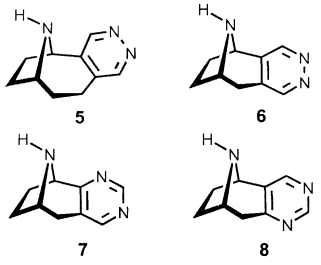
Bioorg. Med. Chem. 10 (2002) 1

Syntheses and Evaluation of Pyridazine and Pyrimidine Containing Bioisosteres of (±)-Pyrido[3.4-b]homotropane and Pyrido-[3.4-b]tropane as Novel nAChR Ligands

Daniela Gündisch,[b] Thomas Kämpchen,[a] Simone Schwarz,[a] Gunther Seitz,[a] Johanna Siegl[a] and Thomas Wegge[a]

[a]*Department of Pharmaceutical Chemistry, Philipps-University, Marbacher Weg 6, D-35032 Marburg, Germany*
[b]*Department of Pharmaceutical Chemistry, Rhein.Friedr.Wilh. University, Kreuzbergweg 26, D-53115 Bonn, Germany*

Bioisosteric replacement of the pyridine moiety in (±)-pyrido[3,4-b]homotropane (PHT) and (+)-pyrido[3,4-b]tropane with the pyridazine and pyrimidine nucleus resulted in hitherto unknown nAChR ligands such as **5**–**8**.



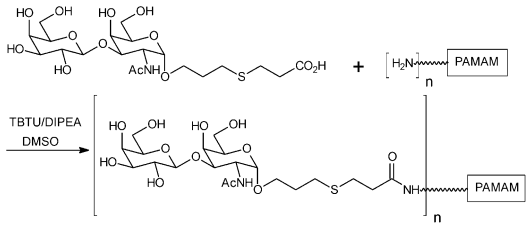
Bioorg. Med. Chem. 10 (2002) 11

Synthesis and Protein Binding Properties of T-Antigen Containing GlycoPAMAM Dendrimers

Myung-Gi Baek and René Roy

Centre for Research in Biopharmaceuticals, Department of Chemistry, University of Ottawa, Ottawa, ON, Canada K1N 6N5

Multivalent glycoPAMAM dendrimers were synthesized from an acid functionalized T-antigen derivative and PAMAM dendritic cores by a peptide coupling stategy providing 4–32 valencies.

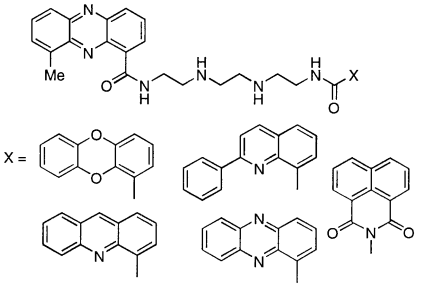


Bioorg. Med. Chem. 10 (2002) 19

Synthesis and Evaluation of Unsymmetrical Bis(arylcarboxamides) Designed as Topoisomerase-Targeted Anticancer Drugs

Julie A. Spicer, Swarna A. Gamage, Graeme J. Finlay and William A. Denny

Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1000, New Zealand

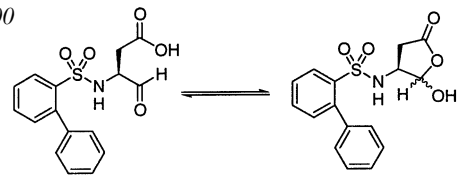


Bioorg. Med. Chem. 10 (2002) 31

Structure-Based Design of Nonpeptide Inhibitors of Interleukin-1β Converting Enzyme (ICE, Caspase-1)

Aurash B. Shahripour,[a] Mark S. Plummer,[a] Elizabeth A. Lunney,[a] Hans P. Albrecht,[b] Sheryl J. Hays,[a] Catherine R. Kostlan,[a] Tomi K. Sawyer,[a] Nigel P. C. Walker,[b] Kenneth D. Brady,[c] Hamish J. Allen,[c] Robert V. Talanian,[c] Winnie W. Wong[c] and Christine Humblet[b]

