United States Patent [19]

Bachovchin et al.

[11] **Patent Number: 4,935,493**

[45] **Date of Patent: Jun. 19, 1990**

[54] PROTEASE INHIBITORS

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[21] Appl. No.: **105,768**

[22] Filed: **Oct. 6, 1987**

[51] **Int. Cl.**[5] **A61K 37/02;** C07K 5/08; C07K 5/10

[52] **U.S. Cl.** **530/331;** 530/330

[58] **Field of Search** 514/2, 18, 19; 530/330, 530/331

[56] **References Cited**

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Yoshimoto et al., 1985, J. Biochem 98:975.

Report of the National Heart Lung and Blood Institute Workshop on Elastase Inhibitors for Treatment of Emphysema held in Rockville, Md. (Jun. 10–11, 1985).

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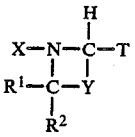
Attorney, Agent, or Firm—Fish & Richardson

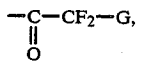
[57] **ABSTRACT**

A compound having the structure



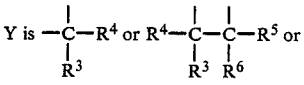
where T is of the fomrula

where each D^1 and D^2, independently, is a hydroxyl group of a group which is capable of being hydrolysed to a hydroxyl group in aqueous solution at physiological pH; a group of the formula



where G is either H,F or an alkyl group containing 1 to about 20 carbon atoms and optional heteroatoms which can be N, S, or O; or a phosphonate group of the formula

where J is O-alkyl, N-alkyl, or alkyl, each comprising about 1–20 carbon atoms and, optionally, heteroatoms which can be N, S, or O; T being able to form a complex with the catalytic site of an enzyme, X is a group having at least one amino acid,



(Abstract continued on next page.)

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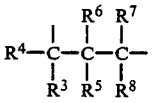
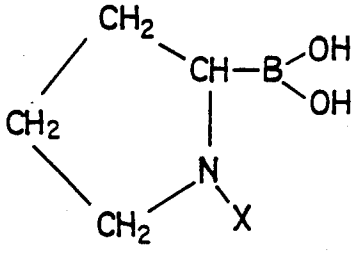
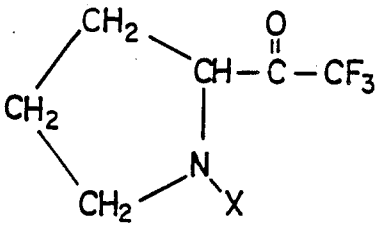


and each R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 is separately a group which does not interfere significantly (i.e., does not lower than Ki of the compound to less than 10^{-7}M) with site-specific recognition of the compound by the enzyme, and allows a complex to be formed with the enzyme.

