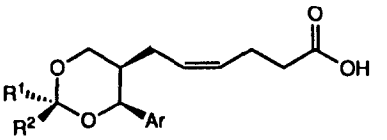
GRAPHICAL ABSTRACTS

BioMed. Chem. Lett. **1992**, *2*, 1181

DUAL-ACTING THROMBOXANE RECEPTOR ANTAGONIST/SYNTHASE INHIBITORS: HETEROCYCLIC VARIATIONS

A.W.Faull, H.Gaskin, P.S.Hadfield, R.Jessup, K.Russell, W.J.Watkins* and M.Wayne
ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England

Abstract: The ability of 1,3-dioxanes bearing a variety of aromatic heterocycles at C4 to inhibit thromboxane synthase has been examined. Potent dual-acting thromboxane receptor antagonist/thromboxane synthase inhibitors have been discovered.

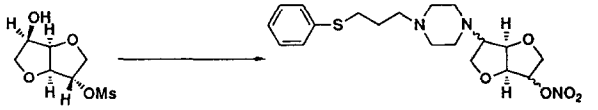


BioMed. Chem. Lett. **1992**, *2*, 1187

SYNTHESIS OF STEREOISOMERS OF 1,4:3,6-DIANHYDROHEXITOL NITRATE DERIVATIVE, KF-14124

Hiroaki Hayashi, Hideo Ueno, and Fumio Suzuki*
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., LTD., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken, 411 Japan

All of the three stereoisomers of 5-deoxy-5-[4-(3-phenylthiopropyl)piperazin-1-yl]-1,4:3,6-dianhydro-L-iditol 2-nitrate [KF-14124; 4 (*exo,exo*)] were synthesized from a common key intermediate (**8**).



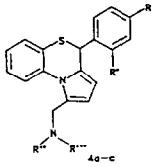
8

BioMed. Chem. Lett. **1992**, *2*, 1193

SYNTHESIS AND PRELIMINARY BIOLOGICAL EVALUATION OF 1-AMINOMETHYL-4-SUBSTITUTED-4H-PYRROLO[2,1-c][1,4]BENZOTHIAZINES, A NEW CLASS OF CALCIUM ANTAGONISTS

G. Campiani[a], V. Nacci*[a], A. Garofalo[a], M Botta[a], I Fiorini[a], A Tafi[a], G. Bruni[b], M R Romeo[b], A Peres[c], L. Bertollini[c]
[a] Dipartimento Farmaco Chimico Tecnologico, Banchi di Sotto 55, [b] Istituto di Farmacologia, via delle Scotte 6, Università di Siena, 53100 Siena, Italy, [c] Dipartimento di Fisiologia e Biochimica Generali, Università di Milano, via Celoria 26 20133 Milano, Italy

The synthesis of conformationally rigid calcium channel blockers is described.

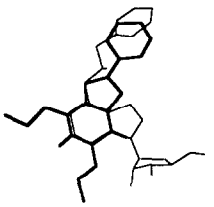


BioMed. Chem. Lett. **1992**, *2*, 1199

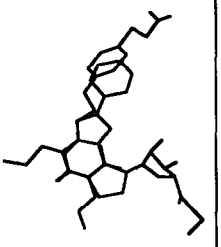
AN EXPLANATION OF THE SUBSTITUENT EFFECT OF 1,3,8-TRISUBSTITUTED XANTHINES ON ADENOSINE A_1/A_2 AFFINITY.

Michael J. Dooley and Ronald J. Quinn*
School of Science, Griffith University, Brisbane, 4111, Australia

At adenosine A_1 receptors both propyl groups contribute to receptor binding.



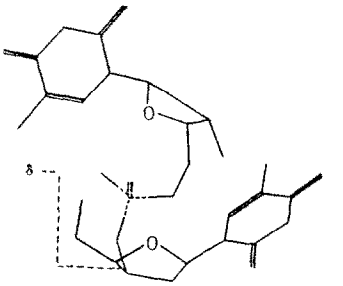
At adenosine A_2 receptors only one propyl group contributes to receptor binding.



