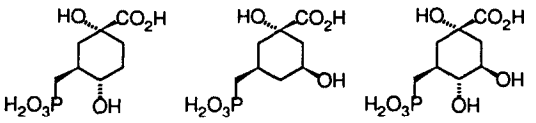
BioMed. Chem. Lett. **1992**, 2, 1349

THE BASIS FOR SLOWLY REVERSIBLE INHIBITION OF DEHYDROQUINATE SYNTHASE: A CASE OF MISTAKEN IDENTITY?

Jean-Luc Montchamp, L. T. Piehler, T. J. Tolbert, and J. W Frost*
Department of Chemistry, Purdue University, West Lafayette, IN 47907

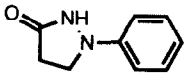
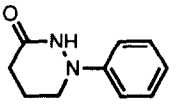


BioMed. Chem. Lett. **1992**, 2, 1353

1-PHENYL-[2H]-TETRAHYDROPYRIDAZIN-3-ONE, A-53612, A SELECTIVE ORALLY ACTIVE 5-LIPOXYGENASE INHIBITOR

Dee W. Brooks*, Daniel H. Albert, Richa d D. Dyer, Jennifer B. Bouska, Patrick Young, Gary Rotert, Joseph M. Machinist and George W. Carter *Immunosciences Research Area, Department 47K, Abbott Laboratories, Abbott Park, Illinois 60064*

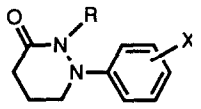
Ring homologation of the known lipoxygenase inhibitor. phenidone (1) provided A-53612 (5), which was discovered to be a selective, orally active 5-lipoxygenase inhibitor.

phenidone   A-53612

BioMed. Chem. Lett. **1992**, 2, 1357

STRUCTURE-ACTIVITY RELATIONSHIPS OF THE PYRIDAZINONE SERIES OF 5-LIPOXYGENASE INHIBITORS

Dee W. Brooks*, Anwer Basha, Francis A. J. Kerdesky, James H. Holms, James D. Ratajcyk, Pramila Bhatia, Jimmie L. Moore, Jonathan G. Martin, Steven P. Schmidt, Daniel H. Albert, Richard D. Dyer, Patrick Young, and George W. Carter *Immunosciences Research Area, Dept 47K, Abbott Laboratories, Abbott Park, Illinois 60064*



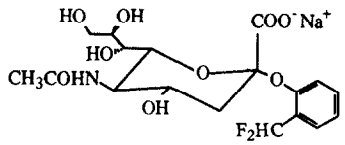
Structure-activity analysis of the pyridazinone series as represented by the initial lead compound A-53612 revealed that the 1-phenyl-2H-tetrahydropyridazin-3-one structure was necessary for 5-lipoxygenase inhibitory activity. Substituents on the phenyl ring had a marked effect on inhibitory activity and methemoglobinemia toxicity.

BioMed. Chem. Lett. **1992**, 2, 1361

Synthesis of Sodium salt of Ortho-(difluoromethyl)phenyl-α-ketoside of N-Acetylneuraminic acid : a Mechanism-based Inhibitor of *Clostridium perfringens* Neuraminidase.

P.-A. Driguez [a], B. Barrere[b], B. Chantegrel[a], C. Deshayes[a], A. Doutheau[a] and G. Quash[b].

[a]Laboratoire de Chimie Organique, INSA, 20 av. A. Einstein, 69621 Villeurbanne-France.
[b]Laboratoire d'Immunochimie INSERM, Chemin du petit Revoyet, 69921 Oullins-France.



7

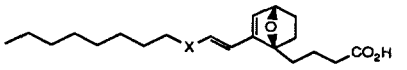
Title compound 7 was prepared in seven steps from N-Acetylneuraminic acid and proven to be an enzyme-activated irreversible inhibitor of *Clostridium perfringens* neuraminidase.

BioMed. Chem. Lett. **1992**, *2*, 1367

Synthesis and Pharmacological Activity of Rationally Designed Inhibitors of the Leukotriene A_4 Hydrolase Enzyme.

Stevan W. Djuric [a*], Renee M. Huff [a], Thomas D. Penning [a], Michael Clare [b], Lydia Swenton [c], James F. Kachur [d], Doreen Villani-Price [d], Gwen G. Krivi [e], E. Yvonne Pyla [e] and Thomas G. Warren [e]. Departments of Chemistry [a], Drug Design [b], Physical Methodology [c], and Immunoinflammatory Diseases [d], Searle R & D, Skokie, Illinois, 60077 USA and Monsanto Corporate Research [e], St. Louis, Missouri, 63198 USA.