[a]*Department of Medicinal Chemistry, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*
[b]*Department of Chemistry BASF AG, Carl-Bosch-Str. 38, 67056 Ludwigshafen, Germany*
[c]*Department of Biochemistry, BASF Bioresearch Corporation, Worcester, MA 01609, USA*



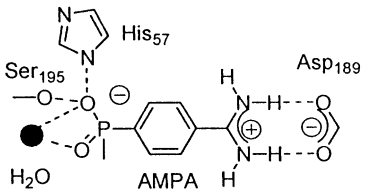
Bioorg. Med. Chem. 10 (2002) 41

An Oxyanion-Hole Selective Serine Protease Inhibitor in Complex with Trypsin

Jian Cui,[a,b] Fatima Marankan,[a] Wentao Fu,[a] David Crich,[b] Andrew Mesecar[a] and Michael E. Johnson[a]

[a]*Center for Pharmaceutical Biotechnology, College of Pharmacy, University of Illinois at Chicago, 900 S. Ashland Avenue, M/C 870, Chicago, IL 60607-7173, USA*
[b]*Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607-7061, USA*

The synthesis and crystal structure of *p*-amidinophenylmethylphosphinic acid (**AMPA**) complexed with trypsin is reported.



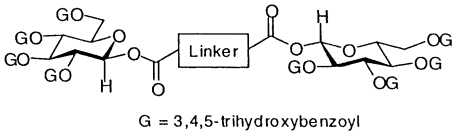
Bioorg. Med. Chem. 10 (2002) 47

In Vitro and In Vivo Inhibition of LPS-Induced Tumor Necrosis Factor-α Production by Dimeric Gallotannin Analogues

Ken S. Feldman,[a] Sarah L. Wilson,[a] Michael D. Lawlor,[a] Charles H. Lang[b] and William J. Scheuchenzuber[c]

[a]*Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA*
[b]*Department of Cellular and Molecular Physiology, The Pennsylvania State University College of Medicine, Hershey, PA 17033, USA*
[c]*Life Sciences Consortium, The Pennsylvania State University, University Park, PA 16802, USA*

Designed dimeric gallotannin analogues as indicated inhibit TNF-α secretion from LPS-stimulated h-PBMCs by up to 53% (5–24 μM) compared to control. Comparable suppression of TNF-α levels (~50% vs control) was observed in the plasma of rats co-treated with LPS and specific tannin analogues.



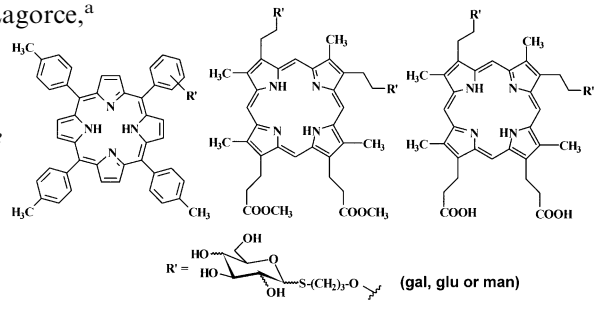
Bioorg. Med. Chem. 10 (2002) 57

Synthesis and Biological Evaluation of Thioglycosylated Porphyrins for an Application in Photodynamic Therapy

I. Sylvain,[a] R. Zerrouki,[a] R. Granet,[a] Y.M. Huang,[a] J.-F. Lagorce,[a] M. Guilloton,[a] J.-C. Blais[b] and P. Krausz[a]

[a]*Université de Limoges, Laboratoire de Chimie des Substances Naturelles, 123 Avenue Albert Thomas F-87060 Limoges, France*
[b]*Université Pierre et Marie Curie, Laboratoire de Chimie Organique Structurale et Biologique, Centre National de la Recherche Scientifique EP 1034, Place Jussieu, F-75005 Paris, France*

Synthesis and biological evaluation of the following porphyrins.