BioMed. Chem. Lett. **1992**, *2*, 1201

2'-DEOXY-ß-D-XYLOTHYMIDINYL-(3', 5')-2'-DEOXY-ß-D-XYLOTHYMIDYLATE: STEREOCHEMICAL COURSE OF DINUCLEOSIDE PHOSPHONATE FORMATION AND CONFORMATIONAL PROPERTIES

Helmut Rosemeyer, Iris Strodtholz, Frank Seela*
Laboratorium für Bioorganische Chemie, Universität Osnabrück, Osnabrück, Germany



d(xTpxT) was synthesized via its protected dinucleoside phosphonate [(asymmetric induction: de (S_P) = 29%)]. It exhibits an inverted CD spectrum compared to d(TpT) but identical stacking thermodynamics. Computer modeling revealed a structure with an endocyclic torsion angle δ [C(5')-C(4')-C(3')-O(3')] of 38° implying a left-handed helical sense.

BioMed. Chem. Lett. **1992**, *2*, 1207

SUBSTITUTED PENTA- AND HEXAPEPTIDES AS POTENT INHIBITORS OF HERPES SIMPLEX VIRUS TYPE 2 RIBONUCLEOTIDE REDUCTASE

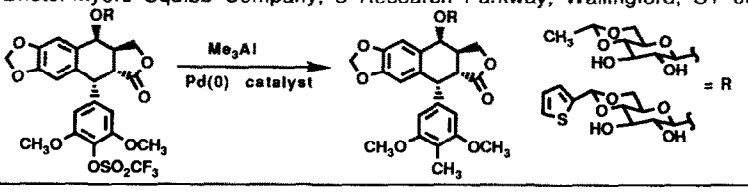
L. L. Chang,* J. Hannah, W. T. Ashton, G. H. Rasmusson, T. J. Ikeler, G. F. Patel, V. Garsky,† C. Uncapher,† G. Yamanaka,† W. L McClements,† and R. L Tolman. Merck Research Laboratories, Rahway, NJ 07065 and †West Point, PA 19486

For the inhibition of herpes simplex virus type 2 ribonucleotide reductase (HSV-2 RR), structure-activity relationship studies on Y, N, and/or L of YVVNDL (equipotent to YAGAVVNDL on HSV-2 RR) using synthetic peptides are reported. The most potent of these, **YVV-N(N^{γ}-Me$_2$)-D-L(γ-Me)**, and **(Bzl)$_2$CHCO-VVND-L(γ-Me)** had relative potencies of 110 and 120, respectively, relative to YAGAVVNDL.

BioMed. Chem. Lett. **1992**, *2*, 1213

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4'-DESHYDROXY-4'-METHYL ETOPOSIDE AND TENIPOSIDE ANALOGS.

Mark G. Saulnier*, Karen L. LeBoulluec, Byron H. Long, Dolatrai M. Vyas, Alfred R. Crosswell, and Terrence. W. Doyle.
Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492-7660.



BioMed. Chem. Lett. **1992**, *2*, 1219

KYNURENINE AMINOTRANSFERASE/HUMAN HEPATIC C-S LYASE: PRELIMINARY STRUCTURE-ACTIVITY RELATIONSHIP STUDIES,

Ian S. Blagbrough*. *School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK.* Lorraine D. Buckberry, Barrie W. Bycroft, and P. Nicholas Shaw. *Department of Pharmaceutical Sciences, School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, UK.*

Abstract: Partially purified human hepatic cytosolic and mitochondrial fractions have been investigated for evidence of C-S lyase (CSL) activity. CSL activity has been characterized with synthetic aliphatic and aromatic L-cysteine conjugates. Preliminary structure-activity relationship studies have shown that aliphatic and aromatic L-cysteine conjugates are substrates.

BioMed. Chem. Lett. **1992**, *2*, 1225

HUMAN HEPATIC C-S LYASE: TRANSAMINATION REACTIONS AND SIGNIFICANT DIFFERENCES BETWEEN KYNURENINE AMINOTRANSFERASE AND KYNURENINASE,

Ian S. Blagbrough*.
School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK. Lorraine D. Buckberry, Barrie W. Bycroft, and P. Nicholas Shaw. *Department of Pharmaceutical Sciences, School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, UK.*

Abstract: Kynurenine aminotransferase and glutamine transaminase K and L activities were assessed in order to identify a physiological role for human hepatic cytosolic C-S lyase (CSL), as the C-C lyase kynureninase, which copurifies with rat hepatic CSL, has shown not to be human hepatic CSL. Kynurenic acid production supports an aminotransferase role for this CSL.

