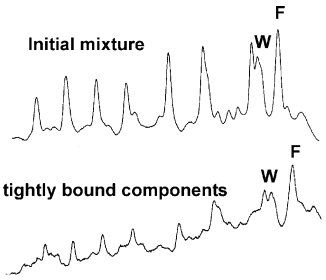
Bioorg. Med. Chem. Lett. 12 (2002) 513

Affinity-Driven Selection of Tripeptide Inhibitors of Ribonucleotide Reductase

Ying Gao, Sebastian Liehr and Barry S. Cooperman*

Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA

Tripeptide libraries of the type Fmoc(W/F)XF were screened for binding to the large subunit of mouse ribonucleotide reductase (mRR), using a new, affinity chromatography method. A high affinity tripeptide, FmocWFF, was found that inhibited mRR activity with a K_i equal to that of AcFTLDADF, the heptapeptide corresponding to the C-terminus of the small subunit of mRR.



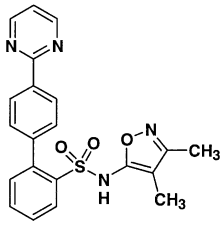
Bioorg. Med. Chem. Lett. 12 (2002) 517

Biphenylsulfonamide Endothelin Receptor Antagonists. Part 3: Structure–Activity Relationship of 4′-Heterocyclic Biphenylsulfonamides

Natesan Murugesan,* Zhengxiang Gu, Philip D. Stein, Steven Spergel, Sharon Bisaha, Eddie C.-K. Liu, Rongan Zhang, Maria L. Webb, Suzanne Moreland and Joel C. Barrish

Department of Chemistry, Cardiovascular Agents, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, USA

A series of 4′-heterocyclic biphenylsulfonamide derivatives was prepared and evaluated for endothelin A (ET_A) receptor antagonist activity. Among the analogues examined, the pyrimidine derivative **18** is the most potent ($K_i = 0.9$ nM) and selective for the ET_A receptor.



18

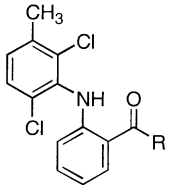
Bioorg. Med. Chem. Lett. 12 (2002) 521

Amide Derivatives of Meclofenamic Acid as Selective Cyclooxygenase-2 Inhibitors

Amit S. Kalgutkar,* Scott W. Rowlinson, Brenda C. Crews and Lawrence J. Marnett

A. B. Hancock, Jr., Memorial Laboratory for Cancer Research, Departments of Biochemistry and Chemistry, Center in Molecular Toxicology and the Vanderbilt Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

A facile strategy for the modification of meclofenamic acid into selective cyclooxygenase-2 inhibitors is reported.



R = OH (meclofenamic acid)
R = $NH(CH_2)_2OC_6H_5$ (amide)

Bioorg. Med. Chem. Lett. 12 (2002) 525

Differential Inhibition of Polymerase and Strand-Transfer Activities of HIV-1 Reverse Transcriptase

L. M. V. Tillekeratne,[a] A. Sherette,[a] J. A. Fulmer,[a] L. Hupe,[b] D. Hupe,[b] S. Gabbara,[b] J. A. Peliska[c] and R. A. Hudson[a,d,*]

[a]*Department of Medicinal and Biological Chemistry, College of Pharmacy, University of Toledo, Toledo, OH 43606, USA*
[b]*Pfizer Global Research and Development, 2800 Plymouth Rd, Ann Arbor, MI 48105, USA*
[c]*Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, MI 48109-0606, USA*
[d]*Departments of Biology and Chemistry, College of Arts and Sciences, University of Toledo, Toledo, OH 43606, USA*

We recently reported a new class of HIV-1-reverse transcriptase inhibitors obtained by the structural simplification of epicatechin and epigallocatechin gallates. By further structural optimization we have defined a subset of these agents in which the capacity to inhibit DNA-strand-transfer is retained, but polymerase inhibitory activity is minimized. DNA-strand-transfer agents may have interesting therapeutic potential.

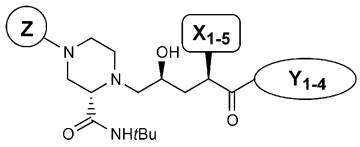
Bioorg. Med. Chem. Lett. 12 (2002) 529

A Combinatorial Library of Indinavir Analogues and Its In Vitro and In Vivo Studies

Yuan Cheng,[a,*] Thomas A. Rano,[a] Tracy T. Huening,[a] Fengqi Zhang,[a] Zhijian Lu,[a] William A. Schleif,[b] Lori Gabryelski,[b] David B. Olsen,[b] Mark Stahlhut,[b] Lawrence C. Kuo,[b] Jiunn H. Lin,[c] Xin Xu,[c] Lixia Jin,[c] Timothy V. Olah,[c] Debra A. McLoughlin,[c] Rick C. King,[c] Kevin T. Chapman[a] and James R. Tata[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

A combinatorial library of HIV protease inhibitors has been prepared. In vitro and in vivo studies of the library identified compounds with greater potency as well as compounds with favorable pharmacokinetic properties.



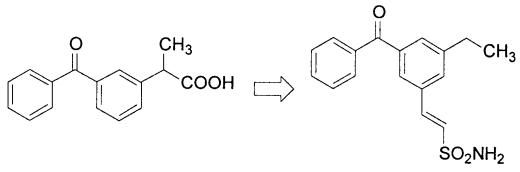
Bioorg. Med. Chem. Lett. 12 (2002) 533

Structure-Based Design of Cyclooxygenase-2 Selectivity into Ketoprofen

Albert Palomer,* Jaume Pascual, Marta Cabré, Liset Borràs, Gracia González, Mònica Aparici, Assumpta Carabaza, Francesc Cabré, M. Luisa García and David Mauleón

R&D Department, Laboratorios Menarini S.A., Alfonso XII 587, 08918 Badalona, Spain

A new family of benzophenone-containing selective COX-2 inhibitors exemplified by **17** has been prepared. The resulting series was designed based on the combined use of pharmacophore models and traditional medicinal chemistry techniques motivated by the comparative modeling of the 3-D structures of the NSAID ketoprofen (**2**) docked into the COX active sites.



