

Bioorganic & Medicinal Chemistry Letters

A Tetrahedron Publication
for Rapid Dissemination of
Preliminary Communications on all aspects of
**Bioorganic Chemistry, Medicinal Chemistry,
Bioinorganic Chemistry** and related disciplines

Editor-in-Chief

DALE L BOGER

The Scripps Research Institute

La Jolla

CA 92037

USA

**Chairman of the Executive
Board of Editors for
Tetrahedron Publications**

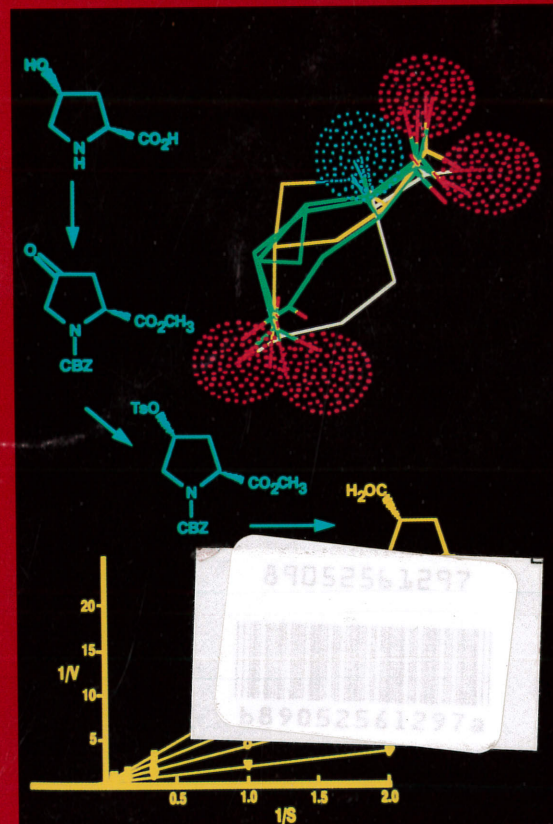
SIR DEREK BARTON

Texas A & M University

USA



PERGAMON



Page 1

Anacor Exhibit 2024

Flatwing Pharmaceuticals, Inc. v. Anacor Pharmaceuticals, Inc.

IPR2018-00171

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Editor-in-Chief: **PROFESSOR D. L. BOGER**

Managing Editor: A. Crown

Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road
La Jolla, California 92037, USA
Fax: (1) 619 554 6401

European Regional Editor: **Professor L. Ghosez**, Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, B-1348 Louvain-la-Neuve, Belgium
Fax: (32) 10 47 41 68

Japanese Regional Editor: **Professor M. Shibasaki**, Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
Fax: (81) 3 5684 5206

EXECUTIVE BOARD OF EDITORS FOR TETRAHEDRON PUBLICATIONS

Chairman: **Professor Sir Derek Barton, FRS**, Department of Chemistry, Texas A & M University, College Station, Texas 77843-3255, USA

Professor J. E. Baldwin, FRS, Dyson Perrins Laboratory, Oxford, OX1 3QY, UK

Dr S. G. Davies, Dyson Perrins Laboratory, Oxford, OX1 3QY, UK

Professor S. Ito, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan
(Associate Editor, Professor Y. Shizuri)

Professor A. R. Katritzky, FRS, Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

Professor N. K. Kochetkov, N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences, Moscow B-334, Russia

Professor Lin Guo-Qiang, Shanghai Institute of Organic Chemistry, Academia Sinica, Shanghai 200032, China

Professor S. F. Martin, Department of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, USA

Professor A. McKillop, University of East Anglia, School of Chemical Sciences, University Plain, Norwich, NR4 7TJ, UK

Professor W. B. Motherwell, Department of Chemistry, University College, 20 Gordon Street, London WC1H 0AJ, UK

Professor A. Nickon, Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, USA

Professor G. Ourisson, Centre National de la Recherche Scientifique, Centre de Neurochimie, 67084 Strasbourg, Cedex, France
(Associate Editor, Professor G. Solladié)

Professor T. Shioiri, Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Professor W. Steglich, Institut für Organische Chemie der Universität München, Karlstr. 23, D-80333 München, Germany

Professor H. H. Wasserman, Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520-8107, USA