BioMed. Chem. Lett. **1992**, *2*, 1231

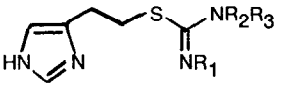
IMETIT, AND N-METHYL DERIVATIVES. THE TRANSITION FROM POTENT AGONIST TO ANTAGONIST AT HISTAMINE H_3 RECEPTORS.

C.R Ganellin,[+] B. Bang-Andersen,[+] Y.S. Khalaf,[+] W. Tertiuk,[+] J.M. Arrang,[++] M. Garbarg,[++] X. Ligneau,[++] A Rouleau[++] and J.C. Schwartz[++]

[+] Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ

[++] Unité de Neurobiologie et Pharmacologie, Centre Paul Broca de l'INSERM, 2 ter rue d'Alésia, 75014 Paris, France

Summary: Imetit {S-[2(imidazol-4-yl)ethyl]isothiourea} ($R_1 = R_2 = R_3 = H$) is a potent H_3-agonist in vitro (on rat brain cortical slices; EC_{50} = 1 nM) and in vivo (ED_{50}~ 1 mg/kg per os in mice). N-Methylimetit is also an agonist (EC_{50} = 15 nM) but dimethyl and trimethyl derivatives are antagonists (K_i = 50 - 500 nM).

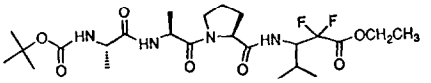


BioMed. Chem. Lett. **1992**, *2*, 1235

SYNTHESIS OF A PEPTIDYL 2,2-DIFLUORO-3-AMINOPROPIONATE

Michael R. Angelastro, Philippe Bey and Norton P. Peet*
Marion Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, OH 45215, USA.

The synthesis of peptidyl 2,2-difluoro-3-amino-propionate 7, a potential proteinase inhibitor is described. Cycloaddition of the Reformatsky reagent prepared from ethyl bromodifluoroacetate with the imine made from isovaleraldehyde and benzylamine was a key step in the construction of 7.

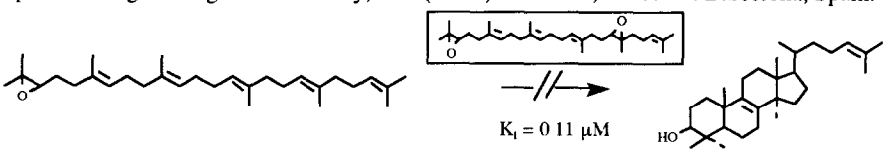


7

BioMed. Chem. Lett. **1992**, *2*, 1239

2,3:18,19-DIOXIDOSQUALENE: SYNTHESIS AND ACTIVITY AS A POTENT INHIBITOR OF 2,3-OXIDOSQUALENE-LANOSTEROL CYCLASE IN RAT LIVER MICROSOMES

José-Luis Abad, Josefina Casas, Francisco Sánchez-Baeza and Angel Messeguer *.
Dpt. of Biological Organic Chemistry, CID (CSIC). J. Girona, 18. 08034 Barcelona, Spain.

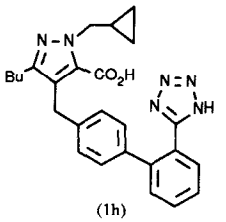


BioMed. Chem. Lett. **1992**, *2*, 1243

C-LINKED BIARYL TETRAZOLES AS ANTAGONISTS OF ANGIOTENSIN II

D. Middlemiss*, B.C. Ross, C. Eldred, J.G. Montana, P. Shah, G.C. Hirst, S.P. Watson, T.A Panchal, J.M.S. Paton, T. Hubbard, G.M. Drew, M.J. Robertson, A. Hilditch, and K.L. Clark.
Glaxo Group Research, Park Road, Ware, Hertfordshire SG12 0DP, U.K.

Abstract: The identification of a novel series of C-linked pyrazole biaryl tetrazoles, e.g. (1h), which are antagonists of angiotensin II, is described. These compounds are highly potent *in vitro* (pK_B ca. 10), and some examples cause significant reductions in blood pressure at $1mgkg^{-1}$ p.o. in hypertensive rats.

