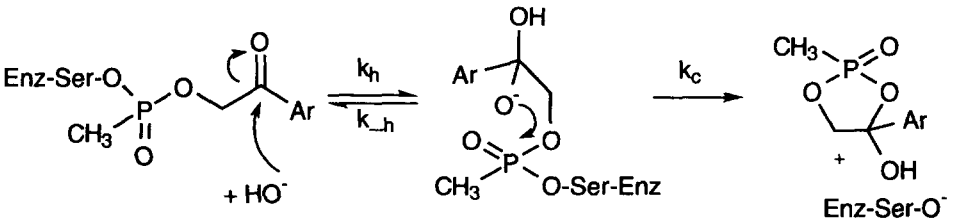
Reversible Modification of Tissue-Type Plasminogen Activator by Methylphosphonate Esters

Bioorg. Med. Chem. **1996**, *4*, 523

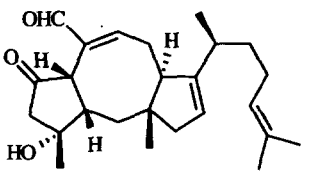
Qinjian Zhao and Ildiko M. Kovach*
Department of Chemistry, The Catholic University of America, Washington, DC 20064, U.S.A.



Ophiobolin M and Analogues, Noncompetitive Inhibitors of Ivermectin Binding with Nematocidal Activity

Bioorg. Med. Chem. **1996**, *4*, 531

Athanasios Tsipouras,* Akinlolu A. Adefarati, Jan S. Tkacz, Easter G. Frazier, Susan P. Rohrer, Elizabeth Birzin, Avery Rosegay, Deborah L. Zink, Michael A. Goetz, Sheo B. Singh and James M. Schaeffer
Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, U.S.A.

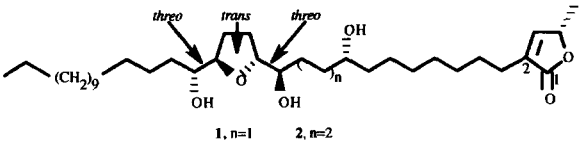


The nematocidal activity of a series of ophiobolins, such as novel ophiobolin M, against *Caenorhabditis elegans* is most likely mediated via their interaction with the nematode ivermectin binding site.

Longifolicin, Longicoricin, and Gigantetroneninone, Three Novel Bioactive Mono-Tetrahydrofuran Annonaceous Acetogenins from *Asimina longifolia* (Annonaceae)

Bioorg. Med. Chem. **1996**, *4*, 537

Qing Ye,[a] Dorothée Alfonso,[a] Dean Evert[b] and Jerry L. McLaughlin,*[,a]
[a]*Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, U.S.A.*, [b]*Department of Horticulture, Georgia Agricultural Experimental Station, The University of Georgia, Tifton, GA 31793, U.S.A.*

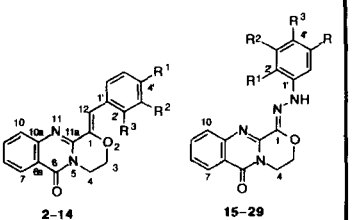


Longifolicin (**1**), longicoricin (**2**), and gigantetroneninone (**3**), three novel annonaceous acetogenins from *Asimina longifolia*, all showed potent cytotoxicities, with (**1**) exhibiting promising selectivity against the human prostate, breast and lung cancer cell lines.

