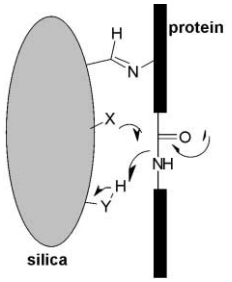
Bioorg. Med. Chem. Lett. 12 (2002) 3247

Effective Artificial Proteases Synthesized by Covering Silica Gel with Aldehyde and Various Other Organic Groups

Hyunsook Kim,[a] Myoung-soon Kim,[a] Hyesun Paik,[a] Yeon-Sook Chung,[a] In Seok Hong[b] and Junghun Suh[a,*]

[a]*School of Chemistry and Center for Molecular Catalysis, Seoul National University, Seoul 151-747, Republic of Korea*
[b]*Artzyme Biotech Corporation, 403-1, Silim-2-Dong, Seoul 151-012, Republic of Korea*

Organic artificial proteases with broad substrate specificity were synthesized by covering silica gel with aldehyde and functional groups present in amino acids.



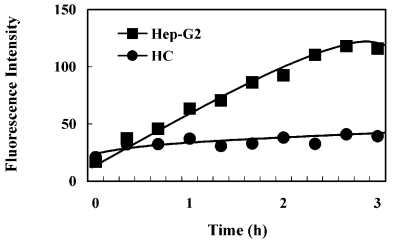
Bioorg. Med. Chem. Lett. 12 (2002) 3251

Specific Accumulation and Growth Inhibitory Effects of Hybrid Liposomes to Hepatoma Cells In Vitro

Koji Nakano, Yasunori Iwamoto, Wataru Takata, Yoko Matsumoto and Ryuichi Ueoka*

Graduate School of Applied Chemistry, Sojo University, 4-22-1 Ikeda, Kumamoto 860-0082, Japan

Specific accumulation and growth inhibitory effects of hybrid liposomes were obtained in human hepatoma (Hep-G2) cells without affecting normal liver (HC) cells at all.



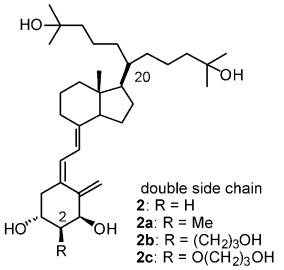
Bioorg. Med. Chem. Lett. 12 (2002) 3255

Synthesis and Testing of 2α-Modified 1α,25-Dihydroxyvitamin D_3 Analogues with a Double Side Chain: Marked Cell Differentiation Activity

Yoshitomo Suhara,[a] Atsushi Kittaka,[a] Seishi Kishimoto,[b] Martin J. Calverley,[c] Toshie Fujishima,[a] Nozomi Saito,[a] Takayuki Sugiura,[b] Keizo Waku[b] and Hiroaki Takayama[a,*]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan*
[b]*Department of Hygienic Chemistry and Nutrition, Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan*
[c]*Department of Medicinal Chemistry, LEO Pharma, DK-2750 Ballerup, Denmark*

New 1α,25-dihydroxyvitamin D_3 analogues **2a**–**c** with strong cell differentiation activity were synthesized.

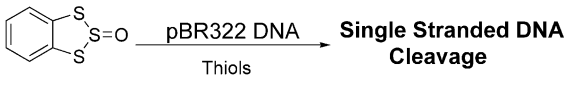


Bioorg. Med. Chem. Lett. 12 (2002) 3259

Benzotrithiole 2-Oxide: A New Family of Thiol-Activated DNA-Cleaving Functionalities

Alex H. F. Lee, Albert S. C. Chan and Tianhu Li*

Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong



1

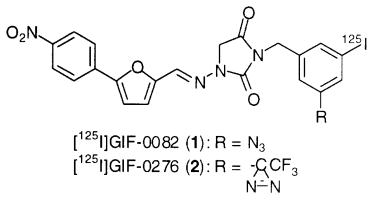
Bioorg. Med. Chem. Lett. 12 (2002) 3265

[^{125}I]-*N*-[(3-Azido-5-iodo)benzyl]dantrolene and [^{125}I]-*N*-{[3-Iodo-5-(3-trifluoromethyl-3*H*-diazirin-3-yl)]benzyl}dantrolene: Photoaffinity Probes Specific for the Physiological Ca^{2+} Release from Sarcoplasmic Reticulum of Skeletal Muscle

