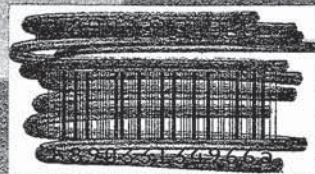


JOURNAL OF  
**MEDICINAL  
CHEMISTRY**

AUGUST 6, 1993  
VOLUME 36 • NUMBER 16  
AMERICAN CHEMICAL SOCIETY  
JMCMAR



JOURNAL OF  
**MEDICINAL  
CHEMISTRY**

**EDITOR-IN-CHIEF**

PHILIP S. PORTOGHESE

Department of Medicinal Chemistry  
College of Pharmacy, Room 8-114  
University of Minnesota  
308 Harvard St. S.E.  
Minneapolis, Minnesota 55455  
(612) 624-6184  
FAX (612) 626-6891

**SENIOR EDITORS**

Raymond E. Counsell  
Laurence H. Hurley  
Herbert T. Nagasawa  
Wendel L. Nelson

**PERSPECTIVES EDITOR**

Michael Williams

**Book Review Editor**

Carl Kaiser

**EDITORIAL ADVISORY BOARD**

Matthew M. Ames  
Stephen J. Benkovic  
Donald B. Boyd  
Peter B. Dervan  
Stephen W. Fesik  
David S. Fries  
Jane F. Griffin  
Ralph F. Hirschmann  
M. Ross Johnson  
Michael Marletta  
David A. Matthews  
Duane Miller  
John H. Musser  
John L. Neumeier  
William Prusoff  
Kenner C. Rice  
Jean Rivier  
C. H. Robinson  
Robert R. Ruffolo, Jr.  
Stuart Schreiber  
John A. Secrist, III  
Robert P. Sheridan  
David J. Triggle  
Daniel F. Veber  
George M. Whitesides  
Dennis M. Zimmerman  
*Ex officio:* James A. Bristol

American Chemical Society  
1155 16th St., N.W.  
Washington, DC 20036  
(202) 872-4600  
TDD (202) 872-8733  
FAX (202) 872-4615

**Journals Department**

American Chemical Society  
2540 Olentangy River Road  
P.O. Box 3330  
Columbus, OH 43210  
(614) 447-3600, Ext. 3171  
TELEX 6842086; FAX (614) 447-3745

**Member & Subscriber Services**

American Chemical Society  
P.O. Box 3337  
Columbus, OH 43210  
(614) 447-3776; FAX (614) 447-3671

*Journal of Medicinal Chemistry* (ISSN 0022-2623) is published biweekly by the American Chemical Society at 1155 16th St., N.W., Washington, DC 20036. Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *Journal of Medicinal Chemistry*, Member & Subscriber Services, P.O. Box 3337, Columbus, OH 43210.

Canadian GST Reg. No. R127571347.

Printed in the USA.

**PUBLICATIONS DIVISION**

Robert H. Marks, Director

*Journals Department:* Charles R. Bertsch, Head

*Editorial Office:* Mary E. Scanlan, Manager; Kathleen E. Duffy, Anne C. O'Melia, and Joseph E. Yurvati, Journals Editing Managers; Mary Jo Lesheski and Diane E. Needham, Assistant Editors

*Advertising Office:* Centcom, Ltd., 1599 Post Road East, P.O. Box 231, Westport, CT 06881

© Copyright 1993 by the American Chemical Society. **Copyright permission:** An individual may make a single reprographic copy of an article in this publication for personal use. Reprographic copying beyond that permitted by Section 107 or 108 of the U.S. Copyright Law is allowed, provided that the appropriate per-copy fee is paid through the Copyright Clearance Center, Inc., 27 Congress St., Salem, MA 01970. For reprint permission, please write to the Copyright Administrator, Publications Division, at the ACS Washington address. Bulk reprints: for quotes and information on placing an order, please call (202) 872-4539 or write to the Distribution Office at the ACS Washington address.

The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48-1984.

**Editorial Information**

**Instructions for authors** and copyright transfer form are printed in the first issue of each volume. Please conform to these instructions when submitting manuscripts.