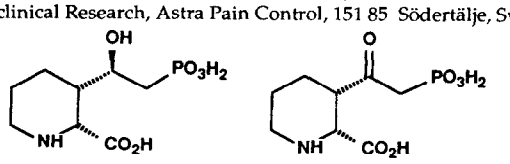


(1h)

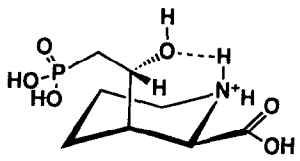
BioMed. Chem. Lett. **1992**, *2*, 1247

Competitive NMDA antagonists that base their activity on a unique conformational effect.

A. Claesson, B-M Swahn, K. M. Edvinsson, H. Molin and M. Sandberg
Preclinical Research, Astra Pain Control, 151 85 Södertälje, Sweden



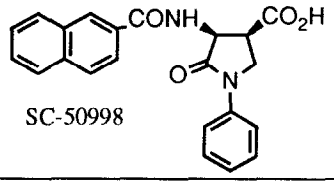
(2R, 3S)



BioMed. Chem. Lett. **1992**, *2*, 1251

1,3,4-TRISUBSTITUTED PYRROLIDINONES AS SCAFFOLDS FOR CONSTRUCTION OF PEPTIDOMIMETIC CHOLECYSTOKININ ANTAGONISTS Daniel L. Flynn*, Clara I. Villamil, Daniel P. Becker, Gary W. Gullikson, Chafiq Moummi, and Dai-Chang Yang,
Departments of Chemistry and Neurological Diseases Research, Searle Research & Development, Skokie, Illinois 60077

A new series of cholecystokinin-A receptor (CCK-A) antagonists are described which utilizes a 1,3,4-trisubstituted pyrrolidinone as a scaffold for appending specific amino acid R group mimics.



SC-50998

BioMed. Chem. Lett. **1992**, *2*, 1257

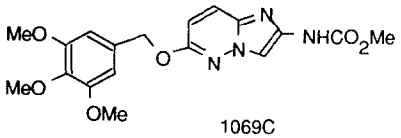
SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1069C: A NEW SYNTHETIC ANTITUMOUR AGENT WITH VERY LOW CROSS-RESISTANCE POTENTIAL

Simon T. Hodgson,* [a] D. Con Jenkins, [a] Vince Knick, [b] Elaine Rapson, [a] and Stuart D.M. Watts, [a]

[a] Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS, UK.

[b] Burroughs-Wellcome, Research Triangle Park, North Carolina 27709, USA

Abstract: *A novel imidazopyridazine carbamate, 1069C, is a potent microtubule inhibitor which binds at the Colchicine site on tubulin and is effective in vivo against murine tumours made resistant to clinically used antitumour drugs.*



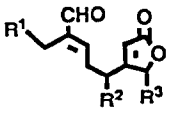
1069C

BioMed. Chem. Lett. **1992**, 2, 1263

PHOSPHOLIPASE A_2 INHIBITION BY MANOALIDE: DEVELOPMENT OF SIMPLE ANALOGUE AND NECESSARY FUNCTIONAL GROUPS FOR INHIBITION

S. Katsumura,[1)*] Q. Han,[1)] H. Kadono,[1)] S. Fujiwara,[2)] S. Isoe,[2)] S. Fujii,[3)] H. Nishimura,[3)] and K. Ikeda,[3)] *1) Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya 662; 2) Faculty of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558 ; and 3) Department of Biochemistry, Osaka University of Pharmaceutical Sciences, Matsubara 580, Japan*

Manoalide analogue 1a inhibited bovine pancreatic phospholipase A_2 to the same extent as seco-manoalide .



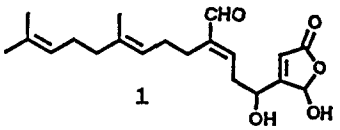
1a R^1=geranyl, R^2=R^3=OH
1b R^1=octyl, R^2=R^3=OH

BioMed. Chem. Lett. **1992**, 2, 1267

TOWARD ELUCIDATION OF THE INHIBITION MECHANISM OF BOVINE PANCREATIC PHOSPHOLIPASE A_2 BY MANOALIDE: AMINO ACID RESIDUES SELECTIVELY MODIFIED BY MANOALIDE ANALOGUES

S. Katsumura,[1)*] Q. Han,[1)] S. Fujiwara,[2)] S. Isoe,[2)] H. Nishimura,[3)] S. Inoue,[3)] and K. Ikeda[3)]
1) Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, 662;
2) Faculty of Science, Osaka City University, Sumiyoshi, Osaka 558; and
3) Department of Biochemistry, Osaka University of Phamaceutical Sciences, Matsubara, 580, Japan

Manoalide analogue 1 selectively modified only two of eleven lysine residues of bovine pancreatic phospholipase A_2.