Takamitsu Hosoya,[a,b] Hiroshi Aoyama,[b] Takaaki Ikemoto,[c] Toshiyuki Hiramatsu,[b] Yasutaka Kihara,[c] Makoto Endo[c] and Masaaki Suzuki[a,b,*]

[a]*Division of Regeneration and Advanced Medical Science, Gifu University Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*
[b]*Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*
[c]*Department of Pharmacology, Saitama Medical School, Moroyama-machi, Saitama 350-0495, Japan*

Photoaffinity probes, **1** and **2**, specific for the physiological Ca^{2+} release from sarcoplasmic reticulum of skeletal muscle have been elaborated.



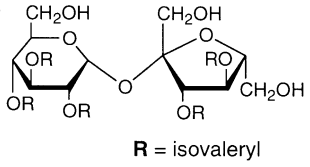
Bioorg. Med. Chem. Lett. 12 (2002) 3267

Facilely Accessible Multidrug Resistance Modulator Derived from Sucrose

Nobutoshi Murakami,[a] Satoru Tamura,[a] Etsuko Iwata,[a] Shunji Aoki,[a] Shin-ichi Akiyama[b] and Motomasa Kobayashi[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan*
[b]*Institute for Cancer Research, Faculty of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima, 890-8520, Japan*

Exploration for new MDR-modulators utilizing atractysucroses as scaffolds disclosed 2,3,4,3′,4′-*O*-pentaisovalerylsucrose as a readily accessible medicinal lead. This lead exhibited more potent MDR modulating activity than verapamil, a representative modulator of MDR mediated by P-gp.

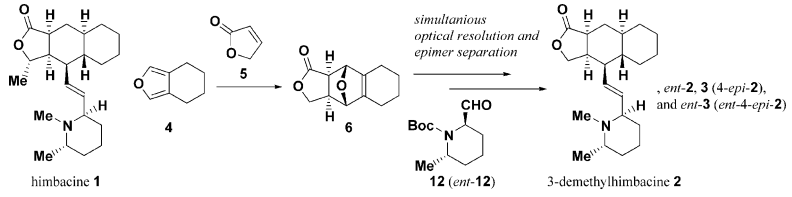


Bioorg. Med. Chem. Lett. 12 (2002) 3271

Synthesis and Muscarinic M_2 Subtype Antagonistic Activity of Enantiomeric Pairs of 3-Demethylhimbacine (3-Norhimbacine) and Its C_4-Epimer

Masanori Takadoi,[a,*] Kentaro Yamaguchi[b] and Shiro Terashima[c]

[a]*Discovery Research Laboratories, Kyorin Pharmaceutical Co. Ltd., 2399-1 Nogi, Nogi-machi, Tochigi 329-0114, Japan*
[b]*Chemical Analysis Center, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263-8522, Japan*
[c]*Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan*



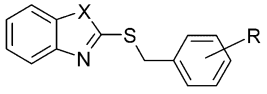
Bioorg. Med. Chem. Lett. 12 (2002) 3275

Heterocyclic Benzazole Derivatives with Antimycobacterial In Vitro Activity

Jan Kočí,[a] Věra Klimešová,[a,*] Karel Waisser,[a] Jarmila Kaustová,[b] Hans-Martin Dahse[c] and Ute Möllmann[c]

[a]*Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, 50005 Hradec Králové, Czech Republic*
[b]*National Reference Laboratory for Mycobacterium kansasii, Regional Institute of Hygiene, Partyzánské náměstí 7, 72892 Ostrava 1, Czech Republic*
[c]*Hans-Knöll-Institut für Naturstoff-Forschung, Beutenbergstr. 11, D-07745 Jena, Germany*

The synthesis and biological activities of benzazole derivatives are reported. The most active compounds are those that contain nitro/thioamide groups.

