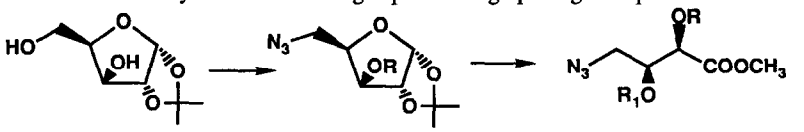
GRAPHICAL ABSTRACTS

BioMed. Chem. Lett. **1992**, 2, 515

VERSATILE SYNTHESIS OF DIHYDROXY γ AND δ AMINO ACIDS FROM CARBOHYDRATES

D. B. Tulshian*, A. F. Gundes and M. Czarniecki,Schering-Plough Research Institute, 60 Orange St., Bloomfield, New Jersey, 07003, USA

The stereospecific syntheses disubstituted derivatives of γ-aminobutanoic acid and δ-aminopentanoic acid are described starting from protected furanose sugars. The keys steps are the introduction of the amine in the form of an alkyl azide and the regiospecific ring opening with periodate.



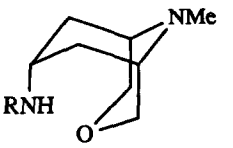
BioMed. Chem. Lett. **1992**, 2, 519

3-OXAGRANATANE (3-OXA-9-AZABICYCLO[3.3.1]NONANE) DERIVATIVES AS HIGHLY POTENT SEROTONIN 5-HT$_3$ RECEPTOR ANTAGONISTS.

J. Bermudez, J.A. Gregory, F.D. King*, S. Starr and R.J. Summersell.

SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex, UK.

The synthesis of 3-oxagranatan-7-amino derivatives and their enhanced potency as 5-HT$_3$ receptor antagonists compared with that of the equivalent tropanes and granatanes is described.



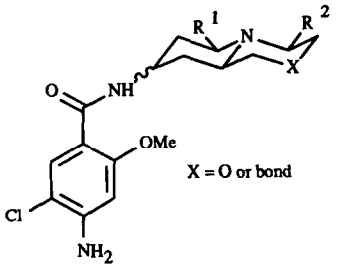
BioMed. Chem. Lett. **1992**, 2, 523

CONFORMATIONALLY RESTRICTED PIPERIDINYL BENZAMIDES AS 5-HT$_3$ RECEPTOR ANTAGONISTS

J. Bermudez, M.S. Hadley, F.D. King* and R.T. Martin

SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, UK

The synthesis and 5-HT$_3$ receptor antagonist potency of indolizidin-7-yl and 8-oxaquinolizidin-2-yl benzamides is described.



BioMed. Chem. Lett. **1992**, 2, 527

NOVEL MOLECULAR PROBES FOR ^{19}F MAGNETIC RESONANCE IMAGING: SYNTHESIS & CHARACTERIZATION OF FLUORINATED POLYMERS, V.D Mehta*, P.V. Kulkarni, R.P. Mason, E.E. Babcock, A. Constantinescu, and P.P. Antich. *Department of Radiology, University of Texas, Southwestern Medical Center at Dallas, Texas 75235*

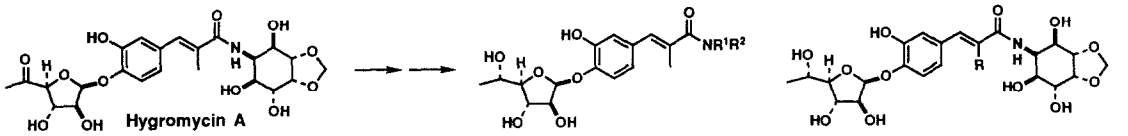
Abstract: Fluorine labeled polymers have been synthesized and characterized to investigate vascular phenomena *in vivo* with ^{19}F Magnetic Resonance Imaging (MRI). The polymers have molecular weights in the range 10 k to 98 k and include polylysines and functionalized dextrans (polyamino dextrans and polyaldehyde dextrans). These fluorinated polymers exhibit a single sharp ^{19}F signal, appropriate ^{19}F MR detection sensitivity, and the biocompatibility necessary for *in vivo* MRI.

