b] Keisuke Takeshita,[b] Toshiro Niki,[b] Masaomi Umeda,[b] Kevin B. Bacon,[b] Karl B. Ziegelbauer[b] and Timothy B. Lowinger[a]

[a]*Department of Chemistry, Research Center Kyoto, Bayer Yakuhin, Ltd., Kizu, Soraku, Kyoto 619-0216, Japan*
[b]*Department of Biology, Research Center Kyoto, Bayer Yakuhin, Ltd., Kizu, Soraku, Kyoto 619-0216, Japan*

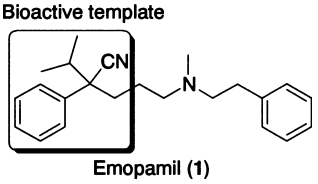


Bioorg. Med. Chem. Lett. 13 (2003) 919

Discovery of Novel Neuronal Voltage-Dependent Calcium Channel Blockers Based on Emopamil Left Hand as a Bioactive Template

Yuichi Suzuki,[a,*] Noboru Yamamoto,[a] Yoichi Iimura,[a] Koki Kawano,[a] Teiji Kimura,[a] Satoshi Nagato,[a] Koichi Ito,[a] Makoto Komatsu,[b] Yoshihiko Norimine,[a] Manami Kimura,[a] Tetsuyuki Teramoto,[a] Yoshihisa Kaneda,[a] Takeshi Hamano,[a] Tetsuhiro Niidome[a] and Masahiro Yonaga[a]

[a]*Tsukuba Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan*
[b]*Ebara Research Co., Ltd, 2-1 Honfujisawa 4-chome, Fujisawa-shi, Kanagawa 251-8502, Japan*



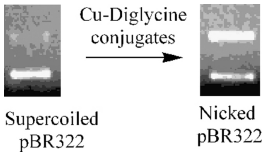
Bioorg. Med. Chem. Lett. 13 (2003) 923

Plasmid Relaxation Induced by Copper Metalated Diglycine Conjugates under Heterogeneous Reaction Conditions

C. Madhavaiah and Sandeep Verma*

Department of Chemistry, Indian Institute of Technology-Kanpur, Kanpur-208016 (UP), India

Heterogeneous catalysis of plasmid relaxation by copper metalated diglycine conjugates is reported.



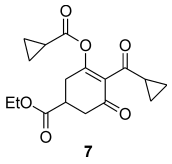
Bioorg. Med. Chem. Lett. 13 (2003) 927

Acylcyclohexanedione Derivatives as Potential In Vivo Sequential Inhibitors of 4-Hydroxyphenylpyruvate Dioxygenase and GA_{20} 3β-Hydroxylase

Jian-Lin Huang, Hun-Ge Liu and Ding-Yah Yang*

Department of Chemistry, Tunghai University, 181 Taichung-Kang Road. Sec.3, Taichung 407, Taiwan

Acylcyclohexanedione derivatives have been synthesized and tested as inhibitors of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD). Compound **7** was found to be a potent inhibitor of 4-HPPD with an IC_{50} value of 40 nM. After metabolism, compound **7** has the potential to become an inhibitor of a second enzyme, GA_{20} 3β-hydroxylase.



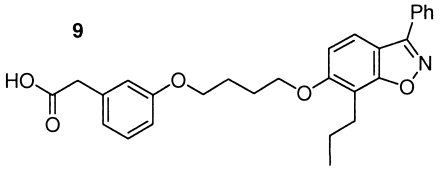
Bioorg. Med. Chem. Lett. 13 (2003) 931

Amphipathic 3-Phenyl-7-propylbenzisoxazoles; Human PPaR γ, δ and α Agonists

Alan D. Adams,[a,*] Winston Yuen,[a] Zao Hu,[a] Conrad Santini,[a] A. Brian Jones,[a] Karen L. MacNaul,[b] Joel P. Berger,[b] Thomas W. Doebber[b] and David E. Moller[b]

[a]*Departments of Basic Chemistry, Merck Research Laboratories, Merck & Co. Inc., PO Box 2000, Rahway, NJ 07065, USA*
[b]*Molecular Endocrinology, Merck Research Laboratories, Merck & Co. Inc., PO Box 2000, Rahway, NJ 07065, USA*

The synthesis and in vitro and in vivo profile of potent PPAR agonists is reported. **9** PPARγK_i 3 nM.

