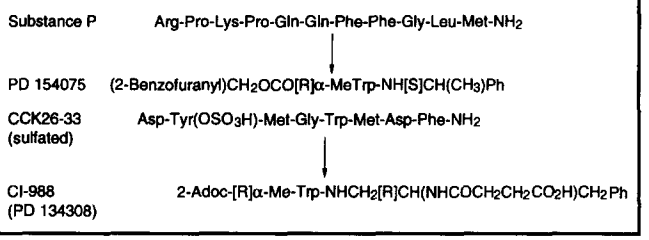
Use of the Chemical Structure of Peptides as the Starting Point to Design Nonpeptide Agonists and Antagonists at Peptide Receptors: Examples with Cholecystokinin and Tachykinins

Bioorg. Med. Chem. **1996**, *4*, 1573

David C. Horwell
Parke-Davis Neuroscience Research Centre, The Forvie Site, Robinson Way, Cambridge CB2 2QB, U.K.

This review summarizes a design strategy to give examples of nonpeptides starting from cholecystokinin (CCK-A and -B) and tachykinins (substance P) (NK-1, -2, -3) as potent functional agonists and antagonists with utility as therapeutic agents.

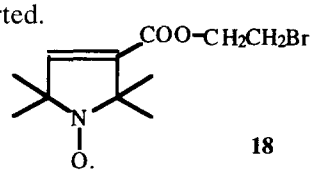


New Amino-Nitroxide Spin Labels

Bioorg. Med. Chem. **1996**, *4*, 1577

Ileana Dragutan,[a,*] Agneta Caragheorgheopol,[b] Filip Chiraleu,[a] and Rolf J. Mehlhorn[c]
[a]*Institute of Organic Chemistry, Romanian Academy, P.O.B. 15-258, Bucharest, Romania*
[b]*Institute of Physical Chemistry, Romanian Academy, Bucharest, Romania*
[c]*University of California, Lawrence Berkeley Laboratory, Berkeley, U.S.A.*

The synthesis of novel amino-nitroxides using *i.a.* **18** as an alkylating agent is reported.



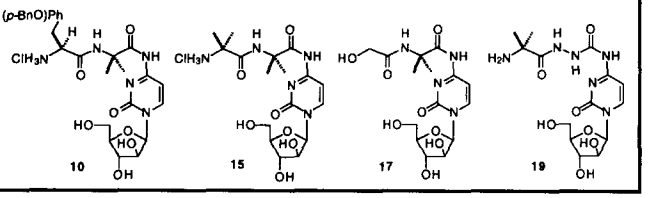
18

Synthesis of Chemoreversible Prodrugs of *ara*-C with Variable Time-Release Profiles. Biological Evaluation of Their Apoptotic Activity

Bioorg. Med. Chem. **1996**, *4*, 1585

Peter Wipf,[a,*] Wenjie Li,[a] Christianah M. Adeyeye,[b] James M. Rusnak[c] and John S. Lazo[c,*]
[a]*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, U.S.A.*
[b]*Department of Pharmaceutics, Duquesne University, Pittsburgh, PA 15282, U.S.A.*
[c]*Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15260, U.S.A.*

N^4-Dipeptidyl and azapeptide slow-release forms of the anticancer drug *ara*-C were prepared by acylation of the lithiated nucleotide. All four prodrugs retained the ability to induce apoptosis in human HL-60 leukemia cells with kinetics dictated by the rate of intramolecular N^4-deacylation.

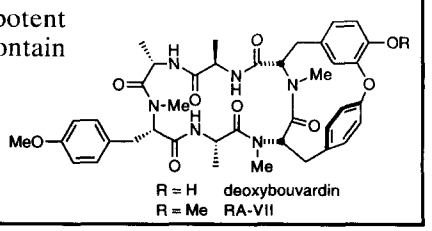


Key Analogues of the Tetrapeptide Subunit of RA-VII and Deoxybouvardin

Bioorg. Med. Chem. **1996**, *4*, 1597

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

The synthesis and evaluation of the two key analogues **3** and **4** of the potent antitumor agents deoxybouvardin (**1**) and RA-VII (**2**) which contain fundamental modifications in the tetrapeptide subunit are described.

