



US007317109B2

(12) **United States Patent**
Campbell et al.

(10) **Patent No.:** **US 7,317,109 B2**
(45) **Date of Patent:** ***Jan. 8, 2008**

(54) **PYRROLIDINE COMPOUNDS AND METHODS FOR SELECTIVE INHIBITION OF DIPEPTIDYL PEPTIDASE-IV**

(75) Inventors: **David Alan Campbell**, San Diego, CA (US); **David T. Winn**, San Diego, CA (US); **Juan Manuel Betancort**, San Diego, CA (US)

(73) Assignee: **Phenomix Corporation**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/381,085**

(22) Filed: **May 1, 2006**

(65) **Prior Publication Data**
US 2006/0264400 A1 Nov. 23, 2006

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/514,575, filed on Oct. 27, 2005.

(60) Provisional application No. 60/519,566, filed on Nov. 12, 2003, provisional application No. 60/557,011, filed on Mar. 25, 2004, provisional application No. 60/592,972, filed on Jul. 30, 2004, provisional application No. 60/676,808, filed on May 2, 2005.

(51) **Int. Cl.**
A61K 31/69 (2006.01)
C07F 5/02 (2006.01)

(52) **U.S. CL.** **548/405; 514/64**

(58) **Field of Classification Search** **548/405**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,674,836 A 7/1972 Creger
3,983,140 A 9/1976 Endo et al.
4,027,009 A 5/1977 Grier et al.
4,231,938 A 11/1980 Monaghan et al.
4,346,227 A 8/1982 Terahara et al.
4,448,784 A 5/1984 Glamkowski et al.
4,450,171 A 5/1984 Hoffman et al.
4,572,912 A 2/1986 Yoshioka et al.
4,681,893 A 7/1987 Roth
4,759,923 A 7/1988 Buntin et al.
4,871,721 A 10/1989 Biller
4,924,024 A 5/1990 Biller
5,006,530 A 4/1991 Angerbauer et al.
5,011,930 A 4/1991 Fujikawa et al.
5,177,080 A 1/1993 Angerbauer et al.
5,260,440 A 11/1993 Hirai et al.
5,273,995 A 12/1993 Roth
5,346,701 A 9/1994 Heiber et al.
5,354,772 A 10/1994 Kathawala

5,385,929 A 1/1995 Borge et al.
5,447,954 A 9/1995 Gribble et al.
5,462,928 A 10/1995 Bachovchin et al.
5,488,064 A 1/1996 Sher
5,491,134 A 2/1996 Sher et al.
5,541,204 A 7/1996 Sher et al.
5,574,017 A 11/1996 Gutheil
5,594,016 A 1/1997 Ueno et al.
5,595,872 A 1/1997 Wetterau, II et al.
5,614,492 A 3/1997 Habener
5,631,224 A 5/1997 Efendic et al.
5,686,104 A 11/1997 Mills et al.
5,712,279 A 1/1998 Biller et al.
5,712,396 A 1/1998 Magnin et al.
5,739,135 A 4/1998 Biller et al.
5,760,246 A 6/1998 Biller et al.
5,770,615 A 6/1998 Cheng et al.
5,776,983 A 7/1998 Washburn et al.
5,827,875 A 10/1998 Dickson, Jr. et al.
5,885,983 A 3/1999 Biller et al.
5,952,301 A 9/1999 Drucker
5,952,322 A 9/1999 Hoover et al.
5,962,440 A 10/1999 Sulsky
5,965,532 A 10/1999 Bachovchin

(Continued)

FOREIGN PATENT DOCUMENTS

DE 19616486 A1 10/1997

(Continued)

OTHER PUBLICATIONS

"Avasimibe: Treatment of Lipoprotein Disorders, ACAT Inhibitor", *Drugs of the Future* 24(1), (1999), 9-15.

(Continued)

Primary Examiner—Laura L. Stockton
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner P.A.

(57) **ABSTRACT**

The present invention is directed to pyrrolidinylaminoacetyl pyrrolidine boronic acid compounds that display selective, potent dipeptidyl peptidase IV inhibitory activity. These compounds are useful for the treatment of disorders that can be regulated or normalized via inhibition of DPP-IV including those characterized by impaired glycemic control such as Diabetes Mellitus and related conditions. The compounds can be administered alone or with another medicament that displays pharmacological activity for treatment of these and other diseases.

