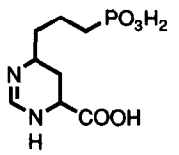
GRAPHICAL ABSTRACTS

BioMed. Chem. Lett. **1992**, *2*, 207

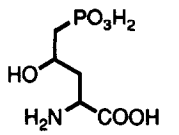
EXCITATORY AMINO ACIDS: 6-PHOSPHONOMETHYLTETRAHYDRO-4-PYRIMIDINECARBOXYLIC ACIDS AND THEIR ACYCLIC ANALOGUES ARE COMPETITIVE N-METHYL-D-ASPARTIC ACID RECEPTOR ANTAGONISTS

Christopher F. Bigge*, Jiang-Ping Wu, James T. Drummond, Linda L. Coughenour, Cynthia M. Hanchin
Parke-Davis Pharmaceutical Research Division
Warner Lambert Company
Ann Arbor, Michigan 48105

Internal hydrogen bonding interactions may influence NMDA receptor affinity.



14 (IC_{50} = 0.42 uM)



16 (IC_{50} = 0.13 uM)

BioMed. Chem. Lett. **1992**, *2*, 213

REGRESSION ANALYSIS FOR QSAR USING NEURAL NETWORKS

David J. Livingstone[1*] and David W. Salt[2]

[1]SmithKline Beecham Research, The Frythe, Welwyn, Herts, AL6 9AR, UK[2]School of Mathematical Studies, Portsmouth Polytechnic, Portsmouth, Hants, PO1 2EG, UK.

Abstract: Neural networks have been used to analyse QSAR data giving promising results. However, there is the danger of chance "correlations" and "over-fitting". We have examined a reported analysis and shown that the size of the hidden layer can be reduced giving more efficient training while maintaining predictive performance .

BioMed. Chem. Lett. **1992**, *2*, 219

NEW POTENT ENKEPHALIN ANALOGS CONTAINING TRIFLUOROMETHYL-AMINO ACID RESIDUES

I. Ojima*[1], K. Kato[1], F. A. Jameison[1], John Conway[1], Kazuaki Nakahashi[2], Masaki Hagiwara[2], Tetsuhisa Miyamae[2], and Hans E. Radunz[3], *[1]Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794; [2]Fuji Chemical Ind. Ltd., 530 Chokeiji, Takaoka, Toyama 933, Japan; [3]E. Merck AG, Pharmazeutische Chemie, Frankfurter Straβe 250, 4119, D-6100 Darmstadt 1, Germany*

Synthesis, *in vivo* analgesic activity and *in vitro* receptor binding assay of new enkephalin analogs bearing trifluoromethyl-amino acid residues.

Tyr-(D)TFNV-Gly-Phe-Met-NH_2 **Tyr-(D)TFNL-Gly-Phe-Met-NH_2**

TFNV = 5,5,5-trifluoronorvaline; TFNL = 6,6,6-trifluoronorleucine

BioMed. Chem. Lett. **1992**, *2*, 223

THE DESIGN AND BIOLOGICAL EVALUATION OF A SERIES OF 3-HYDROXY-3-METHYL-GLUTARYL COENZYME A (HMG-CoA) REDUCTASE INHIBITORS RELATED TO DIHYDROMEVINOLIN.

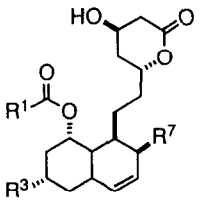
Elisabeth A. Bone, Emer M. Cunningham, Alan H. Davidson, W. Alan Galloway, Christopher N. Lewis,* Elizabeth M. Morrice, Maxwell M. Reeve, Richard S. Todd and Ingrid M. White, Departments of Medicinal Chemistry and Biology, British Bio-technology Limited, Wallington Road, Cowley, Oxford, OX4 5LY

HMG-CoA reductase inhibitors structurally related to dihydromevinolin have been designed and tested. It has been shown that for high inhibitory potency these compounds must possess a methyl group at the C-7 position, but several different alkenes can be tolerated at the C-3 position. These compounds show good activity both in vitro and in vivo.