Professor C.-H. Wong, Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA

BOARD OF CONSULTING EDITORS

R. Abeles, Waltham, MA

P. S. Anderson, Lansdale, PA

M. J. Ashton, Collegeville, PA

J. K. Barton, Pasadena, CA

S. Bell, Raritan, NJ

S. J. Benkovic, Pennsylvania, PA

R. C. Breslow, New York, NY

J. P. Collman, Stanford, CA

P. N. Confalone, Wilmington, DE

E. J. Corey, Cambridge, MA

S. J. Danishefsky, New York, NY

P. B. Dervan, Pasadena, CA

T. W. Doyle, Killingworth, CT

A. Eschenmoser, Zürich

D. M. Floyd, Princeton, NJ

A. K. Ganguly, Bloomfield, NJ

D. Gani, St Andrews

H. B. Gray, Pasadena, CA

J. T. Groves, Princeton, NJ

G. L. Grunewald, Lawrence, KS

H.-J. Hess, Groton, CT

M. Hirobe, Tokyo

R. H. Holm, Cambridge, MA

D. C. Horwell, Cambridge

W. L. Jorgensen, New Haven, CT

D. D. Keith, Nutley, NJ

R. A. Lerner, La Jolla, CA

S. J. Lippard, Cambridge, MA

D. Mansuy, Paris

B. W. Metcalf, King of Prussia, PA

L. A. Mitscher, Lawrence, KS

W. H. Moos, Emeryville, CA

K. Mori, Tokyo

K. Nakanishi, New York, NY

K. C. Nicolaou, La Jolla, CA

T. Ogawa, Saitama

M. Ohno, Ibaragi

H. L. Pearce, Indianapolis, IN

P. Potier, Gif-sur-Yvette

C. D. Poulter, Salt Lake City, UT

A. V. Rama Rao, Hyderabad

J. Rebeck, Jr, Cambridge, MA

R. L. Schowen, Lawrence, KS

S. L. Schreiber, Cambridge, MA

P. G. Schultz, Berkeley, CA

A. I. Scott, College Station, TX

I. Shinkai, Rahway, NJ

T. J. Simpson, Bristol

J. Stubbe, Cambridge, MA

C. T. Walsh, Boston, MA

G. Whitesides, Cambridge, MA

R. V. Wolfenden, Chapel Hill, NC

PUBLISHED TWICE MONTHLY

Publishing, Subscription and Advertising Office:

Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK (Tel: (0865) 843000; Fax: (0865) 843010)

Subscription Rates

Annual Institutional Subscription Rates 1995: North, Central and South America, U.S.\$ 984.00, Rest of World £ 660.00. Associated Personal Subscription Rates are available on request for those whose institutions are library subscribers. Sterling prices exclude VAT. Non-VAT registered customers in the European Community will be charged the appropriate VAT in addition to the price listed. Prices include postage and insurance and are subject to change without notice. Subscription enquiries from customers in North America should be sent to: Elsevier Science Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, USA, and for the remainder of the world to: Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK.

Second Class Postage paid at Newark, NJ. Postmaster send address changes to Elsevier Science Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, USA.

Flatwing Pharmaceuticals, Inc. v. Anacor Pharmaceuticals, Inc
Copyright © 1994 Elsevier Science Ltd