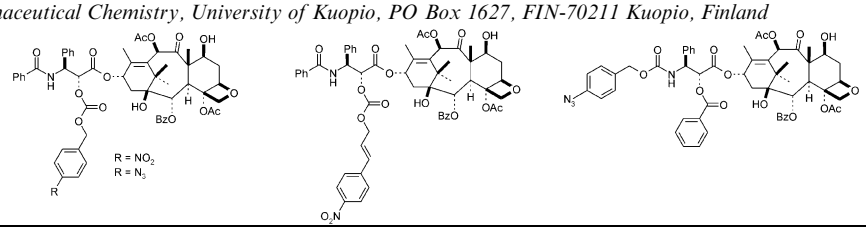


Bioorg. Med. Chem. 10 (2002) 71

Synthesis of Novel Paclitaxel Prodrugs Designed for Bioreductive Activation in Hypoxic Tumour Tissue

Eric W.P. Damen,[a] Tapio J. Nevalainen,[b] Toine J.M. van den Bergh,[a] Franciscus M.H. de Groot[a] and Hans W. Scheeren[a]

[a]*Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands*
[b]*Department of Pharmaceutical Chemistry, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland*



Bioorg. Med. Chem. 10 (2002) 79

Medium-Dependence of the Secondary Structure of Exendin-4 and Glucagon-like-peptide-1

Niels H. Andersen,[a] Yan Brodsky,[a] Jonathan W. Neidigh[a] and Kathryn S. Prickett[b]

[a]*Department of Chemistry, University of Washington, Seattle WA 98195, USA*
[b]*Amylin Pharmaceuticals Inc., 9373 Towne Centre Drive, San Diego CA 92121, USA*

Exendin-4 is a 39-residue peptide from the salivary secretions of *Heloderma suspectum* having some pharmacological properties similar to GLP-1. The synthetic version of this peptide (AC2993) is currently in phase 2 clinical trials as a treatment as a treatment for type 2 diabetes. In contrast to GLP-1, exendin-4 forms monomeric helices in aqueous media. This helical state displays unusual thermal stability due to a hydrophobic C-terminal capping interaction. The absence of this C-capping interaction and the presence of a flexible, helix-destabilizing glycine at residue 16 in GLP-1 are proposed to be the basis for the diminished stability of the monomeric helical state of GLP-1. The greater intrinsic stability of the exendin-4 helix likely reduces the entropic cost of binding at a receptor that requires the C-terminal helix state.

Exendin-4	HGEGTFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS-NH_2
GLP-1	HAEGTFTSDV SSYLEGQAAK EFIAWLVKGR-NH_2

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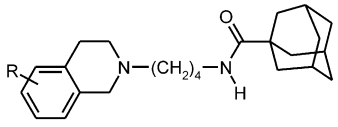
The Influence of Substitution at Aromatic Part of 1,2,3,4-tetrahydroisoquinoline on In Vitro and In Vivo 5-HT_{1A}/5-HT_{2A} Receptor Activities of Its 1-Adamantoyloaminoalkyl Derivatives

Andrzej J. Bojarski,[a] Maria J. Mokrosz,[a] Sijka Charakchieva Minol,[a] Aneta Kozioł,[a] Anna Wesołowska,[b] Ewa Tatarczyńska,[b] Aleksandra Kłodzińska[b] and Ewa Chojnacka-Wójcik[b]

[a]*Department of Medicinal Chemistry Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-143 Kraków, Poland*
[b]*Department of New Drug Research, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-143 Kraków, Poland*



The impact of substituent variations in the aromatic part of 1,2,3,4-tetrahydroisoquinoline moiety on 5-HT_{1A} and 5-HT_{2A} receptor affinities, as well as in vivo functional properties of the investigated compounds are discussed.

