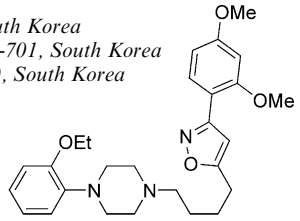
Bioorg. Med. Chem. Lett. 12 (2002) 1327

Design and Synthesis of a Piperazinylalkylisoxazole Library for Subtype Selective Dopamine Receptor Ligands

Mi Young Cha,[a] Byung Chul Choi,[a] Kyung Ho Kang,[b] Ae Nim Pae,[a] Kung Il Choi,[a] Yong Seo Cho,[a] Hun Yeong Koh,[a,*] Hee-Yoon Lee,[b,*] Daeyoung Jung[c] and Jae Yang Kong[c]

[a]*Biochemicals Research Center, Korea Institute of Science and Technology, Cheongrayang, Seoul 130-650, South Korea*
[b]*CMDS, Department of Chemistry (BK21), Korea Advanced Institute of Science and Technology, Daejon 305-701, South Korea*
[c]*Pharmaceutical Screening Research Team, Korea Research Institute of Chemical Technology, Daejon 305-600, South Korea*

A piperazinylbutylisoxazole libary was designed, synthesized and screened for the binding affinities to dopamine D_2, D_3, and D_4 receptors. Several ligands were identified to possess high binding affinity and selectivity for the D_3 and D_4 receptors over the D_2 receptor. Compounds **6s** and **6t** showed K_i values of 2.6 nM and 3.9 nM for the D_3 receptor with 46- and 50-fold selectivity over the D_2 receptor, respectively.



K_i = 2.6 nM

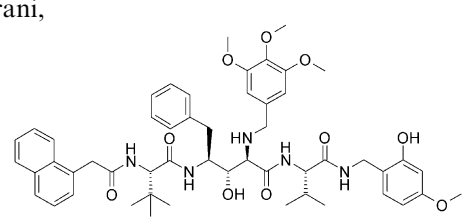
Bioorg. Med. Chem. Lett. 12 (2002) 1331

Structure-Based Optimisation of 2-Aminobenzylstatine Derivatives: Potent and Selective Inhibitors of the Chymotrypsin-Like Activity of the Human 20*S* Proteasome

Pascal Furet,* Patricia Imbach,* Peter Fuerst, Marc Lang, Maria Noorani, Johann Zimmermann and Carlos García-Echeverría*

Oncology Research, Novartis Pharma Inc., CH-4002 Basel, Switzerland

The optimisation of 2-aminobenzylstatine derivatives as non-covalent inhibitors of the chymotryspin-like activity of the 20*S* proteasome is described (e.g., compound **18**, $IC_{50} = 7$ nM).



Compound **18**

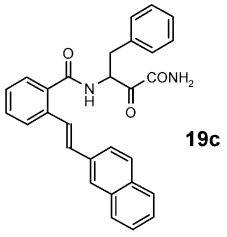
Bioorg. Med. Chem. Lett. 12 (2002) 1335

Discovery of Phenyl Alanine Derived Ketoamides Carrying Benzoyl Residues as Novel Calpain Inhibitors

W. Lubisch* and A. Möller

Department of CNS Discovery Research, Abbott GmbH&Co. KG, PO Box 210805, 67008 Ludwigshafen, Germany

Novel calpain inhibitors derived from phenyl alanine aldehydes or ketoamides carrying a benzoyl residue were prepared and evaluated for their biological potency. A brief structure–activity relationship elucidated the importance of *ortho*-substitutents in the benzoyl moiety. The most potent derivative, the ketoamide **19c**, exhibited a K_i of 6 nM and represents a novel class of reversible, highly potent and non-peptidic calpain inhibitors.



19c

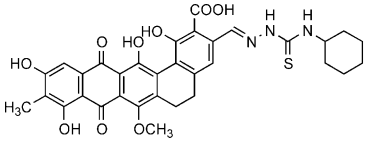
Bioorg. Med. Chem. Lett. 12 (2002) 1339

A Novel Type of Nonsteroidal Estrone Sulfatase Inhibitors

Peter Jütten,* Winfried Schumann, Albert Härtl, Lothar Heinisch, Udo Gräfe,* Walter Werner and Hermann Ulbricht

Hans-Knöll Institute of Natural Products Research, Beutenbergstrasse 1, 07745 Jena, Germany

The cyclohexyl thiosemicarbazone of the natural product madurahydroxylactone is a potent nonsteroidal inhibitor of estrone sulfatase. The compound is devoid of estrogenic properties and shows low acute toxicity.