**Manuscripts for publication** should be submitted to the Editor, Philip S. Portoghesi, at his Minneapolis address.

Correspondence regarding **accepted papers and proofs** should be directed to the Journals Department, at the address below.

**Page charges** of \$25.00 per page may be paid for papers published in this journal. Payment does not affect acceptance or scheduling of papers.

The American Chemical Society and its Editors assume no responsibility for the statements and opinions advanced by contributors.

Registered names and trademarks, etc., used in this publication, even without specific indication thereof, are not to

**Subscription and Business Information**

1993 subscription prices, including postage. (For membership information, contact Office of Member Services at the ACS Washington address.)

	U.S.	Canada and Mexico	Europe*	All Other Countries*
<b>Printed</b>				
Members—1 yr	\$ 54	\$ 79	\$118	\$136
2 yr	\$ 97	\$147	\$225	\$261
Nonmembers	\$586	\$611	\$650	\$668
<b>Microfiche</b>				
Members—1 yr	\$ 54	\$ 54	\$ 79	\$ 79
2 yr	\$ 97	\$ 97	\$147	\$147
Nonmembers	\$586	\$586	\$611	\$611
Supplementary material (microfiche)	\$ 35	\$ 55	\$ 55	\$ 55

\* Air service included.

**New and renewal subscriptions** should be sent with payment to American Chemical Society, Department L-0011, Columbus, OH 43268-0011. Subscriptions are available only on a calendar year basis. Rates quoted do not apply to nonmember subscribers in Japan, who must enter subscription orders with Maruzen Company Ltd., 3-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103, Japan. Tel: (03) 272-7211.

**Printed edition single issue prices:** current year, \$23.00; 1992, \$23.00; prior year, \$45.00. Foreign postage additional. Mail orders and requests for back volume prices should be sent to Microforms & Back Issues Office at the ACS Washington address.

**Phone orders** can be placed for printed, microfiche, and microfilm editions by calling the ACS toll free at (800) 333-9511 from anywhere in the United States and Canada; elsewhere call (614) 447-3776. Phone orders can be charged to Visa, MasterCard, or American Express accounts.

**Changes of address** must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to Member & Subscriber Services. Please allow 6 weeks for change to become effective.

**Claims for missing numbers** will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated (a) North America—more than 90 days beyond issue date, (b) all other foreign—more than 180 days beyond issue date. Claims are handled by Member & Subscriber Services.

**Supplementary material** is noted in the table of contents with a ■. It is available as photocopy (\$10.00 for up to 3 pages and \$1.50 per page for additional pages, plus \$2.00 for foreign postage) or as 24× microfiche (\$10.00, plus \$1.00 for foreign postage). Canadian residents should add 7% GST. See supplementary material notice at end of journal article for number of pages. Orders must state whether for photocopy or for microfiche and give complete title of article, names of authors, journal, issue date, and page numbers. Prepayment is required and prices are subject to change. Order from Microforms & Back Issues Office at the ACS Washington address. Supplementary material except structure factors also appears in

JOURNAL OF  
**MEDICINAL  
CHEMISTRY**<sup>®</sup>

Registered in U.S. Patent and Trademark Office  
© Copyright 1993 by the American Chemical Society

Volume 36, Number 16  
August 6, 1993

JMCMAR 36(16) 2243-2430 (1993)  
ISSN 0022-2623

COMMUNICATIONS TO THE EDITOR

- 2420 Application of a Conformationally Restricted Phe-Leu Dipeptide Mimetic to the Design of a Combined Inhibitor of Angiotensin I-Converting Enzyme and Neutral Endopeptidase 24.11  
Gary A. Flynn,\* Douglas W. Beight, Shujaath Mehdi, Jack R. Koehl, Eugene L. Giroux, John F. French, Paul W. Hake, and Richard C. Dage