27 Claims, No Drawings

U.S. PATENT DOCUMENTS

5,998,463	A	12/1999	Hulin et al.
6,011,155	A	1/2000	Villhauer
6,040,145	A	3/2000	Huber et al.
6,107,317	A	8/2000	Villhauer
6,110,949	A	8/2000	Villhauer
6,124,305	A	9/2000	Villhauer
6,166,063	A	12/2000	Villhauer
6,172,081	B1	1/2001	Damon
6,258,597	B1	7/2001	Bachovchin et al.
6,300,314	B1	10/2001	Wallner et al.
6,303,661	B1	10/2001	Demuth et al.
6,355,614	B1	3/2002	Wallner
6,380,398	B2	4/2002	Kanstrup et al.
6,395,767	B2	5/2002	Robl et al.
6,432,969	B1	8/2002	Villhauer
6,617,340	B1	9/2003	Villhauer
6,989,402	B1	1/2006	Hangeland et al.
2003/0100563	A1	5/2003	Edmondson et al.
2003/0153509	A1	8/2003	Bachovchin et al.
2006/0258621	A1	11/2006	Campbell et al.
2006/0264401	A1	11/2006	Campbell et al.
2006/0276410	A1	12/2006	Campbell et al.
2007/0185061	A1	8/2007	Campbell

FOREIGN PATENT DOCUMENTS

EP	0818448	B1	1/1998
EP	0896538	B1	2/1999
EP	0978279	A1	2/2000
EP	1041068	B1	4/2004
WO	WO-89/03223	A1	4/1989
WO	WO-91/16339	A1	10/1991
WO	WO-93/08259	A2	4/1993
WO	WO-93/10127	A1	5/1993
WO	WO-95/11689	A1	5/1995
WO	WO-95/15309	A1	6/1995
WO	WO-96/39384	A1	12/1996
WO	WO-96/39385	A1	12/1996
WO	WO-97/12613	A1	4/1997
WO	WO-97/12615	A1	4/1997
WO	WO-97/21993	A2	6/1997
WO	WO-98/00439	A2	1/1998
WO	WO-98/19998	A2	5/1998
WO	WO-98/50046	A1	11/1998
WO	WO-99/00353	A1	1/1999
WO	WO-99/03850	A1	1/1999
WO	WO-99/26659	A1	6/1999
WO	WO-99/38501	A2	8/1999
WO	WO-99/43663	A1	9/1999
WO	WO-00/34241	A1	6/2000
WO	WO-00/38722	A1	7/2000
WO	WO-00/47206	A1	8/2000
WO	WO-03/045228	A2	6/2003
WO	WO-03/045977	A2	6/2003
WO	WO-2004/004661	A2	1/2004
WO	WO-2005/047297	A1	5/2005

OTHER PUBLICATIONS

"International Search Report and Written Opinion for PTC Application No. PCT/US04/37820", (Mar. 10, 2005), 9 pgs.
 Bachovchin, W. W., et al., "Inhibition of IgA1 Proteinases from *Neisseria gonorrhoeae* and *Haemophilus influenzae* by Peptide Prolyl Boronic Acids", *Journal of Biological Chemistry*, 265(7), (Mar. 5, 1990), 3738-3743.
 Balkan, B., et al., "Improved Insulin Secretion and Oral Glucose Tolerance after In Vivo Inhibition of DPP-IV in Obese Zucker Rats", *Diabetologia, Suppl. 40, A131 Abstract*, (1977), 1 page, 511.
 Biller, S. A., et al., "Communications to the Editor: Isoprenoid (Phosphorylmethyl)phosphonates as Inhibitors of Squalene Synthetase", *Journal of Medicinal Chemistry*, 31(10), (Oct. 1988), 1869-1871.

Biller, S. A., "Squalene Synthase Inhibitors", *Current Pharmaceutical Design*, 2(1), (1996), 1-40.

Corey, E. J., "Application of Unreactive Analogs of Terpenoid Pyrophosphates to Studies of Multistep Biosynthesis. Demonstration That "Presqualene Pyrophosphate" Is An Essential Intermediate on the Path to Squalene", *Journal of the American Chemical Society*, 98(5), (1976), 1291-1293.

