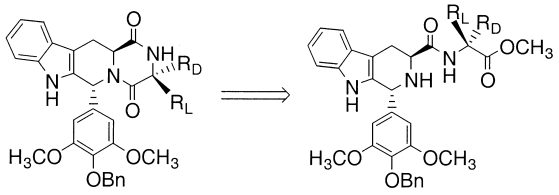
Bioorg. Med. Chem. Lett. 11 (2001) 1251

The Synthesis of Amino-Acid Functionalized β-Carbolines as Topoisomerase II Inhibitors

Amy Morin Deveau, Marc A. Labroli, Christine M. Dieckhaus, Mary T. Barthen, Kirsten S. Smith and Timothy L. Macdonald*

Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22901, USA

The synthesis and biological activity of amino acid functionalized β-carboline derivatives, which are structurally related to azatoxin and the tryprostatins, are reported. These compounds were assayed for their growth inhibition properties in H520 and PC3 cell lines and were examined for their abilities to inhibit topoisomerase II-mediated DNA relaxation.



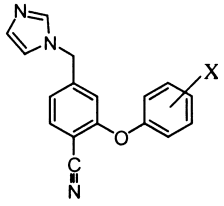
Bioorg. Med. Chem. Lett. 11 (2001) 1257

Diaryl Ether Inhibitors of Farnesyl-Protein Transferase

Suzanne C. MacTough,[a,*] S. Jane deSolms,[a] Anthony W. Shaw,[a] Marc T. Abrams,[b] Terrence M. Ciccarone,[a] Joseph P. Davide,[b] Kelly A. Hamilton,[b] John H. Hutchinson,[a] Kenneth S. Koblan,[b] Nancy E. Kohl,[b] Robert B. Lobell,[b] Ronald G. Robinson[b] and Samuel L. Graham[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA*

A novel series of imidazolemethyl diaryl ethers has been identified as potent inhibitors of FPTase. Rapid parallel synthesis was designed to exploit commercially available substrates.



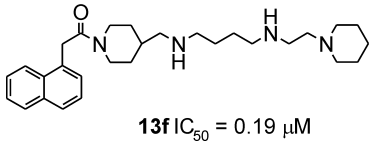
Bioorg. Med. Chem. Lett. 11 (2001) 1261

Synthesis of Polyamine Derivatives Having Non-hypotensive Ca^{2+}-Permeable AMPA Receptor Antagonist Activity

Yoshiyuki Yoneda,* Shinichi Kawajiri, Atushi Hasegawa, Fusako Kito, Sumie Katano, Emi Takano and Tetuya Mimura

Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan

In order to obtain non-hypotensive and selective Ca^{2+}-permeable AMPA receptor antagonists, we have synthesized a series of 1,4-bis(4-piperidinylmethyl)diaminobutanes. Compounds **13b**, **13c**, and **13f** had desirable properties.



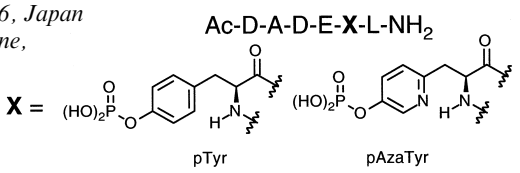
13f IC_{50} = 0.19 μM

Bioorg. Med. Chem. Lett. 11 (2001) 1265

Phospho-Azatyrosine, a Less Effective Protein-Tyrosine Phosphatase Substrate Than Phosphotyrosine

Terrence R. Burke, Jr.,[a,*] Zhu-Jun Yao,[a] Bin Ye,[a] Kengo Miyoshi,[b] Akira Otaka,[b] Li Wu[c] and Zhong-Yin Zhang[c]

[a]*Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bldg. 376, Boyles Street, NCI-FCRDC, PO Box B, Frederick, MD 21702-1201, USA*
[b]*Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan*
[c]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA*