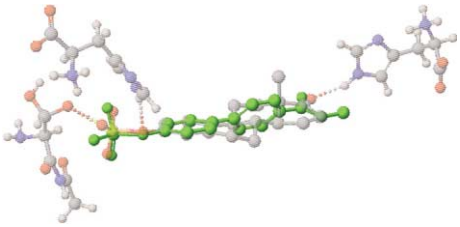
Bioorg. Med. Chem. Lett. 12 (2002) 1343

Design, Synthesis and Biochemical Evaluation of AC Ring Mimics as Novel Inhibitors of the Enzyme Estrone Sulfatase (ES)

Sabbir Ahmed,[a,*] Karen James,[b] Caroline P. Owen[a] and Chirag K. Patel[a]

[a]*School of Chemical and Pharmaceutical Sciences, Kingston University, Penrhyn Road, Kingston upon Thames, Surrey KT1 2EE, UK*
[b]*Institute of Cancer Research, Sutton, UK*

The synthesis and biochemical evaluation of novel inhibitors (as mimics of the AC rings of the steroid backbone) of estrone sulfatase is reported.



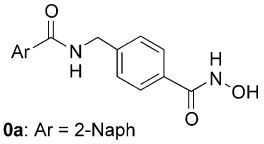
Bioorg. Med. Chem. Lett. 12 (2002) 1347

Novel Histone Deacetylase Inhibitors: *N*-Hydroxycarboxamides Possessing a Terminal Bicyclic Aryl Group

Shinichi Uesato,[a,*] Manabu Kitagawa,[a] Yasuo Nagaoka,[a] Taishi Maeda,[a] Hiroshi Kuwajima[b] and Takao Yamori[c]

[a]*Department of Biotechnology, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan*
[b]*Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashiosaka, Osaka 577-8502, Japan*
[c]*Division of Experimental Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Kamiikebukuro 1-37-1, Toshima-ku, Tokyo 170-8455, Japan*

Synthesis of the promising histone deacetylase inhibitors including **10a** and **10e** is reported. The terminal bicyclic aryl amide groups of these compounds played an important role in increment of their inhibitory activities.



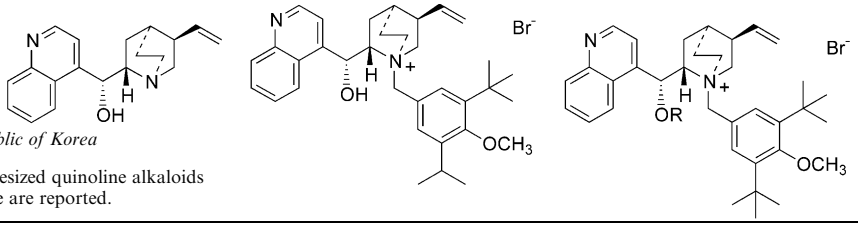
10a: Ar = 2-Naph
10e: Ar = 6-amino-2-Naph

Bioorg. Med. Chem. Lett. 12 (2002) 1351

Synthesis and Evaluation of New Antimalarial Analogues of Quinoline Alkaloids Derived from *Cinchona ledgeriana* Moens ex Trimen

Byeoung-Soo Park,[a] Dae-Young Kim,[b] Philip J. Rosenthal,[c] Sun-Chul Huh,[a] Belinda J. Lee,[c] Eun-Ju Park,[b] Sung-Min Kim,[b] Jang-Eok Kim,[d] Mi-Hee Kim,[b] Tae-Lin Huh,[e] Young-Jae Choi,[b] Ki-Hyung Suh,[b] Won-Sik Choi[a] and Sung-Eun Lee[d,*]

[a]*Department of Life Sciences, Soonchunhyang University, Asan-si, Chungnam 336-600, Republic of Korea*
[b]*Department of Chemistry, Soonchunhyang University, Asan-si, Chungnam 336-600, Republic of Korea*
[c]*Department of Medicine, University of California, San Francisco, CA 94143, USA*
[d]*Department of Agricultural Chemistry, Kyungpook National University, Taegu 702-701, Republic of Korea*
[e]*TG Biotech Institute, 603 Technopark B/D, Kyungpook National University, Taegu 702-701, Republic of Korea*



The in vitro antimalarial activities of a series of synthesized quinoline alkaloids from cinchonidine, cinchonine, quinidine, and quinine are reported.