2 (Ketoprofen) **17**

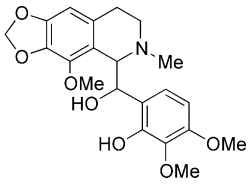
Bioorg. Med. Chem. Lett. 12 (2002) 539

New Anti-Malarial Compounds from Database Searching

Renate Griffith,[a,b,*] Rachada Chanphen,[c] Scott P. Leach[b] and Paul A. Keller[b,*]

[a]*School of Biological and Chemical Sciences, University of Newcastle, Callaghan, NSW 2308, Australia*
[b]*Department of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia*
[c]*National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), 73/1, Rama VI Road, Rajdhevee, Bangkok 10400, Thailand*

The structure and activity of new anti-malarial compounds from database searching are reported.



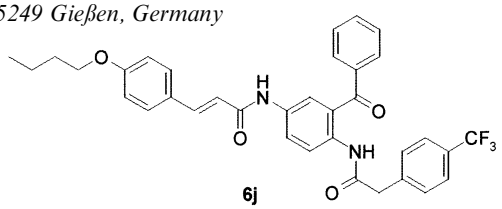
Bioorg. Med. Chem. Lett. 12 (2002) 543

Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 3: *N*-(4-Acylamino-3-benzoylphenyl)-4-propoxycinnamic Acid Amides

Jochen Wiesner,[b,c] Katja Kettler,[a] Hassan Jomaa[c] and Martin Schlitzer[a,*]

[a]*Department für Pharmazie - Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, D-81377 München, Germany*
[b]*Biochemisches Institut der Universitätsklinik Gießen, Friedrichstraße 24, D-35249 Gießen, Germany*
[c]*Jomaa Pharmaka GmbH, Frankfurter Straße 50, D-35249 Gießen, Germany*

We have described 5-(4-propoxycinnamoylamino)-2-(4-tolylacetylamino)-benzophenone as a novel lead for anti-malarial agents. Anti-malarial activity of this type of compounds proved to be quite sensitive against variations of the acyl substituent at the 2-amino group. Best activity was obtained with phenylacetic acid moieties carrying small substituents in the *para*-position. The trifluoromethyl derivative was the most active compound.



6j

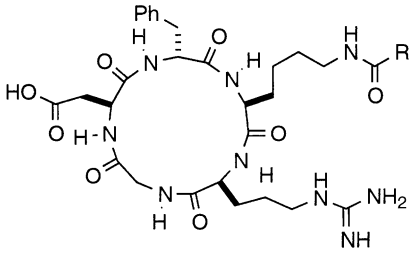
Bioorg. Med. Chem. Lett. 12 (2002) 547

Solid-Phase Synthesis of c(RGDfK) Derivatives: On-Resin Cyclisation and Lysine Functionalisation

Catherine F. McCusker,[a] Philip J. Kocienski,[a,*] F. Thomas Boyle[b] and Andreas G. Schätzlein[c]

[a]*Department of Chemistry, Leeds University, Leeds LS2 9JT, UK*
[b]*AstraZeneca Pharmaceuticals, Alderly Edge, Mereside, Macclesfield, Cheshire SK10 4TG, UK*
[c]*CRC Department of Medical Oncology, Beatson Laboratories, Switchback Road, Glasgow G61 1BD, UK*

The cyclic pentapeptide c(RGDfK), a selective ligand for the $\alpha_v\beta_3$ integrin, was synthesised on solid phase.

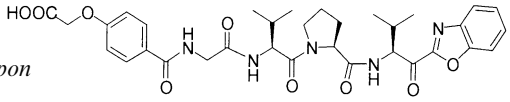


Bioorg. Med. Chem. Lett. 12 (2002) 551

Design and Synthesis of Peptide-Based Carboxylic Acid-Containing Transition-State Inhibitors of Human Neutrophil Elastase

Fuminori Sato,[a,*] Yasunao Inoue,[a] Tomoki Omodani,[a] Kiyomi Imano,[b] Hiroshi Okazaki,[b] Tadashi Takemura[b] and Masanobu Komiya[b]

[a]*Department of Chemistry II, Discovery Research Laboratories, Dainippon Pharmaceutical Co., Ltd. Enoki 33-94, Suita, Osaka 564-0053, Japan*
[b]*Department of Pharmacology III, Discovery Research Laboratories, Dainippon Pharmaceutical Co., Ltd. Enoki 33-94, Suita, Osaka 564-0053, Japan*



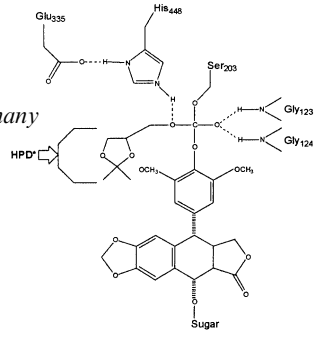
Bioorg. Med. Chem. Lett. 12 (2002) 557

Synthesis, Hydrolytic Activation and Cytotoxicity of Etoposide Prodrugs

Wolf Wrasidlo,[a,*] Ulrike Schröder,[a] Kathrin Bernt,[a] Nicole Hübener,[a] Doron Shabat,[b] Gerhard Gaedicke[a] and Holger Lode[a]

[a]*Charité Children's Hospital, Humboldt University, Augustenburger Platz 1, 13353 Berlin, Germany*
[b]*School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel*

Two prodrugs of the topoisomerase II inhibiting antitumor drug etoposide incorporating either hydrophilic or hydrophobic groups and differing in their substrate specificity for the activating enzyme carboxyl esterase were prepared. These new prodrugs show dramatically different activation kinetics and completely circumvent MDR-1 drug resistance.



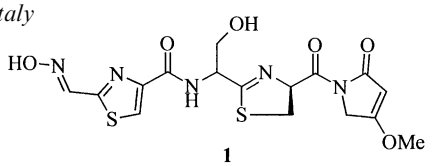
Bioorg. Med. Chem. Lett. 12 (2002) 561

Total Synthesis and Semi-Synthetic Approaches to Analogues of Antibacterial Natural Product Althiomycin

Paola Zarantonello,[a,*] Colin P. Leslie,[a,*] Rafael Ferritto[a] and Wieslaw M. Kazmierski[b]

[a]*GlaxoSmithKline SpA, Medicines Research Centre, Via Fleming 4, 37135 Verona, Italy*
[b]*GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA*

Analogues of the natural antibacterial althiomycin **1** were prepared via both total synthesis and semi-synthetic protocols.



