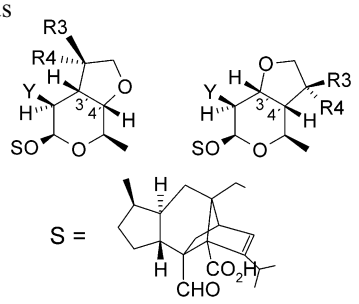
Bioorg. Med. Chem. Lett. 12 (2002) 1697

Antifungal Sordarins. Part 4: Synthesis and Structure–Activity Relationships of 3′,4′-Fused Alkyl-Tetrahydrofuran Derivatives

José M. Bueno, Jesús Chicharro, José M. Fiandor,* Federico Gómez de las Heras and Sophie Huss

GlaxoSmithkline, Research Department, Parque Tecnológico de Madrid, Severo Ochoa, 2.28760 Tres Cantos, Madrid, Spain

A number of novel alkyl substituted 3′,4′ fused tetrahydrofuran sordarin derivatives have been synthesised. Antifungal activity is reported.



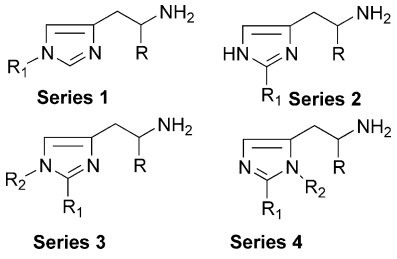
Bioorg. Med. Chem. Lett. 12 (2002) 1701

Antimalarial Activities of Ring-Substituted Bioimidazoles

Rahul Jain,[a,*] Suryanarayana Vangapandu,[a] Meenakshi Jain,[a] Navneet Kaur,[a] Savita Singh[b] and Prati Pal Singh[b]

[a]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India*
[b]*Department of Biotechnology, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India*

The in vitro and in vivo antimalarial activities for four series of ring-substituted bioimidazoles (R = H, CO_2H) are reported.



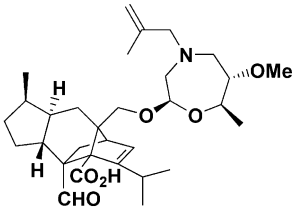
Bioorg. Med. Chem. Lett. 12 (2002) 1705

Synthesis and Evaluation of *N*-Substituted 1,4-Oxazepanyl Sordaricins as Selective Fungal EF-2 Inhibitors

Satoru Kaneko,[a,*] Masami Arai,[a] Takuya Uchida,[a] Tamako Harasaki,[b] Takashi Fukuoka[b] and Toshiyuki Konosu[a]

[a]*Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan*
[b]*Biological Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan*

Sordaricin analogues possessing 6-methoxy-7-methyl-1,4-oxazepane moiety instead of the sugar part were synthesized and evaluated. It was found that *N*-substituents on the oxazepane ring had influence on biological activity. In particular, *N*-(2-methylpropenyl) derivative **12p** exhibited potent in vitro antifungal activity. Furthermore, **12p** maintained significant activity (MIC 0.25 μg/mL) against *Candida albicans* SANK51486 even in the presence of 20% horse serum.



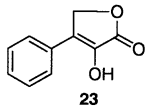
Bioorg. Med. Chem. Lett. 12 (2002) 1709

Design, Synthesis, and Evaluation of Postulated Transient Intermediate and Substrate Analogues as Inhibitors of 4-Hydroxyphenylpyruvate Dioxygenase

Yun-Loung Lin, Jian-Lin Huang, Chung-Shieh Wu, Hung-Ge Liu and Ding-Yah Yang*

Department of Chemistry, Tunghai University, 181, Taichung-Kang Rd. Sec. 3, Taichung, Taiwan 40704, Republic of China

An epoxybenzoquinone, 4-hydroxyphenoxypropionic acid, and 2-hydroxy-3-phenyl-3-butenoic acid derivatives have been synthesized and tested as inhibitors of 4-hydroxyphenylpyruvate dioxygenase. The most potent inhibitor tested was 3-hydroxy-4-phenyl-2(5H)-furanone **23** with an IC_{50} value of 0.5 μM.



