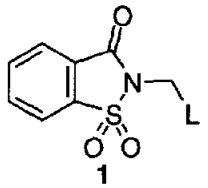
Design, Synthesis, and In Vitro Inhibitory Activity Toward Human Leukocyte Elastase, Cathepsin G, and Proteinase 3 of Saccharin-Derived Sulfones and Congeners

Bioorg. Med. Chem. **1996**, *4*, 1393

William C. Groutas,[a,*] Jeffrey B. Epp,[a] Radhika Venkataraman,[a] Rongze Kuang,[a] Tien My Truong,[a] Jerry J. McClenahan,[a] and Om Prakash[b]
[a]*Department of Chemistry, Wichita State University, Wichita, KS 67260-0051, U.S.A.*
[b]*High-Field NMR Facility, Department of Biochemistry, Kansas State University, Manhattan, KS 66506-3702, U.S.A.*

Structure–activity relationship and mechanistic studies with saccharin derivatives (**1**) and the serine proteinases elastase, cathepsin G, and proteinase 3 have been conducted.



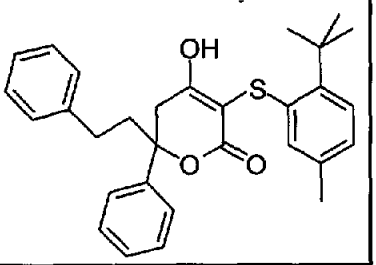
1

Discovery and Optimization of Nonpeptide HIV-1 Protease Inhibitors

Bioorg. Med. Chem. **1996**, *4*, 1401

Peter J. Tummino,[a,*] J. V. N. Vara Prasad,[b] Donna Ferguson,[a] Carolyn Nouhan,[a] Neil Graham,[a] John M. Domagala,[b] Edmund Ellsworth,[b] Christopher Gajda,[b] Susan E. Hagen,[b] Elizabeth A. Lunney,[b] Kimberly S. Para,[b] Bradley D. Tait,[b] Alexander Pavlovsky,[b] John W. Erickson,[d] Stephen Gracheck,[c] Thomas J. McQuade[c] and Donald J. Hupe[a]
Departments of [a]Biochemistry, [b]Chemistry, and [c]Infectious Diseases, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, U.S.A.
[d]Structural Biochemistry Program, NCI-Frederick Cancer Research and Development Center, PRI/DynCorp, Frederick, MD 21702, U.S.A.

A series of 4-hydroxypyranones and 4-hydroxy-5,6-dihydropyranones (example shown) were optimized into low nanomolar HIV-1 protease inhibitors by structure-based design models.

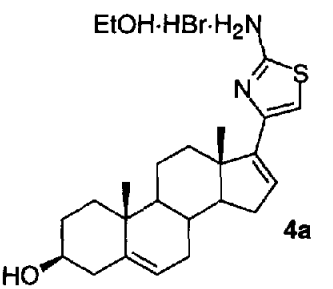


Inhibition of Steroid $C_{17(20)}$ Lyase with C-17-Heteroaryl Steroids

Bioorg. Med. Chem. **1996**, *4*, 1411

Joseph P. Burkhart, Cynthia A. Gates, Marie E. Laughlin, Robert J. Resvick, and Norton P. Peet*
Hoechst Marion Roussel, Inc., 2110 E. Galbraith Road, Cincinnati, OH 45215, U.S.A.

Steroids bearing aminothiazoles, furans and thiophenes at C-17 were synthesized and evaluated as inhibitors of $C_{17(20)}$ lyase. One of the most potent inhibitors of this enzyme was aminothiazole **4a**.



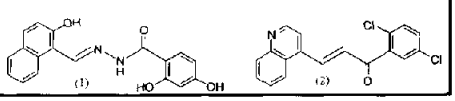
4a

Structure-Based Design of Parasitic Protease Inhibitors

Bioorg. Med. Chem. **1996**, *4*, 1421

Rongshi Li,[a] Xiaowu Chen,[a] Baoqing Gong,[a] Paul M. Selzer,[b] Zhe Li,[a] Eugene Davidson,[c] Gary Kurzban,[c] Robert E. Miller,[d] Edwin O. Nuzum,[d] James H. McKerrow,[a,b] Robert J. Fletterick,[a,c] Sarah A. Gillmor,[a,c] Charles S. Craik,[a,c] Irwin D. Kuntz,[a] Fred E. Cohen,[a,c,d] and George L. Kenyon[a,*]
Departments of [a]Pharmaceutical Chemistry and [b]Pathology, Veterans Affairs Medical Center, [c]Department of Biochemistry and Biophysics, and [d]Pharmacology and Medicine, University of California, San Francisco, CA 94143-0446, U.S.A.
[e]Department of Biochemistry and Molecular Biology, Georgetown University, Washington DC 20007, U.S.A.
[f]Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, U.S.A.