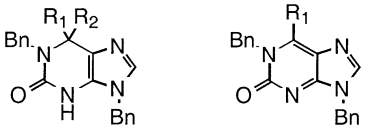
1

Bioorg. Med. Chem. Lett. 12 (2002) 567

Cytotoxic and Antibacterial Activity of 2-Oxopurine Derivatives

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

[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*



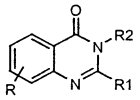
Bioorg. Med. Chem. Lett. 12 (2002) 571

Studies on Quinazolinones as Dual Inhibitors of Pgp and MRP1 in Multidrug Resistance

Shouming Wang,[a,*] Hamish Ryder,[a] Ian Pretswell,[a] Paul Depledge,[b] John Milton,[a] Timothy C. Hancox,[a] Ian Dale,[b] Wendy Dangerfield,[b] Peter Charlton,[b] Richard Faint,[b] Rory Dodd[a] and Stephanie Hassan[b]

[a]*Department of Medicinal Chemistry, Xenova Ltd., 957 Buckingham Avenue, Slough, Berkshire SL1 4NL, UK*
[b]*Department of Pharmacology, Xenova Ltd., 957 Buckingham Avenue, Slough, Berkshire SL1 4NL, UK*

The syntheses and SAR studies of various quinazolinone compounds (**7**) are described for the dual inhibition of Pgp and MRP1 in multidrug resistance.



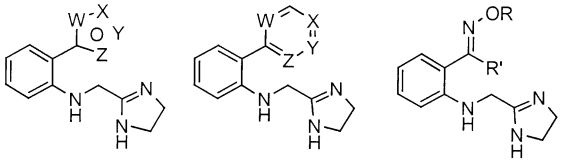
(7)

Bioorg. Med. Chem. Lett. 12 (2002) 575

2-(Anilinomethyl)imidazolines as α_{1A} Adrenergic Receptor Agonists: 2′-Heteroaryl and 2′-Oxime Ether Series

Frank Navas, III,[a,*] Michael J. Bishop,[a] Deanna T. Garrison,[a] Stephen J. Hodson,[a] Jason D. Speake,[a] Eric C. Bigham,[a] David H. Drewry,[a] David L. Saussy,[b] James H. Liacos,[b] Paul E. Irving[b] and M. Jeffrey Gobel[b]

[a]*Division of Chemistry, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[b]*Division of Pharmacology and Molecular Therapeutics, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA*



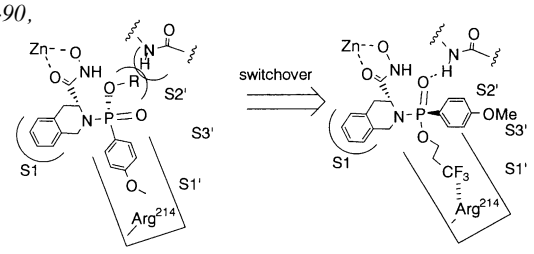
Bioorg. Med. Chem. Lett. 12 (2002) 581

Encounter with Unexpected Collagenase-1 Selective Inhibitor: Switchover of Inhibitor Binding Pocket Induced by Fluorine Atom

Masaaki Sawa,[a,*] Hirosato Kondo[a] and Shin-ichiro Nishimura[b]

[a]*Department of Chemistry, R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan*
[b]*Division of Biological Sciences, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan*

The first example of a highly selective MMP-1 inhibitor by the fluorine atom-induced switching of the binding mode is reported.



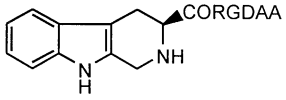
Bioorg. Med. Chem. Lett. 12 (2002) 585

Synthesis and Antithrombotic Activity of Carbolinecarboxyl RGD Sequence

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

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

The syntheses of 3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, RGDS, RGDV, RGDF and their linkers are reported. The antithrombotic activities of these compounds were evaluated.



15-17

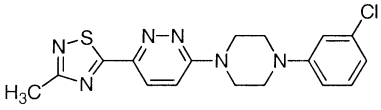
Bioorg. Med. Chem. Lett. 12 (2002) 589

Synthesis and Anti-Angiogenic Activity of 6-(1,2,4-Thiadiazol-5-yl)-3-amino Pyridazine Derivatives

Jean-Pierre Bongartz,[a,*] Raymond Stokbroekx,[a] Marcel Van der Aa,[a] Marcel Luyckx,[a] Marc Willems,[a] Marc Ceusters,[a] Lieven Meerpoel,[a] Gerda Smets,[a] Tine Jansen,[a] Walter Wouters,[a] Charlie Bowden,[a] Lisa Valletta,[b] Mark Herb,[b] Rose Tominovich[b] and Robert Tuman[b]

[a]*Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium*
[b]*RW Johnson Pharmaceutical Research Institute, Drug Discovery, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477-0776, USA*

The synthesis of anti-angiogenic compounds based on the lead structure R 90324 is described.



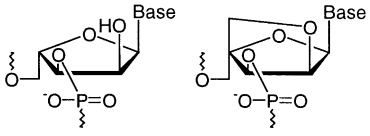
R 90324 IC_{50} = 0.6 nM

Bioorg. Med. Chem. Lett. 12 (2002) 593

α-L-RNA (α-L-*ribo* Configured RNA): Synthesis and RNA-Selective Hybridization of α-L-RNA/α-L-LNA Chimera

Lise Keinicke,[a] Mads D. Sørensen[a] and Jesper Wengel[b,*]

[a]*Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark*
[b]*Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark*



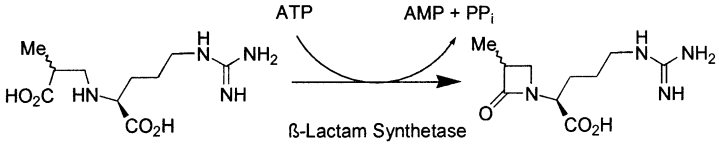
α-L-RNA **α-L-LNA**

Bioorg. Med. Chem. Lett. 12 (2002) 597

Enzymatic Synthesis of Monocyclic β-Lactams

Mark C. Sleeman, Colin H. MacKinnon, Kirsty S. Hewitson* and Christopher J. Schofield*

