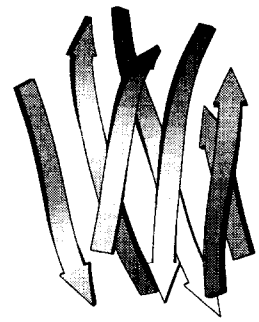
Progress Towards Understanding β-Sheet Structure

Bioorg. Med. Chem. **1996**, *4*, 739

Carey L. Nesloney and Jeffery W. Kelly*
Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, U.S.A.

This review is focused on our current understanding of β-sheet structure, formation, characterization, and design with an emphasis being placed on recent advances.

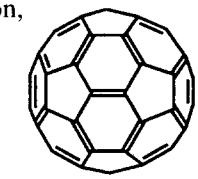


Biological Applications of Fullerenes

Bioorg. Med. Chem. **1996**, *4*, 767

Anton W. Jensen, Stephen R. Wilson* and David I. Schuster*
Department of Chemistry, New York University, Washington Square, New York, NY 10003 6688, U.S.A.

Fullerenes and fullerene derivatives with demonstrated or potential biological applications are surveyed. These applications include: enzyme inhibition, antiviral activity, DNA cleavage, photodynamic therapy, electron transfer, and other in vitro and in vivo biological effects. The metabolism, excretion, and toxicity of C_{60} and its derivatives are also discussed.



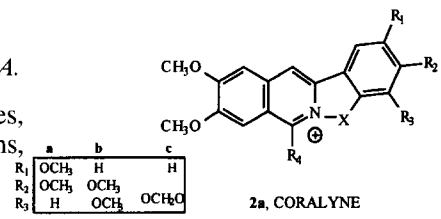
Coralyne and Related Compounds as Mammalian Topoisomerase I and Topoisomerase II Poisons

Bioorg. Med. Chem. **1996**, *4*, 781

Darshan Makhey,[a] Barbara Gatto,[b] Chiang Yu,[b]
Angela Liu,[b] Leroy F. Liu[b] and Edmond J. LaVoie[a,*]
[a]*Dept. of Pharm. Chem., Rutgers University, Piscataway, NJ 08855, U.S.A.*
[b]*Dept. of Pharmacol., UMDNJ-RWJ Medical School, Piscataway, NJ 08855, U.S.A.*

Coralyne and related compounds, including ring opened analogues, were synthesized, evaluated as mammalian topoisomerase I poisons, and their cytotoxicity determined.

2a-c: X = CH = CH, $R_4 = CH_3$ **8a-c**: X = CH_2–CH_2, R_4 = H
7a-c: X = CH_2–CH_2, $R_4 = CH_3$ **10a-c**: X = CH = CH, R_4 = H

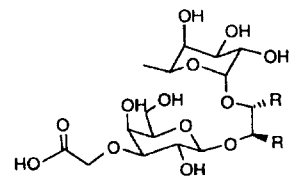


Mimics of the Sialyl Lewis X Tetrasaccharide. Replacement of the *N*-Acetylglucosamine Sugar with Simple C_2-Symmetric 1,2-Diols

Bioorg. Med. Chem. **1996**, *4*, 793

Jeremy C. Prodger,* Mark J. Bamford, Michael I. Bird,[a] Paul M. Gore, Duncan S. Holmes, Richard Priest[a] and Victoria Saez
Departments of Medicinal Chemistry and [a]Molecular Science, Glaxo Research and Development Ltd, Glaxo Wellcome Medicines Resarch Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, U.K.

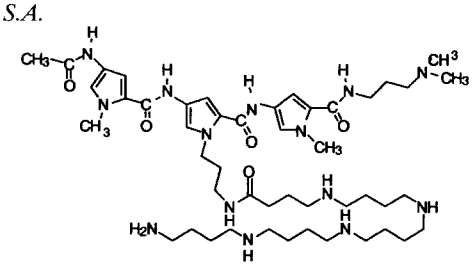
Analogues of sialyl Lewis X (sLe^x) have been synthesized. One mimic which features a cyclohexyl replacement for *N*-acetylglucosamine is equipotent sLe^x.



A Microgonotropen Pentaaza Pentabutylamine and its Interactions with DNA

Bioorg. Med. Chem. **1996**, *4*, 803

Dipanjan Sengupta, Andrei Blaskó and Thomas C. Bruice*
Department of Chemistry, University of California, Santa Barbara, CA 93106, U.S.A.