23

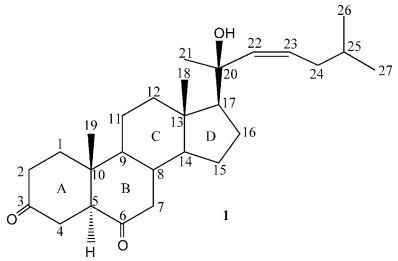
Bioorg. Med. Chem. Lett. 12 (2002) 1715

New Ketosteroids from the Red Alga *Hypnea musciformis*

V. Bultel-Poncé,[a,*] S. Etahiri[b] and M. Guyot[a]

[a]*Laboratoire de Chimie des Substances Naturelles associé au CNRS, Muséum National d'Histoire Naturelle, 63 rue Buffon, 75005 Paris, France*
[b]*Laboratoire de Biochimie Marine, Faculté des Sciences, Université Chouaib Doukkali, BP 20, El Jadida, Maroc*

A new diketosteroid: the 20-hydroxy-5α-cholest-22-ene-3,6-dione exhibited a PPE inhibition (ED_{50} 0.1 mM).



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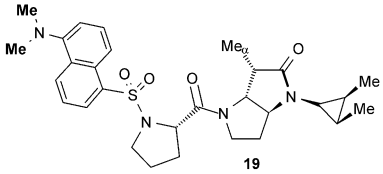
Bioorg. Med. Chem. Lett. 12 (2002) 1719

Pyrrolidine-5,5-*trans*-lactams as Novel Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. Part 3: Potency and Plasma Stability

Alan D. Borthwick,* Anne M. Exall, Terry M. Haley, Deborah L. Jackson, Andrew M. Mason and Gordon G. Weingarten

Department of Medicinal Chemistry CVU UK, GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

Mechanism-based inhibitors of HCMV protease have been developed based on the dansylproline α-methyl pyrrolidine-5,5-*trans*-lactam nucleus, that are stable to human plasma (≥20 h) and have single-figure potency in the μM range against HCMV protease.



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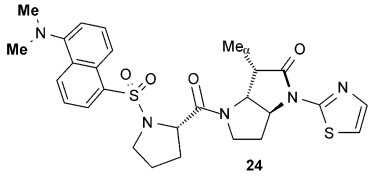


24

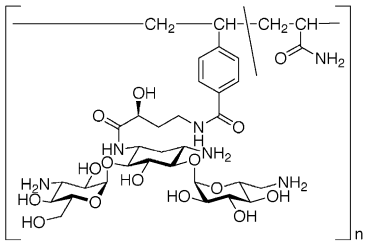
Bioorg. Med. Chem. Lett. 12 (2002) 1723

A Convenient Synthetic Pathway for Multivalent Assembly of Aminoglycoside Antibiotics Starting from Amikacin

Hidehiko Tanaka,[a] Yoshihiro Nishida,[a] Yousuke Furuta[b] and Kazukiyo Kobayashi[a,*]

[a]*Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603, Japan*
[b]*Toyama Kagaku Kogyo Co. Ltd, Toyama City, Toyama 930-8508, Japan*

Vinylpolymers carrying a kanamycin were prepared via regioselective *N*-acylation of amikacin. Two independent biological assays disclosed that the polymers showed neither antibacterial activity nor inhibitory activity of protein synthesis.



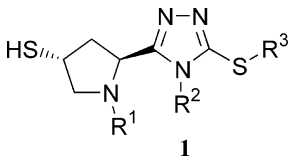
Bioorg. Med. Chem. Lett. 12 (2002) 1727

Synthesis of Triazole-Tethered Pyrrolidine Libraries: Novel ECE Inhibitors

Eric A. Kitas,* Bernd-Michael Löffler, Stefan Daetwyler, Henrietta Dehmlow and Johannes D. Aebi

Pharma Division, Preclinical Research, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland

Compound libraries with general structure **1** were synthesized on solid support. They were found to be a new class of ECE-1 inhibitors.