BioMed. Chem. Lett. **1992**, *2*, 533

SEMISYNTHETIC MODIFICATION OF HYGROMYCIN A. 1. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF VINYL METHYL AND AMIDE ANALOGS.

Scott J. Hecker,* Martha L. Minich, and Kim M. Werner, Pfizer Inc, Central Research Division, Groton, CT 06340.

Hygromycin A is degraded to a benzaldehyde which serves as a key intermediate for preparation of the title analogs.

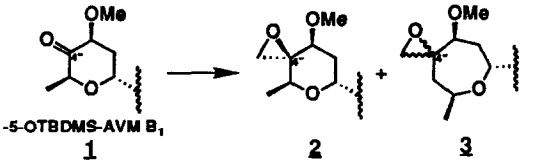


BioMed. Chem. Lett. **1992**, *2*, 537

SYNTHESIS OF AVERMECTIN B_1-4",4"a-OXIDE: A PRECURSOR OF POTENT ANTHELMINTIC AGENTS

Peter T. Meinke*, Peter Sinclair*, Helmut Mrozik, Steve O'Connor, D. A. Ostlind, W. L. Shoop, B. H. Arison and Michael Fisher
Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

Treatment of 4"-oxo-Avermectin B_1 (**1**) with $TMSCH_2N_2$ yielded 4", 4"a-oxide **2** and ring-expanded oxepinyl analog **3**. Oxiranes **2** and **3** were opened regiospecifically with diverse hetero-atomic nucleophiles forming new avermectins exhibiting potent, broad spectrum anthelmintic activity.

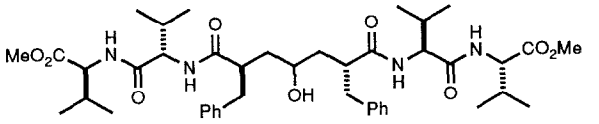


BioMed. Chem. Lett. **1992**, *2*, 541

The Use of HIV-1 Protease Structure in Inhibitor Design

Robert E. Babine*, Nan Zhang, Alex R. Jurgens, Steven R. Schow, Parimal R. Desai, John C. James and M.F.Semmelhack American Cyanamid Company, Medical Research Division, Lederle Laboratories Pearl River, NY 10965

The X-ray structure of HIV-1 protease and molecular dynamics studies were used in the design of pseudo-symmetrical inhibitors of this enzyme. Short bidirectional syntheses of these inhibitors are described.



BioMed. Chem. Lett. **1992**, *2*, 547

TOPOGRAPAHICAL REQUIREMENTS FOR DELTA OPIOID LIGANDS: THE SYNTHESIS AND BIOLOGICAL PROPERTIES OF CYCLIC ANALOGS OF DELTORPHINS AND DERMENKEPHALIN

A. Misicka[+], G. Nikiforovich[+], A. W. Lipkowski[+], R. Horvath[‡], P. Davis[‡], T. H. Kramer[‡], H. I. Yamamura[‡], V. J. Hruby[+], Departments of Chemistry[+] and Pharmacology[‡], University of Arizona, Tucson, AZ 85721

Based on energy calculations and molecular modeling, low energy conformations of Deltorphin I (I) were proposed that led to the design and synthesis of the cyclic analog [D-$\overline{Cys^2,Cys^5}$]Deltorphin (II) that retained high potency at δ opioid receptors.

Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2 (I) → Tyr-D-$\overline{Cys\text{-}Phe\text{-}Asp\text{-}Cys}$-Val-Gly-$NH_2$ (II).