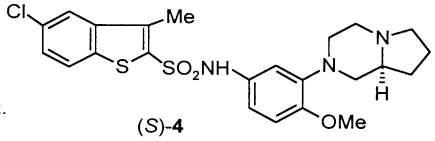
Bioorg. Med. Chem. Lett. 12 (2002) 1357

Bicyclic Piperazinylbenzenesulphonamides are Potent and Selective 5-HT$_6$ Receptor Antagonists

Steven M. Bromidge,[a] Stephen E. Clarke,[b] Frank D. King,[c] Peter J. Lovell,[a] Helen Newman,[d] Graham Riley,[d] Carol Routledge,[a] Halina T. Serafinowska,[a,*] Douglas R. Smith[b] and David R. Thomas[b]

[a]*Department of Psychiatry, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[b]*Department of Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[c]*Department of Neurology, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[d]*Department of Discovery Research, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*

The synthesis of novel conformationally restricted bicyclic piperazinylsulphonamides is described. (*S*)-3-(Hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)-4-methoxyphenyl-2-benzo[*b*]thiophene sulphonamide (*S*)-**4** has been identified as a selective, high affinity 5-HT$_6$ antagonist.



(*S*)-**4**

Bioorg. Med. Chem. Lett. 12 (2002) 1361

Discovery and Initial SAR of Imidazoquinoxalines as Inhibitors of the Src-Family Kinase P56^{Lck}

Ping Chen,[a,*] Derek Norris,[a] Edwin J. Iwanowicz,[a] Steven H. Spergel,[a] James Lin,[a] Henry H. Gu,[a] Zhongqi Shen,[a] John Wityak,[a] Tai-An Lin,[d] Suhong Pang,[d] Henry F. De Fex,[d] Sidney Pitt,[d] Ding Ren Shen,[d] Arthur M. Doweyko,[c] Donna A. Bassolino,[c] Jacques Y. Roberge,[b] Michael A. Poss,[b] Bang-Chi Chen,[a] Gary L. Schieven[d] and Joel C. Barrish[a]

[a]*Department of Discovery Chemistry, Bristol Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*
[b]*Department of Early Discovery Chemistry, Bristol Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*
[c]*Department of Computer Aided Drug Design, Bristol Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*
[d]*Department of Immunology, Inflammation and Pulmonary Drug Discovery, Bristol Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*

We have identified a novel series of 1,5-imidazoquinoxalines as inhibitors of Lck with excellent potency (IC_{50}s < 5 nM) as well as good cellular activity against T-cell proliferation (IC_{50}s < 1 μM). Structure–activity studies demonstrate the requirement for the core heterocycle in addition to an optimal 2,6-disubstituted aniline group.

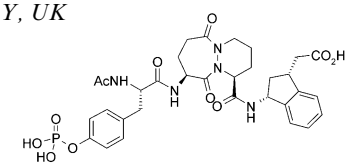
Bioorg. Med. Chem. Lett. 12 (2002) 1365

Structure-Based Design of Peptidomimetic Antagonists of P56^{lck} SH2 Domain

Christopher J. Hobbs,[a,*] Rino A. Bit,[a] Andrew D. Cansfield,[a] Bill Harris,[a] Christopher H. Hill,[a] Katherine L. Hilyard,[a] Ian R. Kilford,[a] Eric Kitas,[b] Antonin Kroehn,[a] Peter Lovell,[a] David Pole,[a] Paul Rugman,[a] Brad S. Sherborne,[a] Ian E. D. Smith,[a] David R. Vesey,[a] D. Lee Walmsley,[a] David Whittaker,[a] Glyn Williams,[a] Fiona Wilson,[a] David Banner,[b] Allan Surgenor[a] and Neera Borkakoti[a]

[a]*Roche Products Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, UK*
[b]*F. Hoffmann-La Roche Ltd, Pharma Division, Preclinical Research, Basel, Switzerland*

The SAR of a novel class of p56^{lck} SH2 domain antagonists is described.