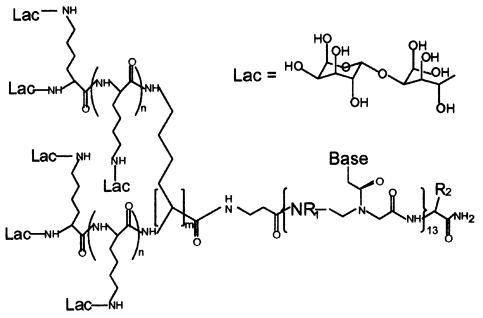
Bioorg. Med. Chem. Lett. 11 (2001) 1269

Liver Cell Specific Targeting of Peptide Nucleic Acid Oligomers

Xiao Zhang, Carla G. Simmons and David R. Corey*

Departments of Pharmacology and Biochemistry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9041, USA

Chimeric molecules consisting of peptide nucleic acid (PNA) and lactose have been synthesized to test the hypothesis that lactose moieties can promote cell-specific uptake of PNAs. Lactose modified PNAs rapidly enter liver-derived HepG2 cells while unmodified PNAs do not and lactose modified PNAs inhibit cellular telomerase.

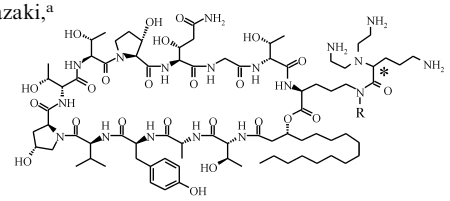


Bioorg. Med. Chem. Lett. 11 (2001) 1273

Synthesis and Antifungal Activities of Novel 1,3-β-D-Glucan Synthase Inhibitors. Part 2

Kazunao Masubuchi,[a] Takehiro Okada,[a] Masami Kohchi,[a] Takeshi Murata,[a] Masao Tsukazaki,[a] Osamu Kondoh,[b] Toshikazu Yamazaki,[b] Yasuko Satoh,[b] Yoshinori Ono,[b] Toshiyuki Tsukaguchi,[b] Kazuko Kobayashi,[c] Naomi Ono,[b] Tomoaki Inoue,[c] Ikuo Horii[c] 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*



7b (*R*) R = -H
10a (*S*) R = -$(CH_2)_3NH_2$
10b (*R*) R = -$(CH_2)_3NH_2$
12 (*S*) R = -$(CH_2)_2NH_2$

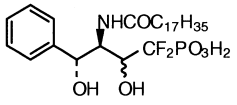
Highly potent 1,3-β-D-glucan synthase inhibitors, **7b**, **10a**, **10b** and **12**, have been identified by the chemical modification of the ornithine residue of a fungicidal macrocyclic lipopeptidolactone, RO-09-3655 (**1**), isolated from the cultured broth of *Deuteromycotinia* spp. These compounds showed stronger antifungal activity against systemic candidiasis as well as pulmonary aspergillosis in mice, and less hepatotoxicity as compared with **1**.

Bioorg. Med. Chem. Lett. 11 (2001) 1277

Synthesis and Evaluation of a Difluoromethylene Analogue of Sphingomyelin as an Inhibitor of Sphingomyelinase

Tsutomu Yokomatsu,[a,*] Hiroaki Takechi,[a] Takeshi Akiyama,[a] Shiroishi Shibuya,[a] Takaaki Kominato,[b] Shinji Soeda[b] and Hiroshi Shimeno[b,*]

[a]*School of Pharmacy, Tokyo University of Pharmacy & Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*
[b]*Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan*



A novel sphingomyelin analogue was prepared and evaluated as an inhibitor of sphingomyelinase. The analogue prevents tumor necrosis factor (TNF)-α-induced cell death of PC-12 neurons at a low concentration of 0.1 μM.

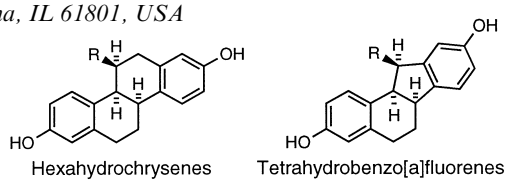
Bioorg. Med. Chem. Lett. 11 (2001) 1281

Synthesis and Evaluation of Hexahydrochrysene and Tetrahydrobenzofluorene Ligands for the Estrogen Receptor

Rosanna Tedesco, Michael K. Youngman, Scott R. Wilson and John A. Katzenellenbogen*

Department of Chemistry, University of Illinois, 600 S. Mathews Ave., Urbana, IL 61801, USA

Derivatives in two bis-phenolic tetracyclic systems have been prepared and evaluated as estrogen receptor ligands and transcriptional activators.