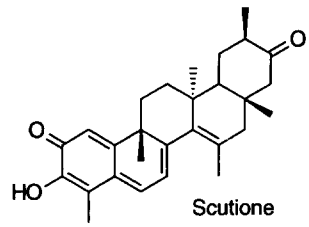


Scutione, a New Bioactive Norquinonemethide Triterpene from *Maytenus scutioides* (Celastraceae)

Bioorg. Med. Chem. **1996**, *4*, 815

Antonio G. González,[a,*] Nelson L. Alvarenga,[a] Angel G. Ravelo,[a] Isabel L. Bazzocchi,[a] Esteban A. Ferro,[b] Angel G. Navarro[c] and Laila M. Moujir[c]
[a]Instituto Universitario de Bio-Orgánica Antonio González, Universidad de La Laguna, Avda. Astrofísico F° Sánchez, 2, 38206, La Laguna, Tenerife, Canary Islands, Spain. [b]Departamento de Investigación, Universidad Nacional de Asunción, San Lorenzo, P.O. Box 1055, Paraguay. [c]Departamento de Microbiología y Biología Celular, Universidad de La Laguna, Tenerife, Canary Islands, Spain

Scutione, a new norquinonemethide triterpene, with a netzahualcoyene type skeleton, has been isolated from the root bark of *Maytenus scutioides* (Celastraceae) by bioactivity-directed fractionation. The structure has been elucidated by means of ^{1}H and ^{13}C NMR spectroscopic studies. Scutione showed antibiotic activity against Gram-positive bacteria and modest cytotoxic activity against HeLa and Hep-2 cell lines. Fluoride derivatives were prepared and assayed for bioactivity.



Bioorg. Med. Chem. **1996**, *4*, 821

The Iron(II)/Reductant (DH_2)-Induced Activation of Dioxygen for the Demethylation of *N*-Methylanilines: Reaction Mimic for the Cytochrome P-450/Reductase System

John P. Hage, Joseph R. Schnelten and Donald T. Sawyer*
Department of Chemistry, Texas A&M University, College Station, TX 77843, U.S.A.

Iron(II) complexes [$Fe^{II}L_x$; e.g., $Fe^{II}(DAPH)_2$ ($DAPH_2$ = 2,6-dicarboxyl pyridine)] in combination with a reductant [DH_2; PhNHNHPh] activate O_2 for the demethylation of *N*-methylanilines.

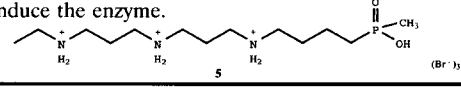
$$PhN(CH_3)_2 + O_2 + DH_2 \xrightarrow{Fe^{II}L_x} PhNH(CH_3) + H_2C{=}O + H_2O + D$$

Synthesis and Evaluation of a Polyamine Phosphinate and Phosphonamidate as Transition State Analogue Inhibitors of Spermidine/Spermine-N^1-Acetyltransferase

Bioorg. Med. Chem. **1996**, *4*, 825

Ronghui Wu,[a] Nada H. Saab,[a] Huatao Huang,[b] Laurie Wiest,[b] Anthony E. Pegg,[b] Robert A. Casero, Jr[c] and Patrick M. Woster*[,a]
[a]Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, Wayne State University, Detroit, MI 48202, U.S.A. [b]Departments of Cellular and Molecular Physiology, College of Medicine, Hershey Medical Center, Pennsylvania State University, Hershey, PA 17033, U.S.A. [c]The Johns Hopkins Oncology Center, Johns Hopkins University, Baltimore, MD 21231, U.S.A.

The synthetic routes leading to polyamine phosphonamidate and phosphinate transition-state mimics for the spermidine/spermine-N^1-acetyltransferase reaction are described. Phosphinate **5** (shown) is an effective inhibitor of the enzyme, with a K_i value of 250 μM. This analogue is a functional inhibitor that, unlike bis(ethyl)spermine, does not superinduce the enzyme.

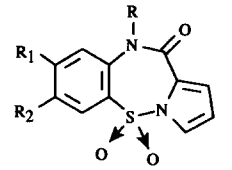


Bioorg. Med. Chem. **1996**, *4*, 837

5*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs): A Novel Class of Non-Nucleoside Reverse Transcriptase Inhibitors

Marino Artico,[a,*] Romano Silvestri,[a] Eugenia Pagnozzi,[a] Giorgio Stefancich,[b] Silvio Massa,[c] Anna Giulia Loi,[d] Monica Putzolu,[d] Simona Corrias,[d] Maria Grazia Spiga[d] and Paolo La Colla[d]
[a]*Università di Roma "La Sapienza", 00185 Roma, Italy.* [b]*Università di Trieste, 34127 Trieste, Italy.* [c]*Università di Siena, 53100 Siena, Italy.* [d]*Università di Cagliari, 00124 Cagliari, Italy*

PBTDs are a new class of specific inhibitors of human immunodeficiency virus type-1 (HIV-1) targeted at the reverse transcriptase (NNRTIs) showing antiviral activity in the range 0.5–1.0 μM. Activities of compounds against the HIV-1 and HIV-2 multiplication in MT-4 cells and recombinant RT in enzyme assays are reported.