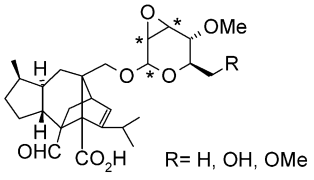
Bioorg. Med. Chem. Lett. 12 (2002) 1371

Antifungal Sordarins. Part 3: Synthesis and Structure–Activity Relationships of 2′,3′-Fused Oxirane Derivatives

Julia Castro, Juan C. Cuevas,* José M[a]. Fiandor, M[a] Teresa Fraile, Federico Gómez de las Heras and José R. Ruiz

GlaxoSmithKline, Research Department, Parque Tecnológico de Madrid, Severo Ochoa, 2. 28760 Tres Cantos, Madrid, Spain

A number of new 2′,3′-fused oxirane and thiirane sordarin derivatives were synthesized. Antifungal activity is reported.



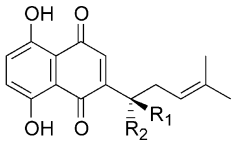
Bioorg. Med. Chem. Lett. 12 (2002) 1375

Shikonin Derivatives: Synthesis and Inhibition of Human Telomerase

Qun Lu, Weijun Liu, Jian Ding, Junchao Cai and Wenhu Duan*

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Science, Shanghai 200031, PR China

We synthesized DL-shikonin, shikonin, alkanin, and their cyclo-derivatives and acyl-derivatives. These compounds have low cytotoxicity, as well as inhibitory activity against the telomerase enzyme, except cyclo-derivatives.



1. R_1=OH, R_2=H
2. R_1=H, R_2=OH

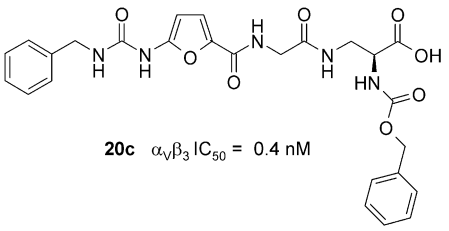
Bioorg. Med. Chem. Lett. 12 (2002) 1379

Synthesis of Highly Potent and Selective Hetaryl Ureas as Integrin $\alpha_V\beta_3$-Receptor Antagonists

Udo E. W. Lange,[a,*] Gisela Backfisch,[b] Jürgen Delzer,[b] Hervé Geneste,[b] Claudia Graef,[a] Wilfried Hornberger,[b] Andreas Kling,[b,*] Arnulf Lauterbach,[a] Thomas Subkowski[a] and Christian Zechel[a]

[a]*BASF AG, D-67056 Ludwigshafen, Germany*
[b]*Abbott GmbH & Co. KG, D-67008 Ludwigshafen, Germany*

SAR and solid-phase synthesis of integrin $\alpha_V\beta_3$-receptor antagonists are presented. Efficacy for selected compounds in functional cellular assays is demonstrated.



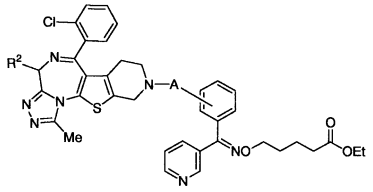
Bioorg. Med. Chem. Lett. 12 (2002) 1383

Syntheses and Bioactivities of Novel Carbamates Combining Platelet Activating Factor (PAF) Receptor Antagonist with Thromboxane Synthase Inhibitor (TxSI)

Masakazu Fujita* and Taketsugu Seki

Omiya Research Laboratory, Nikken Chemicals Co., Ltd., 1-346, Kitabukuro-cho, Saitama-shi, Saitama 330-0835, Japan

Synthesis of carbamates **3b** which possess dual-acting PAF antagonist/TxSI using unstable esters **1**, diazepines **2**, K_2CO_3 and 18-crown-6 is described.



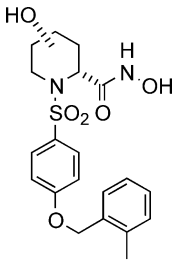
Bioorg. Med. Chem. Lett. 12 (2002) 1387

Synthesis and Biological Activity of Selective Pipecolic Acid-Based TNF-α Converting Enzyme (TACE) Inhibitors

Michael A. Letavic,* Matt Z. Axt, John T. Barberia, Thomas J. Carty, Dennis E. Danley, Kieran F. Geoghegan, Nadia S. Halim, Lise R. Hoth, Ajith V. Kamath, Ellen R. Laird, Lori L. Lopresti-Morrow, Kim F. McClure, Peter G. Mitchell, Vijayalakshmi Natarajan, Mark C. Noe, Jayvardhan Pandit, Lisa Reeves, Gayle K. Schulte, Sheri L. Snow, Francis J. Sweeney, Douglas H. Tan and Chul H. Yu