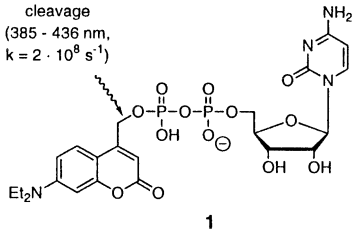
R = H; 7-CH_3; 8-Br, 5-OCH_3; 5-Cl; 6-Cl; 7-Cl; 7-NO_2; 6-OCH_3; 6,7-di-OCH_3

Bioorg. Med. Chem. 10 (2002) 97

Rapid Photolytic Release of Cytidine 5′-Diphosphate from a Coumarin Derivative: a New Tool for the Investigation of Ribonucleotide Reductases

Ralph O. Schönleber,[a] Jürgen Bendig,[b] Volker Hagen[c] and Bernd Giese[a]

[a]*Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland*
[b]*Institute of Chemistry, Humboldt University, Hessische Str. 1-2, D-10115 Berlin, Germany*
[c]*Research Institute of Molecular Pharmacology, A.-Kowalke Str. 4, D-10315 Berlin, Germany*



1

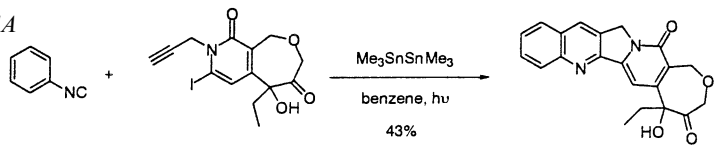
Coumarin protected cytidine 5′-diphosphate (CDP) **1** generates CDP in the ns timescale. Because **1** absorbs light up to 450 nm, this CDP derivative is a suitable probe for the study of the enzyme ribonucleotide reducase.

Bioorg. Med. Chem. 10 (2002) 103

Synthesis and Evaluation of a Novel E-Ring Modified α-Hydroxy Keto Ether Analogue of Camptothecin

Wu Du,[a] Dennis P. Curran,[a,*] Robert L. Bevins,[b] Stephen G. Zimmer,[b] Junhong Zhang[c] and Thomas G. Burke[b,c]

[a]*University of Pittsburgh, Department of Chemistry, Pittsburgh, PA 15260, USA*
[b]*Colleges of Pharmacy Medicine, and Experimental Therapeutics Program, Markey Cancer Center, University of Kentucky, Lexington, KY 40506, USA*
[c]*Tigen Pharmaceuticals, Inc., Lexington, KY 40506, USA*



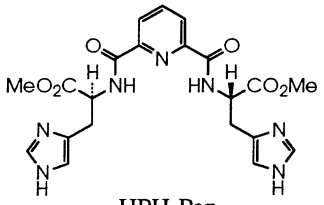
Bioorg. Med. Chem. 10 (2002) 111

Sensitization of Hyperthermic Treatment of Leukemic Cell Lines by a Synthetic Peptide

Yasuharu Hori,[a] Rie Nagai,[b] Naomi Urabe,[b] Toshikazu Yoshikawa[c] and Masami Otsuka[d]

[a]*Research Institute for Advanced Sciences and Technology, Osaka Prefecture University, 1-2 Gakuen-cho, Sakai, Osaka 593-8531, Japan*
[b]*College of Integrated Arts and Sciences, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 593-8531, Japan*
[c]*First Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kaiji-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-0841, Japan*
[d]*Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan*

A synthetic peptide HPH–Pep showed sensitising effect on the hyperthermic treatment of L-1210, Molt-4, and HL60 cells.



HPH-Pep

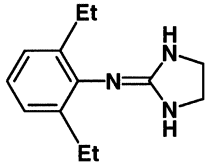
Bioorg. Med. Chem. 10 (2002) 117

Three-Dimensional Common-Feature Hypotheses for Octopamine Agonist 2-(Arylimino)imidazolidines

Akinori Hirashima,[a] Masako Morimoto,[b] Eiichi Kuwano,[a] Eiji Taniguchi[c] and Morifusa Eto[d]

[a]*Department of Applied Genetics and Pest Management, Faculty of Agriculture, Graduate School, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan*
[b]*Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan*
[c]*School of Agriculture, Kyushu Tokai University, Kumamoto 869-1404, Japan*
[d]*Kyushu Women's University, 1-1 Jiyugaoka, Yahatanishi-ku, Kita-Kyushu, Fukuoka 807-8586, Japan*

Three-dimensional pharmacophore hypotheses were built from a set of 10 octopamine (OA) agonist 2-(Arylimino)imidazolidines (AIIs), 2-(Arylimino)thiazolidines (AITs) and 2-(Arylimino)oxazolidines (AIOs). Active OA agonist 2,6-Et_2 AII mapped well onto all the RA, PI and HpAl features of the hypothesis. Taken together, 2,6-Et_2-Ph and foramidine structures are important as OA agonists.



