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(54) **LACTAM-CONTAINING COMPOUNDS AND DERIVATIVES THEREOF AS FACTOR XA INHIBITORS**

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Related U.S. Application Data

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(51) **Int. Cl.**[7] **C07D 471/16**; A61K 31/437; A61P 7/02

(52) **U.S. Cl.** **514/303**; 546/119; 546/120

(58) **Field of Search** 514/303; 546/119, 546/120

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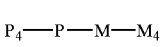
(57) **ABSTRACT**

The present application describes lactam-containing compounds and derivatives thereof of Formula I:



I

or pharmaceutically acceptable salt forms thereof, wherein ring P, if present is a 5–7 membered carbocycle or heterocycle and ring M is a 5–7 membered carbocycle or heterocycle. Compounds of the present invention are useful as inhibitors of trypsin-like serine proteases, specifically factor Xa.

OTHER PUBLICATIONS

Kumar et al., "Ketene dithioacetals. Part II. Reaction of 3–cyano–4–methylthio–2(1H)–pyridones with hydrazine and quanidine: synthesis of novel substituted and fused pyrazolo[4,3–c]pyridone and pyrido[4,3–d]pyrimidine derivatives", Journal of the Chemical Society, Perkin Transactions I: Organic and Bio–Organic Chemistry 1978, No. 8, pp. 857–862 (abstract).

Elodi et al., "Optimization of conditions for the catalytic effect of the factor IXa–factor VIII Complex:Probable role of the complex in the amplification of blood coagulation", *Thromb. Res*., vol. 15, pp. 617–629, 1979.

LACTAM-CONTAINING COMPOUNDS AND DERIVATIVES THEREOF AS FACTOR XA INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

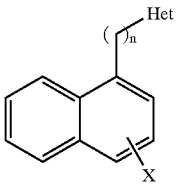
The present application claims the priority of U.S. Provisional Application No. 60/324,165, filed Sep. 21, 2001; and the priority of U.S. Provisional Application No. 60/402,317, filed Aug. 9, 2002. The present application claims the priority benefits of these prior applications, all of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates generally to lactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders.

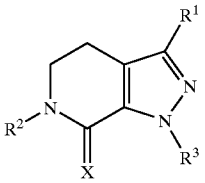
BACKGROUND OF THE INVENTION

WO94/20460 describes angiotensin II compounds of the following formula:



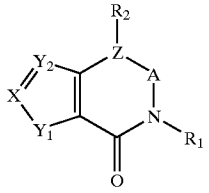
wherein X can be a number of substituents and Het can be a nitrogen-containing heterobicycle. However, WO94/20460 does not suggest Factor Xa inhibition or exemplify compounds like those of the present invention.

WO96/12720 depicts phosphodiesterase type IV and TNF production inhibitors of the following formula:



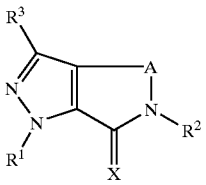
wherein X can be oxygen and R^2 and R^3 can a number of substituents including heterocycle, heterocycloalkyl, and phenyl. However, the presently claimed compounds do not correspond to the compounds of WO96/12720. Furthermore, WO96/12720 does not suggest Factor Xa inhibition.

WO98/52948 details inhibitors of ceramide-mediated sig-



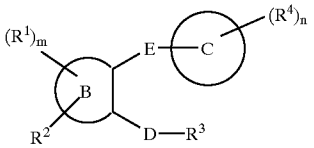
wherein Y_1 can be N—R_6, R_6 can be unsubstituted arylalkyl or unsubstituted heterocyclic-alkyl and R_1 can be a substituted aryl group. WO98/52948 does not mention factor Xa inhibition or show compounds like those of the present invention.

U.S. Pat. Nos. 3,365,459, 3,340,269, and 3,423,414 illustrate anti-inflammatory inhibitors of the following formula:



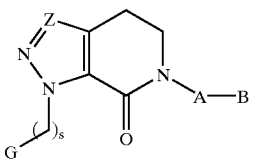
wherein A is 2–3 carbon atoms, X can be O, and R^1 and R^3 can be substituted or unsubstituted aromatic groups. Neither of these patents, however, exemplifies compounds of the present invention.

WO99/32477 reports Factor Xa inhibitors of the following formula:



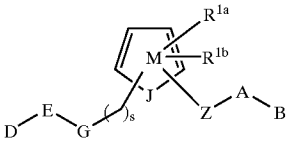
wherein the inhibitors contain at least three aryl or heterocyclic groups (i.e., C, B, and R^3) separated by two linking groups (i.e., E and D). Compounds of this sort are not considered to be part of the present invention.

WO00/39131 describes heterobicyclic Factor Xa inhibitors of which the following is an example formula:



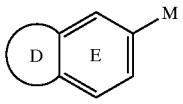
wherein Z is C or N, G is a mono- or bicyclic group, A is a cyclic moiety and B is a basic group or a cyclic moiety. Compounds specifically described in WO00/39131 are not considered to be part of the present invention.

WO98/28269, WO98/28282, WO99/32454, U.S. Pat. No.



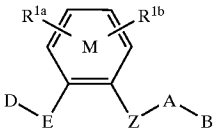
wherein ring M is a heterocycle, Z is a linker, A is a ring, B is a basic or cylic group, D is a basic moiety, and E is a ring. Compounds specifically described in WO98/28269, WO98/28282, WO99/32454, U.S. Pat. No. 6,020,357, and U.S. Pat. No. 6,271,237 are not considered to be part of the present invention.