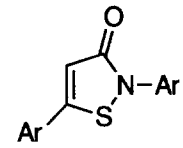
R=H, alkyl; R_1=R_2=H,Cl

Bioorg. Med. Chem. **1996**, *4*, 851

2,5-Diarylisothiazolones: Novel Inhibitors of Cytokine-Induced Cartilage Destruction

S. W. Wright, J. J. Petraitis,* B. Freimark, J. V. Giannaras, M. A. Pratta, S. R. Sherk, J. M. Williams, R. L. Magolda and E. C. Arner
The Du Pont Merck Pharmaceutical Company, Wilmington, DE 19880, U.S.A.

A series of novel 2,5-diarylisothiazolones (**1**) is reported that inhibit the IL-1β induced breakdown of cartilage in an organ culture assay. These compounds appear to inhibit cartilage breakdown by interfering with the proteolytic activation of matrix metalloproteinase.



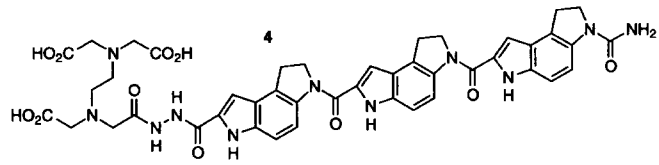
1

Bioorg. Med. Chem. **1996**, *4*, 859

Demonstration and Definition of the Noncovalent Binding Selectivity of Agents Related to CC-1065 by an Affinity Cleavage Agent: Noncovalent Binding Coincidental with Alkylation

Dale L. Boger,* Jiacheng Zhou and Hui Cai
Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

A study of the DNA cleavage efficiency and selectivity of CDPI$_3$–EDTA (**4**), an affinity cleavage agent based on the structure of CC-1065, is described. The studies with **4** provide direct evidence of AT-rich noncovalent binding coincidental with all DNA alkylation sites observed with (+)- or *ent*-(−)-CC-1065.

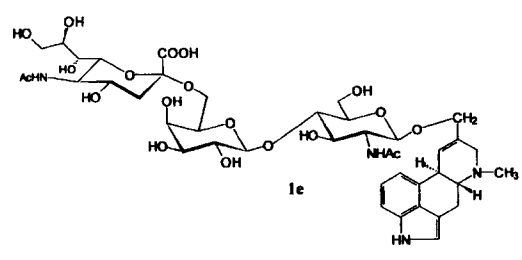


4

Bioorg. Med. Chem. **1996**, *4*, 869

Ergot Alkaloid Glycosides with Immunomodulatory Activities

Vladimír Křen,*[,a] Anna Fišerová,[a] Claudine Augé,[b] Petr Sedmera,[a] Vladimír Havlíček[a] and Petr Šíma[a]
[a]*Institute of Microbiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, CZ-142 20 Prague 4, Czech Republic.* [b]*Université de Paris-Sud, Institut de Chimie Moleculaire d'Orsay, Laboratoire de Chimie Organique Multifonctionnelle, URA CNRS 462, bât. 420, F-91405 Orsay, France*



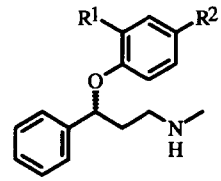
1e

Bioorg. Med. Chem. **1996**, *4*, 877

An Efficient Chemoenzymatic Route to the Antidepressants (*R*)-Fluoxetine and (*R*)-Tomoxetine

Franz Bracher* and Thomas Litz
Institut für Pharmazeutische Chemie der Technischen Universität Braunschweig, Beethovenstr. 55, 38106 Braunschweig, Germany

A new and efficient method for the preparation of (*R*)-fluoxetine (**7a**) and (*R*)-tomoxetine (**7b**) is reported.