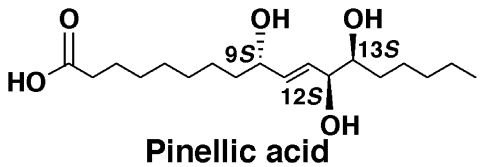


Bioorg. Med. Chem. Lett. 13 (2003) 937

Total Synthesis and Adjuvant Activity of All Stereoisomers of Pinellic Acid

Tatsuya Shirahata, Toshiaki Sunazuka, Kiminari Yoshida, Daisuke Yamamoto, Yoshihiko Harigaya, Takayuki Nagai, Hiroaki Kiyohara, Haruki Yamada, Isao Kuwajima and Satoshi Ōmura*

The Kitasato Institute for Life Science, and School of Pharmaceutical Science, Kitasato University, and The Kitasato Institute, Shirokane, Minatoku, Tokyo 108-8641, Japan



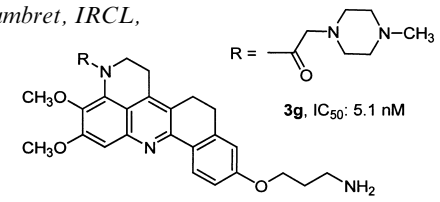
Bioorg. Med. Chem. Lett. 13 (2003) 943

Highly Cytotoxic Benzo[*c*]pyrido[2,3,4-*kl*]acridines

Sarah Chackal,[a] Michael Facompré,[b] Raymond Houssin,[a] Jean-François Goossens,[a] Nicole Pommery,[a] Jean-Pierre Hénichart[a] and Christian Bailly[b,*]

[a]*Institut de Chimie Pharmaceutique Albert Lespagnol, EA 2692, Université de Lille 2, BP 83, 59006 Lille, France*
[b]*Inserm U-524 and Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambret, IRCL, Place de Verdun, 59045 Lille, France*

Benzopyridoacridines were synthesized and evaluated for their capacity to bind to DNA and to inhibit DNA topoisomerases. Potent cytotoxic compounds were discovered.



3g, IC_{50}: 5.1 nM

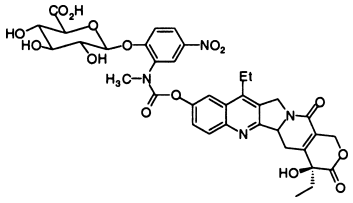
Bioorg. Med. Chem. Lett. 13 (2003) 947

Cancer Chemotherapy: A SN-38 (7-Ethyl-10-hydroxycamptothecin) Glucuronide Prodrug for Treatment by a PMT (Prodrug MonoTherapy) Strategy

Stéphane Angenault,[a] Sylvie Thirot,[a] Frédéric Schmidt,[a,*] Claude Monneret,[a] Bruno Pfeiffer[b] and Pierre Renard[b]

[a]*UMR176 CNRS/Institut Curie, 26, rue d'Ulm, 75248 Paris Cedex 05, France*
[b]*Laboratoires Servier 1, rue Carle Hébert, 92415 Courbevoie Cedex, France*

Synthesis and biological tests for prodrug **7** are reported.



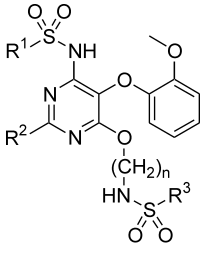
Bioorg. Med. Chem. Lett. 13 (2003) 951

Bis-sulfonamides as Endothelin Receptor Antagonists

Christoph Boss,* Martin H. Bolli, Thomas Weller, Walter Fischli and Martine Clozel

Drug Discovery Chemistry and Preclinical Research, Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil/BL, Switzerland

Structural modifications of bosentan **1** by introduction of a second sulfonamide function at the alkoxy side chain, led to bis-sulfonamides **2**, a new group of endothelin receptor antagonists.