IPR2018-00171

BIOO
CF

A Tetrah
Communication

Chairman of

UW PHARMACY LIBRARY

Bioorganic & Medicinal Chemistry Letters Vol. 4, No. 20, 1994

Contents

- 2365 Contributors to this Issue
- 2367 Graphical Abstracts
- J. Bermudez, L. Gaster, J. Gregory,
J. Jerman, G. F. Joiner, F. D. King and
S. K. Rahman 2373 Synthesis and 5-HT₃ receptor antagonist potency of novel (*endo*) 3,9-diazabicyclo[3.3.1]nonan-7-amino derivatives
- R. Shimazawa, R. Shirai, Y. Hashimoto
and S. Iwasaki 2377 DNA-Binding ability of non-diyne class of dynemicins and aza-anthraquinones
- P. Demonchaux, P. Lenoir, G. Augert
and P. Dupassieux 2383 Design of pyrrolo-1,4-benzoxazine derivatives as inhibitors of 5-lipoxygenase and PAF antagonists with antihistaminic properties
- N.-H. Lin, Y. He, D. J. Anderson,
J. T. Wasicak, R. Kasson, D. Sweeney
and J. P. Sullivan 2389 Synthesis and structure-activity relationships of pyrrolidine-modified analogs of the potent cholinergic channel activator, ABT 418
- T.-S. Wu, S.-C. Huang, P.-L. Wu and
K.-H. Lee 2395 Structure and synthesis of clausenaquinone-A. A novel carbazolequinone alkaloid and bioactive principle from *Clausena excavata*
- G. Romeo, F. Russo, S. Guccione,
R. Chabin, D. Kuo and W. B. Knight 2399 Synthesis of new thiazinoindole derivatives and their evaluation as inhibitors of human leukocyte elastase and other related serine proteases
- J. Lee, N. E. Lewin, P. M. Blumberg and
V. E. Marquez 2405 Conformationally constrained analogues of diacylglycerol—IX. The effect of side-chain orientation on the protein kinase C (PK-C) binding affinity of δ -lactones
- E. K. Lehnert, K. E. Miller,
J. S. Madalengoitia, T. J. Guzi and
T. L. Macdonald 2411 DNA Topoisomerase II inhibition by substituted 1,2,3,4-tetrahydro- β -carboline derivatives
- S. J. Steiner, J. T. Bien and B. D. Smith 2417 Diphenylborinic acid is a strong inhibitor of serine proteases
- J. A. Hartley, M. D. Wyatt,
B. J. Garbiras, C. Richter and M. Lee 2421 Probing the importance of the second chloroethyl arm of a benzoic acid mustard derivative of an imidazole-containing analogue of distamycin
- P. Pradhan, D. L. Luthria and A. Banerji 2425 Pimolin, a new class of natural product from *Pimpinella monoica*: a novel dimeric furochromone
- B. König and M. Grätzel 2429 An immunosensor for the detection of human B-lymphocytes
- G. Adlam, I. S. Blagbrough, S. Taylor,
H. C. Latham, I. S. Haworth and
A. Rodger 2435 Multiple binding modes with DNA of anthracene-9-carbonyl-N¹-spermine probed by LD, CD, normal absorption, and molecular modelling compared with those of spermidine and spermine
- S. K. Thompson, A. M. Eppley,
J. S. Frazee, M. G. Darcy, R. T. Lum,
T. A. Tomaszek, Jr, L. A. Ivanoff,
J. F. Morris, E. J. Sternberg,
D. M. Lambert, A. V. Fernandez,
S. R. Petteway, Jr, T. D. Meek,
B. W. Metcalf and J. G. Gleason 2441 Synthesis and antiviral activity of a novel class of HIV-1 protease inhibitors containing a heterocyclic P₁'-P₂' amide bond isostere

[Continued on inside back cover]



0960-894X(1994)4:20;1-I

BMCLE8 4 (20) 2365-2490 (1994)

Indexed/Abstracted in: Chemical Abstracts, Current Contents,
Science Citation Index, SciSearch, Research Alert, Excerpta Medica Database EMBASE

Pergamon

Page 3

Anacor Exhibit 2024

Printed in Great Britain by Nuffield Press Ltd. Flatwing Pharmaceuticals, Inc. v. Anacor Pharmaceuticals, Inc.

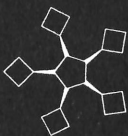
IPR2018-00171

972

Contents [Continued from outside back cover]

