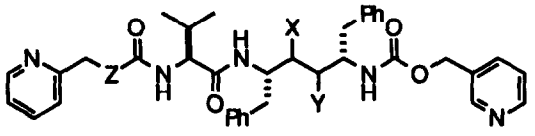
BioMed. Chem. **1994**, *2*, 847

Design of Orally Bioavailable, Symmetry-Based Inhibitors of HIV Protease, Dale J. Kempf,* Kennan C. Marsh, Lynnmarie Codacovi Fino, Pamela Bryant, Adrienne Craig-Kennard, Hing L. Sham, Chen Zhao, Sudthida Vasavanonda, William E. Kohlbrenner, Norman E. Wideburg, Ayda Saldivar, Brian E. Green, Thomas Herrin and Daniel W. Norbeck, *Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064*



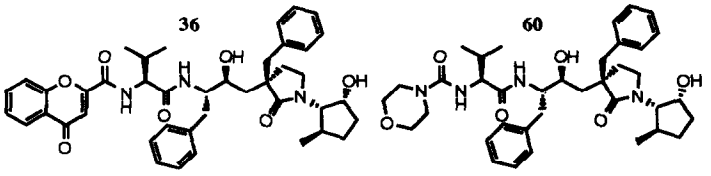
Z = O, N(CH$_3$); X, Y = OH, H

A series of novel, symmetry-based inhibitors of HIV-1 protease with excellent oral bioavailability is described. Systematic evaluation identified the influence of aqueous solubility, molecular size and hydrogen-bonding functionality upon the pharmacokinetic behavior of these inhibitors in rats

BioMed. Chem. **1994**, *2*, 859

SYNTHESIS, ANTIVIRAL ACTIVITY, and BIOAVAILABILITY STUDIES of γ-LACTAM DERIVED HIV PROTEASE INHIBITORS.

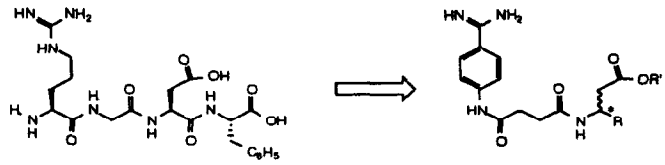
R. W. Hungate*, J. L. Chen, K. E. Starbuck, J. P. Vacca, S. L. McDaniel, R. B. Levin, B. D. Dorsey, J. P. Guare, W. Whitter, M. K. Holloway, P. L. Darke, J. A. Zugay, W. A. Schleif, E. A. Emini, J. C. Quintero, J. H. Lin, I-Wu Chen, P. S. Anderson, J. R. Huff. Merck Research Laboratories, West Point, Pennsylvania 19486



Incorporation of a γ-lactam in hydroxyethylene isosteres results in modest inhibitors of HIV-1 protease. Using 2(S)-amino-1 (R)-hydroxy-3(R)-methylcyclopentane at the C-terminus has produced significantly more potent inhibitors (e.g. **36** and **60**).

BioMed. Chem. **1994**, *2*, 881

Design of Orally Active, Non-Peptide Fibrinogen Receptor Antagonists. An Evolutionary Process from the R-G-D Sequence to Novel Anti-Platelet Aggregation Agents. Bovy, P. R.; Tjoeng, F. S.; Rico, J. G.; Lindmark, R. J.; Rogers, T. E.; Zablocki, J. A.;† Garlan, R. B.;† McMackins, D. E.; Dayringer, H.; Tóth, M. V.; Zupec, M. E.; Rao, S.;† Panzer-Knodle, S. G.;† Nicholson, N. S.;† Salyers, A.;† Taite, B. B.;† Herin, M.;† Miyano, M.;† Feigen, L. P.;† Adams, S. P.; †Thrombosis Research, Searle, 4901 Searle Parkway, Skokie, IL, 60077 and Monsanto Corporate Research, Chemical Sciences, 700 Chesterfield Parkway North, St Louis, MO, 63198, USA



The design of potent, non-peptide fibrinogen receptor antagonists based on the Arg-Gly-Asp (RGD) sequence is presented. An ethyl ester prodrug of several compounds, e.g., where R = (S)-3-pyridyl, were orally active in the dog; in vivo activity was measured with an ex vivo antiaggregatory assay.