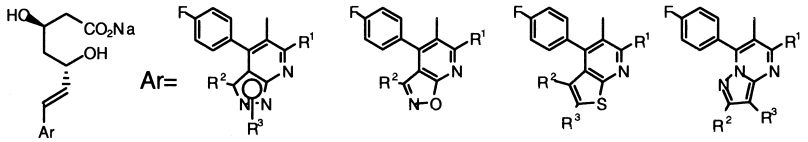
Bioorg. Med. Chem. Lett. 11 (2001) 1285

Synthesis and Biological Evaluations of Condensed Pyridine and Condensed Pyrimidine-Based HMG-CoA Reductase Inhibitors

Mikio Suzuki,[a,*] Hiroshi Iwasaki,[b] Yoshihiro Fujikawa,[b] Mitsuaki Sakashita,[b] Masaki Kitahara[c] and Ryozo Sakoda[a]

[a]*Central Research Institute, Nissan Chemical Industries, Ltd., 722-1 Tsuboi-cho, Funabashi, Chiba 274-8507, Japan*
[b]*Pharmaceuticals Division, Nissan Chemical Industries, Ltd., 7-1, Kanda Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 101-0054, Japan*
[c]*Shiraoka Research Station of Biological Science, Nissan Chemical Industries, Ltd., 1470 Shiraoka, Shiraoka-cho, Minamisaitama-gun, Saitama 349-0294, Japan*

The synthesis and biological evaluations of new pyrazolopyridine, isoxazolopyridine, thienopyridine, and pyrazolopyrimidine-based HMG-CoA reductase inhibitors are reported.



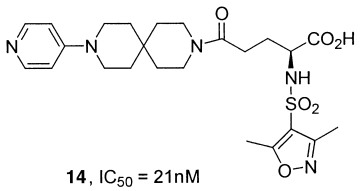
Bioorg. Med. Chem. Lett. 11 (2001) 1289

Spirocyclic Nonpeptide Glycoprotein IIb–IIIa Antagonists. Part 1: Design of Potent and Specific 3,9-Diazaspiro[5.5]undecanes

M. S. Smyth,[a] J. Rose,[a] M. M. Mehrotra,[a] J. Heath,[a] G. Ruhter,[b] T. Schotten,[b] J. Seroogy,[a] D. Volkots,[a] A. Pandey[a] and R. M. Scarborough[a,*]

[a]*COR Therapeutics, Inc., Department of Medicinal Chemistry and Biology, South San Francisco, CA 94080, USA*
[b]*Lilly Research Laboratories, Hamburg, Germany*

The synthesis and biological activity of the potent spirocyclic GPIIb–IIIa antagonists is reported.



14, IC_{50} = 21nM

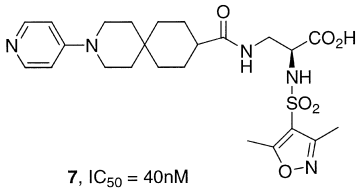
Bioorg. Med. Chem. Lett. 11 (2001) 1293

Spirocyclic Nonpeptide Glycoprotein IIb–IIIa Antagonists. Part 2: Design of Potent Antagonists Containing the 3-Azaspiro[5.5]undec-9-yl Template

A. Pandey,[a] J. Seroogy,[a] D. Volkots,[a] M. S. Smyth,[a] J. Rose,[a] M. M. Mehrotra,[a] J. Heath,[a] G. Ruhter,[b] T. Schotten[b] and R. M. Scarborough[a,*]

[a]*COR Therapeutics, Inc., Department of Medicinal Chemistry and Biology, South San Francisco, CA 94080, USA*
[b]*Lilly Research Laboratories, Hamburg, Germany*

The synthesis and biological activity of the potent spirocyclic GPIIb–IIIa antagonists are presented.