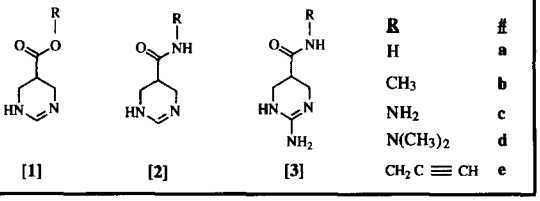


Synthesis and Biochemical Activity of Novel Amidine Derivatives as m1 Muscarinic Receptor Agonists

Bioorg. Med. Chem. **1996**, *4*, 1605

Babatunde Ojo, Philip G. Dunbar, Graham J. Durant, Peter I. Nagy, James J. Huzl, III, Sumudra Periyasamy, Dan O. Ngur, Afif A. El-Assadi, Wayne P. Hoss and William S. Messer, Jr*
Department of Medicinal and Biological Chemistry, Center for Drug Design and Development, College of Pharmacy, The University of Toledo, 2801 West Bancroft Street, Toledo, OH 43606, U.S.A.

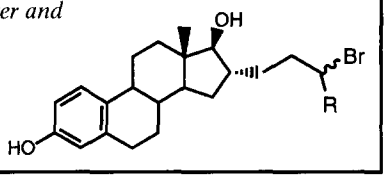
Several amidine derivatives (e.g. **1b** and **1e**) display selective m1 muscarinic agonist activity, and may be useful in the treatment of Alzheimer's disease. To further develop the amidine series, a number of amide and hydrazide derivatives (**2a–e**) and **3b–d**) were synthesized and examined for m1 muscarinic agonist activity.



Bioorg. Med. Chem. **1996**, *4*, 1617

Synthesis and Evaluation of Estradiol Derivatives With 16α-(Bromoalkylamide), 16α-(Bromoalkyl) or 16α-(Bromoalkynyl) Side Chain as Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 1 Without Estrogenic Activity

Joëlle D. Pelletier and Donald Poirier*
Medicinal Chemistry Division, Molecular Endocrinology Laboratory, CHUL Research Center and Laval University, Ste-Foy, PQ G1V 4G2, Canada

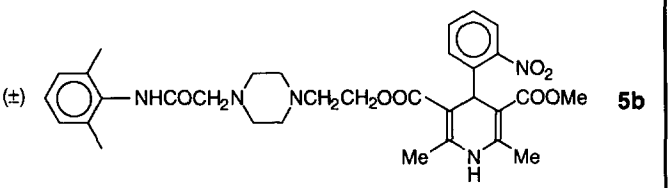


Bioorg. Med. Chem. **1996**, *4*, 1629

1,4-Dihydropyridines Bearing a Pharmacophoric Fragment of Lidoflazine

A. Chiarini, A. Rampa, R. Budriesi, A. Bisi, G. Fabbri, and P. Valenti*
Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy

1,4-Dihydropyridines bearing a pharmacophoric fragment of lidoflazine have been synthesized and found to be negative inotropic and chronotropic agents. A compound of particular interest is **5b**.

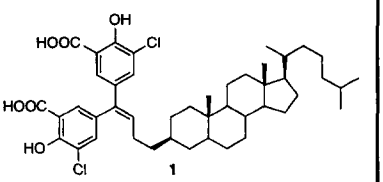


Bioorg. Med. Chem. **1996**, *4*, 1637

Exploration of the Effects of Linker Chain Modifications on Anti-HIV Activities in a Series of Cosalane Analogues

W. Marek Golebiewski, Robert F. Keyes and Mark Cushman*
Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, U.S.A.

The effects of linker chain modifications on anti-HIV activity were investigated in a series of cosalane (**1**) analogues. The modifications included shortening and lengthening the linker chain between the steroid and the dichlorodisalicylmethane pharmacophore, as well as changing the point of attachment of the linker chain to the steroid. The results indicate that the linker chain and attached steroid provide a general lipophilic appendage for the pharmacophore.

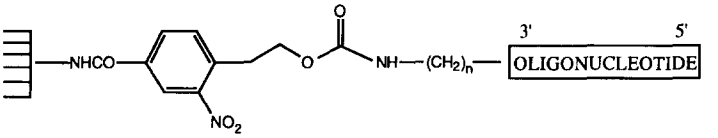


Bioorg. Med. Chem. **1996**, *4*, 1649

New Carbamate Supports for the Preparation of 3′-Amino-modified Oligonucleotides

Anna Aviñó,[a] Ramon Güimil Garcia,[b] Fernando Albericio,[c] Matthias Mann,[b] Matthias Wilm,[b] Gitte Neubauer[b] and Ramon Eritja[b,*]
[a]*Department of Molecular Biology, Centro de Investigación y Desarrollo-CSIC, Jordi Girona 18–26, E-08034 Barcelona, Spain*
[b]*European Molecular Biology Laboratory, Meyerhofstrasse 1, D-69117 Heidelberg, Germany*
[c]*Department of Organic Chemistry, Facultat de Química, Universitat de Barcelona, Martí i Franqués 1–11, E-08028 Barcelona, Spain*

The synthesis of oligonucleotides carrying several amino groups at the 3′-end is reported.

