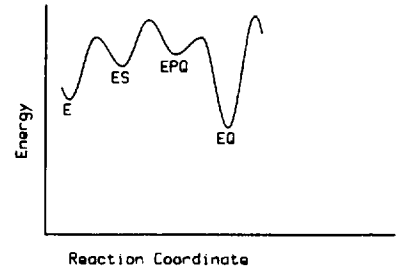
Beyond Enzyme Kinetics: Direct Determination of Mechanisms by Stopped-Flow Mass Spectrometry

Bioorg. Med. Chem. **1997**, *5*, 641

Dexter B. Northrop* and Frank B. Simpson

Division of Pharmaceutical Sciences, School of Pharmacy, University of Wisconsin, Madison, WI 53706, U.S.A.

How to determine the free energy profile for an enzymatic reaction in a single shot.



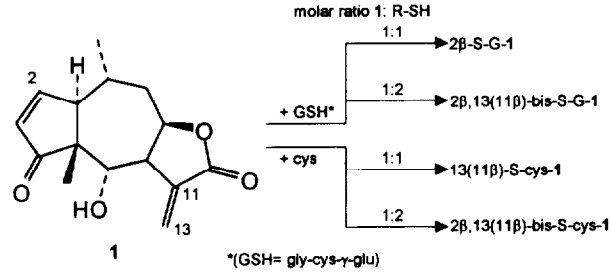
Helenanolide Type Sesquiterpene Lactones—III. Rates and Stereochemistry in the Reaction of Helenalin and Related Helenanolides with Sulfhydryl Containing Biomolecules

Bioorg. Med. Chem. **1997**, *5*, 645

Thomas J. Schmidt

Institut für Pharmazeutische Biologie, Heinrich-Heine-Universität, Universitätsstraße 1, D-40225, Düsseldorf, Germany

The Michael addition of GSH and cys to the two different reactive centers of **1** was shown to be highly stereoselective. Interestingly, the two physiological thiols showed marked differences in reactivity towards the cyclopentenone and the α-methylene-γ-lactone structure.



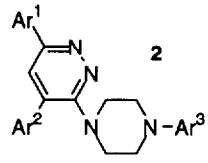
Synthesis and Analgesic Effects of 3-Substituted 4,6-Diarylpyridazine Derivatives of the Arylpiperazine Class

Bioorg. Med. Chem. **1997**, *5*, 655

Florence Rohet,[a] Catherine Rubat,[b] Pascal Coudert,[a] and Jacques Couquelet[a,*]

Groupe de Recherche en Pharmacochimie, [a]Laboratoire de Chimie Thérapeutique and [b]Laboratoire de Pharmacologie, Faculté de Pharmacie, Université d'Auvergne, 28, Place Henri Dunant F63001, Clermont-Ferrand, Cédex, France

Synthesis and antinociceptive activity of pyridazines **2** are reported. Involvement of opiate and serotonergic pathways in analgesic effects of compounds was examined.



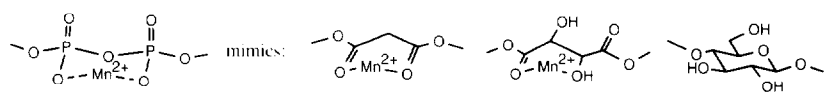
A Search for Pyrophosphate Mimics for the Development of Substrates and Inhibitors of Glycosyltransferases

Bioorg. Med. Chem. **1997**, *5*, 661

Ruo Wang,[a] Darryl H. Steensma,[a,b] Yoshikazu Takaoka,[a] Joanne W. Yun,[a] Tetsuya Kajimoto,[b] and Chi-Huey Wong[a,b,*]

[a]*Department of Chemistry and the Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A. and*

[b]*Frontier Research Program on Glycotechnology, The Institute of Physical and Chemical Research (RIKEN), Saitama, Japan*