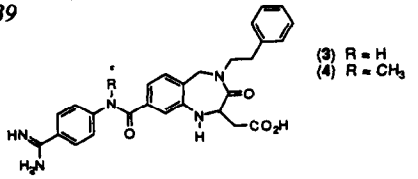
BioMed. Chem. **1994**, *2*, 897

Design of a Potent and Orally Active Nonpeptide Platelet Fibrinogen Receptor (GPIIB/IIIA) Antagonist

W. E. Bondinell,[a*] R. M. Keenan,[a*] W. H. Miller,[a*] F. E. Ali,[a] A. C. Allen,[b] C. W. De Brosse,[b] D. S. Eggleston,[c] K. F. Erhard,[a] R. C. Haltiwanger,[c] W. F. Huffman,[a] S.-M. Hwang,[d] D. R. Jakas,[a] P. F. Koster,[f] T. W. Ku,[a] C. P. Lee,[e] A. J. Nichols,[f] S. T. Ross,[a] J. M. Samanen,[a] R. E. Valocik,[f] J. A. Vasko-Moser,[f] J. W. Venslavsky,[a] A. S. Wong,[d] and C.-K. Yuan[a]

Departments of Medicinal Chemistry,[a] Analytical Sciences,[b] Physical and Structural Chemistry,[c] Cellular Biochemistry,[d] Drug Delivery,[e] and Pharmacology,[f] Research & Development Division, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939

N-Methylation of the potent, nonpeptide GPIIb/IIIa antagonist **3** (SB 207448) gave **4** (SB 208651); both compounds have high affinity for human GPIIb/IIIa and are potent inhibitors of human platelet aggregation *in vitro*, however, only **4** displayed oral activity following intraduodenal administration.



BioMed. Chem. **1994**, *2*, 909

Renin Inhibitor SC-51106 Complexed with Human Renin: Discovery of a New Binding Site Adjacent to P_3

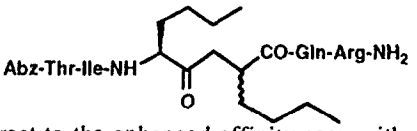
Gunnar J. Hanson* and Michael Clare, *Searle Research,4901 Searle Parkway, Skokie, IL 60077,* Neena L. Summers, Louis W. Lim, David J. Neidhart, Huey S. Shieh and Anna M. Stevens *Monsanto Corporate Research 700 ChesterfieldParkway North, Chesterfield, MO 63017* SC-51106, a "minimal-size" diol-based renin inhibitor lacking a P_4 residue, has been co-crystallized with human renin and the structure of the complex determined by X-ray crystallography. This study defines the mode of binding of this important class of renin inhibitor, and in conjuction with molecular modeling, has led to the discovery of a new binding site adjacent to S_3, which is termed the "S_3 aux(iliary)" subsite.

BioMed. Chem. **1994**, *2*, 919

HIV-1 PROTEASE INHIBITORS: KETOMETHYLENE ISOSTERES WITH UNUSUALLY HIGH AFFINITY COMPARED WITH HYDROXYETHYLENE ISOSTERE ANALOGS

Anne Marinier*, Mihaly V. Toth*, Kathryn Houseman#, Richard Mueller# and Garland R. Marshall*

**Center for Molecular Design and Department of Molecular Biology and Pharmacology, Washington University, St. Louis, MO 63130; #Searle Research and Development, Skokie, IL 60077*

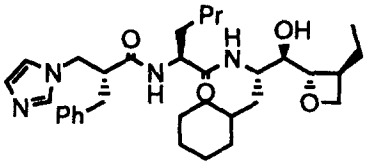


In contrast to the enhanced affinity seen with renin and pepsin upon conversion of the transition-state isostere, ketomethylene, to the hydroxyethylene, a set of HIV protease inhibitors showed a reduction in affinity.