The syntheses and pharmacological activities of rationally designed inhibitors (1 and 2) of the Leukotriene A_4 hydrolase enzyme are discussed.

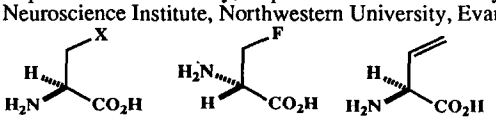


1, X= cis C=C
2, X=CH_2CH_2

BioMed. Chem. Lett. **1992**, *2*, 1371

α-AMINO ACID ANALOGUES AS MECHANISM-BASED INACTIVATORS OF γ-AMINOBUTYRIC ACID AMINOTRANSFERASE

Mark Hans Hopkins+ and Richard B. Silverman*
Department of Chemistry, Department of Biochemistry, Molecular Biology, and Cell Biology, and the Neuroscience Institute, Northwestern University, Evanston, Illinois 60208-3113



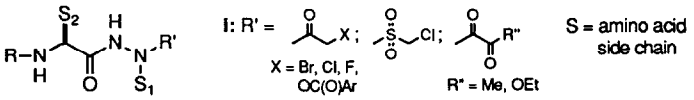
X = a, OSO_3^{-2}; b, OPO_3^{-2}; c, F; d, Cl

Abstract: α-Amino acids are time dependent inactivators of purified γ-aminobutyrate aminotransferase.

BioMed. Chem. Lett. **1992**, *2*, 1375

SYNTHESIS AND EVALUATION OF AZAPEPTIDE-DERIVED INHIBITORS OF SERINE AND CYSTEINE PROTEASES. T. L. Graybill, Mitchell J. Ross, Bruce R. Gauvin, Jill S. Gregory, Alex L. Harris, Mark A. Ator, James M. Rinker and Roland E. Dolle,* Departments of Medicinal Chemistry, Enzymology and Receptor Biochemistry and Special Services, Sterling Winthrop Pharmaceuticals Research Division, 25 Great Valley Parkway, Malvern, PA 19355-1314.

Aza-peptides I were found to be class-specific inhibitors of cysteine proteases.

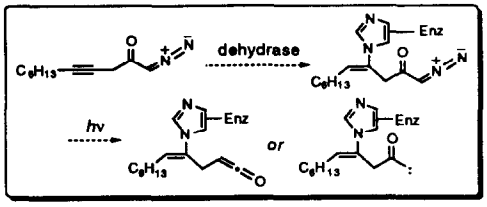


BioMed. Chem. Lett. **1992**, *2*, 1381

A MECHANISM-BASED INACTIVATOR OF *E. COLI* β-HYDROXYDECANOYL THIOLESTER DEHYDRASE DESIGNED TO CROSSLINK ACTIVE SITE AMINO ACIDS

Barry S. Henderson, Kochat Haridas, and John M. Schwab*
Department of Medicinal Chemistry and Pharmacognosy,
School of Pharmacy and Pharmacal Sciences,
Purdue University, West Lafayette, IN 47907

1-Diazo-4-undecyn-2-one, a potential active site crosslinking agent, is shown to be a mechanism-based inactivator of *E. coli* β-hydroxydecanoyl thiolester dehydrase.

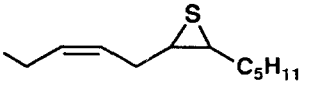


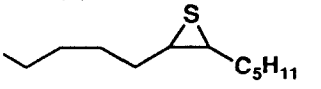
BioMed. Chem. Lett. **1992**, *2*, 1385

Episulfide Inhibitors of Lipoxygenase.

Stephen W. Wright,* Mark J. Nelson
The Du Pont Merck Pharmaceutical Company and Central Research & Development Dept., Du Pont; Experimental Station, Wilmington, DE 19880

Abstract: Epoxide and episulfide substrate mimics were synthesized as inhibitors of soybean lipoxygenase. Regio- and chemoselective enzyme inhibition was observed with 12,13-episulfides (eg, **1a**). Inhibition by **1a** occurred with reduction of the enzyme active site iron from Fe(III) to the inactive Fe(II) with **1a** but not with **4a**.

1a: $HO_2C(CH_2)_6$  C_5H_{11}

4a: $HO_2C(CH_2)_6$  C_5H_{11}

BioMed. Chem. Lett. **1992**, *2*, 1391

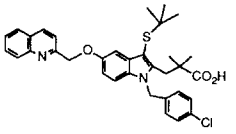
BORINIC ACID INHIBITORS AS PROBES OF THE FACTORS INVOLVED IN BINDING AT THE ACTIVE SITES OF SUBTILISIN CARLSBERG AND α-CHYMOTRYPSIN, Jörg Simpelkamp and J. Bryan Jones*. *Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 1A1*

Abstract: Unsymmetrical borinic acids, with butyl, phenyl and 2-phenylethyl substituents, have been prepared and evaluated as inhibitors of the serine proteases subtilisin Carlsberg and α-chymotrypsin. These borinic acids are powerful inhibitors of each enzyme and the results provide additional information on the factors controlling binding to the active sites of such serine proteases.