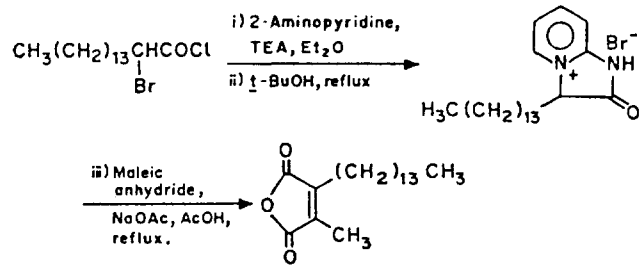
7a: R^1=H, R^2=CF_3
7b: R^1=CH_3, R^2=H

Bioorg. Med. Chem. **1996**, *4*, 881

A Simple and Efficient Synthesis of the Ras Farnesyl-Protein Transferase Inhibitor Chaetomellic Acid A

Narshinha P. Argade* and Rajan H. Naik
Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

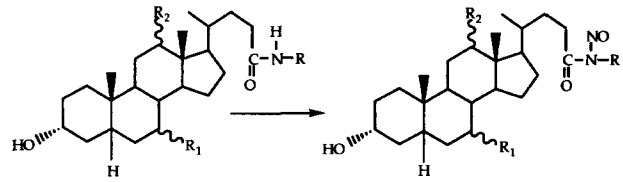
A simple and efficient synthesis of the ras farnesyl-protein transferase inhibitor chaetomellic acid A anhydride is reported.



Bioorg. Med. Chem. **1996**, *4*, 885

Chemical Synthesis, Structural Analysis, and Decomposition of *N*-Nitroso Bile Acid Conjugates

Bishambar Dayal,[a,*] Jalpa Bhojawala,[a] Keshava R. Rapole,[a] Birendra N. Pramanik,[b] Norman H. Ertel,[a] Sarah Shefer[a] and Gerald Salen[a]
[a]*Medical Service, Veterans Administration Medical Center, East Orange, NJ 07019,U.S.A., and Department of Medicine, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ 07103, U.S.A.* [b]*Schering-Plough Research Institute, Kenilworth, NJ 07033, U.S.A.*

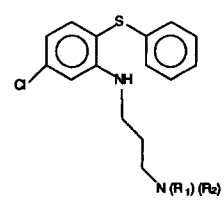


Bioorg. Med. Chem. **1996**, *4*, 891

2-Amino Diphenylsulfides as Inhibitors of Trypanothione Reductase: Modification of the Side Chain

S. Baillet,[a] E. Buisine,[a] D. Horvath,[a,*] L. Maes,[b] B. Bonnet[a] and C. Sergheraert[a]
[a]*Institut Pasteur de Lille, URA 1309 CNRS, Faculté de Pharmacie, 1 rue Calmette, 59019 Lille Cedex, France,* [b]*Janssen Research Foundation, Turnhoutseweg 30, Beerse, Belgium*

A molecular modeling study meant to detect pharmacophore-like patterns in the active site of trypanothione reductase (TR) offered hints about the opportunity of synthesizing and testing diphenylsulfide derivatives with prolonged or branched polyamino side chains as putative TR inhibitors. The inhibition results within the synthesized series confirmed the main working hypothesis inspired by the molecular modeling study. The different compounds were tested in vitro on enzyme, on trypomastigote form of *T. cruzi* and *T. brucei* as well as in vivo on mice.

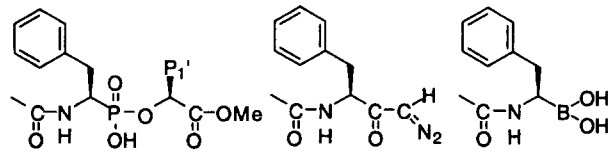


Bioorg. Med. Chem. **1996**, *4*, 901

Synthesis of Five Enantiomerically Pure Haptens Designed for In Vitro Evolution of Antibodies with Peptidase Activity

Jürgen Wagner, Richard A. Lerner* and Carlos F. Barbas, III*
Department of Chemistry and Molecular Biology, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Haptens were designed for the recruitment of serine and cysteine protease reaction mechanisms from combinatorial antibody libraries for the cleavage of dipeptide analogues.

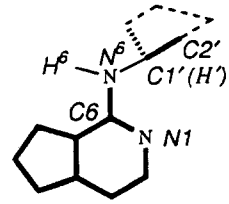


Bioorg. Med. Chem. **1996**, *4*, 917

Conformational Search for the N^6-Substituted Adenosine Analogues and Related Adenosine A_1 Receptor Antagonists

Michael J. Dooley, Motomichi Kono* and Fumio Suzuki*
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co. Ltd, 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken 411, Japan

Newly established global minima for these compounds (C1′-N^6-C6-N1 torsion: 10°) are consistent with retrieved structures from the Cambridge Structural Database and previously published NMR data.



Bioorg. Med. Chem. **1996**, *4*, 923

Theoretical Structure–Activity Studies of Adenosine A_1 Ligands: Requirements For Receptor Affinity

Michael J. Dooley, Motomichi Kono* and Fumio Suzuki*
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co. Ltd, 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken 411, Japan

The 3-D requirements for A_1 adenosine receptor affinity have been studied based on hydrogen-bonding functionality correlation between a group of twelve A_1 adenosine receptor ligands.