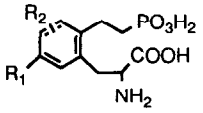


BioMed. Chem. Lett. **1992**, 2, 1269

PHOSPHONOETHYLPHENYLALANINE DERIVATIVES AS NOVEL ANTAGONISTS OF NON-NMDA IONOTROPIC GLUTAMATE RECEPTORS.

G.S. Hamilton*, Z. Huang, R.J. Patch, M.E. Guzewska, R.L. Elliott, S.A. Borosky, D L. Bednar, J.W. Ferkany and E.W. Karbon, *Nova Pharmaceutical Corporation, 6200 Freeport Centre, Baltimore, MD 21224*

Abstract: The synthesis and biological evaluation of substituted phosphonoethylphenylalanines, a new class of KA/AMPA antagonist, is described.

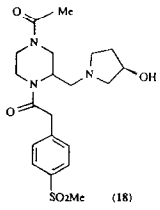


BioMed. Chem. Lett. **1992**, 2, 1275

PREPARATION AND EVALUATION OF SOME HYDROPHILIC PHENYLACETYLPIPERAZINES AS PERIPHERALLY-SELECTIVE KAPPA-OPIOID RECEPTOR AGONISTS.

P J Birch, A G Hayes, M R Johnson*, T A Lea, P J Murray, H Rogers and D I C Scopes Glaxo Group Research, Ware, Herts SG12 ODJ, UK.

The synthesis of a series of hydrophilic phenylacetylpiperazines as potential peripherally-selective κ-opioid receptor agonists is described. Several compounds were potent κ-agonists *in vitro* and one, the sulphone (18), showed significant peripheral selectivity *in vivo*

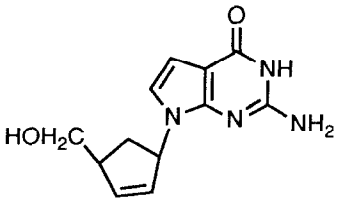


(18)

BioMed. Chem. Lett. **1992**, *2*, 1279

(±)-7-DEAZACARBOVIR AS A COMPOUND WITH POTENTIAL ANTI-HIV AND ANTI-HCMV PROPERTIES

Suhaib M. Siddiqi, Xing Chen, and Stewart W. Schneller*, *Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250*

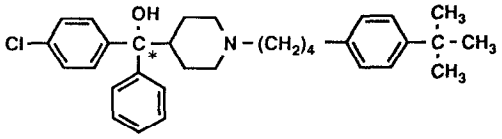


BioMed. Chem. Lett. **1992**, *2*, 1283

NOVEL STEREOSELECTIVE CALCIUM CHANNEL LIGANDS OF THE DIPHENYLALKYLAMINE-TYPE

Ming-Qiang Zhang[1], Patrizia Caldirola[1], Dirk C. Leysen[2], Hendrik Timmerman[1]
[1]Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam;
[2]Department of Medicinal Chemistry II, Organon International B.V., 5340 BH Oss; The Netherlands

[^{3}H]nitrendipine displacement on rat brain membranes
d-enantiomer: $K_D = 8\ 90 \pm 0.14 \times 10^{-6}$ mol/L
l-enantiomer: $K_{D1} = 4.68 \pm 0.18 \times 10^{-8}$ mol/L; $K_{D2} = 8.81 \pm 0.09 \times 10^{-6}$ mol/L

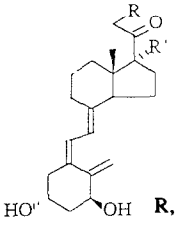


BioMed. Chem. Lett. **1992**, *2*, 1289

SYNTHESIS AND IMMUNOREGULATING ACTIVITY OF VITAMIN D ANALOGUES BEARING PREGNANE SIDE CHAINS

Eigoro Murayama, Katsuhito, Miyamoto, Kiyoshige Ochi, and Noboru Kubodera*
Exploratory Research Laboratories, Chugai Pharm. Co., Ltd. 1-135, Komakado, Gotemba, Shizuoka, 412 Japan

Abstract: The synthesis of vitamin D analogues bearing pregnane side chains and their immunoregulating activity in mice are described.