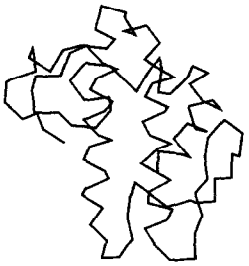
BioMed. Chem. Lett. **1992**, *2*, 553

A PREDICTION OF THE TERTIARY STRUCTURE OF HUMAN PHOSPHOLIPASE A_2 FROM SYNOVIAL FLUID AND A MODEL OF SUBSTRATE BINDING

Mark Kelly, Richard B. Sessions*, Hilary Muirhead

Molecular Recognition Centre and Department of Biochemistry, University of Bristol, School of Medical Sciences, University Walk, Bristol BS8 1TD, U. K.

The tertiary structure of human Phospholipase A_2 from synovial fluid has been predicted by modelling the sequence onto the structure of the homologous snake venom PLA_2 (*Crotalus atrox*). A model of substrate binding has been developed. The structure of these models is discussed.



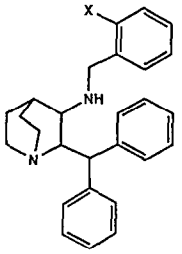
BioMed. Chem. Lett. **1992**, *2*, 559

AN SAR STUDY FOR THE NON-PEPTIDE SUBSTANCE P RECEPTOR (NK_1) ANTAGONIST, CP-96,345.

William Howson,* Julie Hodgson, Reg Richardson, Lesley Walton, Steve Guard and Keith Watling.

Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB, UK.

Results from an SAR study around the novel, non-peptide NK_1 antagonist, CP-96,345 are described. The importance of the 2° nitrogen and the aromatic moieties are clarified. In vitro NK_1 binding data indicate that the rat and guinea-pig brain receptors are different.



BioMed. Chem. Lett. **1992**, *2*, 565

PURINE 8-SUBSTITUTION MODULATES THE RECOGNITION BY RESTRICTION ENDODEOXYRIBONUCLEASE *EcoRI* OF OCTADEOXYRIBONUCLEOTIDES (dGGAATTCC)

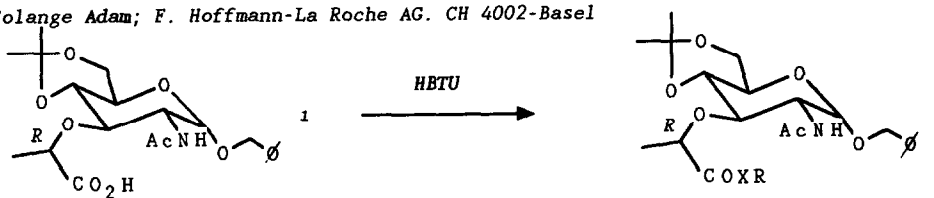
H.Komatsu, S.-G.Kim, I.Sakabe, T.Ichikawa, M.Nakai, and H.Takaku*, Department of Industrial Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275, Japan

The octadeoxyribonucles, d(GGTTAACC) with replacement to deoxy-7,8-dihyroadenosine-8-one (dA^{OH}), 8-methoxy-deoxyadenosine (dA^{OMe}) and 8-methoxydeoxyguanosine (dG^{OMe}) from deoxy-adenosine or deoxyguanosine were used to study their cleavage by the restriction endo-deoxyribonuclease EcoRI. The hydrolysis by EcoRI of the modified oligomers were perfectly resisted compared to d(GGTTAACC).

BioMed. Chem. Lett. **1992**, *2*, 571

HBTU: A MILD ACTIVATING AGENT FOR MURAMIC ACID

Solange Adam; F. Hoffmann-La Roche AG. CH 4002-Basel



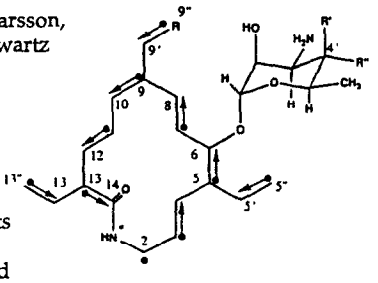
O-Benzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) effects the smooth coupling of 1 with alcohols, peptides and amines in high yields