BioMed. Chem. **1994**, *2*, 927

RENIN INHIBITORS: C-TERMINAL OXETANES AS POTENT TRANSITION-STATE MIMICS

Saul H. Rosenberg,* Kenneth P. Spina, Herman Stein, Jerome Cohen, William R. Baker, and Hollis D. Kleinert *Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064*

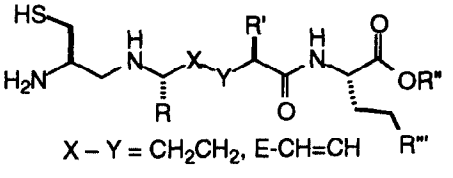


A novel transition-state mimic containing a C-terminal oxetane has been developed. Renin inhibitors incorporating this fragment exhibit enhanced potency against human plasma renin at physiologic pH.

BioMed. Chem. **1994**, *2*, 939

Synthesis and Biological Activity of Ras Farnesyl Protein Transferase Inhibitors. Tetrapeptide Analogs with Amino Methyl and Carbon Linkages.

John S. Wai, Dona L. Bamberger, Thorsten E. Fisher, Samuel L. Graham, Robert L. Smith, Jackson B. Gibbs, Scott D. Mosser, Allen I. Oliff, David L. Pompliano, Elaine Rands, Nancy E. Kohl.
Merck Research Laboratories, West Point, Pennsylvania 19486



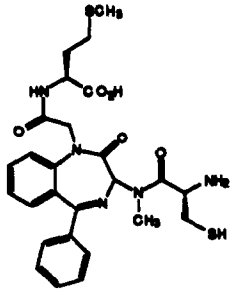
Replacement of the central amino methylene linkage of C[ψCH_2NH]A[ψCH_2NH]AX tetrapeptide inhibitors with carbon tethers led to compounds with potency in the nanomolar range. Some of the more potent olefinic compounds inhibit Ras processing in intact v-*ras* transformed NIH 3T3 cells with IC_{50} values in the 0.1 to 1 μM range, and inhibit selectively the anchorage-independent growth of H-*ras* transformed Rat1 cells at 10 μM.

BioMed. Chem. **1994**, *2*, 949

BENZODIAZEPINE PEPTIDOMIMETIC INHIBITORS OF FARNESYLTRANSFERASE

James C. Manvers, Jr.*, Robert S. McDowell, Mark E. Reynolds, David A. Oare, Todd C. Somers, Mark S. Stanley, Thomas E. Rawson, Martin E. Struble, Daniel J. Burdick, Kathryn S. Chan, Charles M. Duarte, Kenneth J. Paris, Jeff Y. K. Tom, Dairian T. Wan, Yingchun Xue, and John P. Burnier.
Department of Bioorganic Chemistry, Genentech Inc.,
460 Pt. San Bruno Blvd., South San Francisco, CA 94080

Abstract: The synthesis of novel inhibitors of CAAX protein farnesyltransferase in which the central dipeptide (A_1A_2) has been replaced with 3-aminomethyl-1-carboxymethyl-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one (BZA) are described (IC_{50} = 0.3 nM).

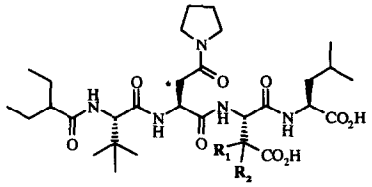


BioMed. Chem. **1994**, *2*, 959

HERPES SIMPLEX VIRUS RIBONUCLEOTIDE REDUCTASE SUBUNIT ASSOCIATION INHIBITORS: THE EFFECT AND CONFORMATION OF β-ALKYLATED ASPARTIC ACID DERIVATIVES

N. Moss[†]*, R. Déziel[†], J.-M. Ferland[†], S. Goulet[†], P. J. Jones[‡], S. Leonard[‡], P. Pitner[‡], and R. Plante[†]. [†]Bio-Méga/Boehringer Ingelheim Research Inc., 2100 Cunard, Laval, Quebec, Canada, H7S 2G5. [‡]Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877.

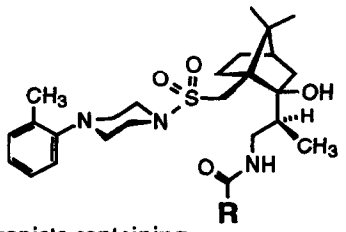
Replacing the aspartic acid moiety in our ribonucleotide reductase inhibitors with β-alkylated aspartic acid derivatives can improve inhibitor potency up to 50 fold. Evidence suggests that appropriate β-alkyl groups (R_1 and R_2) favor the putative bioactive conformation of the important aspartic acid carboxyl group.