ARTICLES

- 2243 Anticonvulsant Activities of Some Arylsemicarbazones Displaying Potent Oral Activity in the Maximal Electroshock Screen in Rats Accompanied by High Protection Indices  
J. R. Dimmock,\* K. K. Sidhu, R. S. Thayer, P. Mack, M. J. Duffy, R. S. Reid, J. W. Quail, U. Pugazhenthii, A. Ong, J. A. Bikker, and D. F. Weaver
- 2253 Nonpeptide Angiotensin II Receptor Antagonists. 2. Design, Synthesis, and Structure-Activity Relationships of 2-Alkyl-4-(1*H*-pyrrol-1-yl)-1*H*-imidazole Derivatives: Profile of 2-Propyl-1-[[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-5-carboxylic Acid (CI-996)  
Ila Sircar,\* John C. Hodges, John Quin III, Amy M. Bunker, R. Thomas Winters, Jeremy J. Edmunds, Catherine R. Kostlan, Cleo Connolly, Stephen J. Kesten, James M. Hamby, John G. Topliss, Joan A. Keiser, and Robert L. Panek
- 2266 Studies on Neurokinin Antagonists. 3. Design and Structure-Activity Relationships of New Branched Tripeptides *N*<sup>α</sup>-(Substituted L-aspartyl, L-ornithyl, or L-lysyl)-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamides as Substance P Antagonists  
Daijiro Hagiwara, Hiroshi Miyake, Kenji Murano, Hiroshi Morimoto, Masako Murai, Takashi Fujii, Isao Nakanishi, and Masaaki Matsuo\*
- 2279 Benzoquinazoline Inhibitors of Thymidylate Synthase: Enzyme Inhibitory Activity and Cytotoxicity of Some 3-Amino- and 3-Methylbenzo[*f*]quinazolin-1(2*H*)-ones  
William Pendergast,\* Jay V. Johnson, Scott H. Dickerson, Inderjit K. Dev, David S. Duch, Robert Ferone, William R. Hall, Joan Humphreys, Joseph M. Kelly, and David C. Wilson
- 2292 Synthesis and Structure-Activity Studies of a Series of Spirooxazolidine-2,4-diones: 4-Oxa Analogues of the Muscarinic Agonist 2-Ethyl-8-methyl-2,8-diazaspiro[4.5]decane-1,3-dione  
Shin-ichi Tsukamoto,\* Masato Ichihara, Fumikazu Wanibuchi, Shinji Usuda, Kazuyuki Hidaka, Masatomi Harada, and Toshinari Tamura
- 2300 Potent HIV Protease Inhibitors: The Development of Tetrahydrofuranlyglycines as Novel P<sub>2</sub>-Ligands and Pyrazine Amides as P<sub>3</sub>-Ligands  
Arun K. Ghosh,\* Wayne J. Thompson, M. Katharine Holloway, Sean P. McKee, Tien T. Duong, Hee Yoon Lee, Peter M. Munson, Anthony M. Smith, Jenny M. Wai, Paul L. Darke, Joan A. Zugay, Emilio A. Emini, William A. Schleif, Joel R. Huff, and Paul S. Anderson
- 2311 Synthesis and Evaluation of Conformationally Restricted *N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamines at  $\sigma$  Receptors. 2. Piperazines, Bicyclic Amines, Bridged Bicyclic Amines, and Miscellaneous Compounds  
Brian R. de Costa,\* Xiao-shu He, Joannes T. M. Linders, Celia Dominguez, Zi Qiang Gu, Wanda Williams, and Wayne D. Bowen
- 2321 A Novel Constrained Reduced-Amide Inhibitor of HIV-1 Protease Derived from the Sequential Incorporation of  $\gamma$ -Turn Mimetics into a Model Substrate  
Kenneth A. Newlander,\* James F. Callahan, Michael L. Moore, Thaddeus A. Tomaszek, Jr., and William F. Huffman

## Potent HIV Protease Inhibitors: The Development of Tetrahydrofuranylglycines as Novel P<sub>2</sub>-Ligands and Pyrazine Amides as P<sub>3</sub>-Ligands