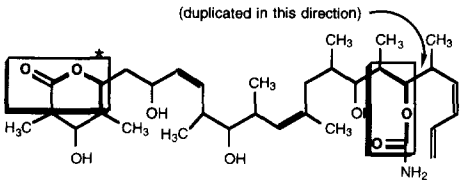


Bioorg. Med. Chem. **1996**, *4*, 1659

Computational and Molecular Modeling Evaluation of the Structural Basis for Tubulin Polymerization Inhibition by Colchicine Site Agents

Ernst ter Haar,[a] Herbert S. Rosenkranz,[a,b] Ernest Hamel[c] and Billy W. Day[a,b,d,*]
[a]*Department of Environmental and Occupational Health, University of Pittsburgh Cancer Institute, University of Pittsburgh, 260 Kappa Drive, Pittsburgh, PA 15238, U.S.A.* [b]*University of Pittsburgh Cancer Institute, University of Pittsburgh, 260 Kappa Drive, Pittsburgh, PA 15238, U.S.A.* [c]*Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, U.S.A.* [d]*Department of Pharmaceutical Sciences, University of Pittsburgh Cancer Institute, University of Pittsburgh, 260 Kappa Drive, Pittsburgh, PA 15238, U.S.A.*

Computational QSAR led to discovery of the potent microtubule stabilizer (+)-discodermolide.



Bioorg. Med. Chem. **1996**, *4*, 1673

Prediction of Relative Potency of Ketone Protease Inhibitors using Molecular Orbital Theory

A. W. Edith Chan[a,b,*] and Julian M. C. Golec[a]
[a]*Hoechst Marion Roussel, Kingfisher Drive, Covingham, Swindon, SN3 5BZ, U.K.* [b]*Selectide, 1580 E. Hanley Blvd, Tucson, AZ 85737-9525, U.S.A.*

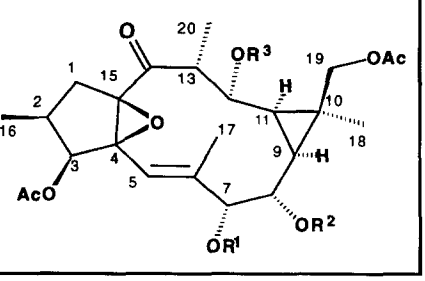
A comparison of the LUMO energy of the model heterocyclic ketone protease inhibitors shows a correlation with the electrophilicity of the carbonyl. The results provide a simple means of predicting relative inhibitor potency.

Bioorg. Med. Chem. **1996**, *4*, 1679

New 19-Acetoxyingol Diterpenes from the Latex of *Euphorbia poisonii* (Euphorbiaceae)

Majekodunmi O. Fatope,[a] Lu Zeng, [b] Joseph E. Ohayagha[a] and Jerry L. McLaughlin[b,*]
[a]*Department of Chemistry, Bayero University, PMB 3011, Kano, Nigeria*
[b]*Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, IN 47907, U.S.A.*

The poisonous latex of *Euphorbia poisonii* gave bioactive 3,12-diacetyl-8-nicotinyl-7-phenylacetyl 19-acetoxyingol (**1**) together with its less active congeners, 3,12-diacetyl-7-phenylacetyl 19-acetoxyingol (**2**) and 3-acetyl-7-phenylacetyl 19-acetoxyingol (**3**). Bioactivity-guided isolation, structure determination and cytotoxic activity of the new ingols are described.



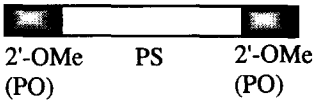
Hybrid Oligonucleotides: Synthesis, Biophysical Properties, Stability Studies, and Biological Activity

Bioorg. Med. Chem. **1996**, *4*, 1685

Dong Yu,[a] Radhakrishnan P. Iyer[a], Denise R. Shaw,[b] Julianna Lisziewicz,[c] Ying Li,[a] Zhiwei Jiang,[a] Allysen Roskey[a] and Sudhir Agrawal[a,*]

[a]Hybridon Inc., One Innovation Drive, Worcester, MA 01605, U.S.A.; [b]Comprehensive Cancer Center, 690 WTI, University of Alabama at Birmingham, AL 35294, U.S.A.; [c]Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, U.S.A.

Hybrid oligonucleotides containing segments of 2′-OMe ribonucleoside phosphoric diester (PO) segments in a deoxynucleoside phosphorothioate (PS) framework shows improved antisense properties.