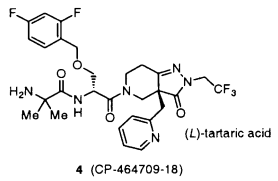


Bioorg. Med. Chem. Lett. 12 (2002) 3279

Discovery and Biological Characterization of Capromorelin Analogues with Extended Half-Lives

Philip A. Carpino,* Bruce A. Lefker, Steven M. Toler, Lydia C. Pan, John R. Hadcock, Marianne C. Murray, Ewell R. Cook, Joseph N. DiBrino, Shari L. DeNinno, Kristin L. Chidsey-Frink, William A. Hada, John Inthavongsay, Sharon K. Lewis, F. Michael Mangano, Michelle A. Mullins, David F. Nickerson, Oicheng Ng, Christine M. Pirie, John A. Ragan, Colin R. Rose, David A. Tess, Ann S. Wright, Li Yu, Michael P. Zawistoski, John C. Pettersen, Paul A. DaSilva-Jardine, Theresa C. Wilson and David D. Thompson

Pfizer Global Research & Development, Groton Labs, MS8220-3004, Eastern Point Rd, Groton, CT 06340, USA



4 (CP-464709-18)

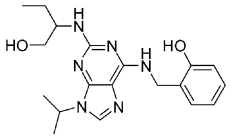
New longer-acting analogues of capromorelin, a dipeptide growth hormone secretagogue (GHS), are described, including **4**.

Bioorg. Med. Chem. Lett. 12 (2002) 3283

Synthesis and Biological Activity of Olomoucine II

Vladimír Kryštof,[a] René Lenobel,[a] Libor Havlíček,[b] Marek Kuzma[c] and Miroslav Strnad[a,*]

[a]*Laboratory of Growth Regulators, Palacký University and Institute of Experimental Botany, Šlechtitelů 11, 783 71 Olomouc, Czech Republic*
[b]*Isotope Laboratory, Institute of Experimental Botany, Czech Academy of Sciences, Vídeňská 1083, 14220 Prague 4, Czech Republic*
[c]*Institute of Microbiology, Czech Academy of Sciences, Vídeňská 1083, 14220 Prague 4, Czech Republic*



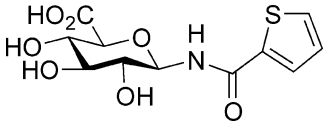
Novel purine derivative olomoucine II exceeds in vitro cytotoxicity of purvalanol A on CEM cell line (IC_{50} $\sim$3.0 μM).

Bioorg. Med. Chem. Lett. 12 (2002) 3287

Identification of Novel Inhibitors of Fibroblast Growth Factor (FGF-2) Binding to Heparin and Endothelial Cell Survival from a Structurally Diverse Carbohybrid Library

Paul V. Murphy,[a,*] Nigel Pitt,[a] Alan O'Brien,[a] Philomena M. Enright,[a] Amanda Dunne,[b] Stephen J. Wilson,[b] Rhona M. Duane[b] and Kathy M. O'Boyle[b,*]

[a]*Department of Chemistry, Centre for Synthesis and Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland*
[b]*Department of Pharmacology, Centre for Integrative Biology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland*



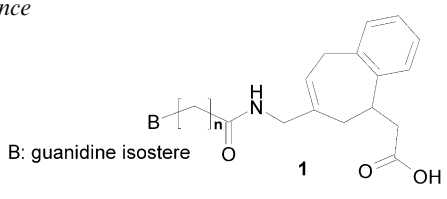
Bioorg. Med. Chem. Lett. 12 (2002) 3291

Substituted Benzocycloheptenes as Potent and Selective α_v Integrin Antagonists

Françoise Perron-Sierra,[a,*] Dominique Saint Dizier,[a] Marc Bertrand,[b] Annie Genton,[a] Gordon C. Tucker[a] and Patrick Casara[a,*]

[a]*Institut de Recherches Servier, 125 chemin de Ronde, 78290 Croissy sur Seine, France*
[b]*Technologie Servier, 25–27 rue E. Vignat, 45007 Orléans, France*

A novel series of potent and specific α_v integrin antagonists **1** has been obtained by aminoalkyl substitutions on benzocycloheptene acetic acids as a rigid GD bioisostere. The preferred compounds showed nano- to subnanomolar IC_{50} values on $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, with favorable pharmacokinetics.