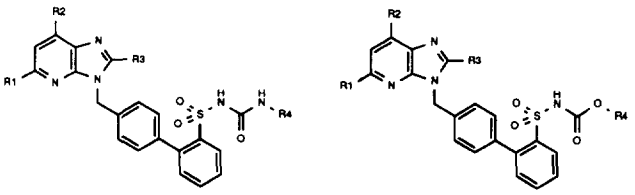


Bioorg. Med. Chem. **1997**, *5*, 673

3*N*-Biphenylsulfonylurea and -Carbamate Substituted Imidazo[4,5-*b*]-Pyridines. Potent Antagonists of ANG II AT_1 Receptors

Holger Heitsch,* Reinhard H. A. Becker, Heinz-Werner Kleemann, and Adalbert Wagner
Hoechst AG, HMR TA Cardiovascular Agents, D-65926 Frankfurt/M., Germany

The synthesis and SAR of 3*N*-biphenylsulfonylurea and -carbamate substituted imidazo[4,5-*b*]pyridines as potent ANG II AT_1 receptor antagonists in vitro and in vivo is described.

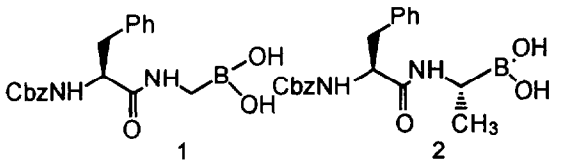


Bioorg. Med. Chem. **1997**, *5*, 679

Cysteine Proteases such as Papain are not Inhibited by Substrate Analog Peptidyl Boronic Acids

Valeri Martichonok and J. Bryan Jones*
Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 1A1

The boronic acid analogs 1 and 2 of good papain substrates have been prepared, but were not found to inhibit the enzyme due to thermodynamic disfavoring of the tetrahedral intermediates of the potential EI-complexes.



Bioorg. Med. Chem. **1997**, *5*, 685

A Microgonotropen Branched Decaaza Decabutylamine and its DNA and DNA/Transcription Factor Interactions

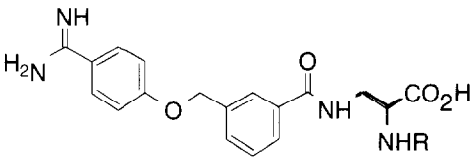
Thomas C. Bruice,[a,*] Dipanjan Sengupta,[a] Andrei Blaskó,[a] S-Y. Chiang,[b] and T. A. Beerman[b,*]
[a]*Department of Chemistry, University of California, Santa Barbara, CA 93106, U.S.A.*
[b]*The Experimental Therapeutics Department, Roswell Park Cancer Institute, Buffalo, NY 14263, U.S.A.*

Decaaza-microgonotropen (**8**) has been synthesized. Its equilibrium binding to d(GGCGCA$_3$T$_3$GGCGG)/(CCGCCA$_3$T$_3$GCGCC) and ctDNA has been measured. The inhibition of binding of transcription factors, TBP, EGR1, and E2F1, to their DNA targets by 8 have been determined. E2F1 transcription factor binding is 50% inhibited at ~2 nM.

Bioorg. Med. Chem. **1997**, *5*, 693

Design, Synthesis, and In Vitro Activities of Benzamide-Core Glycoprotein IIb/IIIa Antagonists: 2,3-Diaminopropionic Acid Derivatives as Surrogates of Aspartic Acid

Chu-Biao Xue,* John Roderick, Sharon Jackson, Maria Rafalski, Arlene Rockwell, Shaker Mousa, Richard E. Olson and William F. DeGrado
Chemical and Physical Sciences and Cardiovascular Diseases, The DuPont Merck Pharmaceutical Company, Experimental Station, P.O. Box 80500, Wilmington, DE 19880, U.S.A.