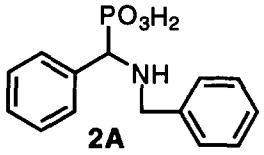
Phosphatase Inhibitors—III. Benzylaminophosphonic Acids as Potent Inhibitors of Human Prostatic Acid Phosphatase

Bioorg. Med. Chem. **1996**, *4*, 1693

Scott A. Beers,* Charles F. Schwender, Deborah A. Loughney, Elizabeth Malloy, Keith Demarest and Jerold Jordan

The R.W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan, NJ 08869, U.S.A.

Compound **2A** has an IC_{50} of 4 nM against the target enzyme. The synthesis, molecular modeling, and SAR of these compounds are detailed.



2A

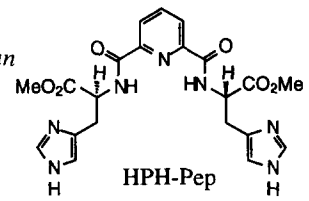
An Artificial Cu^{II} Complex with Intriguing Oxygen Radical-Quenching Profile. X-Ray Structure, Cytochrome c Assay, and ESR Study

Bioorg. Med. Chem. **1996**, *4*, 1703

Masami Otsuka,[a,*] Honoo Satake,[a] Satoru Murakami,[b] Mitsunobu Doi,[c] Toshimasa Ishida,[c] Masakatsu Shibasaki[b] and Yukio Sugiura[a,*]

[a]Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan
[b]Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan
[c]Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-11, Japan

Cu^{II} complex of a novel artificial peptide named HPH-Pep showed superoxide-scavenging activity with a unique profile. HPH-Pep–Cu^{II} did not generate hydrogen peroxide upon scavenging superoxide and the scavenging activity was specific to superoxide.



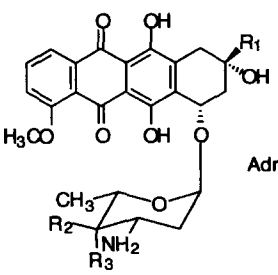
HPH-Pep

Bioorg. Med. Chem. **1996**, *4*, 1709

Some Aspect of the Interactions of Adriamycin with Human Serum Albumin

Lilianna Trynda-Lemiesz and Henryk Kozlowski

Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50383 Wroclaw, Poland



Adriamycin

Bioorg. Med. Chem. **1996**, *4*, 1715

Investigation on QSAR and Binding Mode of a New Class of Human Rhinovirus-14 Inhibitors by CoMFA and Docking Experiments

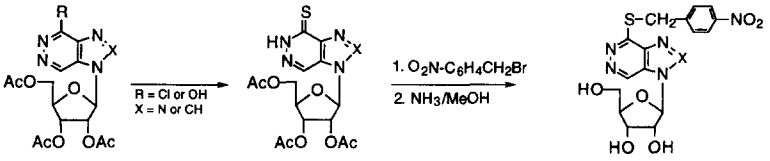
Marino Artico,[a] Maurizio Botta,[b,c,*] Federico Corelli,[b,c,*] Antonello Mai,[a] Silvio Massa[b] and Rino Ragno[b]
[a]Dipartimento di Studi Farmaceutici, Università 'La Sapienza', P.le A. Moro 5, I-00185 Roma, Italy; [b]Dipartimento Farmaco Chimico Tecnologico; and [c]Centro Interdipartimentale per lo Studio Strutturale dei Sistemi Biomolecolari, Università di Siena, Banchi di Sotto 55, I-53100 Siena, Italy

Bioorg. Med. Chem. **1996**, *4*, 1725

The Synthesis and Biological Evaluation of 4-*p*-Nitrobenzylthio-ν-triazolo[4,5-*d*]pyridazine and Imidazo[4,5-*d*]pyridazine Ribosides as Potential Nucleoside Transport Inhibitors

Jacqueline C. Bussolari,[a] Johanna D. Stoeckler[b] and Raymond P. Panzica[a,*]
[a]Departments of Medicinal Chemistry and Chemistry, University of Rhode Island, Kingston, RI 02881, U.S.A.
[b]Division of Biology and Medicine, Brown University, Providence, RI 02912, U.S.A.

Selected S^4-substituted imidazo- and ν-triazolo[4,5-*d*]pyridazine nucleosides were prepared as nucleoside transport inhibitors.