1

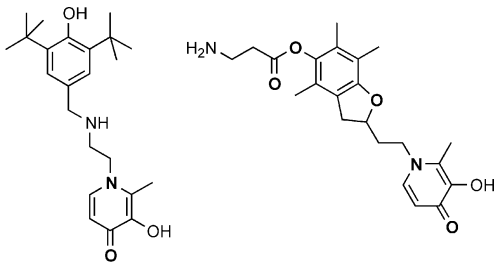
Bioorg. Med. Chem. Lett. 12 (2002) 3297

Prodrug and Covalent Linker Strategies for the Solubilization of Dual-Action Antioxidants/Iron Chelators

David Bebbington, Claire E. Dawson,* Suneel Gaur and John Spencer*

Department of Chemistry, Vernalis Research Limited, Oakdene Court, 613 Reading Road, Winnersh, Wokingham, RG41 5UA, UK

Water soluble prodrugs of hybrid antioxidant/iron chelating molecules have been prepared as well as related hybrid molecules containing a covalent poly(ethylene)glycol or an amine linker.



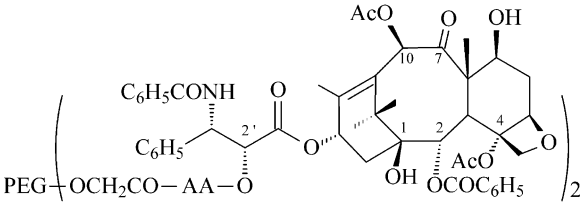
Bioorg. Med. Chem. Lett. 12 (2002) 3301

Synthesis and Evaluation of Water-Soluble Paclitaxel Prodrugs

Xia Feng, Ying-Jin Yuan* and Jin-Chuan Wu

Department of Pharmaceutical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, PR China

Water-soluble paclitaxel prodrugs were synthesized by attaching paclitaxel to PEG through amino acid spacers. The in vitro and in vivo activities of the prodrugs were evaluated in three tumor cell lines, Bcap-37 solid tumor-bearing xenografted mice and B16 melanoma mice.



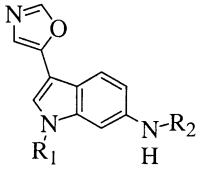
Bioorg. Med. Chem. Lett. 12 (2002) 3305

The TosMIC Approach to 3-(Oxazol-5-yl) Indoles: Application to the Synthesis of Indole Based IMPDH Inhibitors

T. G. Murali Dhar,* Zhongqi Shen, Catherine A. Fleener, Katherine A. Rouleau, Joel C. Barrish, Diane L. Hollenbaugh and Edwin J. Iwanowicz*

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

A modified approach to the synthesis of 3-(oxazolyl-5-yl) indoles is reported. This method was applied to the synthesis of series of novel indole based inhibitors of inosine monophosphate dehydrogenase (IMPDH).



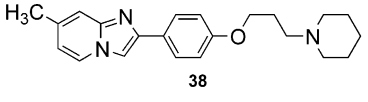
Bioorg. Med. Chem. Lett. 12 (2002) 3309

Novel Human Histamine H_3 Receptor Antagonists

Chandra Shah, Laura McAtee, J. Guy Breitenbucher, Dale Rudolph, Xiaobing Li, Timothy W. Lovenberg, Curt Mazur, Sandy J. Wilson and Nicholas I. Carruthers*

Johnson and Johnson Pharmaceutical Research and Development, L.L.C., 3210 Merryfield Row, San Diego, CA 92121, USA

High throughput screening, using the recombinant human H_3 receptor, was used to identify potent, selective, orally bioavailable, histamine H_3 receptor antagonists (e.g., **38**).