2,6-Et_2 AII

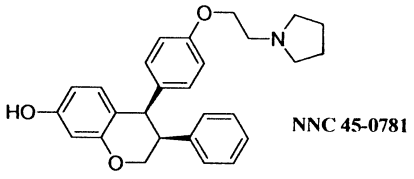
Bioorg. Med. Chem. 10 (2002) 125

Synthesis and Pharmacological Evaluation of Novel *cis*-3,4-Diaryl-hydroxychromanes as High Affinity Partial Agonists for the Estrogen Receptor

Paul S. Bury, Lise B. Christiansen, Poul Jacobsen, Anker S. Jørgensen, Anders Kanstrup, Lars Nærum, Steven Bain, Christian Fledelius, Birgitte Gissel, Birgit S. Hansen, Niels Korsgaard, Susan M. Thorpe and Karsten Wassermann

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

The synthesis and pharmacological evaluation of a series of new tissue-selective estrogens, the *cis*-3,4-diaryl-hydroxy-chromanes, is described.



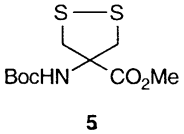
NNC 45-0781

Bioorg. Med. Chem. 10 (2002) 147

Exploring the Interest of 1,2-Dithiolane Ring System in Peptide Chemistry. Synthesis of a Chemotactic Tripeptide and X-ray Crystal Structure of a 4-Amino-1,2-dithiolane-4-carboxylic Acid Derivative

Enrico Morera,[a] Gino Lucente,[a] Giorgio Ortar,[a] Marianna Nalli,[a] Fernando Mazza,[b] Enrico Gavuzzo[b] and Susanna Spisani[c]

[a]*Dipartimento di Studi Farmaceutici and Centro di Studio per la Chimica del Farmaco del CNR, Università degli Studi di Roma "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy*
[b]*Istituto di Strutturistica Chimica, CNR, C.P. n. 10, 00016 Monterotondo Stazione, Rome, Italy*
[c]*Dipartimento di Biochimica e Biologia Molecolare, Università di Ferrara, 44100 Ferrara, Italy*



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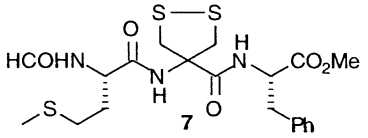


7

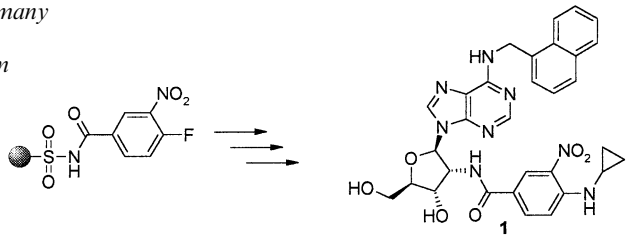
Bioorg. Med. Chem. 10 (2002) 159

Improving an Antitrypanosomal Lead Applying Nucleophilic Substitution on a Safety Catch Linker

Abolfasl Golisade,[a] Claudia Herforth,[a] Ludo Quirijnen,[b] Louis Maes[b] and Andreas Link[a]

[a]*Institut für Pharmazie, Abteilung für Pharmazeutische Chemie, Universität Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany*
[b]*Tibotec Group N.V., Intercity Business Park, Mechelen Noord, Zone L, Generaal de Wittelaan 11B 3, B-2800 Mechelen, Belgium*

Compound **1** obtained via polymer-assisted synthesis using the Kenner safety catch linker displays an IC_{50} of 850 nM on *T. b. brucei* blood stream forms in vitro.