BIOSYNTHESIS OF MACROLACTAM ANTIFUNGAL AGENTS

BioMed. Chem. Lett. **1992**, *2*, 575

M.S. Puar*, V. Gullo, I. Gunnarsson, V. Hegde, M. Patel, and J. Schwartz

Schering-Plough Research,
60 Orange street,
Bloomfield NJ 07003 USA



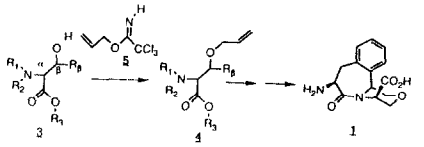
Abstract: The aglycone of the macrolactam antifungal agents is biosynthesized via a combination of ployketide and TCA mechanisms.

BioMed. Chem. Lett. **1992**, *2*, 579

ACID-CATALYZED O-ALLYLATION OF β-HYDROXY-α-AMINO ACIDS: AN ENTRANCE INTO CONFORMATIONALLY CONSTRAINED DIPEPTIDE SURROGATES

Timothy P. Burkholder*, Tieu-Binh Le, Eugene L. Giroux, and Gary A. Flynn
Marion Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215

O-Allylation using allyl trichloroimidate 5 was found to be an effective method for the introduction of an acetaldehyde equivalent onto the hydroxyl group of β-hydroxy-α-amino acid derivatives. Rigid oxygen containing tricyclic anti-phenylalanyl-leucine mimic 1 was efficiently synthesized using this method. This mimetic was further elaborated to provide 7c, a potent inhibitor of angiotensin-1 converting enzyme (ACE).



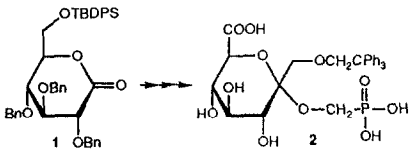
BioMed. Chem. Lett. **1992**, *2*, 583

SYNTHESIS OF A POTENTIAL INHIBITOR OF UDP-GLUCURONOSYLTRANSFERASE

D. Noort[a,b], N.C.R. van Straten[a], G.J P.H. Boons[a], G.A. van der Marel[a], X. Bossuyt[c], N. Blanckaert[c], G.J. Mulder[b], J.H. van Boom[a]

[a]Gorlaeus Laboratories, P O. Box 9502, 2300 RA Leiden; [b]Division of Toxicology, Center for Bio-Pharmaceutical Sciences, P.O. Box 9503, 2300 RA Leiden, The Netherlands; [c]Laboratory of Biological Chemistry, University of Leuven, B-3000 Leuven, Belgium

Compound **1** could be converted in ten steps into the transition-state analogue **2**, which proved to be an inhibitor of UDP-glucuronosyltransferase activity *in vitro*.

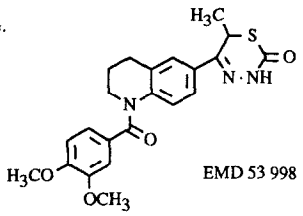


BioMed. Chem. Lett. **1992**, *2*, 589

PREPARATION OF THE ENANTIOMERS OF THE NOVEL CA-SENSITIZER EMD 53 998

R. Jonas*, M. Klockow, and I. Lues
Pharmaceutical Research Department, E. Merck, D-6100 Darmstadt, F. R. G.

The synthesis and preliminary biological evaluation of the enantiomers of EMD 53 998 is described. Solely the (+)-enantiomer EMD 57 033 shows potent Ca-sensitizing activity.



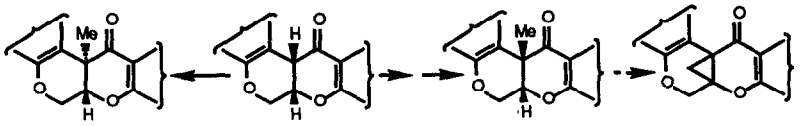
EMD 53 998

BioMed. Chem. Lett. **1992**, *2*, 593

NOVEL SYNTHETIC ROTENOIDS WITH BLOCKED B/C RING SYSTEMS

Jonathan L. Josephs* and John E. Casida
Pesticide Chemistry and Toxicology Laboratory, Department of Entomological Sciences, University of California, Berkeley, California 94720

Blocking the B/C ring fusion of rotenone with either the *cis*-12a-methyl or the 6a,12a-cyclopropyl substituent reduces their potency as inhibitors of NADH dehydrogenase but greatly increases their photostability and the *cis*-12a-methyl compound also has remarkably enhanced toxicity to houseflies.