1

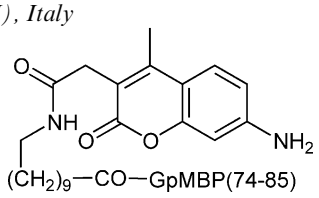
Bioorg. Med. Chem. Lett. 12 (2002) 1731

A New Lipophilic Fluorescent Probe for Interaction Studies of Bioactive Lipopeptides with Membrane Models

Elisa Peroni,[a] Gabriella Caminati,[c] Piero Baglioni,[c] Francesca Nuti,[a] Mario Chelli[b] and Anna M. Papini[a,*]

[a]*Dipartimento di Chimica Organica 'Ugo Schiff', Università degli Studi di Firenze, Polo Scientifico, I-50019 Sesto Fiorentino (FI), Italy*
[b]*CNR-ICCOM, Università degli Studi di Firenze, Polo Scientifico, I-50019 Sesto Fiorentino (FI), Italy*
[c]*Dipartimento di Chimica, Università degli Studi di Firenze, Polo Scientifico, I-50019 Sesto Fiorentino (FI), Italy*

FRET experiments were performed using the lipopeptide AMCA-ωAud-GpMBP(74–85).

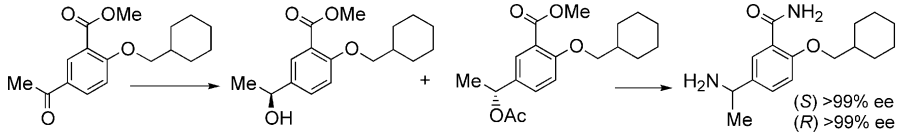


Bioorg. Med. Chem. Lett. 12 (2002) 1735

Efficient Chemoenzymatic Synthesis of (*S*)- and (*R*)-5-(1-Aminoethyl)-2-(cyclohexylmethoxy)benzamide: Key Intermediate for Src-SH2 Inhibitor

Ahmed Kamal* and Mahendra Sandbhor

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India



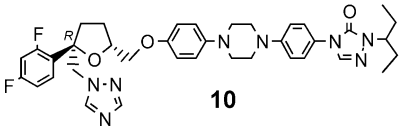
Bioorg. Med. Chem. Lett. 12 (2002) 1739

Synthesis and Antifungal Activity of the 2,2,5-Tetrahydrofuran Regioisomers of SCH 51048

Raymond G. Lovey,[a,*] Anil K. Saksena,[a] Viyyoor M. Girijavallabhan,[a] Paul Blundell,[a] Henry Guzik,[a] David Loebenberg,[b] Raulo M. Parmegiani[b] and Anthony Cacciapuoti[b]

[a]*Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Department of Infectious Diseases and Oncology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

The four 2,2,5-regioisomer counterparts of SCH 51048 are synthesized as antifungal agents. Only the activity of the 2-*R*-isomer (**10**) is significant. The importance of an oxygen at only one of the two possible ring positions benzylic to the difluorobenzene substituent in this family of compounds is discussed.



10

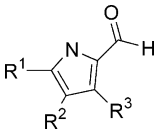
Bioorg. Med. Chem. Lett. 12 (2002) 1743

Discovery of Imidazole Glycerol Phosphate Dehydratase Inhibitors through 3-D Database Searching

Barbara A. Schweitzer,* Paul J. Loida, Claire A. CaJacob, Robert C. Chott, Elizabeth M. Collantes, Shridhar G. Hegde, Philip D. Mosier and Salvatore Profeta

Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63167, USA

We used a pharmacophore model based on known inhibitors and 3-D database searching to identify a class of pyrrole aldehydes as novel inhibitors of imidazole glycerol phosphate dehydratase.