7, IC_{50} = 40nM

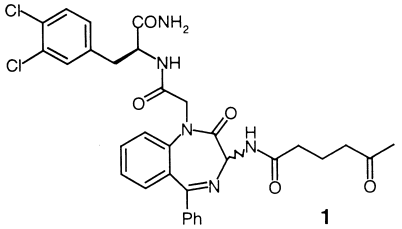
Bioorg. Med. Chem. Lett. 11 (2001) 1297

Identification of a Potent and Selective Oxytocin Antagonist, from Screening a Fully Encoded Differential Release Combinatorial Chemical Library

Brian Evans,* Adrian Pipe, Liz Clark and Martyn Banks

Department of Lead Discovery, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

A library of 1296 1,4-benzodiazepines was prepared on 160 μM Tentagel beads. Compounds are attached to the beads using orthogonally cleavable linkers. The library was first screened as pools of 30 beads where 50% of the material is released and screened. GW405212X (**1**) was identified by picking single beads from active pools.



1

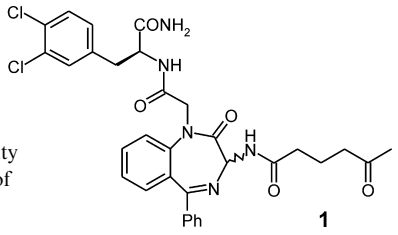
Bioorg. Med. Chem. Lett. 11 (2001) 1301

Structure–Activity Relationship Investigations of a Potent and Selective Benzodiazepine Oxytocin Antagonist

Paul G. Wyatt,[a,*] Michael J. Allen,[b] Josie Chilcott,[c] Gwen Hickin,[a] Neil D. Miller[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*

GW405212X **1** is a potent selective oxytocin antagonist. We have investigated the structure–activity relationship of the 1- and 3-substituents and replacements of the 5-phenyl group of **1**. The effect of these modifications on OT binding antagonism and on pharmacokinetic parameters is reported.



1

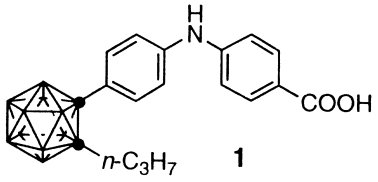
Bioorg. Med. Chem. Lett. 11 (2001) 1307

Structure–Activity Study of Retinoid Agonists Bearing Substituted Dicarba-*closo*-dodecaborane. Relation between Retinoidal Activity and Conformation of Two Aromatic Nuclei

Yasuyuki Endo,[a,*] Toru Iijima,[a] Kyoko Yaguchi,[a] Emiko Kawachi,[a] Noriko Inoue,[a] Hiroyuki Kagechika,[a] Asako Kubo[b] and Akiko Itai[a]

[a]*Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Institute of Medicinal Molecular Design, Key Molecular, Inc., 5-24-5, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Structure–activity study of novel carborane-containing retinoid agonist BR403 (**1**) indicates the planar conformation at the phenyl-*N*-phenyl moiety plays a critical role in the appearance of the biological activity.



1

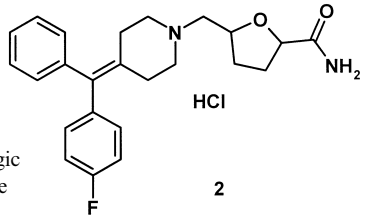
Bioorg. Med. Chem. Lett. 11 (2001) 1313

Pharmacological Evaluation of a Diarylmethylene-Piperidine Derivative: A New Potent Atypical Antipsychotic?

Patrice Talaga,* Alain Matagne and Henrik Klitgaard

UCB S.A., Pharma Sector, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium

A new diaryl-methylene piperidine derivative, **2**, displayed an atypical antipsychotic profile both in vitro and in vivo. The main pharmacological characteristics of this compound appear to reside in a more potent antagonism of the 5-HT_2 serotonergic receptor than of the D2 dopaminergic receptor. This confirms that molecules displaying a D2/5-HT_2 binding ratio <1 possess clozapine-like antipsychotic activity.