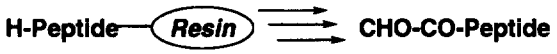
Synthesis of *N*-Glyoxylyl Peptides and Their In Vitro Evaluation as HIV-1 Protease Inhibitors

Bioorg. Med. Chem. **1997**, *5*, 707

Driss Qasmi,[a] Eve de Rosny,[b] Loïc René,[a] Bernard Badet,[a,*] Isabelle Vergely,[b] Nicole Boggetto,[b] and Michèle Reboud-Ravaux[b]

[a]*Institut de Chimie des Substances Naturelles-CNRS, 91198 Gif-sur-Yvette Cedex, France,* [b]*Laboratoire d'Enzymologie Moléculaire et Fonctionelle, Département de Biologie Supramoléculaire et Cellulaire, Institut Jacques Monod & Université Paris VII, 2 place Jussieu 75251, Paris Cedex 05, France*

CHOCO-Peptides synthesized using SPPS were found to be HIV-1 protease inhibitors.



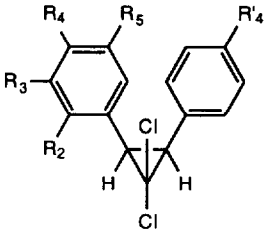
Synthesis and Biological Evaluation of 1,1-Dichloro-2,3-diarylcyclopropanes as Antitubulin and Anti-Breast Cancer Agents

Bioorg. Med. Chem. **1997**, *5*, 715

Sastry S. Jonnalagadda,[a] Ernst ter Haar,[a] Ernest Hamel,[d] Chii M. Lin,[d] Robert A. Magarian,[c] and Billy W. Day[a,b,c,*]

[a,b,c]*University of Pittsburgh, Pittsburgh, PA 15238, U.S.A.;* [d]*National Cancer Institute, Frederick, MD 21702, U.S.A. and* [c]*University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, U.S.A.*

Synthesis of aryl ring substituted derivatives of *Z*-1,1-dichloro-2,3-diphenylcyclopropane led to the discovery of more potent antitubulin and antiproliferative agents.



R = H, OCH_3, OCH_2Ph, F, Cl, Br

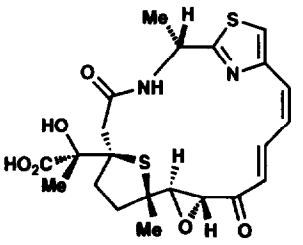
Thiol-independent DNA Cleavage by a Leinamycin Degradation Product

Bioorg. Med. Chem. **1997**, *5*, 723

Akira Asai,* Hiromitsu Saito and Yutaka Saitoh

Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194, Japan

Leinamycin induces single-strand scission of DNA in the presence of thiol. Compound **3** which was obtained from leinamycin treated with thiol showed potent DNA cleavage activity in the absence of thiol. This observation along with the activity of derivatives indicates a novel mechanism of thiol-activiation for DNA-damage by leinamycin.



3

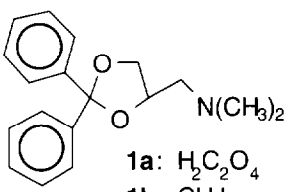
Synthesis and Structure–Activity Relationship Studies in a Series of 2-Substituted 1,3-Dioxolanes Modified at the Cationic Head

Bioorg. Med. Chem. **1997**, *5*, 731

P. Angeli,[a,*] L. Brasili,[b] M. L. Cingolani,[c] G. Marucci,[a] A. Piergentili,[a] M. Pigini[a] and W. Quaglia[a]

[a]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy;* [b]*Dipartimento di Scienze Farmaceutiche, Università di Modena, Via Campi 183, 41100 Modena, Italy; and* [c]*Istituto di Scienze Biomediche, Scuola di Medicina, Università di Ancona, Via Ranieri, 60100 Ancona, Italy*

A series of muscarinic antagonist analogues of **1a** and **1b** bearing a modified cationic head were synthesized and tested on M_1, M_2 and M_3 subtypes. The results show that an ethyl substituent improves the affinity at the three subtypes and a phenethyl substituent seems to lead to M_3 selectivity.