Two chemical series, bis-arylacylhydrazide (e.g., **1**) and chalcone derivatives (e.g., **2**), were identified as antimalarial and anti-Chagas disease agents by both molecular modeling and chemical modification in our structure-based drug design program. They are active against parasites and enzymes in the nanomolar range.



The Rationale for E2020 as a Potent Acetylcholinesterase Inhibitor

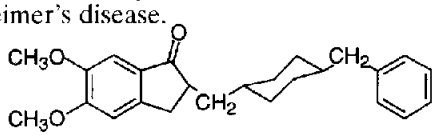
Bioorg. Med. Chem. **1996**, *4*, 1429

Yoshiyuki Kawakami,[a,*] Atsushi Inoue,[a] Takatoshi Kawai,[a] Misako Wakita,[a] Hachiro Sugimoto[a] and Anton J. Hopfinger[b,*]

[a]*Tsukuba Research Laboratories, Eisai Co., Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300-26, Japan*

[b]*Department of Medicinal Chemistry and Pharmacognosy, MC 781, The University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612-7231, U.S.A.*

This paper chronicles the development of E2020 (**I**) as a potent inhibitor of acetylcholinesterase. E2020 is a clinical drug candidate for the treatment of dementias including Alzheimer's disease.



(I)

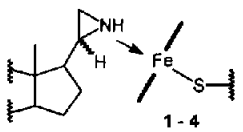
20-Amino and 20,21-Aziridinyl Pregnene Steroids: Development of Potent Inhibitors of 17α-Hydroxylase/C17,20-Lyase (P450 17)

Bioorg. Med. Chem. **1996**, *4*, 1447

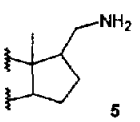
V. C. O. Njar, M. Hector and R. W. Hartmann*

Fachrichtung 12.1 Pharmazeutische Chemie, Universität des Saarlandes, D-66041 Saarbrücken, Germany

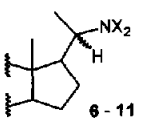
Pregenenolone- and Progesterone-type compounds **1**–**11** (X = H or Ac) were synthesized and tested for P450 17 inhibition. 20(*S*)-20,21-Aziridinylpreg-5-en-3β-ol (**1**) is the most potent inhibitor of the rat testicular enzyme described so far. The nitrogen complexing the heme iron **1** binds reversibly to the enzyme. The dissociation from the active site, however, is rather slow.



1 - 4



5



6 - 11

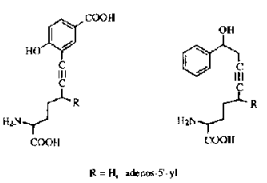
Synthesis of Complex δ-Acetylenic Amino Acids as Potential Multisubstrate Adduct Inhibitors of Methyltransferases

Bioorg. Med. Chem. **1996**, *4*, 1455

Mark R. Burns and James K. Coward*

Department of Chemistry, Interdepartmental Program in Medicinal Chemistry, and College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109 U.S.A.

The synthesis of two types of δ-acetylenic amino acids is described. Key intermediates were derived from common terminal acetylenes via two different routes: 1) palladium-mediated, Heck-type arylation, and 2) Simmons–Smith homologation followed by reaction of the resulting propargylic organometallic with a benzoyltrimethylsilane. Further elaboration to the desired amino acids involved the coupling of carbanions derived from *N*-benzylidene glycine esters to complex alkyl halides. The synthesis of non-nucleoside δ-acetylenic amino acids (R = H) was successfully effected using this chemistry. In the case of the nucleoside-containing amino acids (R = adenos-5′-yl), a potential multisubstrate adduct inhibitor of catechol *O*-methyltransferase was synthesized via this route. Unfortunately, the sensitivity to acid of 5′-deoxy, 5′-carbanucleosides prevented successful completion of the synthesis of a second nucleoside-containing δ-amino acid as a possible inhibitor of phenethanolamine *N*-methyltransferase.



R = H, adenos-5′-yl

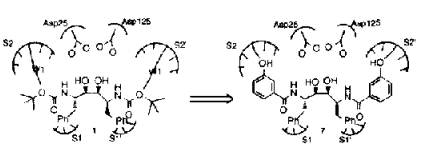
Structure-Based Design of Achiral, Nonpeptidic Hydroxybenzamide as a Novel P2/P2′ Replacement for the Symmetry-Based HIV Protease Inhibitors

Bioorg. Med. Chem. **1996**, *4*, 1471

Ramnarayan S. Randad,* Lucyna Lubkowska, Abelardo M. Silva, Diego M. A. Guerin, Sergei V. Gulnik, Betty Yu and John W. Erickson

Structural Biochemistry Program, SAIC-Frederick, National Cancer Institute — Frederick Cancer Research and Development Center, Frederick, MD 21702, U.S.A.

