GRAPHICAL ABSTRACTS

BioMed. Chem. Lett. **1992**, *2*, 643

DNA - GYRASE INHIBITION AND ANTIBACTERIAL ACTIVITY OF FLUOROQUINOLONES : INFLUENCE OF THE POSITION OF THE FLUORINE(S).

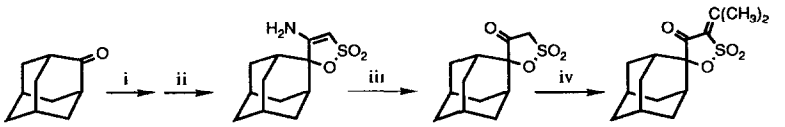
P. Clairefond*[1], D. Bouzard[1], B. Ledoussal[1], E. Coroneos[1], S. Bazile[2] and N. Moreau[2].
[1] Bristol-Myers-Squibb Pharmaceutical Research Institute, 77422 Marne-La-Vallée Cedex 2 , France
[2] CNRS , CERCOA - 2 Rue Henri Dunant, 94320 Thais , France

A series of fluoro-quinolones was evaluated for antibacterial activity and DNA-gyrase inhibitory potency. The influence induced by fluorine substitution on the antibacterial activity cannot be explained by a direct effect on the enzyme target of quinolones.

BioMed. Chem. Lett. **1992**, *2*, 647

SYNTHESIS OF ADAMANTANE SPIRO SULTONES AS POTENTIAL ANTIVIRAL AGENTS

María Jesús Pérez-Pérez[+], Jan Balzarini[§], Mitsuaki Hosoya[§], Erik De Clercq[§] and María José Camarasa[+]
[+]Instituto de Química Médica, Juan de la Cierva 3, 28006 Madrid, Spain. [§] Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

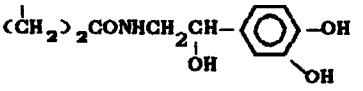


i: NaCN, $NaHCO_3$, ether:H_2O (2:1); ii: CH_3SO_2Cl, pyridine; iii: DBU, CH_3CN; iv: acetone, NaOAc.

BioMed. Chem. Lett. **1992**, *2*, 649

PEPTIDES INDUCING PSYCHOSIS, **A. A. Mazurov*, S. A. Andronati, B. A. Lobasyuk, V. M. Kabanov, A. N. Mokhovikov, *Physico-Chemical Institute, 270080, Odessa, Ukraine***

Abstract: Prolonged behavioral disorders of cats were caused by peptides 1 and 2 after a single intraperitoneal administration.

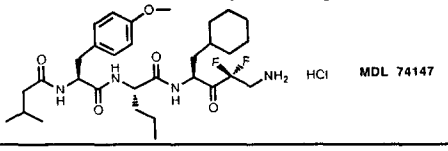
Glp-X-Pro-NH_2 (1) **Pro-X-Gly-NH_2** (2) **X =** 

BioMed. Chem. Lett. **1992**, *2*, 651

MDL 74147, A NOVEL SELECTIVE AND SOLUBLE INHIBITOR OF HUMAN RENIN. SYNTHESIS, STRUCTURE-ACTIVITY RELATIONSHIP, SPECIES AND PROTEASE SELECTIVITIES

D. Schirlin, C. Tarnus, S. Baltzer and J. M. Rémy, Departments of Discovery Chemistry and Enzymology, Marion Merrell Dow Research Institute, 16 rue d'Ankara, 67009 Strasbourg cedex, France

The synthesis of MDL 74147, a novel potent and soluble inhibitor of human renin bearing a β-amino-α,α-difluoroketone functionality is described. Its structure-activity relationship, species and protease solubilities are discussed.

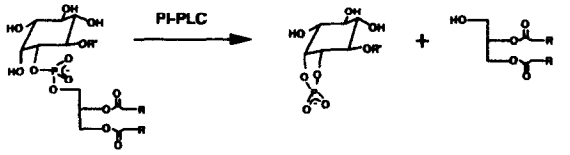


BioMed. Chem. Lett. **1992**, *2*, 655

TETRAVANADATE IS A POTENT INHIBITOR OF PHOSPHATIDYL INOSITOL SPECIFIC PHOSPHOLIPASE C

A. Stewart Campbell and Gregory R.J. Thatcher*
Dept. of Chemistry, Queen's University, Kingston, Canada

Comparison of ^{51}V nmr data with enzyme inhibition data obtained by ^{31}P nmr demonstrates the tetramer of vanadate to be a potent inhibitor of phosphatidyl inositol specific phospholipase C from B. Cereus.