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

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



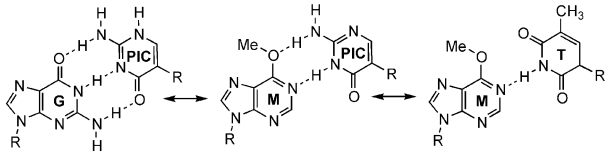
Bioorg. Med. Chem. Lett. 12 (2002) 1391

A Unique Unnatural Base Pair Between a C Analogue, Pseudoisocytosine, and an A Analogue, 6-Methoxypurine, in Replication

Ichiro Hirao,[a,*] Michiko Kimoto,[b,c] Shun-ichi Yamakage,[a] Masahide Ishikawa,[a] Jun Kikuchi[a] and Shigeyuki Yokoyama[a,b,c,*]

[a]*Yokoyama CytoLogic Project, ERATO, JST and RIKEN Genomic Sciences Center, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan*
[b]*RIKEN Harima Institute, 1-1-1 Khoto, Mikazuki-cho, Sayo, Hyogo 679-5148, Japan*
[c]*Department of Biophysics and Biochemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

The interconversion between the G•C and A•T pairs through the unnatural M•PIC pair.



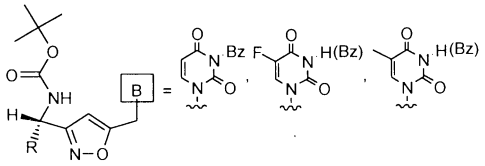
Bioorg. Med. Chem. Lett. 12 (2002) 1395

Heterocyclic Nucleoside Analogues: Design and Synthesis of Antiviral, Modified Nucleosides Containing Isoxazole Heterocycles

Yoon-Suk Lee and Byeang Hyean Kim*

National Research Laboratory, Department of Chemistry, Center for Integrated Molecular Systems, Division of Molecular and Life Sciences, Pohang University of Science and Technology, Pohang 790-784, South Korea

Novel antiviral nucleosides analogues, which consist of isoxazole rings as modified sugars and nucleobases with a methylene linker between them, have been designed, synthesized, and bioassayed.



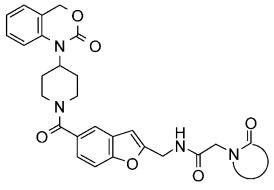
Bioorg. Med. Chem. Lett. 12 (2002) 1399

Identification of Potent and Selective Oxytocin Antagonists. Part 1: Indole and Benzofuran Derivatives

Paul G. Wyatt,[a] Michael J. Allen,[b] Josie Chilcott,[c] Alison Foster,[a] David G. Livermore,[a] Jackie E. Mordaunt,[a,*] Jan Scicinski[a] and Patrick M. Woollard[c]

[a]*Department of Medicinal Chemistry, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK.* [b]*Department of Receptor Pharmacology, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK.* [c]*Department of Research Biometabolism, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

Studies to discover novel, potent and selective oxytocin antagonists are reported. Combinatorial libraries, identified pyrimidine, thiazole, indole and benzofuran as potential alternatives to the benzoic acid moiety of L-371,257. Additional investigations identified indole and benzofuran derivatives with potent oxytocin antagonist activity.



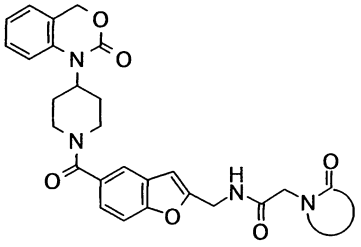
Bioorg. Med. Chem. Lett. 12 (2002) 1405

Identification of Potent and Selective Oxytocin Antagonists. Part 2: Further Investigation of Benzofuran Derivatives

Paul G. Wyatt,[a,*] Michael J. Allen,[b] Josie Chilcott,[c] Christopher J. Gardner,[d] David G. Livermore,[a] Jackie E. Mordaunt,[a,*] Fabrizio Nerozzi,[a] Mamta Patel,[a] Marion J. Perren,[d] Gordon G. Weingarten,[a] Shalia Shabbir,[c] Patrick M. Woollard[c] and Ping Zhou[c]

[a]*Department of Medicinal Chemistry, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*
[b]*Department of Receptor Pharmacology, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*
[c]*Department of Research Biometabolism, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*
[d]*Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*

Further benzofuran derivatives with potent oxytocin antagonist activity and good pharmacokinetic parameters are reported. Efforts to improve the in vivo activity of the series are described.