Heterocondensed Quinazolones: Synthesis and Protein-Tyrosine Kinase Inhibitory Activity of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino-[3,4-*b*]-quinazolin-6-one Derivatives

Bioorg. Med. Chem. **1996**, *4*, 547

László Ôrfi,[a] József Kökösi,[a] György Szász,[a] István Kövesdi,[b] Marianna Mák,[c] István Teplán[d] and György Kéri*[,d]
[a]*Institute for Pharmaceutical Chemistry, Semmelweis University Medical School, Hôgyes E. u. 9, H-1092, Budapest, Hungary,* [b]*EGIS Pharmaceuticals Ltd, P.O. Box 100, H-1475, Budapest, Hungary,* [c]*Central Chemical Research Institute of Hungarian Academy of Science, Pusztaszeri ut 59-67, H-1025, Budapest 2, Hungary,* [d]*1st Institute of Biochemistry, Joint Research Organization of Semmelweis University Medical School and Hungarian Academy of Science, P.O. Box 260, H-1444, Budapest 8, Hungary*



The substances were tested for their ability to inhibit the tyrosine kinase activity of SW-620 (human colon carcinoma) cells. Compounds **8**, **10**, **12**, and **13** showed remarkable inhibitory activity.

Synthesis of 2′-Deoxyuridine 5′-(α,β-Imido)triphosphate: A Substrate Analogue and Potent Inhibitor of dUTPase

Bioorg. Med. Chem. **1996**, *4*, 553

Tina Persson,[a] Gunilla Larsson*[,b] and Per Olof Nyman[b]
Departments of [a]Organic Chemistry and [b]Biochemistry, Chemical Center, Lund University, P.O.B. 124, S-22100 Lund, Sweden

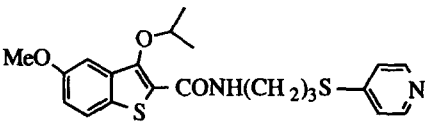
The dUTP and dTTP analogues, 2′-deoxyuridine 5′-(α,β-imido)triphosphate (dUPNPP) and 2′-deoxythymidine 5′-(α,β-imido)triphosphate (dTPNPP) have been synthesized using a combination of chemical and enzymic methods. The properties of dUPNPP have been tested using the enzyme dUTPase from *Escherichia coli*. This enzyme, having a crucial role in the nucleotide metabolism, is strictly specific for its substrate, dUTP, and catalyzes the hydrolysis of the α,β-bridge, resulting in dUMP and pyrophosphate. Replacement of the α,β-bridging oxygen in dUTP with an imido group resulted in a nonhydrolyzable substrate analogue and a potent competitive inhibitor of dUTPase. The analogue prepared (dUPNPP) may be utilized in crystallographic studies of the active site of dUTPase to provide knowledge about specific interactions involved in substrate binding and as a parental compound in design of dUTPase inhibition for medical purposes.

Bioorg. Med. Chem. **1996**, *4*, 557

Inhibition of Adhesion Molecule Expression by *N*-Alkylthiopyridine-benzo[*b*]thiophene-2-carboxamides

Diane H. Boschelli,*[,a] David T. Connor,[a] Mark E. Lesch[b] and Denis J. Schrier[b]
Departments of [a]Medicinal Chemistry and [b]Immunopathology, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105, U.S.A.

The surface levels of ICAM-1 and E-selectin on activated endothelial cells can be reduced by *N*-alkylthiopyridine-benzo[*b*]thiophene-2-carboxamides. In ELISA assays compound **14** had IC_{50}s of 5.7 and 8.4 μM for the inhibition of ICAM-1 and E-selectin expression, respectively.



14

Role of N- and C-Terminal Substituents on the CCK-B Agonist–Antagonist Pharmacological Profile of Boc-Trp-Phg-Asp-Nal-NH_2 Derivatives

Bioorg. Med. Chem. **1996**, *4*, 563

Jian Hui Weng,[a] Armand G.S. Blommaert,[a] Laurent Moizo,[b] André Bado,[b] Bertrand Ducos,[a] Andreas Böhme,[c] Christiane Garbay[a] and Bernard P. Roques*[,a]
[a]Département de Pharmacochimie Moléculaire et Structurale, U266 INSERM — URA D 1500 CNRS, UFR des Sciences Pharmaceutiques et Biologiques, Faculté de Pharmacie — 4, avenue de l'Observatoire, 75270 Paris Cedex 06, France, [b]Laboratoire de Gastro-Entérologie — U10 INSERM - Hôpital Bichat 170, Boulevard Ney — 75877 Paris Cedex 18, France, [c]Rhône Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, 13, quai Jules Guesde — B.P. 14, 94403 Vitry/Seine, France