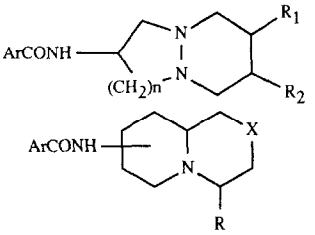
R, R'; H or OH

BioMed. Chem. Lett. **1992**, *2*, 1293

Substituted Benzamides with Conformationally Restricted Side Chains. 4. Hetero-azabicyclo[x.y.0] Derivatives as Gastric Prokinetic Agents.

M.S. Hadley, F.D. King*, B. McRitchie and D.H. Turner
SmithKline Beecham Pharmaceuticals, The Pinnacles, Harlow, Essex CM19 5AD, UK

The gastric prokinetic and dopamine receptor antagonist activity of diazabicyclo[4.3.0], [4.4.0] and oxa- and thia-azabicyclo[4.4.0] benzamides related to the serotonin 5-HT$_4$ receptor agonist BRL 20627 is described.

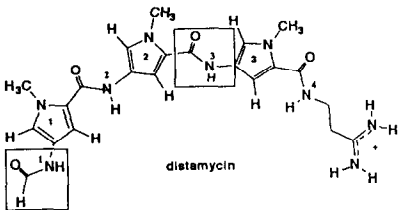


BioMed. Chem. Lett. **1992**, 2, 1299

^{1}H-NMR Studies Of The Interactions Of Two Distamycin Analogues With The Dodecamer d(CGCGAATTCGCG)$_2$

Maria Rosaria Conte, Ernesto Fattorusso*, Luigi Gomez Paloma and Luciano Mayol
Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II, via D. Montesano 49, I-80131 Napoli, Italy

The interaction of two analogues of distamycin containing a retroinversion at the level of the first and third amide bond with the dodecamer d(CGCGAATTCGCG)$_2$ has been studied by ^{1}H-NMR techniques.

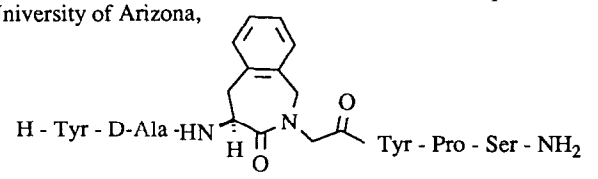


BioMed. Chem. Lett. **1992**, 2, 1305

DERMORPHIN SEQUENCE WITH HIGH δ-AFFINITY BY FIXING THE PHE SIDECHAIN TO TRANS AT χ_1.

D. Tourwé*[a], K. Verschueren[a], G. Van Binst[a], P. Davis[b], F. Porreca[b] and V.J. Hruby[c].
[a]Organische Chemie, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels and Departments of [c]Chemistry and [b]Pharmacology, University of Arizona, AZ 85721, USA

By incorporation of a constrained amino acid into the dermorphin sequence, μ-selectivity is lost by a strong increase in δ-affinity.

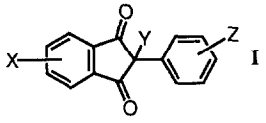


BioMed. Chem. Lett. **1992**, 2, 1309

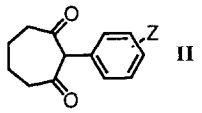
STRUCTURAL ANALYSIS OF 2-ARYL-1,3-DIONE COMPOUNDS AS INHIBITORS OF 5-LIPOXYGENASE

Dee W. Brooks*, Steven P. Schmidt, Richard D. Dyer, Patrick Young and George W. Carter
Immunosciences Research Area, Department 47K, Abbott Laboratories, Abbott Park, Illinois 60064

A variety of 2-aryl-1,3-diones were evaluated for 5-lipoxgyenase inhibitory activity. The well-known 2-phenylindane-1,3-dione system **I** as well as novel seven-membered 1,3-diones **II** were discovered to be inhibitors.



I



II