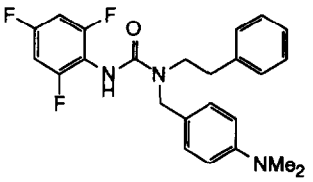


1a: $H_2C_2O_4$
1b: CH_3I

Inhibitors of Acyl-CoA:Cholesterol Acyltransferase: Novel Trisubstituted Ureas as Hypocholesterolemic Agents

Bioorg. Med. Chem. **1997**, *5*, 739

Terri S. Purchase,*[a] Arnold D. Essenburg,[b] Katherine L. Hamelehle,[b] MaryKay S. Hes,[b] Ann Holmes,[a] Brian R. Krause,[b] Richard L. Stanfield[b] and Bharat K. Trivedi[a]
Departments of [a]Medicinal Chemistry and [b]Vascular and Cardiac Diseases, Parke–Davis Pharmaceutical Research, Division of Warner–Lambert Company, Ann Arbor, MI 48105, U.S.A.

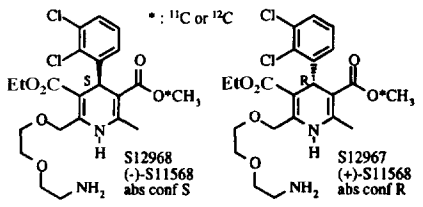


Synthesis of Two Optically Active Calcium Channel Antagonists Labelled with Carbon-11 for In Vivo Cardiac PET Imaging

Bioorg. Med. Chem. **1997**, *5*, 749

F. Dollé,[a,*] F. Hinnen,[a] H. Valette,[a] C. Fuseau,[a] R. Duval,[b,c] J.-L. Péglion,[b] and C. Crouzel[a]
[a]Service Hospitalier Frédéric Joliot, CEA, 4 place du Général Leclerc, F-91406 Orsay, France; [b]Institut de Recherches Servier, 11 rue des Moulineaux, F-92150 Suresnes, France; and [c]Currently: ChiralSep, P. A. de la Boissière, 11 rue de la Boissière, F-76170 La Frenaye, France

S12968 and S12967 have been independently labelled with carbon-11, using [^{11}C]diazomethane or [^{11}C]iodomethane and evaluated as tracers for in vivo imaging with PET of the myocardium low-voltage dependent L-type calcium channel. Optically active labelling precursors have been synthesized using a modified Hantzsch's dihydropyridine synthesis. Separation of the enantiomers was performed using preparative chiral HPLC.

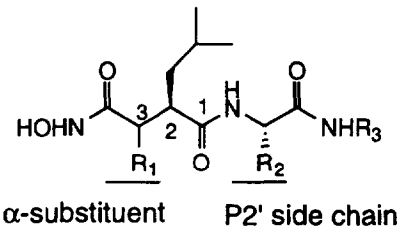


Synthesis and Biological Evaluation of Orally Active Matrix Metalloproteinase Inhibitors

Bioorg. Med. Chem. **1997**, *5*, 765

Ryoichi Hirayama,[c] Minoru Yamamoto,[a] Takahiro Tsukida,[a] Konomi Matsuo,[b] Yuji Obata,[c] Fumio Sakamoto,[b] and Shoji Ikeda[a,*]
[a]New Drug Discovery Research Laboratory, [b]New Drug R & D Laboratory and [c]Product R & D Laboratory, Kanebo, Ltd, 1-5-90 Tomobuchi-Cho, Miyakojima-Ku, Osaka 534, Japan

The synthesis and biological evaluation of orally active inhibitors of matrix metalloproteinase are reported.



N-(5-Substituted) Thiophene-2-alkylsulfonamides as Potent Inhibitors of 5-Lipoxygenase

Bioorg. Med. Chem. **1997**, *5*, 779

Scott A. Beers,* Elizabeth A. Malloy, Wei Wu, Michael Wachter, Justin Ansell, Monica Singer, Michele Steber, Arminda Barbone, Thomas Kircher, David Ritchie, and Dennis Argentieri
The R.W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan NJ 08869, U.S.A.

Compound **4b** is representative of a new and versatile class of 5-LO inhibitors that show dose dependent inhibition of 5-LO with IC_{50}s ranging from 20–100 nM in RBL-1 cell homogenate and submicromolar IC_{50}s in both the PBL whole cell assays.