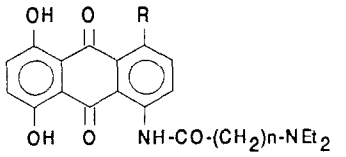


BioMed. Chem. Lett. **1992**, *2*, 659

NEW HYDROXY-AMIDO-ANTHRAQUINONES AS POTENTIAL ANTINEOPLASTIC DRUGS.

G. Zagotto, E. Unarte §, C Antonello, M. T Conconi, S. Marciani Magno, M Palumbo* Department of Pharmaceutical Sciences, University of Padova, Via F. Marzolo 5, 35131 Padova (Italy)
§ Department of Organic Chemistry, University of Santiago de Compostela, Santiago de Compostela (Spain)

The preparation and the preliminary biological results of hydroxy-amido-9,10-anthracenediones, useful as anticancer agents, are described.



n = 1, R = OH
n = 2, R = OH
n = 1, R = NH-CO-(CH$_2$)$_n$-NEt$_2$
n = 2, R = NH-CO-(CH$_2$)$_n$-NEt$_2$

BioMed. Chem. Lett. **1992**, *2*, 663

HIGH-LEVEL SOLUBLE EXPRESSION AND PURIFICATION OF DEACETOXYCEPHALOSPORIN C/ DEACETYLCEPHALOSPORIN C SYNTHASE

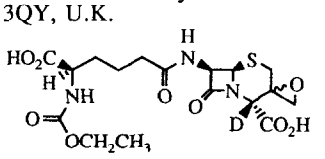
J.E. Baldwin; J.M. Blackburn; R.J. Heath; J.D. Sutherland.The Dyson Perrins Laboratory and The Oxford Centre for Molecular Sciences; South Parks Road, Oxford OX1 3QY, U.K.

The deacetoxycephalosporin C/deacetylcephalosporin C synthase gene from *Cephalosporium acremonium* has been expressed at high levels in *E. coli* under control of the *trc* promoter in a vector modified by PCR. The enzyme is produced in soluble, highly active form in contrast to previously reported expression in insoluble form under control of the λP_L promoter. A three step purification of this unstable enzyme is reported.

BioMed. Chem. Lett. **1992**, *2*, 669

SUBSTRATE SPECIFICITY OF SOLUBLE RECOMBINANT DEACETOXYCEPHALOSPORIN C/ DEACETYLCEPHALOSPORIN C SYNTHASE

J.E. Baldwin; R.M. Adlington; N.P. Crouch; R.J. Heath; I.A.C. Pereira; J.D. Sutherland. The Dyson Perrins Laboratory and The Oxford Centre for Molecular Sciences; South Parks Road, Oxford OX1 3QY, U.K.



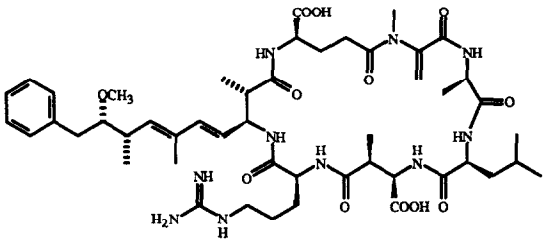
The substrate specificity of DAOC/DACS has been investigated and found to be identical to that of the wild type fungal enzyme. A new metabolite, has been detected on incubation with [4-^{2}H]-exomethylene cephalosporin C. Data obtained after derivatisation are consistent with a spiro-epoxide.

BioMed. Chem. Lett. **1992**, *2*, 673

THE ROLE OF ARGININE IN INTERACTIONS OF MICROCYSTINS WITH PROTEIN PHOSPHATASES 1 AND 2A.

Rie Nishiwaki-Matsushima#, Hirota Fujiki#, Ken-ichi Harada†, Cherie Taylor¶ and Ronald J. Quinn¶*
#National Cancer Center Research Institute, Tokyo 104, Japan,
†Faculty of Pharmacy, Meijo University, Nagoya 468, Japan and
¶School of Science, Griffith University, Brisbane, 4111, Australia.

By comparison with microcystin-LA, the arginine residue in microcystin-LR does not significantly contribute to biological activity. This data allows a refinement of a receptor binding model of the okadaic acid class of protein phosphatase inhibitors.