2

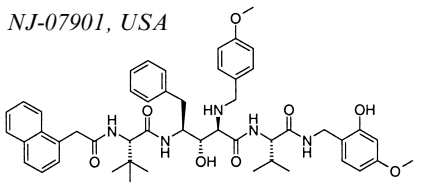
Bioorg. Med. Chem. Lett. 11 (2001) 1317

A New Structural Class of Selective and Non-covalent Inhibitors of the Chymotrypsin-like Activity of the 20S Proteasome

C. García-Echeverría,[a,*] P. Imbach,[a,*] D. France,[a] P. Fürst,[a] M. Lang,[a] M. Noorani,[a] D. Scholz,[b] J. Zimmermann[a] and P. Furet[a,*]

[a]*Oncology Research, Novartis Pharma Inc., CH-4002 Basel, Switzerland and Summit, NJ-07901, USA*
[b]*Novartis Research Institute, A-1235 Vienna, Austria*

We describe the identification and in vitro characterization of a series of 2-aminobenzylstatine derivatives (e.g., **12**) that inhibit non-covalently the chymotrypsin-like activity of the 20S proteasome.



Compound **12**

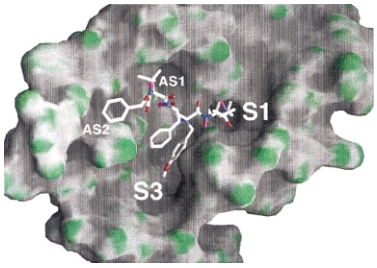
Bioorg. Med. Chem. Lett. 11 (2001) 1321

Modeling of the Binding Mode of a Non-covalent Inhibitor of the 20S Proteasome. Application to Structure-Based Analogue Design

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

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

The binding mode of a novel inhibitor of the chymotrypsin-like activity of the human 20S proteasome has been modelled using the crystal structure of the yeast proteasome. An example of how the model is used to design more potent inhibitors is presented.



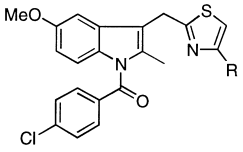
Bioorg. Med. Chem. Lett. 11 (2001) 1325

Thiazole Analogues of the NSAID Indomethacin as Selective COX-2 Inhibitors

Keith W. Woods,* Richard W. McCroskey, Michael R. Michaelides, Carol K. Wada, Keren I. Hulkower and Randy L. Bell

Abbott Laboratories, 100 Abbott Park Rd., D-47S AP10/307, Abbott Park, IL 60064-6101, USA

The carboxyl group of the NSAID indomethacin was replaced with a variety of substituted thiazoles to obtain a series of potent, selective inhibitors of COX-2. Additional substitutions were made at the 1-position and 5-position of the indole of indomethacin.



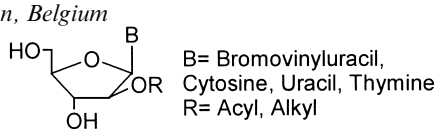
Bioorg. Med. Chem. Lett. 11 (2001) 1329

Design, Synthesis and Enzymatic Activity of Highly Selective Human Mitochondrial Thymidine Kinase Inhibitors

Stefano Manfredini,[a,*] Pier G. Baraldi,[a] Elisa Durini,[a] Luca Porcu,[a] Angela Angusti,[a] Silvia Vertuani,[a] Nicola Solaroli,[a,b] Erik De Clercq,[c] Anna Karlsson[b] and Jan Balzarini[c]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, via Fossato di Mortara 17–19, I-44100 Ferrara, Italy*
[b]*Division of Clinical Virology, Huddinge University Hospital, S-141 86 Huddinge/Stockholm, Sweden*
[c]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

Synthesis, modeling studies and preliminary biological activity of potent and selective inhibitors of the mitochondrial thymidine kinase (TK-2) are described.