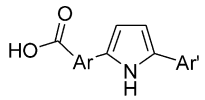


Bioorg. Med. Chem. Lett. 12 (2002) 1747

A Library Construction of 2,5-Disubstituted Pyrrole Compounds by Using Solid/Solution-Phase Syntheses

Naoki Kobayashi,[a,*] Yumiko Kaku,[a] Kunizo Higurashi,[a] Toshihiko Yamauchi,[b] Akira Ishibashi[b] and Yasushi Okamoto[a]

[a]*Discovery Technology Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300-2635, Japan*
[b]*Biology Group, Discovery Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300-2635, Japan*



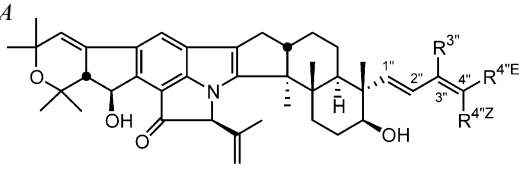
The construction of a library of 2,5-disubstituted pyrrole compounds using solid- and solution-phase synthesis was reported.

Bioorg. Med. Chem. Lett. 12 (2002) 1751

Side-Chain Homologation of Nodulisporic Acid: Synthesis of Potent New Dienyl Derivatives

Dong Ok,* Chunshi Li, Thomas L. Shih, Steve Salva, Michelle B. Ayer, Steven L. Colletti, Prasun K. Chakravarty, Matthew J. Wyvratt, Michael H. Fisher, Lynn Gregory, Michelle Zakson-Aiken, Wesley L. Shoop, Dennis M. Schmatz and Peter T. Meinke*

Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA



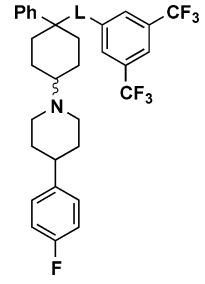
New, diene-modified nodulisporic acid analogues bearing diverse functionality at the 3″- and 4″-sites and exhibiting potent systemic activity against fleas were prepared from the corresponding 3″-aldehyde.

Bioorg. Med. Chem. Lett. 12 (2002) 1755

4,4-Disubstituted Cyclohexylamine NK_1 Receptor Antagonists I

Jason M. Elliott,[a,*] Jose L. Castro,[a] Gary G. Chicchi,[c] Laura C. Cooper,[a] Kevin Dinnell,[a] Gregory J. Hollingworth,[a] Mark P. Ridgill,[a] Wayne Rycroft,[b] Marc M. Kurtz,[c] Duncan E. Shaw,[a] Christopher J. Swain,[a] Kwei-Lan Tsao[c] and Lihu Yang[d]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Biochemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[d]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*

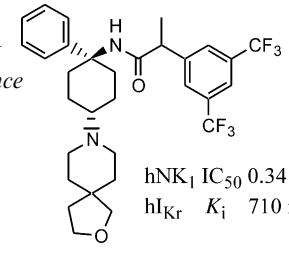


Bioorg. Med. Chem. Lett. 12 (2002) 1759

4,4-Disubstituted Cyclohexylamine NK_1 Receptor Antagonists II

Laura C. Cooper,[a,*] Emma J. Carlson,[b] Jose L. Castro,[a] Gary G. Chicchi,[c] Kevin Dinnell,[a] Jerry Di Salvo,[c] Jason M. Elliott,[a] Gregory J. Hollingworth,[a] Marc M. Kurtz,[c] Mark P. Ridgill,[a] Wayne Rycroft,[b] Kwei-Lan Tsao[c] and Christopher J. Swain[a]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Biochemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*



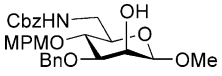
hNK_1 IC_{50} 0.34 nM
hI_{Kr} K_i 710 nM

Bioorg. Med. Chem. Lett. 12 (2002) 1763

Structure-Based Design and Synthesis of HIV-1 Protease Inhibitors Employing β-D-Mannopyranoside Scaffolds

Paul V. Murphy,[a,*] Julie L. O'Brien,[a] Lorraine J. Gorey-Feret[b] and Amos B. Smith, III[c,*]

[a]*Chemistry Department, Centre for Synthesis and Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland*
[b]*Bristol-Myers Squibb Pharmaceutical Company, Wilmington, DE, USA*
[c]*Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, USA*