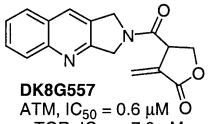


Bioorg. Med. Chem. 10 (2002) 167

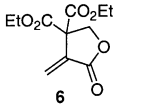
Novel Pyrrolo-quinoline Derivatives as Potent Inhibitors for PI3-Kinase Related Kinases

Hairuo Peng,[a] Doeg-Il Kim,[a] Jann N. Sarkaria,[b] Yong-Seo Cho,[a] Robert T. Abraham[c] and Leon H. Zalkow[a]

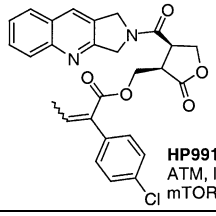
[a]*School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA*
[b]*Department of Oncology, Mayo Clinic, Rochester, MN 55905, USA*
[c]*Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA*



DK8G557
ATM, IC_{50} = 0.6 μM
mTOR, IC_{50} = 7.0 μM



6
ATM, IC_{50} = 0.25 μM
mTOR, IC_{50} > 10 μM



HP9912
ATM, IC_{50} = 6.5 μM
mTOR, IC_{50} = 0.5 μM

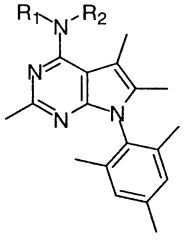
Bioorg. Med. Chem. 10 (2002) 175

$CRHR_1$ Receptor Binding and Lipophilicity of Pyrrolopyrimidines, Potential Nonpeptide Corticotropin-Releasing Hormone Type 1 Receptor Antagonists

Ling-Wei Hsin,[a] Xinrong Tian,[b] Elizabeth L. Webster,[b,c] Andrew Coop,[d] Timothy M. Caldwell,[a] Arthur E. Jacobson,[a] George P. Chrousos,[c] Philip W. Gold,[b] Kamal E. Habib,[b] Alejandro Ayala,[b] William C. Eckelman,[e] Carlo Contoreggi[f] and Kenner C. Rice[a]

[a]*Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 8 Center Drive MSC 0815, Bethesda, MD 20892, USA*
[b]*Clinical Neuroendocrinology Branch, NIMH, National Institutes of Health, 10 Center Drive MSC 1284, Bethesda, MD 20892, USA*
[c]*Pediatric Endocrinology Section, PREB, National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Drive MSC 1583, Bethesda, MD 20892, USA*
[d]*Department of Pharmaceutical Sciences, University of MD, School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, USA*
[e]*PET Department, Clinical Center, Building 10, Room 1C495, National Institutes of Health, 10 Center Drive MSC 1180, Bethesda, MD 20892, USA*
[f]*Molecular Neurobiology Unit, National Institutes on Drug Abuse, National Institutes of Health, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA*

The synthesis of a less lipophilic high affinity $CRHR_1$ ligand is reported.



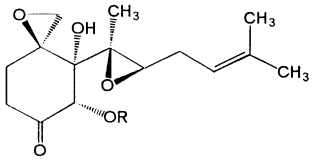
Bioorg. Med. Chem. 10 (2002) 185

5-Demethylovalicin, as a Methionine Aminopeptidase-2 Inhibitor Produced by *Chrysosporium*

Kwang-Hee Son,[a] Ju-Young Kwon,[a] Ha-Won Jeong,[a] Hyae-Kyeong Kim,[a] Chang-Jin Kim,[a] Yie-Hwa Chang,[b] Jung-Do Choi[c] and Byoung-Mog Kwon[a]

[a]*Korea Research Institute of Bioscience and Biotechnology, 52-Eundong, Yusong, Taejon 305-333, Republic of Korea*
[b]*Health Sciences Center, School of Medicine, St. Louis University, 1402 S. Grand Blvd., St. Louis, MO 63104, USA*
[c]*Department of Biochemistry, Chungbuk National University, Cheongju 361-763, Republic of Korea*

5-Demethylovalicin, isolated from the fermentation broth *Chrysosporium* inhibited the recombinant human MetAP-2 (IC_{50} = 17.7 nM) and the growth of human umbilical vein endothelial cells (HUVEC; IC_{50} = 100 nM) in cell proliferation assay without cytotoxicity on the transformed cell lines.