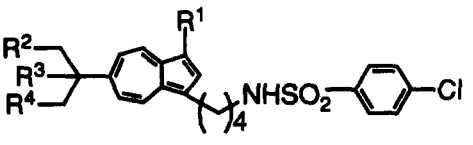
Pseudopeptides derived from CCK4 have been synthesized by liquid phase synthesis. Among these peptides, ^{2}Adoc-D-αMeTrp-Phg-Asp-Nal-NH_2 presents a CCK-B agonist profile, while ^{2}Adoc-D-αMeTrp-Phg-Asp-Nal-$N(CH_3)_2$ behaves as a very potent CCK-B antagonist. This study emphasizes the role of the N- and C-terminal amino acid substituents on the pharmacological profile of these peptides.

Bioorg. Med. Chem. **1996**, *4*, 575

Azulene Derivatives as TXA_2/PGH_2 Receptor Antagonists — II. Synthesis and Biological Activity of 6-Mono- and 6-Dihydroxylated-isopropylazulenes

Masayuki Yokota, Satoko Uchibori, Hiromi Hayashi, Rei Koyama, Kazuhiro Kosakai, Shuichi Wakabayashi and Tsuyoshi Tomiyama
Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd, 6351 Sakaki-machi, Nagano 389-06, Japan

A series of 6-hydroxylated-isopropylazulenes were synthesized and evaluated for their TXA_2/PGH_2 receptor antagonistic activity.



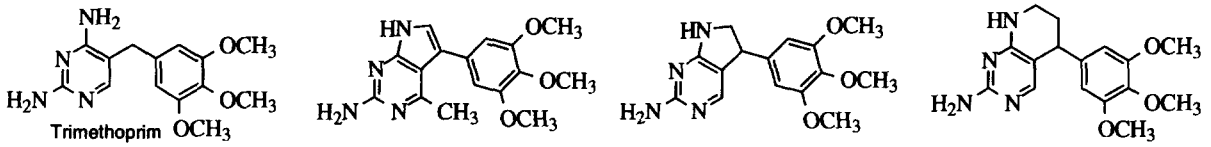
R^1 = COOH or SO_3Na
R^2, R^3, R^4 = H or OH

Pyrrolo[2,3-*d*]pyrimidines and Pyrido[2,3-*d*]pyrimidines as Conformationally Restricted Analogues of the Antibacterial Agent Trimethoprim

Bioorg. Med. Chem. **1996**, *4*, 593

Lee F. Kuyper,*[a] Janice M. Garvey,[a] David P. Baccanari,[a] John N. Champness,[b] David K. Stammers[b] and Christopher R. Beddell[b]

[a]*Wellcome Research Laboratories, Research Triangle Park, NC 27709, U.S.A.*
[b]*Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, U.K.*



5′-Linked Lipid-oligodeoxyribonucleotide Derivatives as Inhibitors of Human Immunodeficiency Virus Replication

Bioorg. Med. Chem. **1996**, *4*, 603

Sang-Gug Kim,[a] Hideki Nakashima,[b] Yoko Shoji,[c] Takabumi Inagawa,[a,b] Naoki Yamamoto,[d] Yasuhiro Kinzuka,[a] Kazuyuki Takai[a] and Hiroshi Takaku*[,a]

[a]*Department of Industrial Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275, Japan,* [b]*Department of Microbiology, Yamanashi Medical University, Nakakoma-gun, Yamanashi 409-38, Japan,* [c]*Institute of Medical Science, St Marianna University School of Medicine, Sugao, Miyamae-ku, Kawasaki 261, Japan,* [d]*Department of Microbiology, Tokyo Medical and Dental University School of Medicine, Yushima, Bunkyo-ku, Tokyo 113, Japan*