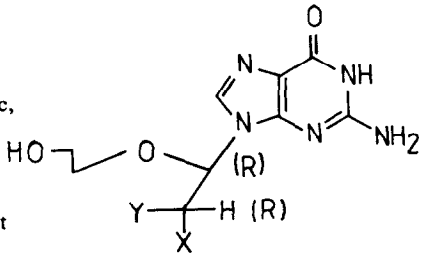
BioMed. Chem. Lett. **1992**, *2*, 677

STEREOSPECIFIC SYNTHESIS OF CHIRAL ACYCLIC ANALOGUES OF GUANOSINE

Christian Périgaud, Gilles Gosselin* and Jean-Louis Imbach

Université de Montpellier II, Sciences et Techniques du Languedoc, place E. Bataillon, 34095 Montpellier Cédex 5, France

The title compounds (X = OH or H, Y = CH_2OH or H) have been synthesized by ring opening of suitably protected 9-α-L-arabinopyranosylguanines. None of them showed significant activity against a variety of DNA and RNA viruses.



BioMed. Chem. Lett. **1992**, *2*, 681

THE EFFECT OF N-ACYL SUBSTITUENTS ON THE STABILITY OF MONOCYCLIC β-LACTAM INHIBITORS OF HUMAN LEUKOCYTE ELASTASE

William K. Hagmann*, Kevan R. Thompson, Shrenik K. Shah, Paul E. Finke, Bonnie M. Ashe, Hazel Weston, Alan L. Maycock, James B. Doherty, Merck Research Laboratories, Rahway, NJ 07065

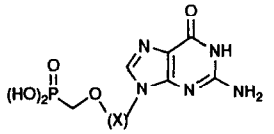
Simple N-acetyl-2-azetidinone inhibitors of human leukocyte elastase (**I**) were found to undergo N-deacylation as well as β-lactam ring opening. The development of the N-carbamoyl-2-azetidinone nucleus in **5** was crucial to the stability of these compounds for effective oral bioavailability.

BioMed. Chem. Lett. **1992**, *2*, 685

Synthesis and Biological Activity of Carbocyclic Derivatives of the Potent Antiviral Agent 9-[2-(Phosphonomethoxyethyl]guanine (PMEG)

Joanne J. Bronson, Louis M. Ferrara, John C. Martin, and Muzammil M. Mansuri
Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492-7660

Cyclopentane derivatives (**2-5**) of 9-[2-phosphonomethoxy)ethyl]guanine were prepared and evaluated for activity against HSV-2 and HIV.



1: PMEG: X = CH_2CH_2
2: X = 1,2-trans-cyclopentane
3: X = 1,2-cis-cyclopentane
4: X = 1,3-cis cyclopentane
5: X = 1,3-cis-cyclopentene

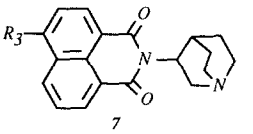
BioMed. Chem. Lett. **1992**, *2*, 691

DERIVATIVES OF NAPHTALIMIDE: NEW POTENT CONFORMATIONALLY RESTRICTED ANTAGONISTS OF 5-HT$_3$ RECEPTORS.

M. Langlois[1], J.L. Soulier[1], B. Brémont[1], S.Shen[1], V. Rampillon[1] and A. Giudice[2]

[1]CNRS-CERCOA, UPR 2621, 2-8 rue Henri Dunant, 94320, Thiais, France.
[2]SANOFI, 38 via G.B. Piranesi, 20137, Milan, Italy.

New potent 5-HT$_3$ antagonists 7 were synthesized from naphtalic anhydride and racemic or (R) and (S) 3-aminoquinuclidines. In contrast to zacopride, the activity resided essentially in the (R) enantiomer.



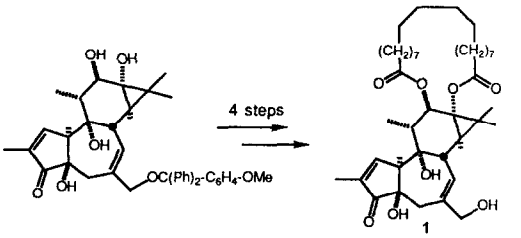
7

BioMed. Chem. Lett. **1992**, *2*, 695

THE SYNTHESIS OF A PHORBOL 12,13-BIS-LACTONE

Thomas E. Rawson and Timothy P. Kogan*
Bioorganic Chemistry, Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, California 94080.