The Dyson Perrins Laboratory and the Oxford Centre for Molecular Sciences, South Parks Road, Oxford OX1 3QY, UK

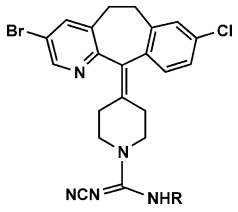


Bioorg. Med. Chem. Lett. 12 (2002) 601

Synthesis of 5,6-Dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*] pyridin-11-ylidene)-1-piperidine-*N*-cyanoguanidine Derivatives as Inhibitors of Ras Farnesyl Protein Transferase

Alan B. Cooper,* Corey L. Strickland,* James Wang, Jagdish Desai, Paul Kirschmeier, Robert Patton, W. Robert Bishop, Patricia C. Weber and V. Girijavallabhan

Schering-Plough Research Institute, Departments of Chemistry, Structural Chemistry and Tumor Biology, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA



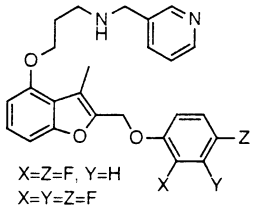
A series of novel *N*-cyanoguanidine tricyclic farnesyl protein transferase (FPT) inhibitors was prepared. Replacement of a piperidine amide-group with a *N*-cyanoguanidine functionality increased FPT activity. X-ray crystal structure determination of **42** complexed with FPT revealed differences in the interactions of the amide and *N*-cyanoguanidine groups with the protein.

Bioorg. Med. Chem. Lett. 12 (2002) 607

Design and Synthesis of Novel Benzofurans as a New Class of Antifungal Agents Targeting Fungal *N*-Myristoyltransferase. Part 2

Hirosato Ebiike,[a] Miyako Masubuchi,[a] Pingli Liu,[a] Ken-ichi Kawasaki,[a] Kenji Morikami,[a] Satoshi Sogabe,[a] Michiko Hayase,[b] Toshihiko Fujii,[b] Kiyoaki Sakata,[b] Hidetoshi Shindoh,[c] Yasuhiko Shiratori,[a] Yuko Aoki,[b] Tatsuo Ohtsuka[a,*] and Nobuo Shimma[a]

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



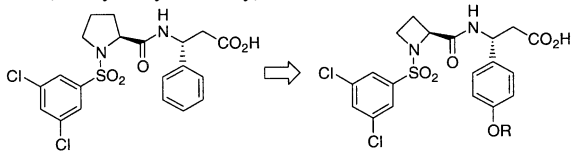
Modification of the C-2 position of a benzofuran derivative **6** (RO-09-4609), an *N*-myristoyltransferase (Nmt) inhibitor, has led us to discover antifungal agents that are active in a murine systemic candidiasis model. The drug design is based on the analysis of a crystal structure of a *Candida* Nmt complex with **2**. The optimization has been guided by various biological evaluations including a quasi in vivo assay and pharmacokinetic analysis.

Bioorg. Med. Chem. Lett. 12 (2002) 611

The Discovery of Acylated β-Amino Acids as Potent and Orally Bioavailable VLA-4 Antagonists

Linus S. Lin,[a,*] Ihor E. Kopka,[a] Richard A. Mumford,[b] Plato A. Magriotis,[a] Thomas Lanza, Jr.,[a] Philippe L. Durette,[a] Theodore Kamenecka,[a] David N. Young,[a] Stephen E. de Laszlo,[a] Ermenegilda McCauley,[b] Gail Van Riper,[b] Usha Kidambi,[b] Linda A. Egger,[b] Xinchun Tong,[a] Kathryn Lyons,[c] Stella Vincent,[c] Ralph Stearns,[c] Adria Colletti,[c] Yohannes Teffera,[c] Judy Fenyk-Melody,[d] John A. Schmidt,[b] Malcolm MacCoss[a] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Inflammation and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, USA*
[d]*Department of Comparative Medicine, Merck Research Laboratories, Rahway, NJ 07065, USA*



2
IC_{50} = 2.4 nM

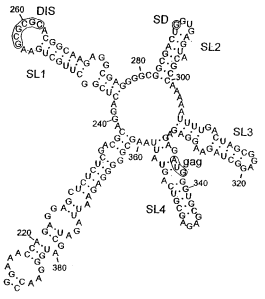
7g: R = Me, 0.49 nM
7h: R= Et, 0.27 nM

Bioorg. Med. Chem. Lett. 12 (2002) 615

Absorption Studies on Aminoglycoside Binding to the Packaging Region of Human Immunodeficiency Virus Type-1

Julie M. Sullivan, Jerry Goodisman and James C. Dabrowiak*

Department of Chemistry, CST 1-014, Syracuse University, Syracuse, NY 13244, USA



Bioorg. Med. Chem. Lett. 12 (2002) 619

A Novel Series of Hybrid Compounds Derived by Combining 2-Aminotetralin and Piperazine Fragments: Binding Activity at D_2 and D_3 Receptors

Aloke K. Dutta,[a,*] Xiang-Shu Fei[a] and Maarten E. A. Reith[b]

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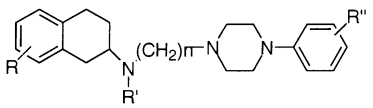
[b]*University of Illinois, College of Medicine, Department of Biomedical and Therapeutic Sciences, Peoria, IL 61605, USA*

A series of 7-hydroxy-2-[*N*-alkyl-(*N*-(4-phenylpiperazine)alkyl)amino]tetralins was developed based on a novel hybrid approach which combined 2-aminotetralin and arylpiperazine pharmacophoric moieties. Structure–activity studies led to a novel template showing 50- to 100-fold selectivity for the D_3 receptor.