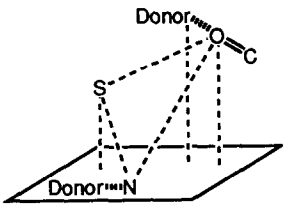


BioMed. Chem. Lett. **1992**, *2*, 597

A PARTIAL PHARMACOPHORE FOR THE PLATELET ACTIVATING FACTOR (PAF) RECEPTOR

Edward E. Hodgkin, Andrew Miller and Mark Whittaker,* British Bio-technology Ltd., Watlington Road, Cowley, Oxford, OX4 5LY, UK

A partial pharmacophore for the platelet activating factor receptor has been generated by a molecular modelling comparison of five heterocyclic sp2 nitrogen PAF antagonists using a Monte Carlo 'Boltzmann Jump' technique. This pharmacophore defines the relative spatial orientation of the plane of the heterocyclic ring, the sp2 nitrogen, a carbonyl/sulphonyl pharmacophoric group and a sulphur atom.

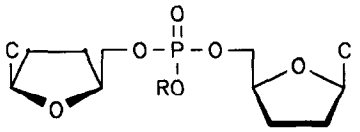


BioMed. Chem. Lett. **1992**, *2*, 603

NUCLEOTIDIC PRODRUGS OF ANTI-HIV DIDEOXYNUCLEOSIDES

F. Puech, A. Pompon, I. Lefebvre, G. Gosselin and J.L. Imbach*
U.M.R. 112 Synthélabo - C.N.R.S .- Université Montpellier.2
Place E. Bataillon, 34095 Montpellier Cedex 5, France

Abstract. The kinetics of decomposition of dinucleoside phosphodi- and triester of ddC in culture medium and in cellular extract have been determined by HPLC. The anti-HIV activities of those compounds are related to the obtained results.

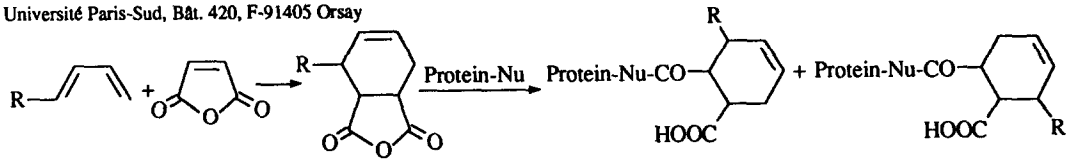


R : CH_3, H

BioMed. Chem. Lett. **1992**, *2*, 607

A NEW CLASS OF REAGENTS FOR THE CHEMICAL MODIFICATION OF PROTEINS

André LUBINEAU, David BONNAFFE and Michel THERISOD
Laboratoire de chimie Organique Multifonctionnelle, associé au CNRS, Institut de Chimie Moléculaire d'Orsay, Université Paris-Sud, Bât. 420, F-91405 Orsay



BioMed. Chem. Lett. **1992**, *2*, 609

SYNTHESIS OF FLUORESCEINYL-NEUROKININ-A, A BIOLOGICALLY ACTIVE PROBE FOR NK_2 RECEPTORS

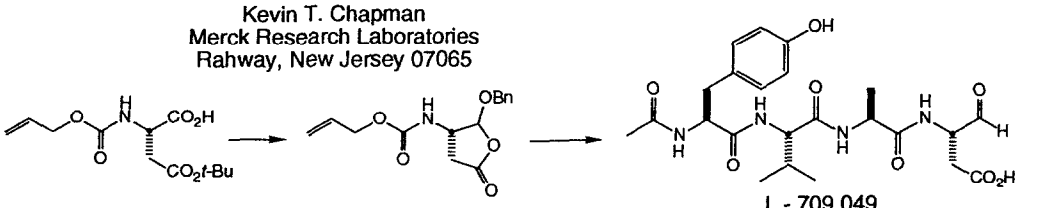
Karin Ceszkowski and Andre Chollet *
Glaxo Institute for Molecular Biology S.A.
Chemin des Aulx 14, CH-1228 Plan-les-Ouates, Switzerland