Coutts, S. J., "Structure-Activity Relationships of Boronic Acid Inhibitors of Dipeptidyl Peptidase IV. I. Variation of the P₂ Position of X_n-boroPro Dipeptides", *J. Med. Chem.* 39(10), (1996), 2087-2094.

Coutts, S. J., et al., "Two Efficient Methods for the Cleavage of Pinanediol boronate Esters Yielding the Free Boronic Acids", *Tetrahedron Letters*, 35(29), (1994), 5109-5112.

Deacon, C. F., et al., "Both Subcutaneously and Intravenously Administered Glucagon-Like Peptide I are Rapidly Degraded From the NH₂-Terminus in Type II Diabetic Patients and in Healthy Subjects", *Diabetes*, 44(9), Retrieved from the Internet: <http://gateway.ut.ovid.com.floyd.lib.umn.edu/gw2/ovidweb.cgi>, (1995), 1126-1131, (11 pgs.).

Deacon, C. F., et al., "Dipeptidyl Peptidase IV Inhibition as an Approach to the Treatment and Prevention of Type 2 Diabetes: a Historical Perspective", *Biochemical and Biophysical Research Communications* 294, (2002), 1-4.

Demuth, H.-U., et al., "Rebuttal to Deacon and Holst: "Metformin Effects on Dipeptidyl Peptidase IV Degradation of Glucagon-like Peptide-1" Versus "Dipeptidyl Peptidase Inhibition as an Approach to the Treatment and Prevention of Type 2 Diabetes: a Historical Perspective", *Biochemical and Biophysical Research Communications* 296, (2002), 229-232, p. 229 only.

Ghiselli, G., "The Pharmacological Profile of FCE 27677: A Novel ACAT Inhibitor with Potent Hypolipidemic Activity Mediated by Selective Suppression of the Hepatic Secretion of ApoB-100-Containing Lipoprotein", *Cardiovascular Drug Reviews*, 16(1), (1998), 16-30.

Hara, S., "Ileal Na⁺/bile Acid Cotransporter Inhibitors", *Drugs of the Future*, 24(4), (1999), 425-430.

Hinke, S. A., et al., "Metformin Effects on Dipeptidyl-Peptidase IV Degradation of Glucagon-like Peptide-1", *Biochemical and Biophysical Research Communications* 291, (2002), 1302-1308.

Holst, Jens J., et al., "Perspectives in Diabetes: Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes", *Diabetes*, vol. 47, From the Department of Medical Physiology, University of Copenhagen, Copenhagen, Denmark, (Nov. 1998), 1663-1670.

Kelly, T. A., et al., "Immunosuppressive Boronic Acid Dipeptides Correlation Between Conformation and Activity", *Journal of the American Chemical Society*, 115(26), (1993), 12637-12638.

Krause, B. R., "ACAT Inhibitors: Physiologic Mechanisms for Hypolipidemic and Anti-Atherosclerotic Activities in Experimental Animals", *Inflammation: Mediators and Pathways*, Ruffolo, Jr., et al., Editors, published by CRC Press, Boca Raton, FL, (1995), 173-198.

Kubota, T., et al., "Dipeptidyl Peptidase IV (DP IV) Activity in Serum and on Lymphocytes of MRL/Mp-lpr/lpr Mice Correlates With Disease Onset", *Clin Exp Immunol* 96, (1994), 292-296.

McClard, R. W., "Novel Phosphonylphosphinyl (P-C-P-C-) Analogues of Biochemically Interesting Diphosphates. Syntheses and Properties of P-C-P-C- Analogues of Isopentenyl Diphosphate and Dimethylallyl Diphosphate", *J. Am. Chem. Soc.*, vol. 109, (1987), 5544-5545.

Murakami, K., "A Novel Insulin Sensitizer Acts as a Coligand for Peroxisome Proliferation-activated Receptor- α (PPAR- α) and PPAR- γ —Effect on PPAR- α Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", *Diabetes*, vol. 47, (Dec. 1998), 1841-1847.