Bis-Sulfonamides **2**

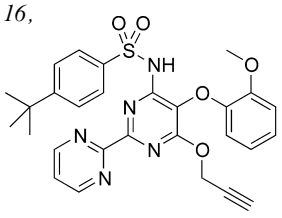
Bioorg. Med. Chem. Lett. 13 (2003) 955

The Use of Sulfonylamido Pyrimidines Incorporating an Unsaturated Side Chain as Endothelin Receptor Antagonists

Martin H. Bolli,* Christoph Boss, Martine Clozel, Walter Fischli, Patrick Hess and Thomas Weller

Drug Discovery Chemistry and Preclinical Research, Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil/BL, Switzerland

A series of compounds structurally related to bosentan **1** featuring an unsaturated side chain at position 6 of the core pyrimidine have been studied for their potential to block the ET_A and ET_B receptor. The propargyl derivative **26** significantly reduced blood pressure in in vivo model studies with hypertensive salt-sensitive Dahl rats.



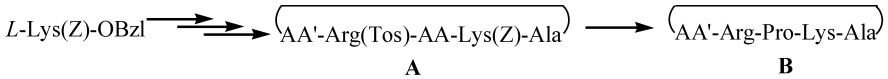
26

Bioorg. Med. Chem. Lett. 13 (2003) 961

Synthesis and Thrombolytic Activity of Fibrinogen Fragment Related Cyclopeptides

Ming Zhao, Na Lin, Chao Wang and Shiqi Peng*

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



in **A** when AA' = Ala, Gly, Gln, Lys(Z), AA = Pro; when AA' = Pro, AA = Ala, Gly, Gln, Lys(Z); in **B** AA' = Ala, Gly, Gln, Lys

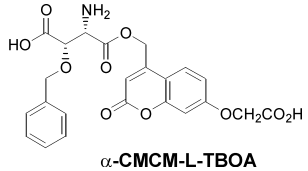
Bioorg. Med. Chem. Lett. 13 (2003) 965

Synthesis and Photoreactivity of Caged Blockers for Glutamate Transporters

Kiyo Takaoka,[a,b] Yoshiro Tatsu,[c] Noboru Yumoto,[c] Terumi Nakajima[a] and Keiko Shimamoto[a,*]

[a]*Suntory Institute for Bioorganic Research, 1-1-1 Wakayamadai, Shimamoto, Osaka 618-8503, Japan*
[b]*Japan Society for the Promotion of Science, 1-1-1 Wakayamadai, Shimamoto, Osaka 618-8503, Japan*
[c]*National Institute of Advanced Industrial Science and Technology, Midorigaoka, Ikeda 563-8577, Japan*

The photolysis of α-CMCM-L-TBOA, a caged blocker for glutamate transporters, immediately released L-TBOA to show glutamate uptake inhibition.



α-CMCM-L-TBOA

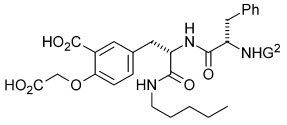
Bioorg. Med. Chem. Lett. 13 (2003) 973

Modification of the N-Terminus of Peptidomimetic Protein Tyrosine Phosphatase 1B (PTP1B) Inhibitors: Identification of Analogues with Cellular Activity

Scott D. Larsen,[a,*] F. Craig Stevens,[a] Thomas J. Lindberg,[a] Paul M. Bodnar,[a] Theresa J. O'Sullivan,[a] Heinrich J. Schostarez,[a] Barbara J. Palazuk[b] and John E. Bleasdale[b]

[a]*Medicinal Chemistry Research, Pharmacia Corporation, 333 Portage St., Kalamazoo, MI 49007, USA*
[b]*Cell & Molecular Biology, Pharmacia Corporation, 333 Portage St., Kalamazoo, MI 49007, USA*

Modification of the N-terminus of PTP1B inhibitor **3** led to the identification of analogues **61** and **62**, which were demonstrated to induce modest augmentation of 2-deoxyglucose uptake into L6 myocytes.



3: G^2 = Boc
61: G^2 = $COCH_2$-4-CF_3-Ph
62: G^2 = $COCH_2$-4-MeO-Ph