Arun K. Ghosh,<sup>\*,†</sup> Wayne J. Thompson,<sup>†</sup> M. Katharine Holloway,<sup>‡</sup> Sean P. McKee,<sup>†</sup> Tien T. Duong,<sup>†</sup> Hee Yoon Lee,<sup>†</sup> Peter M. Munson,<sup>†</sup> Anthony M. Smith,<sup>†</sup> Jenny M. Wai,<sup>†</sup> Paul L. Darke,<sup>§</sup> Joan A. Zugay,<sup>§</sup> Emilio A. Emini,<sup>‡</sup> William A. Schleif,<sup>‡</sup> Joel R. Huff,<sup>†</sup> and Paul S. Anderson<sup>†</sup>

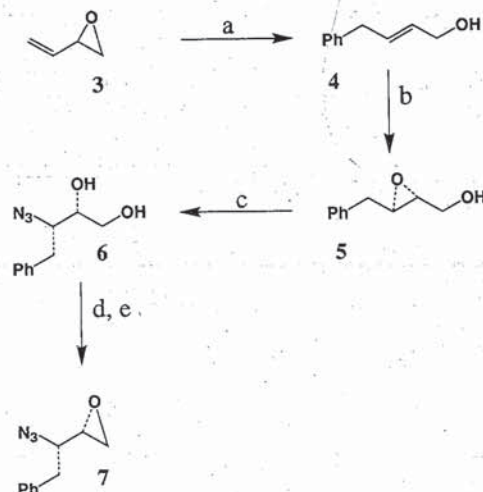
Departments of Medicinal Chemistry, Molecular Biology, Molecular Systems, and Virus and Cell Biology, Merck Research Laboratories, West Point, Pennsylvania 19486

Received April 5, 1993

A series of protease inhibitors bearing constrained unnatural amino acids at the P<sub>2</sub>-position and novel heterocycles at the P<sub>3</sub>-position of compound 1 (Ro 31-8959) were synthesized, and their *in vitro* enzyme inhibitory and antiviral activities were evaluated. Replacement of P<sub>2</sub>-asparagine of compound 1 with (2*S*,3'*R*)-tetrahydrofuranylglycine resulted in improvement in enzyme inhibitory as well as antiviral potencies (compound 23). Interestingly, incorporation of (2*S*,3'*S*)-tetrahydrofuranylglycine at the P<sub>2</sub>-position proved to be less effective. The resulting compound 24 was 100-fold less potent than the 2*S*,3'*R*-isomer (compound 23). This stereochemical preference indicated a hydrogen-bonding interaction between the tetrahydrofuranyl oxygen and the residues of the S<sub>2</sub>-region of the enzyme active site. Furthermore, replacement of P<sub>3</sub>-quinolinoyl ligand of 1 with various novel heterocycles resulted in potent inhibitors of HIV proteases. Of particular interest, compound 2 with (2*S*,3'*R*)-tetrahydrofuranylglycine at P<sub>2</sub> and pyrazine derivative at P<sub>3</sub> is one of the most potent inhibitors of HIV-1 (IC<sub>50</sub> value 0.07 nM) and HIV-2 (IC<sub>50</sub> value 0.18 nM) proteases. Another important result in this series is the identification of compound 27 in which the P<sub>2</sub>-P<sub>3</sub>-amide carbonyl has been removed. The resulting compound 27 has exhibited improvement in antiviral potency while retaining the enzyme inhibitory potency similar to compound 1.