WO98/57951 describes Factor Xa inhibitors of the following formula:



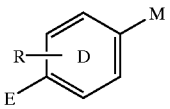
wherein ring M can be a variety of heterocycles and rings D–E represent a heterobicyclic group. Compounds specifically described in WO98/57951 are not considered to be part of the present invention.

WO98/57934 and U.S. Pat. No. 6,060,491 describe Factor Xa inhibitors of the following formula:



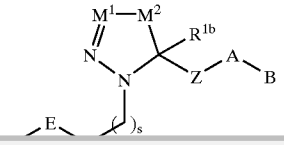
wherein ring M is a 6-membered heteroaryl, Z is a linker, A is a ring, B is a basic or cylic group, D is a basic moiety, and E is a ring. Compounds specifically described in WO98/57934 and U.S. Pat. No. 6,060,491 are not considered to be part of the present invention.

WO98/57937 and U.S. Pat. No. 5,998,424 describe Factor Xa inhibitors of the following formula:



wherein ring M is a variety of rings, ring D is an aromatic ring, and R and E are non-basic groups. Compounds specifically described in WO98/57937 and U.S. Pat. No. 5,998,424 are not considered to be part of the present invention.

WO99/50255 and U.S. Pat. No. 6,191,159 describe pyrazoline and triazoline Factor Xa inhibitors of the following formulas:



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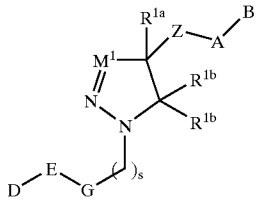
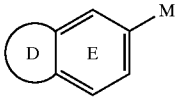


Compounds specifically described in WO99/50255 and U.S. Pat. No. 6,191,159 are not considered to be part of the present invention.

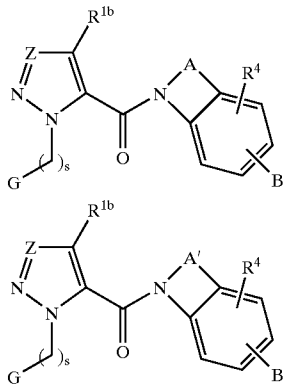
WO00/59902 describes Factor Xa inhibitors of the following formula:



wherein ring M can be a variety of rings all of which are substituted with Z—A—B, Z is a linker, A is a ring, B is a sulfonyl-containing heterobicycle, and rings D–E represent a heterobicyclic group or a 6-membered ring. Compounds specifically described in WO00/59902 are not considered to be part of the present invention.

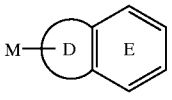
WO01/32628 describes cyano-pyrroles, cyano-imidazoles, cyano-pyrazoles, and cyano-triazoles that are Factor Xa inhibitors. Compounds specifically described in WO01/32628 are not considered to be part of the present invention.

WO01/05784 describes Factor Xa inhibitors of the following formulas:



wherein Z is C or N, G is a mono- or bicyclic ring M, A is a linker, B is a basic or cyclic group. Compounds specifically described in WO01/05784 are not considered to be part of the present invention.

WO00/39108 describes Factor Xa inhibitors of the following formula:



wherein ring M can be a variety of heterocycles and rings D–E represent a heterobicyclic group. Compounds specifi-

WO01/19798 describes factor Xa inhibitors of the following formula:

A—Q—D—E—G—J—X

wherein A, D, G, and X can be phenyl or heterocycle. However, none of the presently claimed compounds are exemplified or suggested in WO01/19798.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* 1979, 15, 617–629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peak-to-trough characteristics (e.g., clearance and/or volume of distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e) factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side-effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing costs or feasibility (e.g., difficulty of synthesis, number of chiral centers, chemical stability, and ease of handling).

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel lactam-containing compounds and derivatives thereof that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present

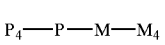
The present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

The present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

The present invention provides novel lactam-containing compounds and derivatives thereof for use in therapy.

The present invention provides the use of novel lactam-containing compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that lactam-containing compounds of Formula I:



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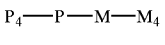
wherein P_4, P, M, and M_4 are defined below, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] In an embodiment, the present invention provides a novel compound of Formula I:



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or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

M is a 3–10 membered carbocycle or a 4–10 membered heterocycle, consisting of: carbon atoms and 1–3 heteroatoms selected from O, $S(O)_p$, N, and NZ^2;

ring M is substituted with 0–3 R^{1a} and 0–2 carbonyl groups, and there are 0–3 ring double bonds;

P is fused onto ring M and is a 5, 6, or 7 membered carbocycle or a 5, 6, or 7 membered heterocycle, consisting of: carbon atoms and 1–3 heteroatoms selected from O, $S(O)_p$, and N;

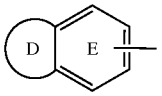
ring P is substituted with 0–3 R^{1a} and 0–2 carbonyl groups, and there are 0–3 ring double bonds;

alternatively, ring P is absent and P_4 is directly attached to ring M, provided that when ring P is absent, P_4 and M_4 are attached to the 1,2, 1,3, or 1,4 positions of ring M;

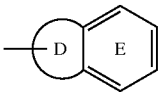
one of P_4 and M_4 is —Z—A—B and the other —G_1—G;

G is a group of Formula IIa or IIb:

IIa



IIb



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