Nicolosi, R. J., et al., "The ACAT Inhibitor, CI-1011 is Effective in the Prevention and Regression of Aortic Fatty Streak Area in Hamsters", *Atherosclerosis* 137, (1998), 77-85.

Ortiz De Montellano, P. R., "Inhibition of Squalene Synthetase by Farnesyl Pyrophosphate Analogues", *Journal of Medicinal Chemistry*, 20(2), (1977), 243-249.

- Pauly, R. P., et al., "Inhibition of Dipeptidyl Peptidase IV (DP IV) in Rat Results in Improved Glucose Tolerance", *Abstracts from the 11th International Symposium on Regulatory Peptides*, (1996), p. 148.
- Rosenblum, S. B., "Discovery of 1-(4-Fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A Designed, Potent, Orally Active Inhibitor of Cholesterol Absorption", *J. Med. Chem.* 41, (1998), 973-980.
- Salisbury, B. G., "Hypocholesterolemic Activity of a Novel Inhibitor of Cholesterol Absorption, SCH 48461", *Atherosclerosis* 115, (1995), 45-63.
- Sendobry, S. M., "Attenuation of Diet-Induced Atherosclerosis in Rabbits with a Highly Selective 15-lipoxygenase Inhibitor Lacking Significant Antioxidant Properties", *British Journal of Pharmacology* 120, (1997), 1199-1206.
- Sliskovic, D. R., "ACAT Inhibitors: Potential Anti-atherosclerotic Agents", *Current Medicinal Chemistry*, 1(3), (1994), 204-225.
- Smith, C., "RP 73163: A Bioavailable Alkylsulphonyl-Diphenylimidazole ACAT Inhibitor", *Bioorganic & Medicinal Chemistry Letters*, 6(1), (1996), 47-50.
- Stout, D. M., et al., "Inhibitors of Acyl-CoA: Cholesterol O-Acyl Transferase (ACAT) as Hypocholesterolemic Agents. 6. The First Water-Soluble ACAT Inhibitor With Lipid-Regulating Activity", *Chemtracts-Organic Chemistry*, vol. 8, (1995), 359-362.
- Tanaka, S., et al., "Suppression of Arthritis by the Inhibitors of Dipeptidyl Peptidase IV", *International Journal of Immunopharmacology*, 19(1), (1997), 15-24.
- Tanaka, S., et al., "Suppression of Arthritis by the Inhibitors of Dipeptidyl Peptidase IV", *Ensho—Japanese Journal of Inflammation*, 18(3), (1998), 199-202.
- Application Serial No. 04810839.3 (EPO), Non-Final Office Action mailed Jul. 18, 2007, 4 p.
- Application Serial No. 04810839.3 (EPO), Supplemental European Search Report mailed Dec. 13, 2006, 3 p.

1
**PYRROLIDINE COMPOUNDS AND
METHODS FOR SELECTIVE INHIBITION
OF DIPEPTIDYL PEPTIDASE-IV**

CROSS REFERENCE TO RELATED
APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 10/514,575, filed on Oct. 27, 2005, which is a national stage application of PCT/US04/037820, which claims priority to U.S. provisional application No. 60/519,566, filed on Nov. 12, 2003; U.S. provisional application No. 60/557,011, filed on Mar. 25, 2004; and U.S. provisional application No. 60/592,972, filed on Jul. 30, 2004. This application is also a continuation-in-part of U.S. application Ser. No. 60/676,808, filed on May 2, 2005. These applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a pyrrolidinylaminoacetyl pyrrolidine boronic acid compound and its use as a selective inhibitor of post-proline/alanine cleaving amino-dipeptidases, particularly dipeptidyl peptidase-IV (DPP-IV). The invention also relates to methodology for employing a pyrrolidine compound, alone or with another medicament, to treat a DPP-IV-related disease, including but not limited to disorders characterized by impaired glycemic control, especially Diabetes Mellitus and related conditions. Thus, the invention has applications in the medicinal, chemical, pharmacological, and medical fields.

BACKGROUND OF THE INVENTION

Dipeptidyl peptidase-IV (DPP-IV) is a serine protease that belongs to a group of post-proline/alanine cleaving amino-dipeptidases. DPP-IV catalyzes the release of an N-terminal dipeptide of any configuration from proteins, and preferably, the dipeptide contains an N-terminal penultimate proline or alanine.