Using a crystal structure of the HIV PR/1 complex, achiral, nonpeptidic 2-hydroxyphenylacetamide and 3-hydroxybenzamide groups were modeled as novel P2/P2′ ligands to replace the crystallographic water molecules and to provide direct interactions with the NH groups of the Asp29/129 residues. The results obtained from kinetic and crystallographic studies on HIV PR/7 complex partly confirm our initial hypothesis.



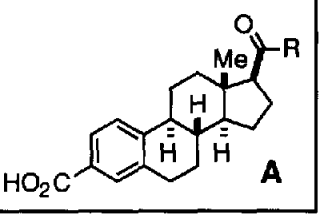
3-Carboxy-20-Keto Steroids are Dual Uncompetitive Inhibitors of Human Steroid 5α-Reductase Types 1 and 2

Bioorg. Med. Chem. **1996**, *4*, 1481

Dennis S. Yamashita,* Dennis A. Holt, Hye-Ja Oh, Dinu Shah, Hwa-Kwo Yen, Martin Brandt and Mark A. Levy*

Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406-0939, U.S.A.

Steroidal 3-carboxy-20-ketones have been prepared within two structural series, the estra-1,3,5-trienes (**A**) and the androsta-3,5-dienes, as potential inhibitors of types 1 and 2 steroid 5α-reductase, the activities responsible for the final step in biosynthesis of dihydrotestosterone. These compounds are potent uncompetitive inhibitors of both human recombinant enzymes, defining a novel class of dual 5α-reductase inhibitors.



A

Properties of Analogues of an Intermediate in the Process of Mechanism-Based Inactivation of Carboxypeptidase A

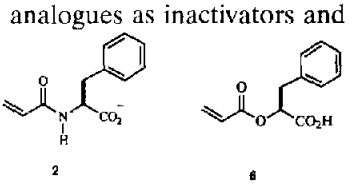
Bioorg. Med. Chem. **1996**, *4*, 1487

Soumitra S. Ghosh,[a] Srikanth Dakoji,[b] Yasuhiro Tanaka,[b] Young J. Cho[b] and Shahriar Mobashery[b,*]

[a]*Applied Genetics, San Diego, CA 92121, U.S.A.*

[b]*Department of Chemistry, Wayne State University, Detroit, MI 48202, U.S.A.*

Kinetic analyses and molecular modeling of *N*-acryloylphenylalanine (**2**) and its analogues as inactivators and substrates for carboxypeptidase A are reported.



2 **6**

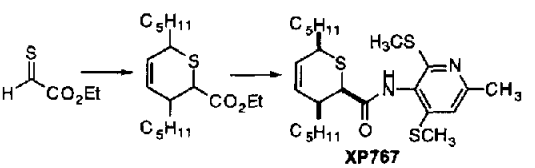
ACAT Inhibitors Derived from Hetero-Diels–Alder Cycloadducts of Thioaldehydes

Bioorg. Med. Chem. **1996**, *4*, 1493

Richard G. Wilde,* Jeffrey T. Billheimer, Sandie J. Germain, Elizabeth A. Hausner, Paul C. Meunier, Deborah A. Munzer, Janet K. Stoltenborg, Peter J. Gillies, Deborah L. Burcham, Shiew-Mai Huang, John D. Klaczkiewicz, Soo S. Ko and Ruth R. Wexler

The DuPont Merck Pharmaceutical Company, DuPont Experimental Station, P.O. Box 500, Wilmington, DE 19880-0500, U.S.A.

Cycloaddition of thioaldehydes gave rise to compounds (such as XP767) that were evaluated for inhibition of acyl-CoA:cholesterol acyltransferase.



XP767

Quiescent Affinity Inactivators of Protein Tyrosine Phosphatases

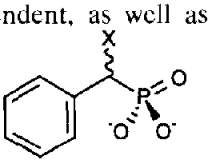
Bioorg. Med. Chem. **1996**, *4*, 1515

William P. Taylor,[a] Zhong-Yin Zhang[b] and Theodore S. Widlanski[a,*]

[a]*Department of Chemistry, Indiana University, Bloomington, IN 47405, U.S.A.*

[b]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY 10461, U.S.A.*

The α-halobenzylphosphonates **1–3** are irreversible inactivators of the protein tyrosine phosphatase Yop51*Δ162. The inactivation is shown to be time- and concentration-dependent, as well as active site directed.