BioMed. Chem. **1994**, *2*, 971

CONFORMATIONALLY CONSTRAINED o-TOLYLPIPERAZINE CAMPHORSULFONAMIDE OXYTOCIN ANTAGONISTS. STRUCTURAL MODIFICATIONS THAT PROVIDE HIGH RECEPTOR AFFINITY AND SUGGEST A BIOACTIVE CONFORMATION.

Peter D. Williams,* Richard G. Ball, Bradley V. Clineschmidt, J. Chris Culberson, Jill M. Erb, Roger M. Freidinger, Joseph M. Pawluczyk, Debra S. Perlow, Douglas J. Pettibone, and Daniel F. Veber.
Departments of Medicinal Chemistry, New Lead Pharmacology, Molecular Systems, Biophysical Chemistry, Merck Research Laboratories, West Point, PA 19486, and Rahway, NJ 07065 USA



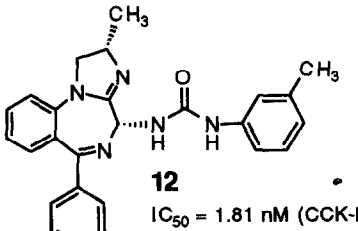
Abstract: A series of novel *o*-tolylpiperazine camphorsulfonamide oxytocin antagonists containing rotationally restricted 1-acylamino-2-propyl substituents at the C2-*endo* position on camphor is described.

BioMed. Chem. **1994**, *2*, 987

Selective Non-peptide Ligands for an Accommodating Peptide Receptor. Imidazobenzodiazepines as Potent Cholecystokinin Type B Receptor Antagonists.

M. G. Bock,* R. M. DiPardo, R. C. Newton, J. M. Bergman, D. F. Veber, S. B. Freedman,[£] A.J . Smith,[£] K. L. Chapman,[£] S. Patel,[£] J. A. Kemp,[£] G. R. Marshall, [£]R. M. Freidinger Departments of Medicinal Chemistry and [£]Biochemistry Merck Research Laboratories, West Point, PA 19486 [£]Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, England

New imidazobenzodiazepine CCK-B receptor antagonists, exemplified by the potent and selective compound **12**, are described.

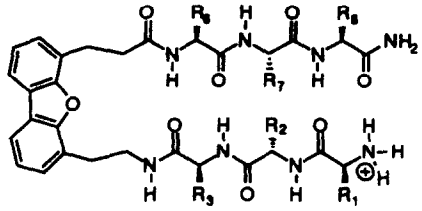


12
IC_{50} = 1.81 nM (CCK-B)
CCK B/A selectivity = 861

BioMed. Chem. **1994,** *2,* 999

AMINO ACIDS THAT SPECIFY SECONDARY STRUCTURE THROUGH HYDROPHOBIC CLUSTERING AND HISTIDINE-AROMATIC INTERACTIONS LEAD TO BIOLOGICALLY ACTIVE PEPTIDOMIMETICS

N.R. Graciani, K.Y. Tsang, S.L. McCutchen and Jeffery W. Kelly
Department of Chemistry, Texas A&M University



Acyclic β-sheets can be nucleated in heptapeptides when the 4-(2-aminoethyl)-6-dibenzofuran propanoic acid residue is flanked in sequence by two His residues, a His residue and a hydrophobic residue or by hydrophobic residues. Peptidomimetics with the antimicrobial activity of gramicidin S are reported.

BioMed. Chem. **1994,** *2,* 1007

Peptidomimetic Antagonists Designed To Inhibit The Binding Of CD4 To HIV gp120

Savithri Ramurthy‡, Min S. Lee†‡, Hiroshi Nakanishi†‡, Richard Shen‡, and Michael Kahn†‡*
†Department of Pathobiology, University of Washington, Seattle, WA 98195, and the
‡Molecumetics Institute, 2023 120th Avenue N. E., Suite 400, Bellevue, Washington 98005