R^1 = CH_3, $C(CH_3)_2CH_2CH_3$, (S)-$CH(CH_3)CH_2CH_3$

R^3 = CH_3, $CH{=}CHCH_3$, $CH{=}CHCH_2CH_3$, $CH{=}CH(CH_2)_3CH_3$, $CH{=}CHCH_2Ph$, $CH{=}CHCH(CH_3)_2$

R^7 = H, CH_3, $CH(CH_3)_2$

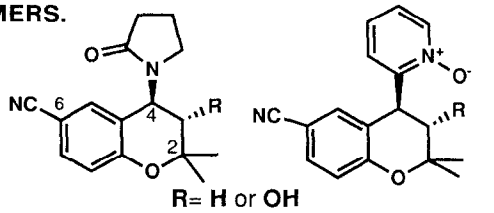


BioMed. Chem. Lett. **1992**, *2*, 229

SYNTHESIS OF HOMOCHIRAL POTASSIUM CHANNEL OPENERS: ROLE OF THE BENZOPYRANYL 3-HYDROXYL IN CROMAKALIM AND PYRIDINE N-OXIDES IN DETERMINING THE ACTIVITIES OF ENANTIOMERS.

M R Attwood, B S Brown, R M Dunsdon, D N Hurst, P S Jones* and P B Kay
Roche Products Limited, Welwyn Garden City, Herts. AL7 3AY

Abstract: The preparation of several homochiral benzopyranyl potassium channel openers is described A subtle stereochemical effect of the 3-hydroxyl on the biological activities of the enantiomers was observed.

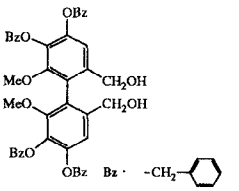


BioMed. Chem. Lett. **1992**, *2*, 235

NEW HEXAHYDROXYDIPHENYL DERIVATIVES AS POTENT INHIBITORS OF HIV REPLICATION IN H9 LYMPHOCYTES

Yoshiki Kashiwada,[a] Li Huang,[a] Robert E. Kilkuskie,[b] Anne J. Bodner,[b] and Kuo-Hsiung Lee[a]*
[a]*Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599,*
[b]*Cambridge Biotech Corporation, 1600 East Gude Drive, Rockville, Maryland 20850*

A series of hexahydroxydiphenyl derivatives of ellagic acid have been synthesized as simple analogs of ellagitannins and evaluated for their inhibitory activity against HIV replication in H9 lymphocytes. Compound **10** was found to be a potent inhibitor of HIV replication in infected H9 lymphocytes with little cytotoxicity.



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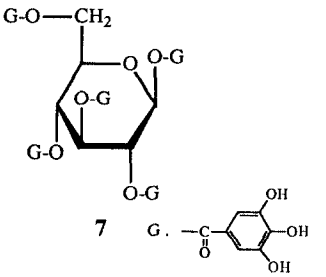
BioMed. Chem. Lett. **1992**, *2*, 239

TANNINS AS SELECTIVE INHIBITORS OF PROTEIN KINASE C

Yoshiki Kashiwada,[a] Gen-ichiro Nonaka,[b] Itsuo Nishioka,[b] Lawrence M. Ballas,[c] Jack B. Jiang,[c] William P. Janzen,[c] and Kuo-Hsiung Lee[a]*
[a]*Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599*
[b]*Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan*
[c]*Sphinx Pharmaceuticals Corporation, Durham, North Carolina 27717*

Fifty-six tannins were evaluated for their inhibitory effects against protein kinase C (PKC). Ellagitannins and complex tannins were found to be potent inhibitors of PKC, while gallotannins (e.g. 7) and condensed tannins, having a relatively large number of phenolic hydroxy groups, showed some inhibitory effects on PKC. Phorbol displacement assay suggested that the active tannins interact with the regulatory site of the enzyme.



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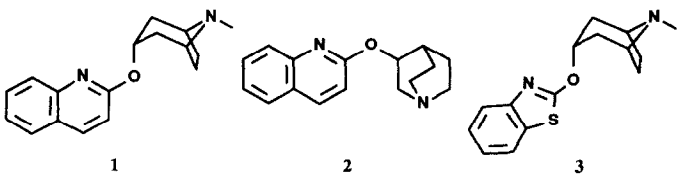
BioMed. Chem. Lett. **1992**, *2*, 245

AZAHETEROAROMATIC ETHERS AS CARBONYL BIOISOSTERES. SYNTHESIS AND EVALUATION OF A NOVEL CLASS OF 5-HT$_3$ RECEPTOR ANTAGONISTS

Ian A Cliffe,* Neil Brammer, Vicki Middlefell, Panchanadam Swaminathan,[a] and Alan C. White.
Wyeth Research (U.K.) Ltd., Huntercombe Lane South, Taplow, Berkshire, SL6 OPH, England and [a]*Wyeth-Ayerst Research, CN-8000, Princeton, NJ08540, USA*

Quinolin-2-yl and benzothiazol-2-yl derivatives of 3-tropane and 3-quinuclidine **1-3** are novel 5-HT$_3$ receptor antagonists. The heteroaromatic groups behave as bioisosteres of the carbonyl groups found in many 5-HT$_3$ receptor antagonists.