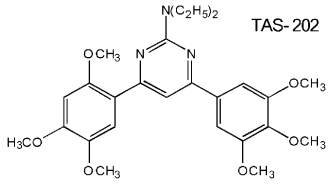
Bioorg. Med. Chem. Lett. 12 (2002) 623

Synthesis of a Magnosalin Derivative, 4-(3,4,5-Trimethoxyphenyl)-6-(2,4,5-trimethoxyphenyl)-2-diethylaminopyrimidine, and the Anti-Angiogenic and Anti-Rheumatic Effect on Mice by Oral Administration

Katsunao Tanaka,[a,b,*] Yasuo Konno,[a] Yasushi Kuraishi,[b] Ikuko Kimura,[c] Takashi Suzuki[a] and Mamoru Kiniwa[a]

[a]*Pharmacobioregulation Research Laboratory, Taiho Pharmaceutical Co., Ltd., 1-27 Misugidai, Hanno-City, Saitama 357-8527, Japan*
[b]*Department of Applied Pharmacology, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*
[c]*Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan*

TAS-202, a magnosalin derivative, inhibited the proliferation of vascular endothelial cells selectively, and prevented angiogenesis and arthritis on mice by oral administration.



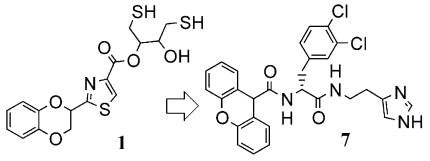
Bioorg. Med. Chem. Lett. 12 (2002) 629

A New Class of Type I Protein Geranylgeranyltransferase (GGTase I) Inhibitor

Satoshi Sunami,* Mitsuru Ohkubo, Takeshi Sagara, Jun Ono, Shuichi Asahi, Seita Koito and Hajime Morishima

Banyu Tsukuba Research Institute, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

Replacement of the thiol groups of **1** with an imidazole ring was achieved by using combinatorial library methods to find a new class of GGTase I inhibitor (**7**).



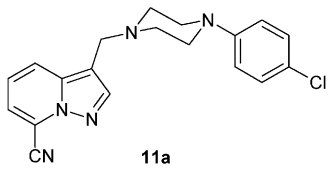
Bioorg. Med. Chem. Lett. 12 (2002) 633

Di- and Trisubstituted Pyrazolo[1,5-*a*]pyridine Derivatives: Synthesis, Dopamine Receptor Binding and Ligand Efficacy

Stefan Löber, Tarek Aboul-Fadl, Harald Hübner and Peter Gmeiner*

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

The 7-cyanopyrazolo[1,5-*a*]pyridine **11a** (FAUC 327) had high D4 affinity and subtype selectivity as well as substantial intrinsic activity in the low nanomolar range.



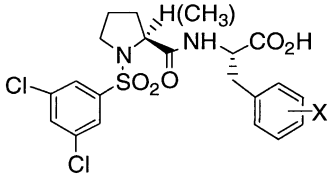
Bioorg. Med. Chem. Lett. 12 (2002) 637

Substituted *N*-(3,5-Dichlorobenzenesulfonyl)-L-prolyl-phenylalanine Analogues as Potent VLA-4 Antagonists

Ihor E. Kopka,[a,*] David N. Young,[a] Linus S. Lin,[a] Richard A. Mumford,[b] Plato A. Magriotis,[a] Malcolm MacCoss,[a] Sander G. Mills,[a] Gail Van Riper,[b] Ermengilda McCauley,[b] Linda E. Egger,[b] Usha Kidambi,[b] John A. Schmidt,[b] Kathryn Lyons,[c] Ralph Stearns,[c] Stella Vincent,[c] Adria Colletti,[c] Zhen Wang,[c] Sharon Tong,[a] Junying Wang,[a] Song Zheng,[a] Karen Owens,[a] Dorothy Levorse[a] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Inflammation and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of substituted *N*-(3,5-dichlorobenzenesulfonyl)-L-prolyl- and α-methyl-L-prolyl-phenylalanine derivatives was prepared as VLA-4/VCAM antagonists. The compounds showed excellent potency with a wide variety of neutral, polar, electron withdrawing or donating groups on the phenylalanine ring ($IC_{50} \sim 1$ nM). Heteroaryl ring substitution for phenylalanine was also well tolerated. Pharmacokinetic studies in rat were performed on a representative set of compounds in both series.



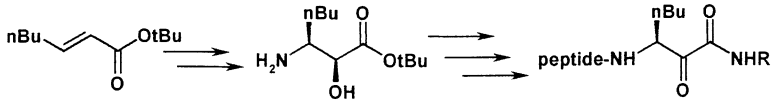
Bioorg. Med. Chem. Lett. 12 (2002) 641

Solution and Solid-Phase Synthesis of Potent Inhibitors of Hepatitis C Virus NS3 Proteinase

Rebekah Beevers, Maria G. Carr, Philip S. Jones, Steven Jordan, Paul B. Kay, Robert C. Lazell and Tony M. Raynham*

Department of Chemistry, Roche Discovery Welwyn, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, UK

A versatile route for the synthesis of homochiral α-ketoamide analogues of amino acids is described. Incorporation of this functionality into peptide sequences using either solution or solid-phase chemistry led to potent inhibitors of HCV proteinase.



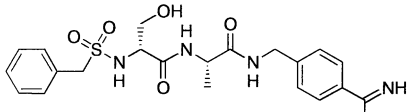
Bioorg. Med. Chem. Lett. 12 (2002) 645

4-Amidinobenzylamine-Based Inhibitors of Urokinase

Sebastian Künzel,[a] Andrea Schweinitz,[b] Siegmund Reißmann,[a] Jörg Stürzebecher[b] and Torsten Steinmetzer[a,*]

[a]*Institut für Biochemie und Biophysik, Universität Jena, Philosophenweg 12, D-07743 Jena, Germany*
[b]*Zentrum für Vaskuläre Biologie und Medizin, Universität Jena, Nordhäuser Str. 78, D-99089 Erfurt, Germany*

A series of 4-amidinobenzylamine-based peptidomimetic inhibitors of urokinase was synthesized. The most potent one, benzylsulfonyl-D-Ser-Ala-4-amidinobenzylamide **16**, inhibits uPA with a K_i of 7.7 nM but is less selective than **10** with a Gly as P2 residue. Hydroxyamidine and carbonate prodrugs were prepared, which are rapidly converted into the active inhibitors in rats after subcutaneous application.