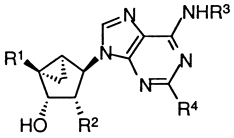
Bioorg. Med. Chem. Lett. 11 (2001) 1333

Ring-Constrained (N)-Methanocarba Nucleosides as Adenosine Receptor Agonists: Independent 5′-Uronamide and 2′-Deoxy Modifications

Kyeong Lee,[a] Gnana Ravi,[a] Xiao-duo Ji,[a] Victor E. Marquez[b] and Kenneth A. Jacobson[a,*]

[a]*Molecular Recognition Section, LBC, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA*
[b]*Laboratory of Medicinal Chemistry, National Cancer Institute, Frederick, MD 21702, USA*

Novel methanocarba adenosine analogues, having the pseudo-ribose northern (N) conformation preferred at adenosine receptors (ARs), were synthesized and testing in binding assays. The 5′-uronamide modification preserved [N^6-(3-iodobenzyl)] or enhanced (N^6-methyl) affinity at A_3ARs, while the 2′-deoxy modification reduced affinity and efficacy in a functional assay.



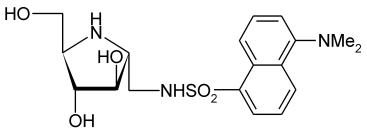
R^1 = CH_2OH, CONH-alkyl
R^2 = OH, H
R^3 = H, CH_3, cyclopentyl, 3-I-benzyl
R^4 = H, Cl

Bioorg. Med. Chem. Lett. 11 (2001) 1339

Powerful Probes for Glycosidases: Novel, Fluorescently Tagged Glycosidase Inhibitors

Albin Hermetter,[a] Hubert Scholze,[a] Arnold E. Stütz,[b,*] Stephen G. Withers[c] and Tanja M. Wrodnigg[b]

[a]*Institut für Biochemie der Technischen Universität Graz, Petersgasse 12, A-8010 Graz, Austria*
[b]*Glycogroup, Institut für Organische Chemie der Technischen Universität Graz, Stremayrgasse 16, A-8010 Graz, Austria*
[c]*Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1*



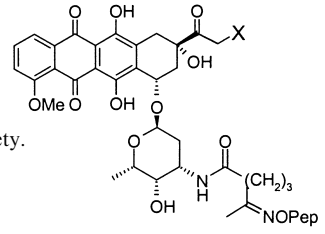
1-*N*-Dansyl derivatives of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol exhibiting K_i values in the low nanomolar range are reported. An enzyme/inhibitor complex with *Agrobacterium* sp. β-glucosidase was characterised by fluorescence spectrometry.

Bioorg. Med. Chem. Lett. 11 (2001) 1343

A New Method for Chemoselective Conjugation of Unprotected Peptides to Dauno- and Doxorubicin

Paolo Ingallinella, Annalise Di Marco, Marina Taliani, Daniela Fattori* and Antonello Pessi

Istituto di Ricerche di Biologia Molecolare P. Angeletti (IRBM) Via Pontina Km 30.600, Pomezia, Rome, Italy



A new method for chemoselective conjugation of unprotected peptides to dauno- and doxorubicin through an oxime bond is presented. This method does not require protecting groups on the peptide moiety.

Bioorg. Med. Chem. Lett. 11 (2001) 1347

Anodic Oxidation of Ifosfamide and Cyclophosphamide: A Biomimetic Metabolism Model of the Oxazaphosphorinane Anticancer Drugs

Angelo Paci, Thierry Martens and Jacques Royer*

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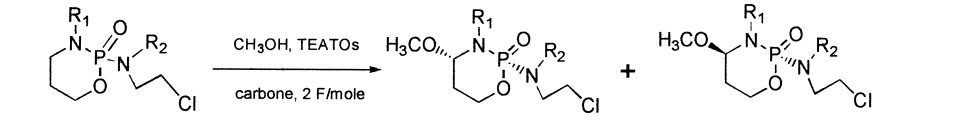

$R_1 = (CH_2)_2$-Cl, R_2 =H , **1a**
R_1 = H, $R_2 = (CH_2)_2$-Cl, **1b**

$R_1 = (CH_2)_2$-Cl, R_2 =H , **6α** (48%, yield)
R_1 = H, $R_2 = (CH_2)_2$-Cl, **7α** (0%, yield)

$R_1 = (CH_2)_2$-Cl, R_2 =H , **6β** (36%, yield)
R_1 = H, $R_2 = (CH_2)_2$-Cl, **7β** (40%, yield, 70% conversion)