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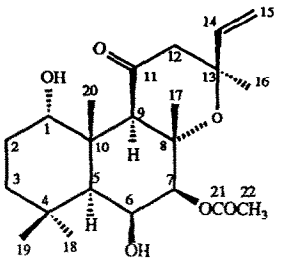
BioMed. Chem. Lett. **1992**, *2*, 249

EPI-DEOXYCOLEONOL, A NEW ANTIHYPERTENSIVE LABDANE DITERPENOID FROM *COLEUS FORSKOHLII*

J.S.Tandon[a],R.Roy[a],S.Balachandran[a] and R.A.Vishwakarma[b,*]
[a]*Medicinal Chemistry Division,Central Drug Research Institute, Lucknow 226001, India,* [b]*Bio-organic Chemistry Laboratory, National Institute of Immunology, New Delhi 110067, India*

A new blood-pressure lowering labdane diterpenoid 13-epi-9-deoxycoleonol (13-epi-9-deoxyforskolin) has been isolated from the Indian medicinal plant *Coleus forskohlii* and the stereostructure determined by various two-dimensional NMR techniques



BioMed. Chem. Lett. **1992**, *2*, 255

A SYNTHETIC OCTASACCHARIDE MIMICS THE NATIVE, O-SPECIFIC DETERMINANT OF THE *Shigella dysenteriae* TYPE 1 LIPOPOLYSACCHARIDE

Vince Pozsgay,* Cornelis P.J. Glaudemans, John B. Robbins, and Rachel Schneerson
National Institutes of Health, NIDDK and NICHD, Bethesda, MD 20892 U.S.A.

[-3)-α-L-Rha*p*-(1,2)-α-D-Gal*p*-(1,3)-α-D-Glc*p*NAc-(1,3)-α-L-Rha*p*-(1-]$_2$-OMe

1

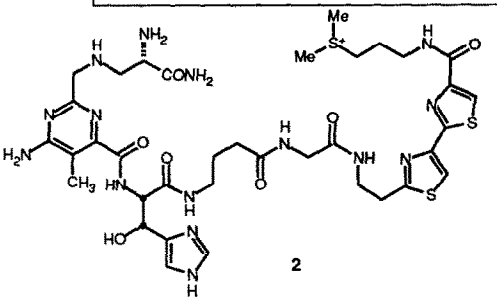
^{1}H-NMR data indicate that the octasaccharide **1** possesses conformational features of the O-specific determinant of *Shigella dysenteriae* type 1.

BioMed. Chem. Lett. **1992**, *2*, 261

DEGLYCO GABA, GLY-DESACETAMIDOBLEOMYCIN A_2: A SIMPLIFIED SYNTHETIC MODEL FOR BLEOMYCIN A_2

Dale L. Boger, * Royce F. Menezes, Qun Dang, and Wenjin Yang. *Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037*

Abstract: The synthesis of **2**, a simplified synthetic model for bleomycin A_2, and the preliminary demonstration of its functional cleavage of duplex DNA are detailed.



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BioMed. Chem. Lett. **1992**, *2*, 267

SOLID PHASE SYNTHESIS OF 5′ NON RADIOACTIVE MULTIPLE LABELLED OLIGODESOXYRIBONUCLEOTIDES

C. Pierlot and C. Sergheraert*
Institut Pasteur, Service de Chimie des Biomolécules, Faculté de Pharmacie: Laboratoire de Chimie Générale, URA CNRS 1309, BP 245, 59019 Lille Cédex, France

Abstract: The convenient solid phase synthesis of oligodesoxyribonucleotides carrying multiple amine groups at their 5′ end was described using a branching lysine core. The possiblity of attachment of non radioactive label was demonstrated by synthesis of a 5′-tetrathymidilate. The identity of the derivatives was proved by Plasma Desorption Mass Spectrometry