16 K_i 7.7 nM

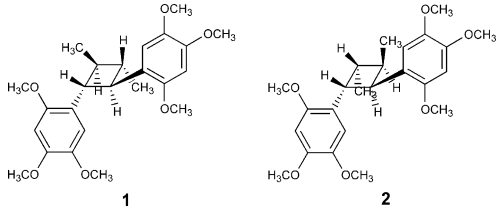
Bioorg. Med. Chem. Lett. 12 (2002) 649

Two Neolignans from *Perilla frutescens* and Their Inhibition of Nitric Oxide Synthase and Tumor Necrosis Factor-α Expression in Murine Macrophage Cell Line RAW 264.7

Jae-Ha Ryu,[a,*] Haeng Ja Son,[a] Sook Hyun Lee[a] and Dong Hwan Sohn[b]

[a] *College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Republic of Korea*
[b] *College of Pharmacy and Medicinal Resources Research Center, Wonkwang University, Iksan-City, Geonbuk 570-749, Republic of Korea*

Inhibitors (**1** and **2**) of iNOS ($IC_{50} = 5.9$ and 53.5 μM, respectively) and TNF-α expression were identified from medicinal plant, *Perilla frutescens*.

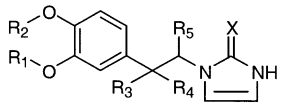


Bioorg. Med. Chem. Lett. 12 (2002) 653

Synthesis and Biological Evaluation of Imidazol-2-one and 2-Cyanoiminoimidazole Derivatives: Novel Series of PDE4 Inhibitors

J. Ignacio Andrés,[a,*] José M. Alonso,[a] Adolfo Díaz,[a] Javier Fernández,[a] Laura Iturrino,[a] Pedro Martínez,[a] Encarna Matesanz,[a] Eddy J. Freyne,[b] Frederik Deroose,[b] Gustaaf Boeckx,[b] Davy Petit,[b] Gaston Diels,[b] Anton Megens,[b] Marijke Somers,[b] Jean Van Wauwe,[b] Paul Stoppie,[b] Marina Cools,[b] Fred De Clerck,[b] Danielle Peeters[b] and Didier de Chaffoy[b]

[a]*Janssen-Cilag, Basic Research Centre, Jarama s/n, 45007 Toledo, Spain*
[b]*Janssen Research Foundation, B2340, Belgium*



The synthesis and in vitro PDE4 inhibitor activity of a novel series of imidazol-2-one and 2-cyanoiminoimidazole derivatives are described. The ani-inflammatory activity after topical application of some selected compounds as well as the gastro-intestinal side effects were also evaluated in in vivo models. Some of the 2-cyanoiminoimidazoles showed potent PDE4 inhibitor activity and less side effects than reference compounds.

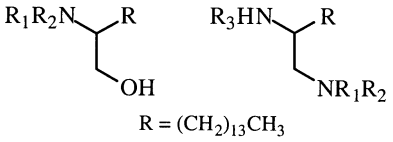
Bioorg. Med. Chem. Lett. 12 (2002) 659

Leishmanicidal Activity of Some Aliphatic Diamines and Amino-Alcohols

Esther del Olmo,[a,*] Mario Alves,[a] José L. López,[a] Alba Inchaustti,[b] Gloria Yaluff,[b] Antonieta Rojas de Arias[b,*] and Arturo San Feliciano[a]

[a]*Departamento de Química Farmacéutica, Facultad de Farmacia, Univ. de Salamanca, 37007 Salamanca, Spain*
[b]*Instituto de Investigaciones en Ciencias de la Salud (IICS), Univ. Nacional de Asunción, Paraguay*

Some aliphatic diamine and amino-alcohols and related alkyl, acyl and carbamoyl derivatives have been synthesised and tested in vitro on cultures of cutaneous, muco-cutaneous and visceral strains of *Leishmania* spp.



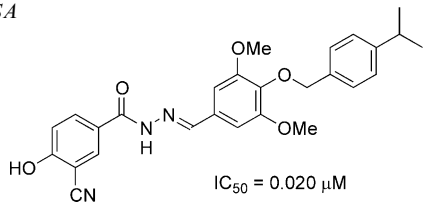
Bioorg. Med. Chem. Lett. 12 (2002) 663

Human Glucagon Receptor Antagonists Based on Alkylidene Hydrazides

Anthony Ling,[a,*] Michael Plewe,[a] Javier Gonzalez,[a] Peter Madsen,[b] Christian K. Sams,[b] Jesper Lau,[b] Vlad Gregor,[c] Doug Murphy,[a] Kimberly Teston,[a] Atsuo Kuki,[a] Shenghua Shi,[a] Larry Truesdale,[a] Dan Kiel,[a] John May,[a] James Lakis,[a] Kenna Anderes,[a] Eugenia Iatsimirskaia,[a] Ulla G. Sidelmann,[b] Lotte B. Knudsen,[b] Christian L. Brand[b] and Alex Polinsky[a]

[a]*Pfizer Global Research and Development, 10770 Science Center Dr., San Diego, CA 92121, USA*
[b]*Novo Nordisk, Novo Nordisk Park, 2760 Maaloev, Denmark*
[c]*Anadys Pharmaceuticals Inc., 9050 Camino Santa Fe, San Diego, CA 92121, USA*

Further optimization of a series of alkylidene hydrazides having affinity for the human glucagon receptor, representative in vitro metabolism, and pharmacodynamic results are described.



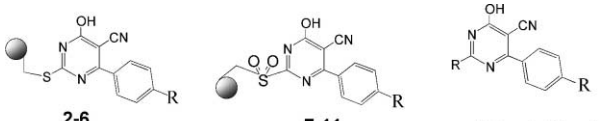
Bioorg. Med. Chem. Lett. 12 (2002) 667

Syntheses of Novel Antimycobacterial Combinatorial Libraries of Structurally Diverse Substituted Pyrimidines by Three-Component Solid-Phase Reactions

Arun Kumar,[a] Sudhir Sinha[b] and Prem M. S. Chauhan[a,*]

[a]*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226001, U.P., India*
[b]*Biochemistry Division, Central Drug Research Institute, Lucknow-226001, U.P., India*

A library of 80 new pyrimidine based scaffolds has been developed by three-component solid-phase syntheses. Six compounds, **12i**, **13c**, **14d**, **14e**, **14o**, and **15d** have shown in vitro activity against *Mycobacterium tuberculosis* (MABA) at a concentration of 50 and 25 μg/mL.