The inhibition of the enzyme HIV-1 protease, which cleaves the *gag* and *gag-pol* polyproteins into the functional proteins of infectious virions, continues to be a major therapeutic target for the treatment of AIDS and related ailments.<sup>1</sup> Of the numerous potent protease inhibitors that have been reported recently,<sup>2</sup> the present clinical candidate (2*S*,4*aS*,8*aS*,2'*R*,3'*S*)-*N*-*tert*-butyl-2-(2'-hydroxy-4'-phenyl-3'-((*N*-(2-quinolinylcarbonyl)-*L*-asparaginyl)-amino)butyl)decahydroisoquinoline-3-carboxamide (1) (Ro 31-8959) is particularly unique because of its effectiveness against both the enzymes HIV-1 and HIV-2 proteases.<sup>3</sup> Since these are the genetically most divergent strains of HIV known to exist to date, a protease inhibitor with this property may result in reduced susceptibility to clinical resistance. Subsequently, we have investigated the effect of incorporation of conformationally constrained unnatural amino acids in place of asparagine at the P<sub>2</sub> subsite of compound 1. As reported in a recent paper,<sup>4</sup> the replacement of asparagine with (2*S*,3'*R*)-tetrahydrofuranylglycine not only increased the enzyme affinities for HIV-1 and HIV-2 proteases but led to significant enhancement of antiviral potencies compared to 1. We now report the synthesis, enzyme inhibition, and antiviral potencies of a structurally novel class of protease inhibitors in which various constrained unnatural amino acids and novel heterocyclic derivatives were incorporated at the P<sub>2</sub>- and P<sub>3</sub>-positions of the present clinical candidate 1 (Ro 31-8959). This study has resulted in protease inhibitors with improved enzyme inhibitory and antiviral potencies. Particularly noteworthy is the inhibitor 2 which is very potent against HIV-1 (IC<sub>50</sub> = 0.07 nM) and HIV-2 (IC<sub>50</sub> = 0.18 nM).

### Scheme I. Synthesis of Azido Epoxide<sup>a</sup>

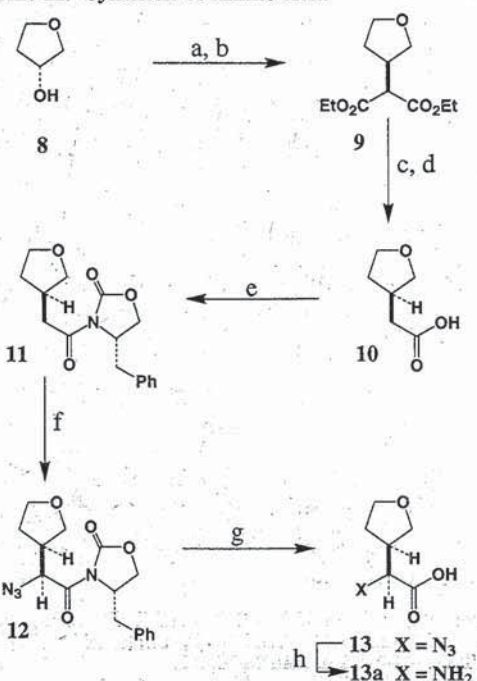


<sup>a</sup> Key: (a) PhMgBr, CuCN, THF, -78 °C; (b) tBuOOH, (-)-DET, Ti(OiPr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -22 °C; (c) Ti(OiPr)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>, PhH, 80 °C; (d) AcOCMe<sub>2</sub>COCl, CHCl<sub>3</sub>, 23 °C; (e) NaOMe, THF, 23 °C.

### Chemistry

The desired (2*R*,3*S*)-azido epoxide 7 was prepared as shown in Scheme I. The commercially available butadiene monoxide 3 was converted to allylic alcohol 4 by reaction with phenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide. The allylic alcohol 4 was then subjected to the Sharpless epoxidation<sup>5</sup> condition with (-)-diethyl D-tartrate to furnish the epoxide 5. Regioselective ring opening of epoxide 5 with diisopropoxytitanium diazide in benzene at 75 °C, as described by Sharpless and co-workers,<sup>6</sup> afforded the azidodiol 6 in very good yield. Azidodiol 6 was then converted efficiently to the desired azidoepoxide 7 by treatment with 2-acetox-

<sup>†</sup> Department of Medicinal Chemistry.  
<sup>‡</sup> Department of Molecular Systems.  
<sup>§</sup> Department of Molecular Biology.  
<sup>‡</sup> Department of Virus and Cell Biology.