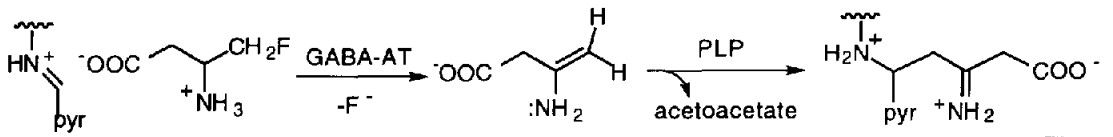
1 X = F
2 X = Cl
3 X = Br

Mechanism-Based Inactivation of γ-Aminobutyric Acid Aminotransferase by 3-Amino-4-fluorobutanoic Acid

Bioorg. Med. Chem. **1996**, *4*, 1521

Richard B. Silverman* and Cheryl L. Chamberlain Roscher
Department of Chemistry, Department of Biochemistry, Molecular Biology, and Cell Biology, and the Institute of Neuroscience, Northwestern University, Evanston, IL 60208-3113, U.S.A.

3-Amino-4-fluorobutanoic acid inactivates γ-aminobutyric acid (GABA) aminotransferase by an enamine mechanism, but five out of every seven turnovers it releases the enamine, producing acetoacetic acid.

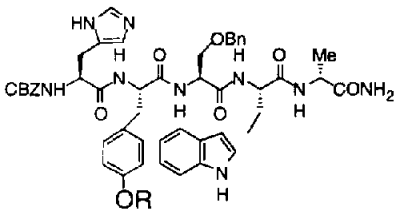


Inhibitors of Farnesyl:Protein Transferase—A Possible Cancer Chemotherapeutic

Bioorg. Med. Chem. **1996**, *4*, 1537

Jeffrey D. Scholten,[a,*] Karen Zimmerman,[a] Maritza Oxender,[a] Judith Sebolt-Leopold,[a] Richard Gowan,[a] Daniele Leonard[b] and Donald J. Hupe[a]
Departments of [a]Biochemistry and [b]Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, U.S.A.

This paper will explore how advances in our understanding of FPTase mediated catalysis has affected the design of FPTase inhibitors as possible cancer therapeutic agents.



13a = benzyl
13b = hydrogen
13c = phosphate

Bioorg. Med. Chem. **1996**, *4*, 1545

A New Class of HIV-1 Protease Inhibitor: The Crystallographic Structure, Inhibition and Chemical Synthesis of an Aminimide Peptide Isostere

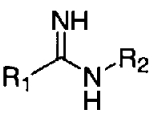
Earl E. Rutenber,[a] Fiona McPhee,[b] Alan P. Kaplan,[c] Steven L. Gallion,[c] Joseph C. Hogan, Jr.,[c] Charles S. Craik[a,b,*] and Robert M. Stroud[a,b]
[a]Department of Biochemistry and Biophysics. [b]Department of Pharmaceutical Chemistry, University of California at San Francisco, San Francisco, CA 94143 U.S.A.
[c]ArQule, Inc., Medford, MA 02155 U.S.A.

Bioorg. Med. Chem. **1996**, *4*, 1559

Inhibitors of Human Nitric Oxide Synthase Isoforms with the Carbamidine Moiety as a Common Structural Element

William M. Moore,[a,*] R. Keith Webber,[b] Kam F. Fok,[b] Gina M. Jerome,[a] Christine M. Kornmeier,[a] Foe S. Tjoeng[b] and Mark G. Currie[a]
Departments of [a]Inflammatory Diseases Research and [b]Medicinal Chemistry, G. D. Searle Research and Development, Monsanto Company, Mail Zone T3G, 800 North Lindbergh Boulevard, St. Louis, MO 63167, U.S.A.

Amino acid and nonamino acid-based compounds, including a novel series of substituted amidines (R_1 = carbon and R_2 = H), are compared as inhibitors of human NOS isoforms.

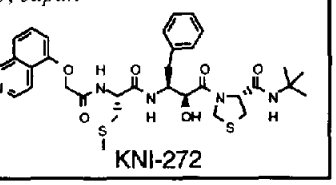


Bioorg. Med. Chem. **1996**, *4*, 1565

Solution Conformations of KNI-272, a Tripeptide HIV Protease Inhibitor Designed on the Basis of Substrate Transition State: Determined by NMR Spectroscopy and Simulated Annealing Calculations

Yasushi Ohno,[a] Yoshiaki Kiso[b] and Yuji Kobayashi[a,*]
[a]*Institute for Protein Research and Faculty of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565, Japan*
[b]*Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan*

KNI-272, a highly selective and potent HIV protease inhibitor containing allophenylnorstatine, has been studied in DMSO-d_6 by NMR spectroscopy and simulated annealing calculations.



KNI-272