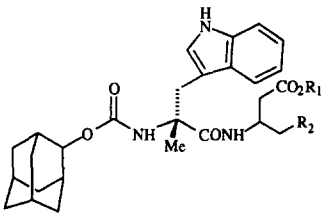


Bioorg. Med. Chem. **1996**, *4*, 1733

Cholecystokinin B Antagonists. Synthesis and Quantitative Structure–Activity Relationships of a Series of C-Terminal Analogues of CI-988

C. E. Augelli-Szafran,[a,*] D. C. Horwell,[b] C. Kneen,[b] D. F. Ortwine,[a] M. C. Pritchard,[b] T. S. Purchase,[a] B. D. Roth,[a] B. K. Trivedi,[a] D. Hill,[c] N. Suman-Chauhan[b] and L. Webdale[b]
[a]Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan, 48105, U.S.A.; [b]Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB, U.K.; [c]Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, U.K.

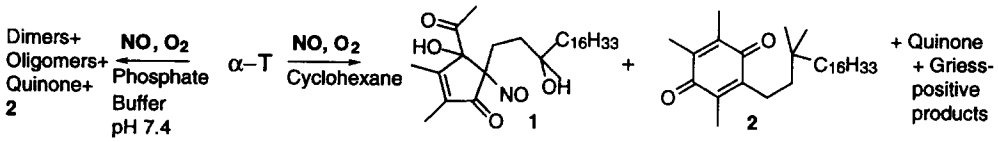
Continued interest in the synthesis of potent, highly selective, nonpeptide antagonists for the central (CCK-B) receptor has led to the development of this series of C-terminal analogues of CI-988.



Bioorg. Med. Chem. **1996**, *4*, 1747

Nitric Oxide-Induced Oxidation of α-Tocopherol

Marco d'Ischia* and Luisa Novellino
Department of Organic and Biological Chemistry, University of Naples Federico II, via Mezzocannone 16, I-80134 Naples, Italy

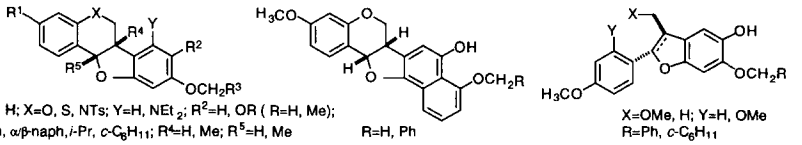


Stereoselective Syntheses of Substituted Pterocarpans with Anti-HIV Activity, and 5-Aza-/5-Thia-pterocarpan and 2-Aryl-2,3-dihydrobenzofuran Analogues

Bioorg. Med. Chem. **1996**, *4*, 1755

Thomas A. Engler, Kenneth O. LaTessa, Rajesh Iyengar, Wenying Chai and Konstantinos Agrios
Department of Chemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

Syntheses of several examples of molecules of the general structures shown are reported.

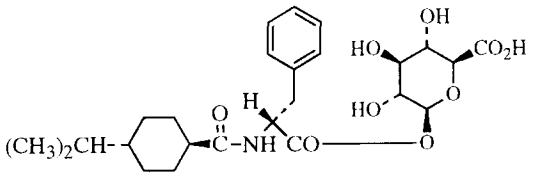


Structure Determination of Metabolites Isolated from Urine and Bile after Administration of AY4166, a Novel D-Phenylalanine-Derivative Hypoglycemic Agent

Bioorg. Med. Chem. **1996**, *4*, 1771

H. Takesada, K. Matsuda, R. Ohtake, R. Mihara, I. Ono, K. Tanaka, M. Naito, M. Yatagai and E. Suzuki*
Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan

Among 10 metabolities of AY4166 (*N-trans*-4-isopropyl-cyclohexane carbonyl)-D-phenylalanine), four were hydroxyl, three were glucronides, two were carboxylate and the other was dehydro derivative.



Conformational Analysis of Phthalein Derivatives Acting as Thymidylate Synthase Inhibitors by Means of ^{1}H NMR and Quantum Chemical Calculations

Bioorg. Med. Chem. **1996**, *4*, 1783

S. Ghelli,[a,*] G. Rastelli,[b] D. Barlocco,[c] M. Rinaldi,[b] D. Tondi,[b] P. Pecorari[b] and M. P. Costi[b,*]
[a]*Dipartimento di Chimica, Universita' di Modena, Via Campi 183, 41100 Modena, Italy*
[b]*Dipartimento di Scienze Farmaceutiche, Universita' di Modena, Via Campi 183, 41100 Modena, Italy*
[c]*Istituto Chimico Farmaceutico, Università di Milano, Viale Abruzzi 42, 20143, Italy*

^{1}H NMR and quantum chemical calculations have been performed to study the conformations of a set of phthalein derivatives acting as thymidylate synthase inhibitors. The relationships between the conformational results and the biological activity of the compounds has also been proposed.