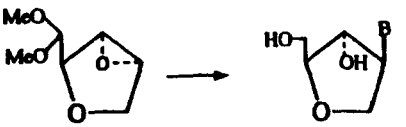
The lipid-phosphorothioate oligonucleotides (LS-ODNs) showed higher anti-HIV activities than non-lipid-phosphorothioate oligonucleotides, at the low concentrations of 0.04 μM. LS-ODNs can inhibit HIV-1 reverse transcriptase activity through interactions with the enzyme.

Studies on the Synthesis and Biological Activities of 4′-(*R*)-Hydroxy-5′-(*S*)-hydroxymethyl-tetrahydrofuranyl Purines and Pyrimidines

Bioorg. Med. Chem. **1996**, *4*, 609

Hong-Wu Yu, Liang-Ren Zhang, Ji-Chang Zhou, Ling-Tai Ma and Li-He Zhang*
School of Pharmaceutical Sciences, Beijing Medical University, Beijing 100083, People's Republic of China

A series of 4′-(*R*)-hydroxy-5′-(*S*)-hydroxymethyl-tetrahydrofuranyl purines and pyrimidines were synthesized by the reaction of 3,4-epoxy-5-(*S,trans*)-dimethoxymethyl-tetrahydrofuran and nucleobases. Compounds **6a**, **6c** and **7b** have shown significant inhibition on the growth of HL-60 cells.

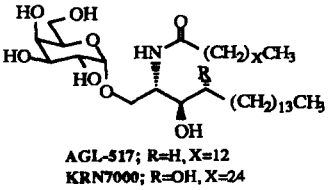


Enhancing Effects of α-, β-Monoglycosylceramides on Natural Killer Cell Activity

Bioorg. Med. Chem. **1996**, *4*, 615

Eiichi Kobayashi, Kazuhiro Motoki, Yasunori Yamaguchi, Takeshi Uchida, Hideaki Fukushima and Yasuhiko Koezuka*
Pharmaceutical Research Laboratory, Kirin Brewery Co., Ltd, 3 Miyahara-cho, Takasaki-shi, Gunma 370-12, Japan

We examined the enhancing effects of six kinds of α- and β-monoglycosylceramides (MonoCers) on in vitro and in vivo natural killer (NK) cell activity, and found that α-MonoCers show stronger enhancing activities than β-MonoCers. These results suggest that the manner of combination between sugar and ceramide plays an important role in the manifestation of enhancing activities of MonoCers on NK cell activity.

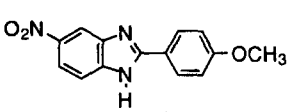


Structure–Activity Relationships of Benzimidazoles and Related Heterocycles as Topoisomerase I Poisons

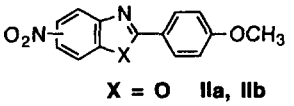
Bioorg. Med. Chem. **1996**, *4*, 621

Jung Sun Kim,[a] Qun Sun,[a] Barbara Gatto,[b] Chiang Yu,[b] Angela Liu,[b] Leroy F. Liu[b] and Edmond J. LaVoie*[,a]
[a]Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08855, U.S.A., [b]Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08855, U.S.A.

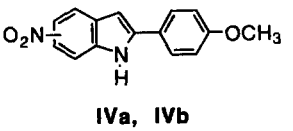
A series of substituted 2-(4-methoxyphenyl)-1*H*-benzimidazoles was synthesized and evaluated as inhibitors of topoisomerase I. Compound **I** exhibited the highest activity while none of its heterocyclic analogues (**II**, **III**, and **IV**) were active.



I



X = O IIa, IIb
X = S IIIa, IIIb



IVa, IVb