The synthesis of a phorbol derivative (1) containing a 24-membered ring 12,13-bis-lactone was achieved via bis-acylation of 20-methoxytritylphorbol with decynoic acid, followed by a copper mediated macrocyclic ring closure.



1

BioMed. Chem. Lett. **1992**, *2*, 697

ENANTIOSELECTIVE DEPROTECTION OF N-PROTECTED AMINO ACIDS BY D-AMINOACYLASE

Hao-Ping Chen[a], Shih-Hsiung Wu*[ac], Ying-Chieh Tsai[b], Yunn-Bor Yang[b] and Kung-Tsung Wang[ac]
[a]Graduate Institute of Biochemical Sciences, National Taiwan University,
[b]Institute of Biochmistry, National Yang-Ming Medical College and
[c]Institute of Biological Chemistry, Academia Sinica, P.O.Box 23-106, Taipei, Taiwan

N-protected-DL-amino acids $\xrightarrow[\text{from } \textit{Alcaligenes faecalis}]{\text{D-aminoacylase}}$ D-amino acids + N-protected-L-amino acids

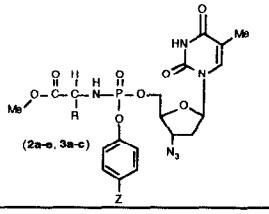
N-protected groups including acetyl (Ac), benzoyl (Bz) and benzyloxycarbonyl (Z).

BioMed. Chem. Lett. **1992**, *2*, 701

ARYL PHOSPHATE DERIVATIVES OF AZT INHIBIT HIV REPLICATION IN CELLS WHERE THE NUCLEOSIDE IS POORLY ACTIVE

Chnstopher McGuigan*, Ranjith N Pathirana, Naheed Mahmood† and Alan J Hay$^{\phi}$
Department of Chemistry, University of Southampton, Southampton, SO9 5NH, UK, † Medical Research Council Collaborative Centre, Burtonhole Lane, Mill Hill, London, NW7 1AD, UK, ϕ National Institute for Medical Research, The Ridgeway, London, NW7 1AA, UK

Aryl phosphate derivatives of the anti-HIV agent AZT have been prepared as membrane soluble pro-drugs for the bio-active nucleotide forms. In contrast to AZT, several of the compounds are very active in kinase deficient (JM) cells Activity may correlate with the π hydrophobicity parameter for the aryl substituent.



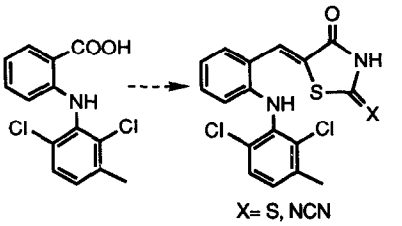
Compound	HIV-1 ED_{50} / μM
1	100
2a	0 8
2b	0 4
2c	0 32
2d	0 8
2e	40
3a	8
3b	1 6
3c	100

BioMed. Chem. Lett. **1992**, *2*, 705

SYNTHESIS AND CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITORY ACTIVITY OF SOME THIAZOLIDENE-4-ONE ANALOGS OF MECLOFENAMIC ACID

Diane H. Boschelli*#, David T. Connor#, Paul J. Kuipers% and Clifford D. Wright%, Departments of Chemistry# and Immunopathology%, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Rd., Ann Arbor, MI 48105

Replacing the carboxylic acid functionality of meclofenamic acid with select heterocycles converted this cyclooxygenase (CO) inhibitor into dual inhibitors of CO and 5-lipoxygenase (5-LO).

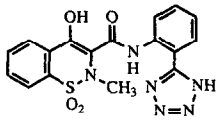


X= S, NCN

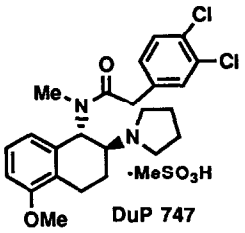
BioMed. Chem. Lett. **1992**, *2*, 709

Anti-allergic and Anti-inflammatory Actions of 2'-(tetrazole-5-yl)-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide 1,1-dioxid T. Ikeda, H. Kakegawa, H. Miyataka, H. Matsumoto and T. Satoh, *Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770 Japan*

2'-(Tetrazole-5-yl)-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide 1,1-dioxide showed the inhibitory effects on the antigen-induced histamine release from rat PEC, 48 h homorogous PCA in rats and the carrageenin-induced paw edema in mice



BioMed. Chem. Lett. **1992**, *2*, 715



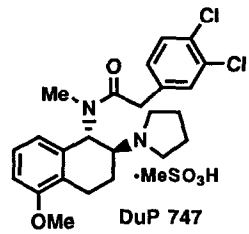
DuP 747

DuP 747: A NEW, POTENT, KAPPA, OPIOID ANALGESIC SYNTHESIS AND PHARMACOLOGY.