The physiological role of DPP-IV has not been established fully. It is believed to play an important role in regulatory peptide metabolism, which, among other things, controls various physiological functions including but not limited to glycemic control and insulin sensitivity. In particular, DPP-IV has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones, glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which are inactivated by removal of their two N-terminal amino acids.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of insulinotropic hormones including, GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, consequent improved glucose tolerance. Therefore, such inhibitors have been proposed for the treatment of patients with impaired glycemic control such as Diabetes Mellitus and related conditions.

This proposal has significant difficulties, however. Additional dipeptide cleaving amino-dipeptidases have also been discovered, including DPP-VII, DPP-VIII, DPP-IX, and fibroblast activation protein (FAP), which can have substrate and inhibitor specificity similar to DPP-IV. The precise physiological role of each of these dipeptide cleaving enzymes is not well defined. But, their propensity to cleave N-terminus dipeptides from proteins in general indicates that these amino-dipeptidases are involved in many physiologi-

2

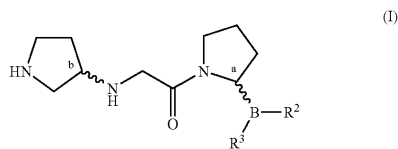
cal cycles. Thus, the difficulty concerning inhibitors of DPP-IV is that they can also affect the other members of the enzyme group. The evidence indicates that, for example, other inhibitors of DPP-IV, which also inhibit the other amino-dipeptidases such as DPP-VIII, will cause toxic effects in animals.

Accordingly, a need exists for compounds that are useful for inhibiting DPP-IV without an adverse event profile that precludes chronic administration.

SUMMARY OF THE INVENTION

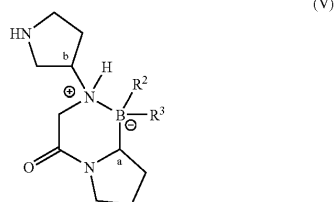
The present invention is directed to a selective DPP-IV inhibitor and methods of use that are effective in treating conditions that may be regulated or normalized by inhibition of DPP-IV. More particularly, the invention is directed to a pyrrolidinylaminoacetyl pyrrolidine boronic acid compound. This pyrrolidinylaminoacetyl pyrrolidine boronic acid compound is useful at effective doses for treatment of malconditions associated with DPP-IV activity and is a selective inhibitor of DPP-IV.

A pyrrolidinylaminoacetyl boronic acid compound of the invention (hereinafter the pyrrolidine compound of the invention) has a structure represented in part by Formula I.



The substituents and bond designations of formula I include R² and R³, which, independently or together, are —OH, —O[−]M⁺ wherein M⁺ is a cation, a hydroxyl bearing a boronic acid protecting group, or a group capable of being hydrolyzed to a hydroxyl group in an aqueous solution at physiological pH or in biological fluids; and the wavy lines at asymmetric carbons C^a and C^b, which independently indicate for each asymmetric carbon an R configuration, an S configuration, or a mixture of both configurations such that all stereoisomers and all stereomeric mixtures are included. Also included within the scope of the invention are a cyclic isomer thereof, any pharmaceutically acceptable salt thereof, any prodrug thereof, and any solvate thereof.

A pyrrolidine compound of the invention may exist in either of two forms, the linear form represented by formula I above and the cyclic isomer form represented by formula V below.



The cyclic isomer form and the linear form are in thermodynamic equilibrium when in solution. The equilibrium

3

shifts depending upon pH. Thus, the predominance of one form over the other in solution depends upon the pH so that at acidic pH, the linear isomer predominates while at basic pH, the cyclic isomer predominates. The linear and cyclic isomers are also stable such that either form may be isolated as a solid. The isolated cyclic isomer can function as a prodrug.

The invention also is directed to a pharmaceutical composition containing a pyrrolidine compound of the invention and a pharmaceutical carrier. The pharmaceutical composition may be formulated to be dosed by any administrative route including but not limited to parenteral injection, oral, buccal, rectal and the like.