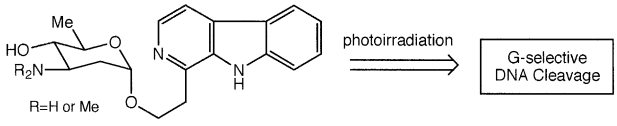


Bioorg. Med. Chem. Lett. 12 (2002) 671

β-Carboline–Carbohydrate Hybrids: Molecular Design, Chemical Synthesis and Evaluation of Novel DNA Photocleavers

Kazunobu Toshima,* Yukiko Okuno, Yoko Nakajima and Shuichi Matsumura

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

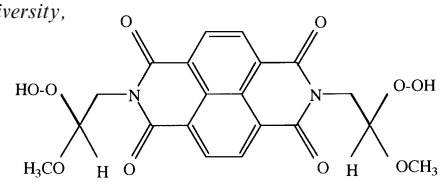


Bioorg. Med. Chem. Lett. 12 (2002) 675

Induction of Apoptosis in HL-60 Cells by Photochemically Generated Hydroxyl Radicals

Sakiko Haruna,[a] Rie Kuroi,[a] Kazumi Kajiwara,[a] Ryoko Hashimoto,[a] Seiichi Matsugo,[b] Sadako Tokumaru[c] and Shosuke Kojo[a,*]

[a]*Department of Food Science and Nutrition, Nara Women's University, Nara 630-8506, Japan*
[b]*Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Yamanashi University, Yamanashi 400-8511, Japan*
[c]*Department of Life and Health Sciences, Joetsu University of Education, Joetsu, Niigata 943-8512, Japan*



NP-III

Hydroxyl radicals generated selectively by photolysis of a photo-Fenton reagent, *N*,*N*′-bis(2-hydroperoxy-2-methoxyethyl)-1,4,5,8-naphthaldiimide (NP-III), induce apoptosis in HL-60 (human promyelocytic leukemia) cells involving the activation of caspase-3.

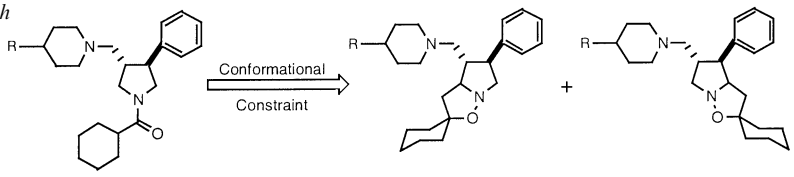
NP-III + hν→·OH→HL-60 cells→Activation of caspase-3→Apoptosis.

Bioorg. Med. Chem. Lett. 12 (2002) 677

CCR5 Antagonists: Bicyclic Isoxazolidines as Conformationally Constrained *N*-1-Substituted Pyrrolidines

Christopher L. Lynch,[a,*] Amy L. Gentry,[a] Jeffrey J. Hale,[a] Sander G. Mills,[a] Malcolm MacCoss,[a] Lorraine Malkowitz,[b] Martin S. Springer,[b] Sandra L. Gould,[b] Julie A. DeMartino,[b] Salvatore J. Siciliano,[b] Margaret A. Cascieri,[b] George Doss,[c] Anthony Carella,[d] Gwen Carver,[d] Karen Holmes,[d] William A. Schleif,[d] Renee Danzeisen,[d] Daria Hazuda,[d] Joseph Kessler,[d] Janet Lineberger,[d] Michael Miller[d] and Emilio A. Emini[d]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Immunology Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism-NMR Spectroscopy, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[d]*Department of Antiviral Research, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*



Bioorg. Med. Chem. Lett. 12 (2002) 681

An Additional 2′-Ribofuranose Residue at a Specific Position of the DNA Primer Prevents Its Elongation by HIV-1 Reverse Transcriptase

O. I. Andreeva,[a] A. S. Golubeva,[a] S. N. Kochetkov,[a] A. Van Aerschot,[b] P. Herdewijn,[b] E. V. Efimtseva,[a] B. S. Ermolinsky[a] and S. N. Mikhailov[a,*]

[a]*Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Vavilov str. 32, Moscow 119991, Russia*
[b]*Rega Institute, Katholieke Universiteit Leuven, Minderbroedersstraat, B-3000 Leuven, Belgium*

5′-dGXC-GTT-GTX-XXX-CG-3′ (X = dAdo or 2′-*O*-β-D-ribofuranosyladenosine residues) were prepared and used as modified primers in DNA synthesis reaction catalyzing by HIV RT on RNA template.

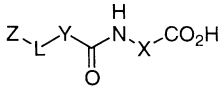
Bioorg. Med. Chem. Lett. 12 (2002) 685

Identification of Unique VLA-4 Antagonists from a Combinatorial Library

Stephen E. de Laszlo,[a] Bing Li,[a] Ermengilda McCauley,[b] Gail Van Riper,[b] and William K. Hagmann[a,*]

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

A combinatorial library of 28 pools of 180 compounds (345 diastereomers) was designed and prepared in support of the delineation of the SAR of two prototypical VLA-4 antagonists. Deconvolution of the active pools led to the identification of three novel series of VLA-4 antagonists with low nanomolar potencies.



Z = alkyl, aryl, aralkyl
L = -NH(C=O)-, -SO_2-, -C(=O)-
Y, X = amino acids

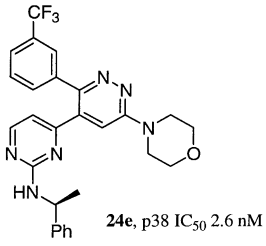
Bioorg. Med. Chem. Lett. 12 (2002) 689

Pyridazine Based Inhibitors of p38 MAPK

Charles J. McIntyre,[a,*] Gerald S. Ponticello,[a] Nigel J. Liverton,[a] Stephen J. O'Keefe,[b] Edward A. O'Neill,[b] Margaret Pang,[b] Cheryl D. Schwartz[b] and David A. Claremon[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Inflammation Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

Trisubstituted pyridazines were synthesized and evaluated as in vitro inhibitors of p38 MAPK.