P.Rajagopalan*, R.M. Scrinbner, P. Pennev, W.K. Schmidt,S.W. Tam
G.F. Steinfels and L. Cook
CNS Diseases Research, The DuPont Merck PharmaceuticalCompany, Wilmington, DE 19880-0353

The synthesis and pharmacology of (±)-trans-3,4-dichloro-N-methyl-N-[5-methoxy-2-(pyrrolidin-1-yl)-1,2,3,4-tetrahydronapthalen-1-yl]benzeneacetamide methanesulfonate (DuP 747), a novel kappa agonist analgesic, are described.

BioMed. Chem. Lett. **1992**, *2*, 721



DuP 747

DuP 747: SAR STUDY

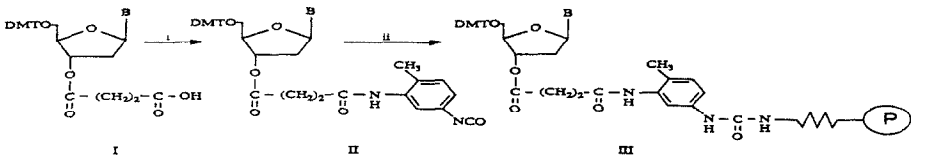
P. Rajagopalan*, R.M. Scribner, P.Pennev, P.L. Mattei, H.S. Kezar, C.Y. Cheng, R.S. Cheeseman, V.R. Ganti,A.L. Johnson, M.A. Wuonola, W.K. Schmidt, S.W. Tam, G.F. Steinfels and L. Cook
CNS Diseases Research, The DuPont Merck Pharmaceutical Company, Wilmington, DE 19880-0353

The structure-activity relationships in the seriers of compounds represented by DuP 747 are described in detail.

BioMed. Chem. Lett. **1992**, *2*, 727

A SIMPLE METHOD FOR THE DERIVATISATION OF LONG CHAIN ALKYLAMINE-CONTROLLED PORE GLASS (LCAA-CPG) FOR SOLID PHASE SYNTHESIS OF OLIGONUCLEOTIDES

K.C.Gupta* and Pradeep Kumar
Nucleic Acids Research Laboratory, CSIR Centre for Biochemicals, Delhi University Campus, Mall Road, Delhi - 110 007, India.



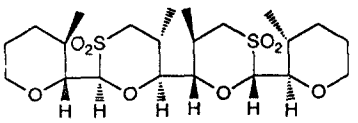
I II III

BioMed. Chem. Lett. **1992**, *2*, 731

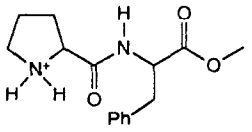
Dipeptidic Ammonium Ion Binding by a Synthetic Receptor.

G. Li and W.C. Still, Department of Chemistry, Columbia University, New York, NY 10027 USA

The conformationally homogeneous podand receptor binds dipeptide-like substrates enantioselectively and diastereoselectively



Podand Receptor



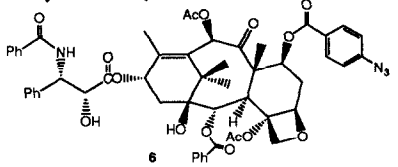
Typical Substrate

BioMed. Chem. Lett. **1992**, *2*, 735

TAXOL PHOTOAFFINITY LABEL: 7-(*p*-AZIDOBENZOYL)TAXOL SYNTHESIS AND BIOLOGICAL EVALUATION

Gunda I. Georg* and Geraldine C. B. Harriman, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045
Richard H. Himes and Magdalena R. Mejillano, Department of Biochemistry, University of Kansas, Lawrence, KS 66045

Summary: *An efficient semi-synthetic approach utilizing the appropriately functionalized (3R,4S)-3-hydroxy-4-phenyl-2-azetidinone and 7-(p-azidobenzoyl)baccatin III is described which leads to the targeted biologically active taxol photoaffinity label* ***6****.*



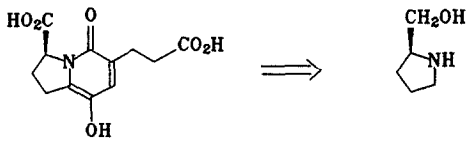
6

BioMed. Chem. Lett. **1992**, *2*, 739

ANODIC AMIDE OXIDATIONS: A NOVEL SYNTHESIS OF THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR A58365A.