The invention is as well directed to a method of treatment of a malcondition that can be regulated or normalized via inhibition of DPP-IV. The method involves administration of an effective amount of a pyrrolidine compound of the invention, such as would be present in a pharmaceutical composition of the invention, to mammals, especially humans, to affect a malcondition that can be regulated or normalized via inhibition of DPP-IV. Preferably, an effective amount of a pyrrolidine compound of the invention exhibits lower toxicity than do non-selective inhibitors of DPP-IV, particularly in comparison to boronic acid inhibitors of DPP-IV that also display inhibition of other DPP enzymes and FAP. Therefore, the invention is directed to methods for selectively inhibiting DPP-IV including administering to a patient in need of such treatment a therapeutically effective amount of a pyrrolidine compound of the invention.

The invention further is directed to a pharmaceutical combination of a pyrrolidine compound of the invention and one or more other medicaments that are useful for treatment of a malcondition that can be regulated or normalized via inhibition of DPP-IV. Such malconditions are associated with impairments in glycemic control especially Diabetes Mellitus and related conditions. A pharmaceutical combination may be formulated according to the invention as a pharmaceutical composition.

The invention is also directed to a process for preparing a pyrrolidine compound of the invention, a method for preparing a pharmaceutical composition of the invention, and the use of a pyrrolidine compound of the invention in a method for the preparation of a medicament for treating a malcondition that can be regulated or normalized via inhibition of DPP-IV.

DEFINITIONS

The term "absolute configuration" in connection with an asymmetric carbon is determined by considering the tetrahedral shape of the asymmetric carbon bonds, assigning a priority of 1 through 4 to each of the groups bound to the asymmetric carbon with the group having the highest atomic number having the first priority. If the tetrahedron is viewed from a side remote from group 4, an R absolute configuration is assigned when groups 1-3 are in a clockwise arrangement and an S absolute configuration is assigned when groups 1-3 are in a counterclockwise arrangement.

The term "asymmetric carbon" means a carbon atom covalently bound to four different groups.

The term "beta cell degeneration" is intended to mean loss of beta cell function, beta cell dysfunction, and death of beta cells, such as necrosis or apoptosis of beta cells.

The term "Diabetes Mellitus and related conditions" refers to Type 1 diabetes, Type 2 diabetes, gestational diabetes, MODY, impaired glucose tolerance, impaired fast-

4

ing glucose, hyperglycemia, impaired glucose metabolism, insulin resistance, obesity, diabetic complications, and the like.

The term "diabetic complications" refers to conditions, diseases and maladies associated with diabetes including retinopathies, neuropathies, nephropathies, cardiomyopathies, dermopathies, arteriosclerosis, coronary artery disease and other known complications of diabetes.

The term "diastereomer" means one member of a group of two or more stereoisomers having at least two asymmetric carbons such that these stereoisomers are not mirror images of each other.

The terms "DPP-VII, DPP-VIII, DPP-IX and FAP" mean respectively amino dipeptidyl peptidase VII, VIII, IX and fibroblast activation protein. The DPP enzymes cleave dipeptide moieties at the N-terminus of their protein or oligopeptide substrates. In particular, the term "DPP-IV" denotes dipeptidyl peptidase IV (EC 3.4.14.5; DPP-IV), also known as "CD-26." DPP-IV preferentially cleaves a dipeptide from the N terminus of a polypeptide chain containing a proline or alanine residue in the penultimate position.

The term "enantiomer" means one member of a pair of stereoisomers having the same molecular structure and at least one asymmetric carbon such that the stereoisomers of the pair are the mirror images of each other. If the enantiomer contains two or more asymmetric carbons, the enantiomeric pair will have opposing asymmetry at each asymmetric carbon.

The term "group that can be hydrolyzed to a hydroxyl" as used herein refers to an ester group formed from the combination of an aliphatic or aromatic alcohol or diol and a boronic acid.

The term "inhibitor" (and its corresponding verb and gerund) means a compound that will reversibly, irreversibly or temporarily interact with an enzyme so as to reduce, modify, slow down or block its enzymatic activity upon its normal substrate. The interaction may occur within or at the enzymatic site or at an allosteric site associated with the enzyme.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in T.W. Greene, P. G. Wuts, "Protective Groups In Organic Synthesis, 3rd Ed." (John Wiley & Sons, New York (1999)), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxycarbonyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl,

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.