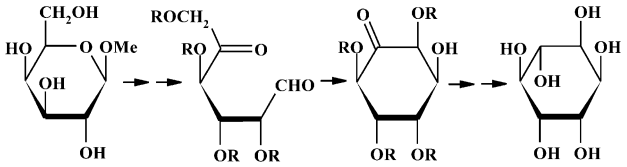
38

Bioorg. Med. Chem. Lett. 12 (2002) 3313

Intramolecular Aldol Cyclization of L-*lyxo*-Hexos-5-ulose Derivatives: A New Diastereoselective Synthesis of D-*chiro*-Inositol

Giorgio Catelani,[a,*] Antonino Corsaro,[b] Felicia D'Andrea,[a] Manuela Mariani[a] and Venerando Pistarà[b]

[a]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università degli Studi di Pisa, Via Bonanno, 33, I-56126 Pisa, Italy*
[b]*Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale A. Doria, I-95125 Catania, Italy*



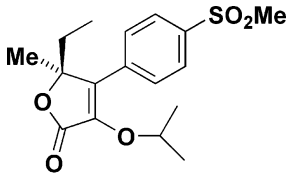
Bioorg. Med. Chem. Lett. 12 (2002) 3317

Discovery of a Potent and Selective COX-2 Inhibitor in the Alkoxy Lactone Series with Optimized Metabolic Profile

Yves Leblanc,[a,*] Patrick Roy,[a] Zhaoyin Wang,[a] Chun Sing Li,[a] Nathalie Chauret,[a] Deborah A. Nicoll-Griffith,[a] José M. Silva,[a] Yves Aubin,[a] James A. Yergey,[a] Chi Chung Chan,[a] Denis Riendeau,[a] Christine Brideau,[a] Robert Gordon,[a] Lijing Xu,[a] Janine Webb,[b] Denise M. Visco[c] and Petpiboon Prasit[a]

[a]*Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe Claire-Dorval, Quebec, Canada H9R 4P8*
[b]*Merck Research Laboratories, Harlow, Essex, UK*
[c]*Merck Research Laboratories, Rahway, NJ, USA*

5(*S*)-(5-Ethyl-5-methyl-3-(2-propoxy)-4-methanesulfonylphenyl)-2(5H)-furanone **11** is a potent and selective COX-2 inhibitor with optimized metabolic profile.



11

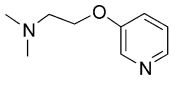
Bioorg. Med. Chem. Lett. 12 (2002) 3321

Synthesis and Biological Evaluation of Pyridine-Modified Analogues of 3-(2-Aminoethoxy)pyridine as Novel Nicotinic Receptor Ligands

Nan-Horng Lin,* Liming Dong, William H. Bunnelle, David J. Anderson and Michael D. Meyer

Neurological and Urological Diseases Research, D-47W, Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, USA

Analogues of compound **1** were synthesized and tested in vitro for nicotinic receptor binding affinity.



1

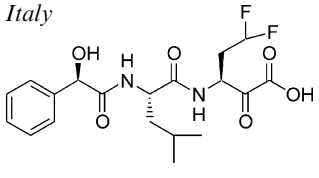
Bioorg. Med. Chem. Lett. 12 (2002) 3325

Capped Dipeptide α-Ketoacid Inhibitors of the HCV NS3 Protease

Emanuela Nizi, Uwe Koch, Simona Ponzi, Victor G. Matassa and Cristina Gardelli*

Department of Chemistry, IRBM, MRL Rome, Via Pontina Km 30,600, Pomezia, 00040 Rome, Italy

The N-terminal aminoacid of α-ketotripeptide inhibitors of the hepatitis C virus NS3 protease can be replaced with an α-hydroxy acid. The highest affinity of the capping residue with R configuration has been explained by molecular modeling studies.



IC_{50} = 3 μM

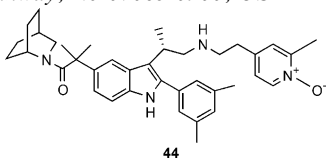
Bioorg. Med. Chem. Lett. 12 (2002) 3329

Modification of the Pyridine Moiety of Non-peptidyl Indole GnRH Receptor Antagonists

Joseph P. Simeone,[a,*] Robert L. Bugianesi,[a] Mitree M. Ponpipom,[a] Yi Tien Yang,[b] Jane-Ling Lo,[b] Joel B. Yudkovitz,[b] Jisong Cui,[b] George R. Mount,[b] Rena Ning Ren,[b] Mellissa Creighton,[c] An-Hua Mao,[c] Stella H. Vincent,[c] Kang Cheng[b] and Mark T. Goulet[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Department of Biochemistry and Physiology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*

The synthesis and biological evaluation of a series of indole GnRH receptor antagonists are described. Several potent binders of the human GnRH receptor were discovered, including compound **44**, which also exhibited acceptable oral bioavailability in both rats and dogs.