BioMed. Chem. Lett. **1992**, *2*, 1395

A New Class of Leukotriene Biosynthesis Inhibitors: The Discovery of MK0591,

P. Prasit *, M Belley, C. Brideau, C. Chan, S Charleson, J. F. Evans, R Fortin, A W Ford-Hutchinson, J.W. Gillard, J Guay, J.H. Hutchinson, S Léger, D Riendeau, R N. Young and R Zamboni *Merck Frosst Centre for Therapeutic Research, P.O Box 1005, Pointe Claire-Dorval, Québec H9R 4P8, CANADA.*

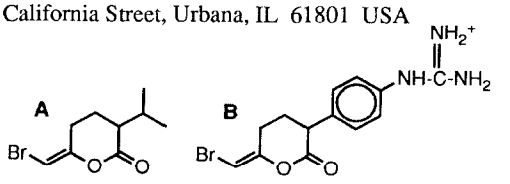


BioMed. Chem. Lett. **1992**, *2*, 1399

ENOL LACTONE DERIVATIVES AS INHIBITORS OF HUMAN NEUTROPHIL ELASTASE AND TRYPSIN-LIKE PROTEASES

John A. Katzenellenbogen*, Roopa Rai, and Wei Dai
Department of Chemistry, University of Illinois, 1209 West California Street, Urbana, IL 61801 USA

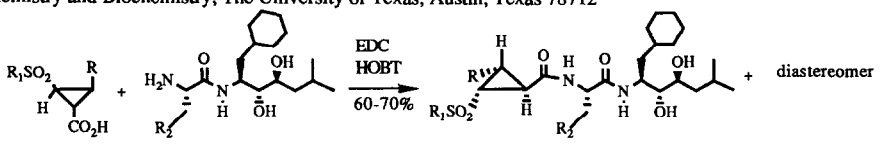
We report on the development of substituted valero enol lactones as powerful inhibitors of human neutrophil elastase (HNE) by valine mimic enol lactones (such as **A**) and trypsin-like enzymes (trypsin, plasmin, urokinase, t-PA, and thrombin) by guanidino-aryl substituted enol lactones (such as **B**).



BioMed. Chem. Lett. **1992**, *2*, 1405

CONFORMATIONALLY RESTRICTED PEPTIDE ISOSTERES. 2. SYNTHESIS AND IN VITRO POTENCY OF DIPEPTIDE RENIN INHIBITORS EMPLOYING A 2-ALKYLSULFONYL-3-PHENYLCYCLOPROPANE CARBOXAMIDE AS A P_3 AMINO ACID REPLACEMENT.

William R. Baker,* Hwan-Soo Jae, Stephen F. Martin,* Stephen L. Condon, Herman H. Stein, Jerome Cohen, and Hollis D. Kleinert, Pharmaceutical Products Division, Abbott Laboratories, One Abbott Park Road, Abbott Park, IL 60064 and Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712



BioMed. Chem. Lett. **1992**, *2*, 1411

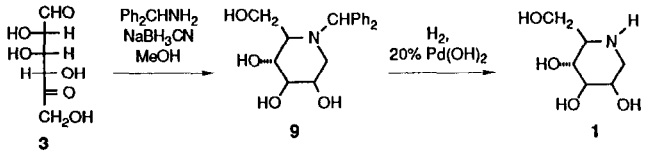
MECHANISM-BASED INACTIVATION OF MANDELATE RACEMASE BY PROPARGYLGLYCOLATE, James A. Landro, George L. Kenyon,[1]* and John W. Kozarich*. *Dept. of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742. [1]Dept. of Pharmaceutical Chemistry, University of California, San Francisco, California 94143.*

Abstract: Propargylglycolate (2-hydroxy-3-butynoic acid) has been determined to be both a substrate and an inactivator of mandelate racemase. The partition ratio for racemization/inactivation has been estimated to be ~17,000. Inactivation of the racemase appears to require the rapid covalent addition of 1 substrate molecule; however, a slower labeling process is observed that results in the attachment of up to 5 molecules of substrate per active site. The process is consistent with an enzyme-catalyzed rearrangement of the acetylenic substrate to an allenic-enol that affords 2-keto-3-butenoate as the ultimate electrophile.