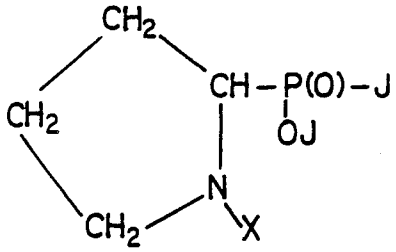
12 Claims, 2 Drawing Sheets



Prolyl Boronate

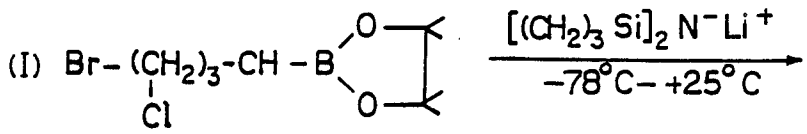


Prolyl Trifluoro alkyl ketone

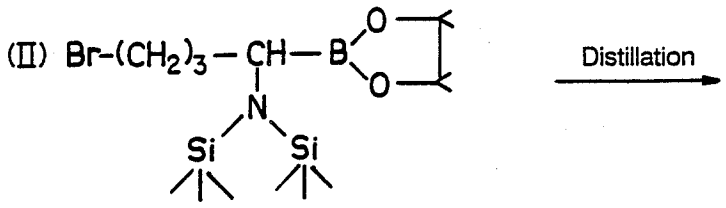


Prolyl phosphonate

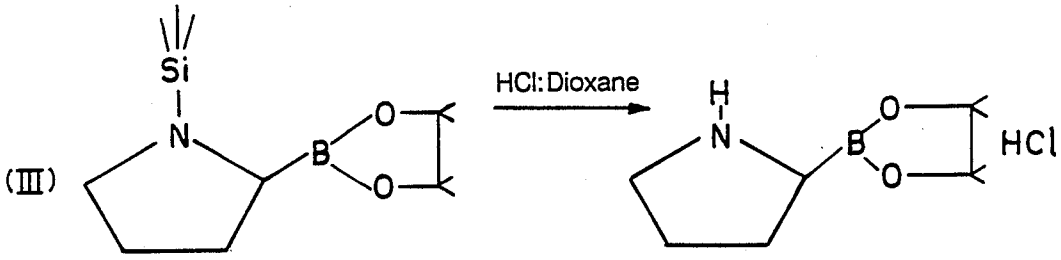
FIG. 1



4-bromo-1-chlorobutyl boronate pinacol



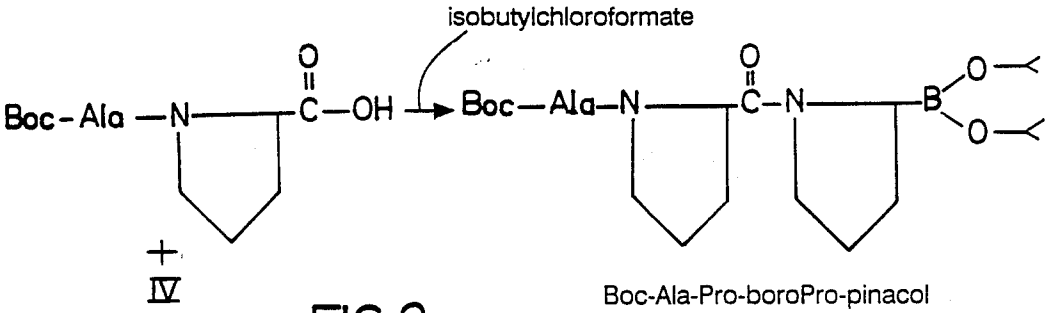
4-bromo-1 [(bistrimethylsilyl) amino] butyl bornonate pinacol



1-trimethylsilyl-boroProline pinacol

IV

boroProline-pinacol-HCl



Boc-Ala-Pro-boroPro-pinacol

FIG.2

PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

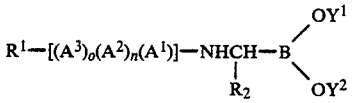
This invention relates to protease inhibitors, and particularly to transition state analogs.

Transition state analogs, compounds which are thought to resemble the substrates of enzymes, are thought to bind more tightly to the enzymes than the substrates themselves. Transition state analogs form complexes with enzymes at their catalytic sites.

Baugh et al. (Proteinases and Tumor Invasion ed. Strauli et al., Raven Press, N.Y., 1980, p. 165) state that transition state analogs containing boronic acid moieties or aldehydes form tetrahedral adducts with serine proteases and are thus good inhibitors of these enzymes. Further, they state that some peptide aldehydes have been synthetically prepared, that most are of microbial origin, and that "it would appear that changing the R-group [of synthetic peptides] to satisfy the specific requirements of a given protease should result in both potent and specific inhibitors." They also state that transition state analogs containing cyclic ester moieties have been used to inhibit chymotrypsin and that "variations thereof may become useful as inhibitors of cathepsin G."

Yoshimoto et al. (J. Biochem .98: 975, 1985) describe prolyl endopeptidase inhibitors containing a protinal moiety. These inhibitors appear to act non-competitively.

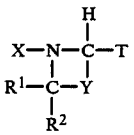
Shenvi et al., U.S. Pat. No. 4,499,082, describe peptides having an α-amino boronic acid residue. These peptides are reversible inhibitors of elastase. They have the structureal formula



where R_2 is an alkyl group of one to six carbons which may have an aromatic substituent or an in-chain bivalent group.

SUMMARY OF THE INVENTION

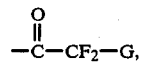
In a first aspect, the invention features compounds having the structure



(1)

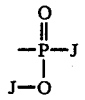
and salts thereof, where T is a boronate group of the formula

where each D^1 and D^2, independently, is a hydroxyl group or a group which is capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH; or T is a group of the formula



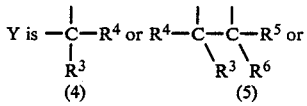
(2)

where G is either H,F or an alkyl group containing 1 to about 20 carbon atoms and optional heteroatoms which can be N, S, or O; or T is a phosphonate group of the formula

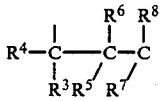


(3)

where each J, independently, is O-alkyl, N-alkyl, or alkyl (each containing about 1–20 carbon atoms) and, optionally, heteroatoms which can be N, S, or O; where T is a group able to form a complex with the catalytic site of an enzyme; X includes one or more amino acids,



(4) (5)

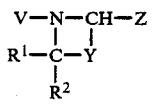


(6)

and each R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, independently, is a group which does not interfere significantly (i.e., does not raise the Ki of the compound to greater than 10^{-5}M) with site-specific recognition of the compound by the enzyme, while permitting a complex to be formed between the compound and the enzyme.

In preferred embodiments, T is a boronate group, each D^1 and D^2, independently, is OH or F or D^1 and D^2 together form a ring containing 1 to about 20 carbon atoms, and optionally heteratoms which can be N, S, or O; each R^{1-8} is H; X mimics the substrate recognized by the enzyme, for example X is pro-, thr-pro-, ala-pro-, ala-ala-pro, ser-thr-pro-, pro-ser-, pro-thr- or ser-pro- (pro=proline, thr=threonine, and ser=serine); X contains both an amino acid and a blocking group, such as an acetyl group; the enzymes inhibited by the compounds of the invention are post prolyl cleaving enzymes, most preferably serine proteases, even more preferably IgA1 proteases; and the analog has a binding constant of at least 10^{-7}M, most preferably 10^{-10}M.

In a second aspect, the invention features a compound, which is useful as an intermediate in the synthesis of compounds of Formula (1), having the formula



(7)

where V is $(CH_3)_3$ Si— or H—,
Y is

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