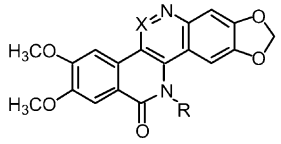
44

Bioorg. Med. Chem. Lett. 12 (2002) 3333

Diaza- and Triazachrysenes: Potent Topoisomerase-Targeting Agents with Exceptional Antitumor Activity against the Human Tumor Xenograft, MDA-MB-435

Alexander L. Ruchelman,[a] Sudhir K. Singh,[a] Xiaohua Wu,[a,b] Abhijit Ray,[a] Jin-Ming Yang,[b,c] Tsai-Kun Li,[c] Angela Liu,[c] Leroy F. Liu[b,c] and Edmond J. LaVoie[a,b,*]

[a]*Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020, USA*
[b]*The Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA*
[c]*Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854, USA*



Where X = CH; or N

R = $CH_2CH_2N(CH_3)_2$; $CHCH_3CH_2N(CH_3)_2$; CH_2(-$CHOCH_2$ CH_2CH_2-); and X = N; R = $CH_2CH_2CH_2CH_3$

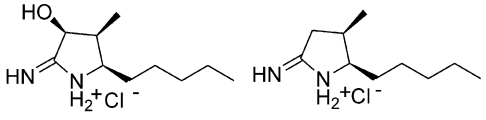
Bioorg. Med. Chem. Lett. 12 (2002) 3337

3-Hydroxy-4-methyl-5-pentyl-2-iminopyrrolidine: A Potent and Highly Selective Inducible Nitric Oxide Synthase Inhibitor

Sofya Tsymbalov,[a] Timothy J. Hagen,[a] William M. Moore,[b] Gina M. Jerome,[b] Jane R. Connor,[b] Pamela T. Manning,[b] Barnett S. Pitzele[a] and E. Ann Hallinan[a,*]

[a]*Department of Discovery Medicinal Chemistry, Pharmacia, 4901 Searle Parkway, Skokie, IL 60077, USA*
[b]*Department of Discovery Pharmacology, 800 North Lindbergh Boulevard, St. Louis, MO 63167, USA*

Introduction of a hydroxyl moiety into the iminopyrrolidine ring of i-NOS inhibitor **2** affords **1**, which is three times more selective an i-NOS inhibitor as its parent.



1 **2**

Bioorg. Med. Chem. Lett. 12 (2002) 3341

SB-656104-A: A Novel 5-HT_7 Receptor Antagonist with Improved In Vivo Properties

Ian T. Forbes,* Sara Douglas, Andrew D. Gribble, Robert J. Ife, Andrew P. Lightfoot, Ashley E. Garner, Graham J. Riley, Phillip Jeffrey, Alexander J. Stevens, Tania O. Stean and David R. Thomas

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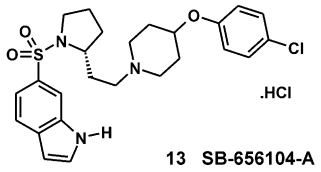
An SAR study around the previously reported selective 5-HT_7 receptor antagonist SB-269970-A has resulted in the identification of SB-656104-A, a structurally related analogue having an improved pharmacokinetic profile.



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Bioorg. Med. Chem. Lett. 12 (2002) 3345

Scaleable and Efficient Synthesis of 2′-Deoxy-2′-*N*-phthaloyl Nucleoside Phosphoramidites for Oligonucleotide Synthesis

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2′-Deoxy-2′-*N*-phthaloyl nucleosides were prepared from arabino nucleosides by triflate displacement with phthalimide in the presence of DBU. The corresponding phosphoramidites suitable for automated oligonucleotide synthesis were also synthesized. Described procedure allows preparation of title compounds on 100-g scale.