24e, p38 IC_{50} 2.6 nM

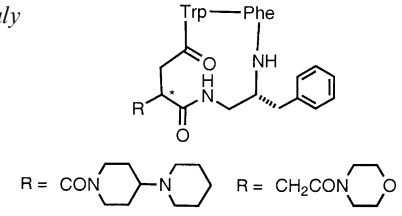
Bioorg. Med. Chem. Lett. 12 (2002) 693

Insertion of 2-Carboxysuccinate and Tricarballylic Acid Fragments into Cyclic-Pseudopeptides: New Antagonists for the Human Tachykinin NK-2 Receptor

Nicholas J.S. Harmat,* Danilo Giannotti, Rossano Nannicini, Enzo Perrotta, Marco Criscuoli, Riccardo Patacchini, Anna-Rita Renzetti, Sandro Giuliani, Maria Altamura and Carlo A. Maggi

Menarini Ricerche S.p.A. Laboratori di Firenze, Via Rismondo 12/A, 50131 Firenze, Italy

The sequence-Trp-Phe-(D)PheΨCH_2NH- was bound at its terminal ends with either 2-carboxy succinate or enantiomerically enriched tricarballylic acid (TCA) to give cyclic pseudo-peptides which were active h-NK2 receptor antagonists. The best activity was given by one isolated epimer in the 2-carboxy succinate series by the 4-piperidinyl piperidinoyl derivatve **8e**, and in the TCA series by the morpholinoyl derivative **12d**.



8e **12d**

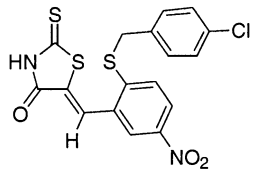
Bioorg. Med. Chem. Lett. 12 (2002) 697

Benzylidene Rhodanines as Novel Inhibitors of UDP-*N*-Acetylmuramate/L-Alanine Ligase

Mui Mui Sim,[a,*] Siew Bee Ng,[b] Antony David Buss,[b] Sharon Carmelita Crasta,[b] Kah Lin Goh[b] and Sue Kim Lee[b]

[a]*Medicinal and Combinatorial Chemistry Laboratory, Institute of Molecular and Cell Biology, 30 Medical Drive, Singapore 117609, Singapore*
[b]*Center for Natural Product Research, Institute of Molecular and Cell Biology, 30 Medical Drive, Singapore 117609, Singapore*

Benzylidene rhodanine **1** inhibits MurC (IC_{50} = 27 μM) and shows whole-cell activity against MRSA (MIC = 31 μM).



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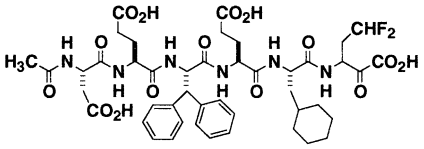
Bioorg. Med. Chem. Lett. 12 (2002) 701

A Designed P_1 Cysteine Mimetic for Covalent and Non-Covalent Inhibitors of HCV NS3 Protease

Frank Narjes,[a,*] Konrad F. Koehler,[a] Uwe Koch,[a] Benjamin Gerlach,[a] Stefania Colarusso,[a] Christian Steinkühler,[b] Mirko Brunetti,[b] Sergio Altamura,[b] Raffaele De Francesco[b] and Victor G. Matassa[a]

[a]*Department of Chemistry, IRBM, MRL Rome, Via Pontina Km 30.600, Pomezia, 00040 Rome, Italy*
[b]*Department of Biochemistry, IRBM, MRL Rome, Via Pontina Km 30.600, Pomezia, 00040 Rome, Italy*

The difluoromethyl group was designed by computational chemistry methods as a mimetic of the canonical P_1 cysteine thiol for inhibitors of the hepatitis C virus serine protease. This modification led to the development of competitive covalent inhibitor **8**.



8 $K_i^* = 10$ pM

Bioorg. Med. Chem. Lett. 12 (2002) 705

Evolution, Synthesis and SAR of Tripeptide α-Ketoacid Inhibitors of the Hepatitis C Virus NS3/NS4A Serine Protease

Stefania Colarusso, Benjamin Gerlach, Uwe Koch, Ester Muraglia, Immacolata Conte, Ian Stansfield, Victor G. Matassa and Frank Narjes*

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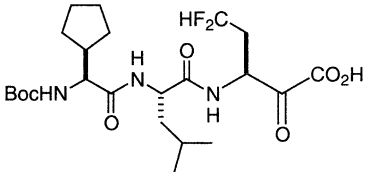
N-Terminal truncation of a hexapeptide ketoacid gave rise to potent tripeptide inhibitors of the hepatitis C virus NS3 protease/NS4A cofactor complex. Optimization of these tripeptides led to ketoacid **30**.



30 $IC_{50} = 0.38$ μM

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New Indene-Derivatives with Anti-Proliferative Properties

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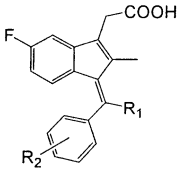
The synthesis and the biological evaluation of new indene derivatives derived from the Sulindac structure are reported.



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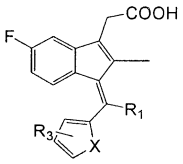

II

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Meiosis Activating Sterols Derived from Diosgenin

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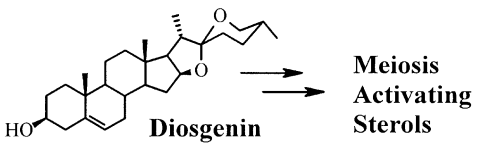
The synthesis and in vitro meiosis promoting activity of a series of sterols based on the initial lead FF-MAS is reported using Diosgenin as a starting material.



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Synthesis and Cytotoxicity of 3,4-Diaryl-2(5*H*)-furanones

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A series of 3,4-diaryl-2(5*H*)-furanone derivatives were synthesized and evaluated for their cytotoxicity in a small panel of cancer cell lines. Four out of 10 compounds in this series, for example 3-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-, 3-(3,4,5-trimethoxyphenyl)-4-(3-hydroxy-4-methoxyphenyl)-, 3-(3,4,5-trimethoxyphenyl)-4-(3-amino-4-methoxyphenyl)-, and 3-(3,4,5-trimeoxy-phenyl)-4-(2-naphthyl)-2(5*H*)-furanones, were found to have potent cytotoxic activities with ED_{50} values of less than 20 nM in most of the cell lines tested.