BioMed. Chem. Lett. **1992**, *2*, 1419

CONCISE SYNTHESIS OF 1-DEOXYMANNOJIRIMYCIN

Ellen W. Baxter and Allen B. Reitz*, R. W. Johnson Pharm. Res. Inst., Spring House, PA 19477.



3 9 1

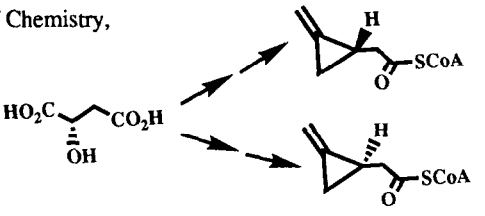
The important enzyme inhibitor 1-deoxymannojirimycin (**1**) was prepared from 5-keto-D-mannose (**3**) in two steps. The key double reductive amination displays a marked divergence in stereocontrol relative to that reported for similar reactions performed under catalytic conditions.

BioMed. Chem. Lett. **1992**, *2*, 1423

Studies of the Inactivation of General Acyl-CoA Dehydrogenase by (1*R*)- and (1*S*)-(Methylenecyclopropyl)acetyl-CoA

Ming-tain Lai, Eugene Oh and Hung-wen Liu,* Department of Chemistry, University of Minnesota, Minneapolis, MN 55455-0431

Studies of the effects of the title compounds on the inactivation of general acyl-CoA dehydrogenase under saturation conditions showed that the association of the 1*S* isomer is weaker than that of the 1*R* isomer.

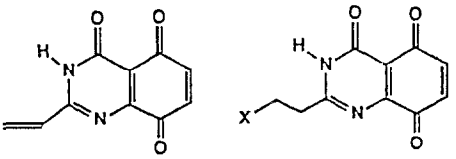


BioMed. Chem. Lett. **1992**, *2*, 1427

RATIONAL DESIGN OF PURINE NUCLEOSIDE PHOSPHORYLASE INHIBITORS: DESIGN OF 2-(2'-HALOETHYL) AND 2-ETHENYL SUBSTITUTED QUINAZOLINONE ALKYLATING AGENTS,

Robert O. Dempcy and Edward B. Skibo*, *Department of Chemistry and Biochemistry, Arizona State University, Tempe, Arizona 85287-1604*

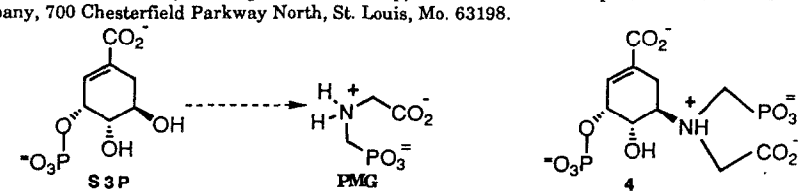
Abstract: The synthesis, addition/elimination chemistry, and purine nucleoside phosphorylase inhibitory properties of 2-(2'-bromoethyl) and 2-ethenyl substituted quinazolinone-based quinones are described.



BioMed. Chem. Lett. **1992**, *2*, 1435

DESIGN & SYNTHESIS OF A NOVEL EPSP SYNTHASE INHIBITOR BASED ON ITS TERNARY COMPLEX WITH SHIKIMATE 3-PHOSPHATE AND GLYPHOSATE

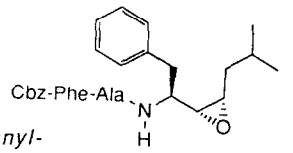
Mohammad R. Marzabadi,‡ Jose' L. Font,‡ Kenneth J. Gruys,‡ Paul D. Pansegrau‡ and James A. Sikorski§*
‡New Products Division, The Agricultural Group, and §Monsanto Corporate Research: Units of Monsanto Company, 700 Chesterfield Parkway North, St. Louis, Mo. 63198.



BioMed. Chem. Lett. **1992**, *2*, 1441

INACTIVATION OF HIV-1 PROTEASE BY A TRIPEPTIDYL EPOXIDE

Stephan K. Grant, Michael L. Moore, Stephen A. Fakhoury, Thaddeus A. Tomaszek, Jr., and Thomas D. Meek* *Department of* Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, Pennsylvania, U.S.A.



Abstract: *(2S,3R,4S)-N-[N-(N-benzyloxycarbonyl)-L-phenylalanyl]-L-alanyl-1-phenyl-2-amino-3,4-epoxy-6-methylheptane, a tripeptidyl epoxide analogue of peptide substrates of the retroviral protease of the human immunodeficiency virus-1, is a potent, active-site directed, irreversible inactivator of this enzyme.*