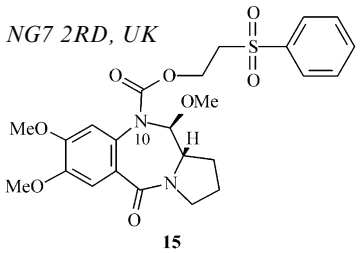
Bioorg. Med. Chem. Lett. 12 (2002) 1413

Synthesis and Biological Evaluation of an N10-Psec Substituted Pyrrolo[2,1-*c*][1,4]benzodiazepine Prodrug

Jane M. Berry,[a] Philip W. Howard,[a,*] Lloyd R. Kelland[b] and David E. Thurston[a,*]

[a]*CRUK Gene Targeted Drug Design Research Group, Cancer Research Laboratories, School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[b]*CRUK Centre for Cancer Therapeutics, Institute for Cancer Research, Clifton Avenue, Sutton, Surrey SM2 5PX, UK*

The first example of an N10-protected (e.g., Psec, **15**) pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) analogue that retains significant cytotoxicity in a number of tumour cell lines is reported. This prototype could lead to a new generation of clinically useful N10-protected PBD prodrugs.



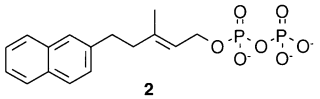
15

Bioorg. Med. Chem. Lett. 12 (2002) 1417

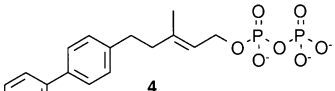
Aromatic Farnesyl Diphosphate Analogues: Vinyl Triflate-Mediated Synthesis and Preliminary Enzymatic Evaluation

Chunmei Zhou, Ying Shao and Richard A. Gibbs*

Department of Pharmaceutical Sciences, College of Pharmacy and AHP, Wayne State University, Detroit, MI 48202, USA



2
FTase Inhibitor



4
FTase Substrate

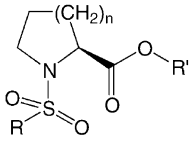
Bioorg. Med. Chem. Lett. 12 (2002) 1421

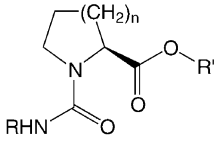
Use of Parallel-Synthesis Combinatorial Libraries for Rapid Identification of Potent FKBP12 Inhibitors

Chi Choi, Jia-He Li, Mark Vaal, Christine Thomas, David Limburg, Yong-Qian Wu,* Yi Chen, Raj Soni, Chad Scott, Douglas T. Ross, Hong Guo, Pamela Howorth, Heather Valentine, Shi Liang, Dawn Spicer, Mike Fuller, Joseph Steiner and Gregory S. Hamilton

Guilford Pharmaceuticals Inc., Research Department, 6611 Tributary Street, Baltimore, MD 21224, USA

Using simple, inexpensive equipment, we have used solution-phase, parallel synthesis to rapidly prepare hundreds of sulfonamide- and urea-containing FKBP inhibitors, resulting in rapid identification of extremely potent compounds in these series.





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Solid-Phase Synthesis of FKBP12 Inhibitors: *N*-Sulfonyl and *N*-Carbamoylprolyl/pipecolyl Amides

Ling Wei, Yong-Qian Wu,* Douglas E. Wilkinson, Yi Chen, Raj Soni, Chad Scott, Douglas T. Ross, Hong Guo, Pamela Howorth, Heather Valentine, Shi Liang, Dawn Spicer, Mike Fuller, Joseph Steiner and Gregory S. Hamilton

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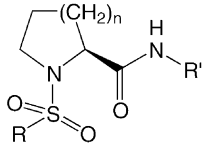
In parallel with our work on solution-phase parallel synthesis of ligands for the rotamase enzyme FKBP12, we herein report a methodology for the solid-phase synthesis of two classes of inhibitor, *N*-sulfonyl and *N*-carbamoylprolyl and pipecolyl amides along with their in vitro/in vivo biological results.



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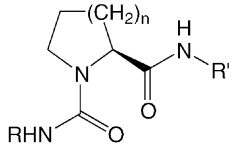

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