15 IC_{50} 4.48 μM

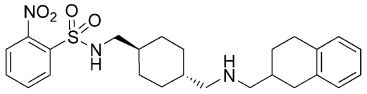
Bioorg. Med. Chem. Lett. 12 (2002) 1767

Discovery of Potent and Selective Small Molecule NPY Y5 Receptor Antagonists

Imadul Islam, Dale Dhanoa, John Finn,* Ping Du, Mary W. Walker, John A. Salon, Jack Zhang and Charles Gluchowski

Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, NJ 07652, USA

The discovery of a new class of sulfonamide NPY Y5 receptor antagonists is described. Optimization of this series led to the identification of compounds with high affinity for the hY5 subtype and excellent selectivity over the other NPY receptor subtypes. The SAR for this series was examined and a model for understanding the ligand–receptor interactions was developed.



11 K_i hY5 6 nM

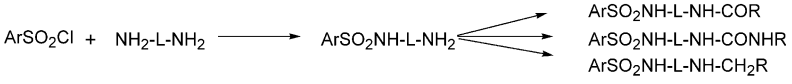
Bioorg. Med. Chem. Lett. 12 (2002) 1771

High-Throughput Synthesis Optimization of Sulfonamide NPY Y5 Antagonists

John Finn,* David Pelham, Mary W. Walker and Charles Gluchowski

Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, NJ 07652, USA

A series of sulfonamide neuropeptide Y Y5 antagonists was optimized by preparation of sets of analogues using high-throughput synthesis and purification techniques.



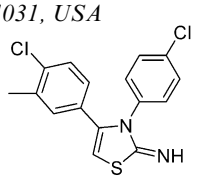
Bioorg. Med. Chem. Lett. 12 (2002) 1775

Discovery of Substituted 3,4-Diphenyl-thiazoles as a Novel Class of Monoamine Transporter Inhibitors through 3-D Pharmacophore Search Using a New Pharmacophore Model Derived from Mazindol

Istvan J. Enyedy,[a] Jiansuo Wang,[a] Wahiduz A. Zaman,[b] Kenneth M. Johnson[b] and Shaomeng Wang[a,*]

[a]*Departments of Internal Medicine and Medicinal Chemistry, University of Michigan, Ann Arbor, MI 48109-0934, USA*
[b]*Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX 77555-1031, USA*

3,4-Diphenyl-thiazoles were identified as a novel class of monoamine transporter inhibitors (K_i = 24 nM at DAT).



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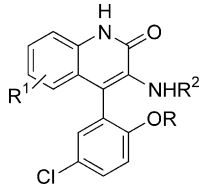
Bioorg. Med. Chem. Lett. 12 (2002) 1779

The Synthesis and Structure–Activity Relationships of 4-Aryl-3-aminoquinolin-2-ones: A New Class of Calcium-Dependent, Large Conductance, Potassium (Maxi-K) Channel Openers Targeted for Post-Stroke Neuroprotection

Piyasena Hewawasam,[a,*] Wenhong Fan,[a] Jay Knipe,[c] Sandra L. Moon,[b] Christopher G. Boissard,[b] Valentin K. Gribkoff[b] and John E. Starrett, Jr.[a]

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



Bioorg. Med. Chem. Lett. 12 (2002) 1785

CCR3 Antagonists: A Potential New Therapy for the Treatment of Asthma. Discovery and Structure–Activity Relationships

Dean A. Wacker,* Joseph B. Santella, III, Daniel S. Gardner, Jeffrey G. Varnes, Melissa Estrella, George V. DeLucca, Soo S. Ko, Keiichi Tanabe, Paul S. Watson, Patricia K. Welch, Maryanne Covington, Nicole C. Stowell, Eric A. Wadman, Paul Davies, Kimberly A. Solomon, Robert C. Newton, George L. Trainor, Steven M. Friedman, Carl P. Decicco and John V. Duncia*

Bristol-Myers Squibb Company, Experimental Station, PO Box 80336, Wilmington, DE 19880-0336, USA