The synthesis and characterization of a fluoresceinated derivative of the neuropeptide NKA are described. N-α-[fluoresceinyl]-(His^1)NKA specifically labels NK_2 receptors and retains NKA biological activity.

BioMed. Chem. Lett. **1992**, *2*, 613

Synthesis of a Potent, Reversible Inhibitor of Interleukin-1β Converting Enzyme

Kevin T. Chapman
Merck Research Laboratories
Rahway, New Jersey 07065



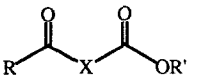
L - 709,049
K_i = 0.76 ± 0.16 nM vs ICE

BioMed. Chem. Lett. **1992**, *2*, 619

ASYMMETRIC REDUCTION OF KETOESTERS WITH ALCOHOL DEHYDROGENASE FROM *THERMOANAEROBACTER ETHANOLICUS*

Changsheng Zheng, Van T. Pham and Robert S. Phillips*
Department of Chemistry, University of Georgia, Athens, GA 30602

Chiral hydroxyesters and lactones were obtained by the asymmetric reduction of ketoesters catalyzed by secondary alcohol dehydrogenase from *T. ethanolicus*.



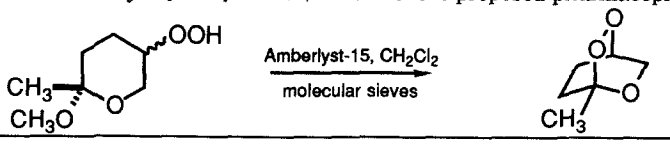
R = CH_3, C_2H_5, i-C_3H_7
X = CH_2, $(CH_2)_2$, $(CH_2)_3$, $CHCH_3$
R' = CH_3, C_2H_5, n-C_4H_9

BioMed. Chem. Lett. **1992**, *2*, 623

SYNTHESIS AND ANTIMALARIAL EVALUATION OF 2,3,5-TRIOXABICYCLO[2.2.2]OCTANES. MODELS FOR THE PUTATIVE PHARMACOPHORE OF QINGHAOSU (ARTEMISININ)

Dee Ann Casteel,* Kyeong-Eun Jung, Division of Medicinal and Natural Products Chemistry, College of Pharmacy, University of Iowa, Iowa City, IA 52242; and Lucia Gerena and Wilbur Milhous, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100

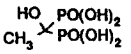
5-Hydroperoxy-2-methoxytetrahydropyrans are cyclized with transacetalization in the presence of Amberlyst-15 and molecular sieves to 2,3,5-trioxabicyclo[2.2.2]octanes, models of the proposed pharmacophore of qinghaosu.



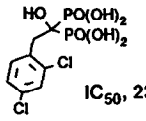
BioMed. Chem. Lett. **1992**, *2*, 627

INHIBITORS OF *myo*-INOSITOL MONOPHOSPHATASE UNRELATED TO THE ENZYME SUBSTRATE **S.R. Fletcher, R. Baker, P.D. Leeson, M.Teall, E.A. Harley and C.I. Ragan.** The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Harlow, UK.

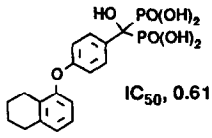
Hydroxymethylenebisphosphonate derivatives have been found to be competitive inhibitors of myo-inositol monophosphatase



IC_{50}, 110 nM



IC_{50}, 23 nM



IC_{50}, 0.61 nM