Scheme II. Synthesis of Amino Acid<sup>a</sup>

<sup>a</sup> Key: (a) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -10 °C; (b) NaH, CH<sub>2</sub>(CO<sub>2</sub>Et)<sub>2</sub>, DMF; (c) 1 N NaOH then H<sub>3</sub>O<sup>+</sup>; (d) Cu<sub>2</sub>O (cat), CH<sub>3</sub>CN, 80 °C; (e) Me<sub>3</sub>COCl, Et<sub>3</sub>N, THF, -78 °C then *N*-lithio-(*S*)-(-)-4-benzyloxazolidinone; (f) KN(TMS)<sub>2</sub>, THF, -78 °C, 30 min, then trisyl azide, -78 °C, 2 min, then AcOH, 30 °C, 1 h; (g) LiOH, THF-H<sub>2</sub>O; (h) 5% Pd-C, EtOH-H<sub>2</sub>O.

ysisobutyryl chloride in chloroform at 23 °C followed by exposure of the resulting chloroacetate derivative to an excess of sodium methoxide in tetrahydrofuran at 23 °C for 3 h.<sup>7</sup>

The synthetic route leading to the (2*S*,3'*R*)-tetrahydrofuranylglycine equivalent is described in Scheme II. Readily prepared<sup>8</sup> enantiomerically pure (*S*)-(+)-3-hydroxytetrahydrofuran (8) was mesylated with mesyl chloride and triethylamine in methylene chloride at 0 °C for 20 min. Displacement<sup>9</sup> of the resulting mesylate with the sodium salt of diethyl malonate in DMF at 100 °C furnished the malonate derivative 9. Ester hydrolysis followed by copper ion promoted decarboxylation<sup>10</sup> furnished the (*R*)-tetrahydrofuranylacetic acid (10) in very good yield. The highly diastereoselective azidation protocol developed by Evans<sup>11</sup> was then employed to introduce the  $\alpha$ -amine functionality. Thus, deprotonation of the (*S*)-(-)-4-benzyloxazolidinone with *n*-BuLi followed by acylation with the mixed anhydride resulting from the reaction of acid 10 with pivaloyl chloride in the presence of triethylamine provided the carboximide 11 after silica gel chromatography. Treatment of this carboximide with potassium hexamethyldisilazide in tetrahydrofuran at -78 °C for 30 min provided the potassium enolate which was reacted with trisyl azide at -78 °C for 2 min and then quenched with glacial acetic acid and warmed to 30 °C. The  $\alpha$ -azido carboximide thus obtained was purified by silica gel chromatography to furnish the azide 12 as a single diastereomer by HPLC and <sup>1</sup>H-NMR (400-MHz) analysis. Removal of the chiral auxiliary was effected by exposure to lithium hydroxide in aqueous tetrahydrofuran to provide the desired acid 13. The resulting azido acid was hydrolyzed over 5% palladium on charcoal in a mixture of

Table I. Structure and Inhibitory Potencies of Various Constrained P<sub>2</sub>-Ligands

Compd	R	IC <sub>50</sub> (nM)	CIC <sub>95</sub> (nM)
1.		0.23±0.1 (n=3)	22±7 (n=10)
23.		0.054±0.027 (n=4)	8±4 (n=8)
24.		5.4	100
25.		2.6	---
26.		0.7	100
31.		0.6	50
32.		3.3	>200
33.		0.5	---
34.		39	---
35.		67.9	---

ethanol and water (2:1) to furnish the amino acid 13a. The corresponding (2*S*,3'*S*)-tetrahydrofuranylglycine equivalent was obtained utilizing (*R*)-(-)-3-hydroxytetrahydrofuran as the starting material. Similarly, diastereomeric azido acid 28 and other cyclic amino acids utilized in Table I were prepared following a similar course of reaction as described in Scheme II. Various pyrazine derivatives were synthesized as shown in Scheme III. The known<sup>12</sup> dichloropyrazine derivative 14 was heated with dimethylamine or 1-methyl piperazine in 2-propanol at 85 °C for 12 h to furnish the pyrazine derivative 15a or 15b. Hydrolysis of the corresponding methyl ester with aqueous NaOH in ethanol and subsequent acidification provided the acid derivative. For the preparation of pyrazine derivative 17, pyrazine 15b was first converted to bromide

# 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.