Bioorg. Med. Chem. **1995**, *3*, 1009

CRYSTALLOGRAPHIC STRUCTURE OF A PEPTIDYL KETO ACID INHIBITOR AND HUMAN α-THROMBIN

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Department of Chemistry, Michigan State University,
East Lansing, MI 48824-1322;
M.M.Abelman, T.A. Miller, G.P. Vlasuk, P.W. Bergum,
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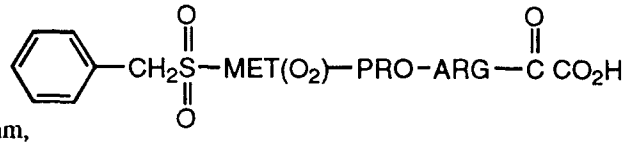
Corvas International, Inc., 3030 Science Park Road,
San Diego, CA 92121-1102



The binding of the α-keto acid peptide in the active site of human α-thrombin is described.

Bioorg. Med. Chem. **1995**, *3*, 1019

NEW TRIPEPTIDIC THROMBIN INHIBITORS. INFLUENCE OF P2 AND P3 RESIDUES ON ACTIVITY AND SELECTIVITY

Guillaume De Nanteuil*°, Philippe Gloanec°, Christine Lila°, Bernard Portevin°, Alain Boudon+, Alain Rupin# and Tony J. Verbeuren#
Divisions of Medicinal Chemistry°, Molecular Modeling+ and Angiology#
Institut de Recherche Servier, 11 Rue des Moulineaux 92150 Suresnes, FRANCE

Replacement of the P2 proline residue in tripeptidic thrombin inhibitors by non natural amino acids (PHI, ABO, N-cycloalkyl glycines) afforded compounds with similar potency than reference compound DuP 714, but with enhanced selectivity for thrombin as compared to plasmin.

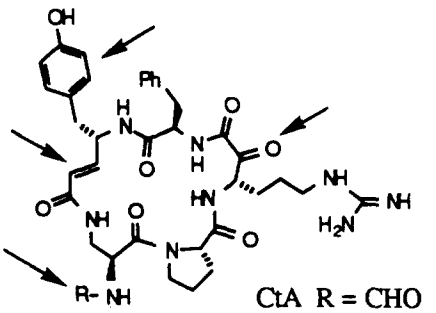
Ac-D-Phe-Pro-boroArg (DuP 714) ⇒ ⇒ Ac-D-Phe-"original P2 residue"-boroArg

Bioorg. Med. Chem. **1995**, *3*, 1025

CYCLOTHEONAMIDE DERIVATIVES: SYNTHESIS AND THROMBIN INHIBITION. EXPLORATION OF SPECIFIC STRUCTURE-FUNCTION ISSUES

Bruce E. Maryanoff,* Han-Cheng Zhang, Michael N. Greco, Karen A. Glover, Jack A. Kauffman, and Patricia Andrade-Gordon, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477 USA

Analogues of cyclotheonamide A (CtA), modified at positions marked by the arrows, were synthesized by our published convergent protocol and tested for thrombin inhibition under two sets of conditions.



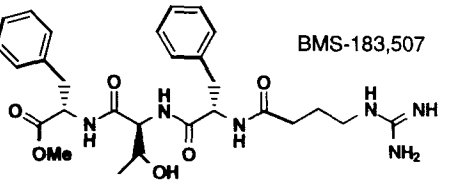
CtA R = CHO

Bioorg. Med. Chem. **1995**, *3*, 1039

MOLECULAR MODELING STUDIES OF NOVEL RETRO-BINDING TRIPEPTIDE ACTIVE-SITE INHIBITORS OF THROMBIN.

Wan F. Lau ,* Lydia Tabernero, John S. Sack, and Edwin J. Iwanowicz.
Bristol-Myers Squibb Pharmaceutical Research Institute,
P.O. Box 4000, Princeton, New Jersey 08543-4000, U.S.A.

BMS-183,507 is a potent member of a series of retro-binding inhibitors of thrombin. We describe the modeling studies of these inhibitors and compare the crystal structure of BMS-183,507/thrombin with the crystal structure of hirudin/thrombin and with the computational binding model.



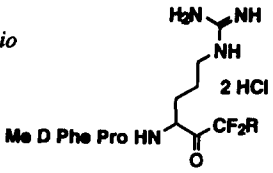
BMS-183,507

SYNTHESIS AND COMPARISON OF TRIPEPTIDYLFLUOROALKANE THROMBIN INHIBITORS

Bioorg. Med. Chem. **1995**, *3*, 1049

B. Neises*, R. J. Broersma[1], C. Tarnus, F. Piriou, J. M. Remy, C. Lintz, E. F. Heminger[1] and L. W. Kutcher[1]

Marion Merrell Dow Research Institute 16, rue d'Ankara 67080 Strasbourg, France
Marion Merrell Dow Research Institute [1] 2210 East Galbraith Road, Cincinnati, Ohio 45215 USA



1 R= F
2 R= CF_3
3 R= $CH_2CH_2CH_3$

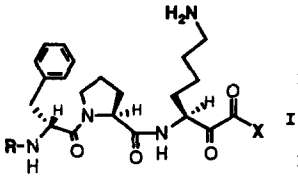
Synthesis and biological activity of three new tripeptidylfluoroketones are described.

AMIDE AND α-KETO CARBONYL INHIBITORS OF THROMBIN BASED ON ARGININE AND LYSINE: SYNTHESIS, STABILITY, AND BIOLOGICAL CHARACTERIZATION.

Bioorg. Med. Chem. **1995**, *3*, 1063

S.F. Brady*, J.T. Sisko*, K.J. Stauffer*, C.D. Colton*, H. Qiu*, S.D. Lewis@, A.S. Ng@, J.A. Shafer@, M.J. Bogusky*, D.F. Veber*, and R.F. Nutt* Departments of Medicinal Chemistry* and Biological Chemistry@, Merck Research Laboratories, West Point, PA 19486

Extrapolation from a set of thrombin-inhibitory amides, H-P_3-P_2-Arg-NH_2, has afforded the prototype inhibitor **I** with the aminobutyl side chain of lysine replacing the guanidinopropyl side chain of arginine. Selected modifications of **I** have led to analogs (**II**-**IV**) exhibiting nanomolar K_i (thrombin). Factors which affect chemical stability and racemization in this class have been evaluated. Optimal structures have been realized in keto amides **II** and **III**.

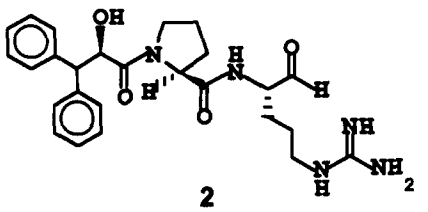


I: R = H, X = OCH_3
II: R = CH_3, X = $NHCH_3$
III: R = CH_3, X = NH_2
IV: R = CH_3, X = $N<(CH_2)_4$

ACTIVE SITE-DIRECTED THROMBIN INHIBITORS: α-HYDROXYACYL-PROLYL-ARGINALS. NEW ORALLY ACTIVE ANALOGUES OF D-Phe-Pro-Arg-H, S. Bajusz*, E. Barabás, I. Fauszt, A. Fehér, Gy. Horváth, A. Juhász, A. G. Szabó, and E. Széll, Institute for Drug Research, P.O. Box 82, Budapest, H-1325, Hungary

Bioorg. Med. Chem. **1995**, *3*, 1079

Abstract: Synthesis and evaluation of title compounds are described. Some analogues (e.g. **2**) are potent anticoagulants in vitro and show significant oral activities in a dose of 5 mg/kg, i.e. delay clotting times and inhibit thrombus formation.

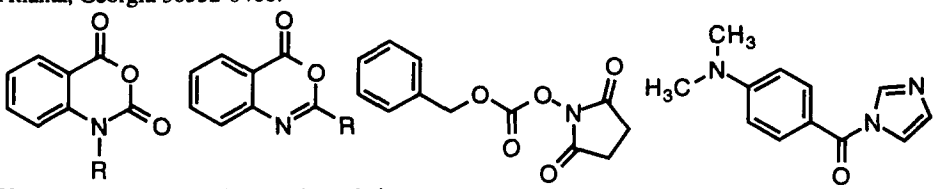


2

Rates Of Thrombin Acylation And Deacylation Upon Reaction With Low Molecular Weight Acylating Agents, Carbamylating Agents And Carbonylating Agents.

Bioorg. Med. Chem. **1995**, *3*, 1091

Audra D. Brown and James C. Powers, School of Chemistry & Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332-0400.



Various heterocyclic and aromatic acylating agents were used to acylate the active site serine of thrombin. The rates of acylation and deacylation were determined.

PEPTIDE-DERIVED TRANSITION STATE ANALOGUE INHIBITORS OF THROMBIN

Bioorg. Med. Chem. **1995**, *3*, 1099

Mieke Jetten, Co A.M. Peters, A. Visser, Peter D.J. Grootenhuis, Jan W. van Nispen and Harry C.J. Ottenheijm* *N.V. Organon, P.O.Box 20, 5340 BH Oss, The Netherlands*

H-D-Phe-Pro-Arg-ψ-Gly-Q

ψ = C(O)NH, C(O)-CH_2, CH(OH)-CH_2, CH(OH); Q = OH, Phe, Phe-Lys

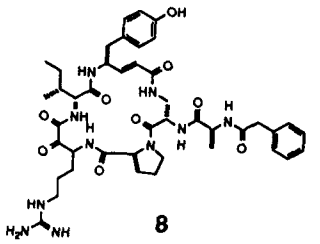
A series of peptide-derived transition state analogue inhibitors of thrombin has been synthesized and tested. Compound **47a** (ψ =C(O)-CH_2, Q= Phe-Lys) was found to be the most potent thrombin inhibitor of the series studied (K_i= 29 nM).

Bioorg. Med. Chem. **1995**, *3*, 1115

THREE MORE CYCLOTHEONAMIDES, C, D, AND E, POTENT THROMBIN INHIBITORS FROM THE MARINE SPONGE *THEONELLA SWINHOEI*

Youichi Nakao, Shigeki Matsunaga, and Nobuhiro Fusetani*
Laboratory of Marine Biochemistry,
Faculty of Agriculture, The University
of Tokyo, Bunkyo-ku, Tokyo, Japan

Abstract: Three new thrombin and trypsin inhibitors, cyclotheonamides C, D, and E (**8**) were isolated from the marine sponge *Theonella swinhoei*.



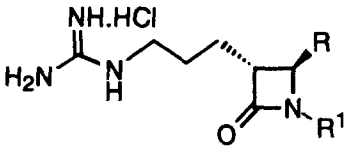
8

Bioorg. Med. Chem. **1995**, *3*, 1123

AZETIDIN-2-ONE DERIVATIVES AS INHIBITORS OF THROMBIN.

William T. Han,* Ashok K. Trehan, J.J. Kim Wright, Marianne E. Federici,† Steven M. Seiler† and Nicholas A. Meanwell,* Division of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5, Research Parkway, Wallingford, Connecticut, 06492-7660 and Department of Cardiovascular Biochemistry,† The Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000.

A series of 3-(3-guanidinopropyl)-azetidin-2-one derivatives was prepared and characterized as potent, time-dependent inhibitors of cleavage of synthetic substrates *in vitro* by the serine proteases thrombin, trypsin and plasmin.



Bioorg. Med. Chem. **1995**, *3*, 1145

ACTIVE SITE-DIRECTED THROMBIN INHIBITORS 2. STUDIES RELATED TO ARGININE/GUANIDINE BIOISOSTERES.

D. R. St. Laurent, N. Balasubramanian*, W. T. Han, A. Trehan, M. E. Federici, N. A. Meanwell, J. J. Wright, and S. M. Seiler The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492-7660 and P. O. Box 4000, Princeton, New Jersey 08543.

Isosteric replacement of the guanidine/arginine moiety in N-arylsulfonylarginine amides was examined. The chemistry and biological activity of a series of isosteres are also discussed.