K. A. Alvi, M. Jaspars, P. Crews, B. Strulovici and E. Oto	2447	Penazetidine A, an alkaloid inhibitor of protein kinase C
J. P. Demers, W. E. Hageman, S. G. Johnson, D. H. Klaubert, R. A. Look and J. B. Moore	2451	Selective inhibitors of protein kinase C in a model of Graft-vs-Host disease
S. Sabesan	2457	Synthesis and neuraminidase inhibition studies of 4-azido, amino and acetamido substituted sialosides
J. Aubé, B. Gülgeze and X. Peng	2461	Synthesis of <i>cis</i> - δ -phenylmethyl-D-proline using a nitrogen-centered radical derived from a chiral oxaziridine
R. B. Greenwald, A. Pendri, D. Bolikal and C. W. Gilbert	2465	Highly water soluble taxol derivatives: 2'-polyethyleneglycol esters as potential prodrugs
R. P. Iyer, D. Yu and S. Agrawal	2471	Stereospecific bio-reversibility of dinucleoside S-alkyl phosphorothiolates to dinucleoside phosphorothioates
R. D. Clark, A. Jahangir, J. A. Langston, K. K. Weinhardt, A. B. Miller, E. Leung and R. M. Eglen	2477	Ketones related to the benzoate 5-HT ₄ receptor antagonist RS-23597 are high affinity partial agonists
R. D. Clark, A. Jahangir, J. A. Langston, K. K. Weinhardt, A. B. Miller, E. Leung, D. W. Bonhaus, E. H. F. Wong and R. M. Eglen	2481	Synthesis and preliminary pharmacological evaluation of 2-benzyloxy substituted aryl ketones as 5-HT ₄ receptor antagonists
T. Nakajima, T. Kashiwabara, T. Izawa and S. Nakajima	2485	Structure-activity studies of <i>N</i> -cyano-3-pyridinecarboxamides and their amide and thioamide congeners
	2489	Additions and Corrections
	I	Instructions to Contributors

First
ce on
ganic
mistry



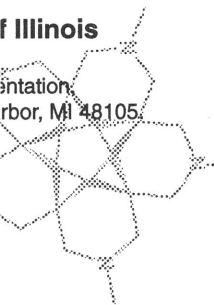
cs
nsas

erloo

nsin

f Illinois

entation,
rbor, MI 48105





0960-894X(94)00350-5

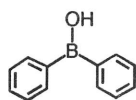
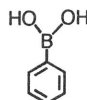
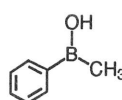
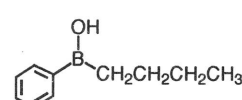
**DIPHENYLBORINIC ACID IS A STRONG INHIBITOR OF SERINE
PROTEASES[‡]**Steven J. Steiner,[‡] Jeffrey T. Bien, Bradley D. Smith*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556, USA

Abstract. Diphenylborinic acid, a commercially available and reasonably air stable compound, was found to be a strong competitive inhibitor of three serine proteases. Compared to phenylborinic acid, it was a thirty-fold better inhibitor of α -chymotrypsin, a fifteen-fold better inhibitor of subtilisin BPN', and a sixty-fold better inhibitor of bovine trypsin. The pK_a and inhibitory ability of methylphenylborinic acid was also determined.

Boronic acids have been studied as competitive inhibitors of serine proteases for more than twenty-five years.¹ Nonetheless, interest in these compounds remains high due to their potential clinical uses,² and their ability to act as structural probes of enzyme binding sites.³ Despite numerous X-ray and NMR studies, some of the details concerning the structures of the enzyme/inhibitor complexes remain controversial, particularly when the inhibitors are simple, "non substrate-like" boronic acids.⁴ In some cases there is clear evidence for a covalent tetrahedral adduct with the active-site serine hydroxyl.^{4,5} In other cases there is no doubt that the boron is coordinated to the active-site histidine.⁶

Our interest in this area stems from our recent efforts to develop molecular transport devices using boron acids.⁷ While conducting experiments with diphenylborinic acid, **1**, we became curious about its ability to inhibit serine proteases. Inhibition with asymmetric boronic acids has been reported before,⁸ the most recent study by the Jones research group.⁹ In general, borinic acids are better inhibitors than boronic acids. The major detraction with borinic acids is their susceptibility to air oxidation. Diarylborinic acids, however, are reasonably air stable compounds. For example, a solution of **1** in phosphate buffer, at pH 7.4, was found to be > 90 % pure after standing on the bench top for 24 hours. Compound **1** has a pK_a of 6.2.¹⁰ At neutral pH it readily combines with vicinal diols to form anionic, tetrahedral "ate" complexes.⁷ The expected inhibitory ability of **1** was hard to predict, *a priori*, since it was difficult to estimate the relative importance of various opposing factors such as increased acidity, enzyme binding site specificity, inhibitor hydrophobicity, loss of a potential active-site hydrogen, etc. We felt that if **1** were a good protease binder then it may have utility in clarifying some of the structural and mechanistic ambiguities concerning this class of transition-state-analogue inhibitors.

**1****2****3****4**

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.