Kevin D. Moeller* and Poh Lee Wong, Department of Chemistry, Washington University, St. Louis, MO 63130

An anodic amide oxidation based procedure for annulating lactam rings onto amino acid derivatives has been used to construct the angiotensin-converting enzyme inhibitor A58365A.

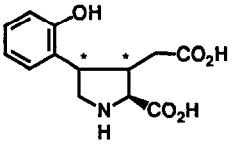


A58365A

BioMed. Chem. Lett. **1992**, 2, 743

CONFIGURATIONAL VARIANTS OF HYDROXYPHENYL-KAINOIDS: THEIR POTENT DEPOLARIZING ACTIVITY IN THE RAT CENTRAL NERVOUS SYSTEM

K. Hashimoto, M. Horikawa, M. Ishida†, H. Shinozaki† and H. Shirahama*
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan, †The Tokyo Metropolitan Institute of Medical Science, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113, Japan



Four stereoisomers of the title compound were synthesized and their depolarizing activities were estimated.

BioMed. Chem. Lett. **1992**, 2, 747

THE CONFORMATION OF CYCLOSPORIN A BOUND TO CYCLOPHILIN IS ALTERED (ONCE AGAIN) FOLLOWING BINDING TO CALCINEURIN: AN ANALYSIS OF RECEPTOR-LIGAND-RECEPTOR INTERACTIONS

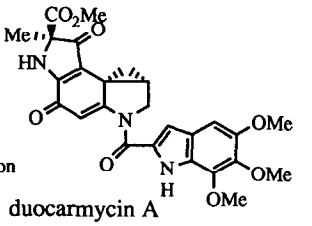
Michael K. Rosen, Peter J. Belshaw, David G. Alberg, Stuart L. Schreiber*
Department of Chemistry, Harvard University, Cambridge, MA 02138

Abstract Analyses of the complexation of cyclosporin A (CsA) by cyclophilin and the unusual properties of MeBm$_2$t^1-CsA lead us to propose a conformational change upon binding of the cyclophilin-CsA complex to the protein phosphatase, calcineurin.

BioMed. Chem. Lett. **1992**, 2, 755

SYNTHESIS AND CYTOTOXICITY OF ENANTIOMERIC PAIRS OF DUOCARMYCIN A AND ITS 2-EPIMER

Yasumichi Fukuda,[1] Kazuhiko Nakatani,[2] and Shiro Terashima[2]* Central Research Laboratories, Kyorin Pharmaceutical Co. LTD., Mitarai, Nogi, Tochigi 329-01, JAPAN[1] Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara 229, JAPAN[2]

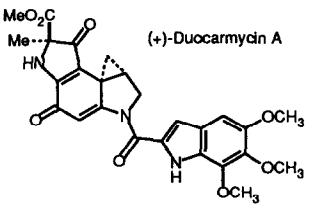


duocarmycin A

Abstract. The synthesis of the four possible diastereomers of duocarmycin A was achieved through optical resolution of a tricyclic synthetic intermediate. The stereochemical configuration of the cyclopropane ring was found to be closely related with their cytotoxicity against P388 murine leukemia.

BioMed. Chem. Lett. **1992**, 2, 759

DNA Alkylation Properties of the Duocarmycins: (+)-Duocarmycin A, *Epi*-(+)-Duocarmycin A, *Ent*-(-)-Duocarmycin A and *Epi,Ent*-(-)-Duocarmycin A, Dale L. Boger,* Weiya Yun, *Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037, USA.* Shiro Terashima, Yasumichi Fukuda, Kazuhiko Nakatani, *Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, JAPAN.* Paul A. Kitos, Qing Jin, *Department of Biochemistry, University of Kansas, Lawrence, Kansas 66045, USA.*



(+)-Duocarmycin A

Abstract. A study of the comparative in vitro cytotoxic activity and DNA alkylation properties of both enantiomers of the two diastereomers of (+)-duocarmycin A are detailed. The DNA alkylation efficiency and in vitro cytotoxic potency of the natural enantiomers ((+)-duocarmycin A > *epi*-(+)-duocarmycin A, 3-8x) exceed those of the unnatural enantiomers (*ent*-(-)-duocarmycin A, *epi,ent*-(-)-duocarmycin A) by at least 100x.