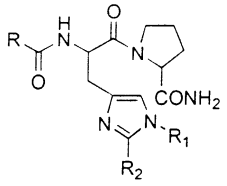
Bioorg. Med. Chem. 10 (2002) 189

Synthesis and Biology of New Thyrotropin-Releasing Hormone (TRH) Analogues

Rahul Jain,[a] Jatinder Singh,[a] Jeffery H. Perlman[b] and Marvin C. Gershengorn[b]

[a]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India*
[b]*Division of Molecular Medicine, Department of Medicine, Weill Medical College of Cornell University, New York, NY 10021, USA*

The synthesis of the several novel TRH analogues and their binding affinities and activation potencies to TRH-R are reported.



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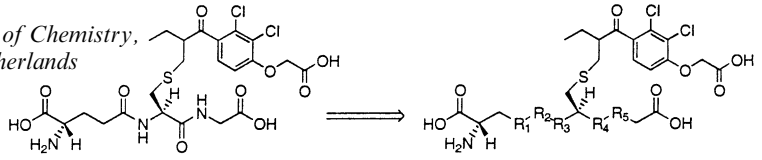
Peptidomimetic Glutathione Analogues as Novel γGT Stable GST Inhibitors

Danny Burg,[a] Dmitri V. Filippov,[b] Ralph Hermanns,[a] Gijs A. van der Marel,[b] Jacques H. van Boom[b] and Gerard J. Mulder[a]

[a]*Division of Toxicology, Leiden/Amsterdam Center for Drug Research, Leiden University, PO Box 9503, 2300RA, Leiden, The Netherlands*
[b]*Division of Bio-Organic Synthesis, Leiden Institute of Chemistry, PO Box 9502, 2300RA, Leiden University, The Netherlands*



Glutathione-Ethacrynic acid

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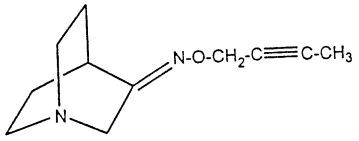
Quinuclidinone *O*-Alkynyloximes with Muscarinic Agonist Activity

Brinda Somanadhan,[a] Weng-Keong Loke,[b] Meng-Kwoon Sim[c] and Mei-Lin Go[a]

[a]*Department of Pharmacy, National University of Singapore, Republic of Singapore*
[b]*Defence Science National Laboratories, Republic of Singapore*
[c]*Department of Pharmacology, National University of Singapore, Republic of Singapore*



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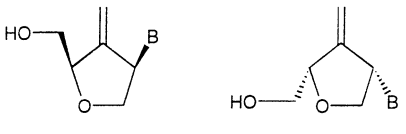
Synthesis of Novel (2*R*,4*R*)- and (2*S*,4*S*)-*iso* Dideoxynucleosides with Exocyclic Methylene as Potential Antiviral Agents

Su Jeong Yoo,[a] Hea Ok Kim,[b] Yoongho Lim,[c] Jeongmin Kim[d] and Lak Shin Jeong[a]

[a]*Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea*
[b]*Division of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Republic of Korea*
[c]*Department of Applied Biology & Chemistry, Konkuk University, Seoul 143-701, Republic of Korea*
[d]*LG Chem/Biotech Research Institute, Taejon, 305-380, Republic of Korea*



B = Pyrimidines and Purines

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New Chemical and Biological Aspects of Artemisinin-Derived Trioxane Dimers

Gary H. Posner,[a] John Northrop,[a] Ik-Hyeon Paik,[a] Kristina Borstnik,[a] Patrick Dolan,[b] Thomas W. Kensler,[b] Suji Xie[c] and Theresa A. Shapiro[c]

[a]*Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, MD 21218, USA*
[b]*Division of Toxicological Sciences and The Environmental Health Sciences Center, Department of Environmental Health Sciences, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD 21205, USA*
[c]*Division of Clinical Pharmacology, Department of Medicine, School of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA*