US006297233B1

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

(10) **Patent No.: US 6,297,233 B1**
(45) **Date of Patent: Oct. 2, 2001**

(54) **LACTAM INHIBITORS OF FXA AND METHOD**

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

(21) Appl. No.: **09/496,571**

(22) Filed: **Feb. 2, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/167,428, filed on Nov. 24, 1999, and provisional application No. 60/119,372, filed on Feb. 9, 1999.

(51) **Int. Cl.**[7] **C07D 223/12**; C07D 223/10; C07D 403/06; A61K 31/55

(52) **U.S. Cl.** **514/212.03**; 514/212.08; 540/524; 540/527

(58) **Field of Search** 540/524, 527; 514/212.03, 212.08

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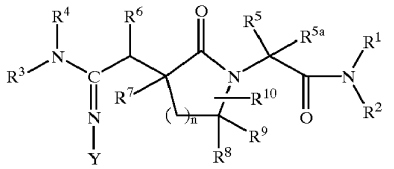
(57) **ABSTRACT**

Caprolactam inhibitors are provided which have the structure



including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrugs thereof, wherein n is 1 to 5; and

and Y R^1, R^2, R^3, R^5, R^{5a}, R^6, R^7, R^8, R^9 and R^{10} are as defined herein. These compounds are inhibitors of Factor Xa and thus are useful as anticoagulants. A method for treating cardiovascular diseases associated with thromboses is also provided.

18 Claims, No Drawings

LACTAM INHIBITORS OF FXA AND METHOD

This application claims priority from application Ser. Nos. 60/119,372 filed Feb. 9, 1999 and 60/167,428 filed No. 24, 1999.

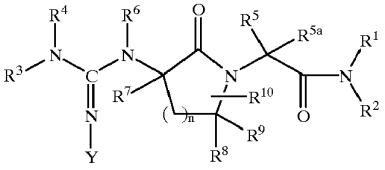
FIELD OF THE INVENTION

The present invention relates to lactam inhibitors of the enzyme Factor Xa which are useful as anticoagulants in the treatment of cardiovascular diseases associated with thromboses.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, novel lactam derivatives are provided which are inhibitors of the enzyme Factor Xa and have the structure I

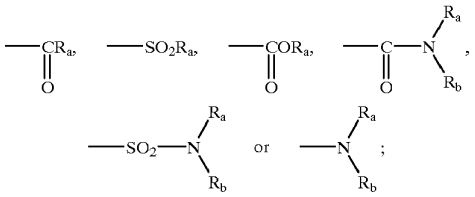
(I)



including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrugs thereof, wherein

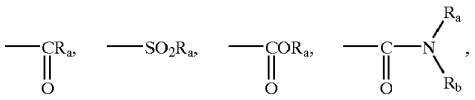
n is an integer from 1 to 5;

Y is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl, cycloheteroalkyl, cyano, nitro, hydroxy, amino, —ORa, —SRa,



R^1, R^2, R^4, R^6, R^8, and R^9 are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl cycloheteroalkyl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, substituted alkylcarbonyl, cycloheteroalkylcarbonyl and heteroarylcarbonyl;

R^3 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, cyano, nitro, hydroxy, —ORa, —SRa,



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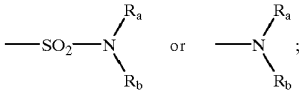
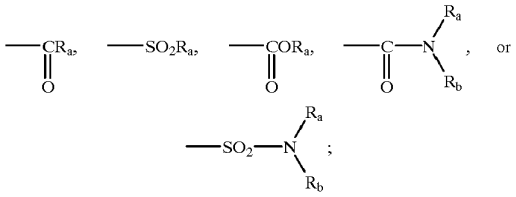
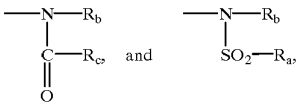


R^5, R^{5a}, and R^7 are the same or different and are independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, cycloalkyl, aryl, cycloheteroalkyl,



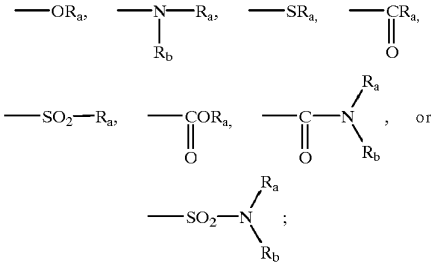
R^{10} is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloheteroalkyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl, heteroarylcarbonyl,



or when R^9 is hydrogen and R^8 and R^{10} are on adjacent carbons they join to complete a cycloalkyl or phenyl ring;

R_a and R_b are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, cycloheteroalkyl, cycloalkyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, substituted alkyl-carbonyl, cycloheteroalkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, alkylaminocarbonyl and dialkylaminocarbonyl;

R_c is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, cycloalkyl, cycloheteroaryl,



and wherein R^1 and R^2, and/or R^3 and R^4 and/or R_a and R_b can be taken together with the nitrogen to which they are attached, i.e.

to form a cycloheteroalkyl ring or a heteroaryl ring;

R^3 and Y can be taken together to form a heteroaryl ring;

R^3 or R^4 or Y can form a ring with R^6 which can be a cycloheteroalkyl or a heteroaryl ring;

R^5 and R^{5a} can be taken together to the carbon to which they are attached to form a cycloalkyl ring, a heteroaryl ring or a cycloheteroalkyl ring; and

where one or more of R^3 R^4 or R^6 are H, then double bond isomers are possible which are included in the present invention.

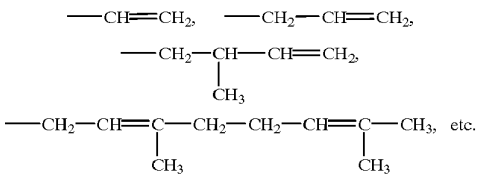
In addition, in accordance with the present invention, a method for preventing, inhibiting or treating cardiovascular diseases associated with thromboses is provided, wherein a compound of formula I is administered in a therapeutically effective amount which inhibits Factor Xa.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 20 carbons, preferably 1 to 12 carbons, more preferably 1 to 8 carbons in the normal chain. Examples include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the various additional branched chain isomers thereof. The term "lower alkyl" includes both straight and branched chain hydrocarbons containing 1 to 4 carbons.

The term "alkenyl" as employed herein alone or as part of another group includes both straight and branched hydrocarbons having one or more double bonds, preferably one or two, and being of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain. Examples include



The term "alkynyl" as employed herein alone or as part of another group includes both straight and branched hydrocarbons having one or more triple bonds, preferably one or two, and being of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain. Examples include

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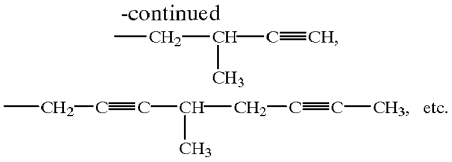
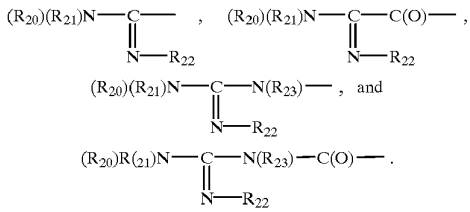
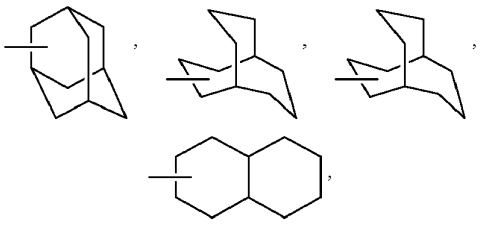


The terms "substituted alkyl", "substituted lower alkyl", "substituted alkenyl" and "substituted alkynyl" refer to such groups as defined above having one, two, or three substituents selected from halo, alkoxy, haloalkoxy, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylcycloalkyl, aryloxy, arylalkoxy, heteroaryloxo, hydroxy, —N_3, nitro, cyano, $(R_{20})(R_{21})N$—, carboxy, thio, alkylthio, arylthio, arylalkylthio, heteroarylthio, alkyl-C(O)—, alkoxycarbonyl, $(R_{20})(R_{21})N$—C(O)—, arylcarbonyloxy, alkyl-C(O)—NH—, alkyl-C(O)—N(alkyl)—, aryl-C(O)—NH—, aryl-C(O)—N(alkyl)—, aryl-C(O)—, arylalkoxycarbonyl, alkoxycarbonyl-NH—, alkoxycarbonyl-N(alkyl)—, cycloalkyl-C(O)—, cycloheteroalkyl-C(O)—, heteroaryl-C(O)—, cycloalkyl-C(O)—NH—, cycloalkyl-C(O)—N(alkyl), cycloheteroalkyl-C(O)—NH—, cycloheteroalkyl-C(O)—N(alkyl)—, heteroaryl-C(O)—NH—, heteroaryl-C(O)—N(alkyl)—, arylsulfinyl, alkylsulfinyl, cycloalkylsulfinyl, cycloheteroalkylsulfinyl, heteroarylsulfinyl, arylsulfonyl, alkylsulfonyl, cycloalkylsulfinyl, cycloheteroalkylsulfinyl, heteroarylsulfinyl, $(R_{20})(R_{21})$N-sulfinyl, (R_{20}) (R_{21})N-sulfonyl, alkyl-SO_2—NH—, alkyl-SO_2-N(alkyl)—, aryl-SO_2—NH—, aryl-SO_2—N(alkyl)—, cycloalkyl-SO_2—NH—, cycloalkyl-SO_2-N(alkyl)—, cycloheteroalkyl-SO_2—NH—, cycloheteroalkyl-SO_2—N(alkyl)—, heteroaryl-SO_2—NH—, heteroaryl-SO_2—N(alkyl)—, (R_{20}) (R_{21})N—C(O)—NH—, (R_{20}) (R_{21})N—C(O)—N(alkyl)—, hydroxy-NH—C(O)—, hydroxy-N(alkyl)—C(O)—,



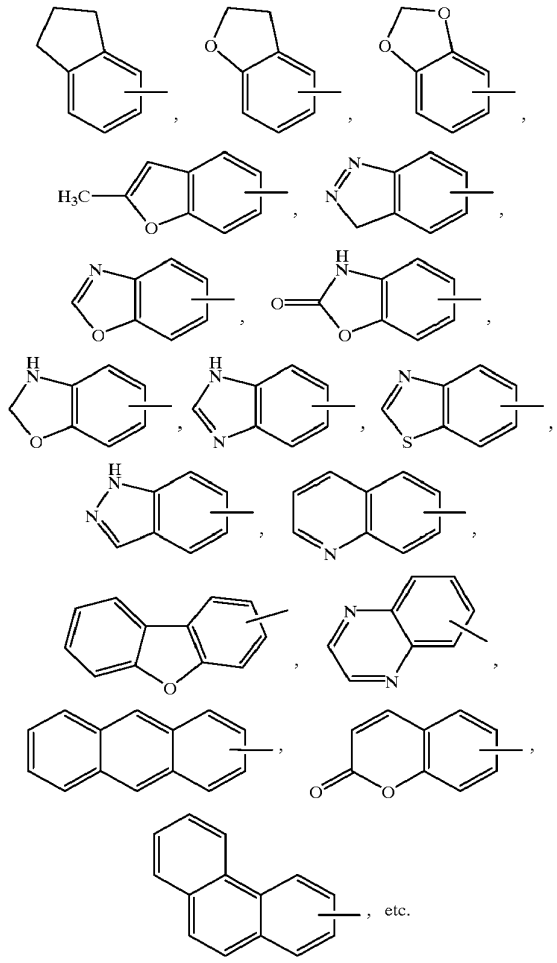
The term "halo" refers to chloro, bromo, fluoro and iodo.

The term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds and/or 1 or 2 triple bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons forming the rings. Also included within the definition of "cycloalkyl" are such rings fused to an aryl, cycloheteroalkyl, or heteroaryl ring and bridged multicyclic rings containing 5 to 20 carbons, preferably 6 to 12 carbons, and 1 or 2 bridges. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

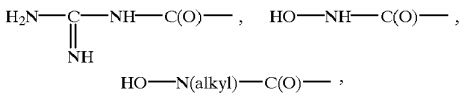


cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cycloheptadienyl, cyclopentynyl, cyclohexynyl, cycloheptynyl, cyclooctynyl, etc. Also included within the definition of "cycloalkyl" are such groups having one, two or three substituents selected from alkyl, substituted alkyl, halo, hydroxy, (R_{20}) (R_{21}) N—, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylthio, heteroaryl and cycloheteroalkyl.

The term "aryl" as employed herein alone or as part of another group refers to phenyl, 1-naphthyl, and 2-naphthyl as well as such rings fused to a cycloalkyl, aryl, cycloheteroalkyl, or heteroaryl ring. Examples include

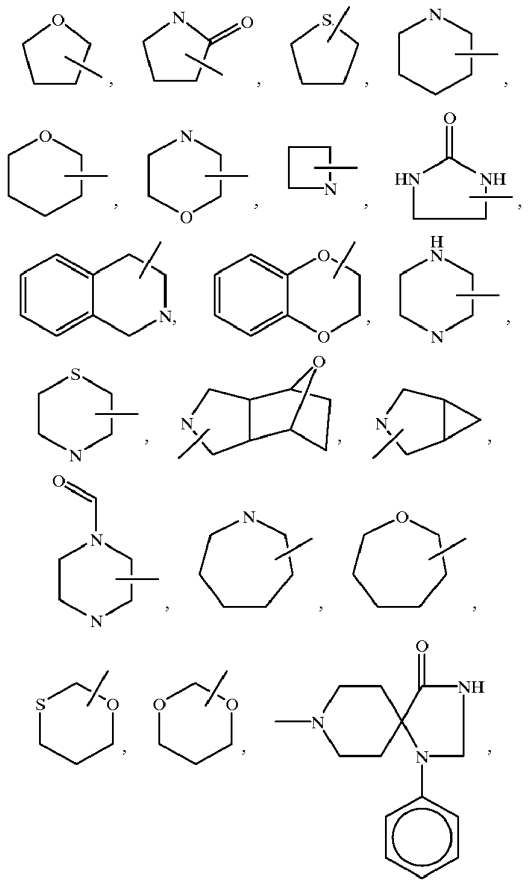


The term "aryl" also includes such ring systems wherein the phenyl, 1-naphthyl, or 2-naphthyl has one two, or three substitutents selected from halo, hydroxy, alkyl, alkenyl, alkoxy, haloalkoxy, carboxy, cyano, nitro, substituted alkyl, substituted alkenyl, alkylcarbonyl, (substituted alkyl)—C(O)—, aryloxy, arylalkoxy, arylthio, arylalkylthio, cycloheteroalkyl, heteroaryl, —N(R_{20}) (R_{21}), alkyl-SO_2—, (substituted alkyl)-SO_2—, aryl-SO_2—, cycloalkyl-SO_2—, cycloheteroalkyl-So_2—, heteroaryl-SO_2—, alkyl-SO_2—NH—, aryl-SO_2—NH—, cycloheteroalkyl-SO_2—NH—, heteroaryl-SO_2—NH—, alkyl-SO_2—N(alkyl)—, (substituted alkyl)-SO_2—N(alkyl)—, cycloalkyl-SO_2—N(alkyl)—, aryl-SO_2—N(alkyl)—, cycloheteroalkyl-SO_2—N(alkyl)—, heteroaryl-SO_2—N(alkyl)—, (R_{20}) (R_{21})N—C(O)—, (R_{20}) (R_{21})N—C(O)—NH—, aryl-C(O)—, cycloalkyl-C(O)—, cycloheteroalkyl-C(O)—, heteroaryl-C(O)—, (R_{20}) (R_{21})N—C(O)—N(alkyl)—,



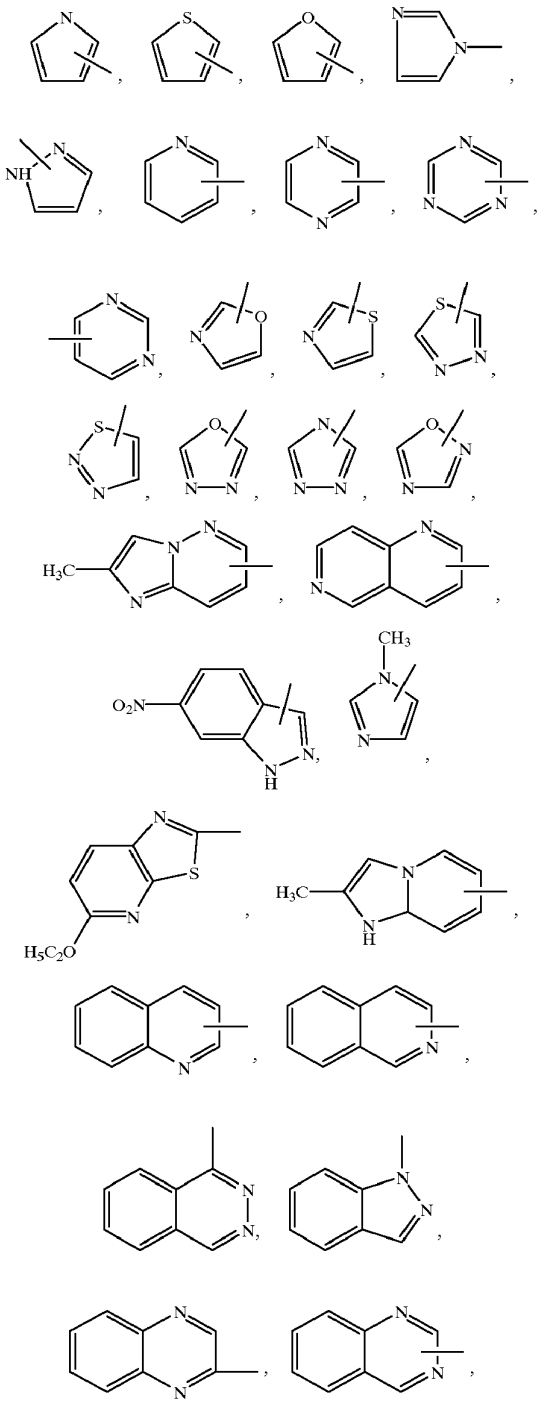
formyl, HC(O)—NH—, arylalkoxycarbonyl-NH—C(O)—, arylalkoxycarbonyl-N(alkyl)—C(O)—, (R_{20})(R_{21})N—C(O)-alkyl-NH—C(O)—, (R_{20})(R_{21})N—C(O)—alkyl-N(alkyl)—C(O)—, aryl-C(O)—NH—SO_2—, aryl-C(O)—N(alkyl)—SO_2—, cycloalkyl-C(O)—NH—SO_2—, cycloalkyl-C(O)—N(alkyl)—SO_2—, heteroaryl-C(O)—NH—SO_2—, cycloheteroalkyl-C(O)—NH—SO_2—, heteroaryl-C(O)—N(alkyl)—SO_2—, cycloheteroalkyl-C(O)—N(alkyl)—SO_2—, alkyl-C(O)—NH—SO_2—, alkyl-C(O)—N(alkyl)—SO_2—, substituted alkyl-C(O)—NH—SO_2—, substituted alkyl-C(O)—N(alkyl)—SO_2—, (R_{20})(R_{21})N—C(O)—alkyl-NH—C(O)-alkyl—NH—C(O)—, (R_{20}) (R_{21})N—C(O)-alkyl-N(alkyl)—C(O)-alkyl—NH—C(O)—, and (R_{20})(R_{21})N—C(O)-alkyl-NH—C(O)-alkyl-N(alkyl)—C(O)—, as well as pentafluorophenyl. Phenyl and substituted phenyl are the preferred aryl groups.

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to 3-, 4-, 5-, 6- or 7- membered saturated or partially unsaturated rings which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or an available nitrogen atom. Also included within the definition of cycloheteroalkyl are such rings fused to a cycloalkyl or aryl ring and spiro cycloheteroalkyl rings. One, two, or three available carbon or nitrogen atoms in the cycloheteroalkyl ring can be substituted with an alkyl, substituted alkyl, (R_{20}) (R_{21})N—, aryl, cycloalkyl, keto, alkoxycarbonyl, arylalkoxycarbonyl, alkoxycarbonyl-NH—, alkoxycarbonyl-N(alkyl)—, arylalkoxycarbonyl-NH—arylalkoxycarbonyl-N(alkyl)—, alkylcarbonyl—NH—, alkylcarbonyl-N(alkyl)—, arylcarbonyl, alkylsulfonyl, arylsulfonyl, substituted alkylsulfonyl, HO—N═, alkoxy-N═, (O)CH—, or (R_{20}) (R_{21})N—C(O)—. Also, an available nitrogen or sulfur atom in the cycloheteroalkyl ring can be oxidized. Examples of cycloheteroalkyl rings include



etc. Depending on the point of attachment, a hydrogen may be missing from the nitrogen atom in the above rings.

The term "heteroaryl" as used herein alone or as part of another group refers to a 5- 6- or 7-membered aromatic rings containing from 1 to 4 nitrotgen atoms and/or 1 or 2 oxygen or sulfur atoms provided that the ring contains at least 1 carbon atom and no more than 4 heteroatoms. The heteroaryl ring is linked through an available carbon or nitrogen atom. Also included within the definition of heteroaryl are such rings fused to a cycloalkyl, aryl, cycloheteroalkyl, or another heteroaryl ring. One, two, or three available carbon or nitrogen atoms in the heteroaryl ring can be substituted with an alkyl, substituted alkyl, alkoxy, alkylthio, keto, halo, hydroxy, cycloalkyl, aryl, cycloheteroalkyl, heteroaryl, $(R_{20})(R_{21})N$—, nitro, carboxy, cyano, alkoxycarbonyl, aryloxycarbonyl, alkylcarbonyl, substituted alkyl-C(O)—, arylcarbonyl, cycloalkylcarbonyl, $(R_{20})(R_{21})N$—C(O)—, guanidinylcarbonyl, $(R_{20})(R_{21})N$—C(O)-alkyl-NH—C(O)—, $(R_{20})(R_{21})N$—C(O)-alkyl-N(alkyl)—C(O)—, alkyl-C(O)—NH—, alkyl-C(O)—N(alkyl)—, substituted alkyl-C(O)—NH—, substituted alkyl-C(O)—N(alkyl)—, cycloalkyl-C(O)—NH—, cycloalkyl-C(O)—N(alkyl)—, aryl-C(O)—NH—, aryl-C(O)—N(alkyl)—, heteroaryl-C(O)—NH—, heteroaryl-C(O)—N(alkyl)—, cycloheteroalkyl-C(O)—NH—, cycloheteroalkyl-C(O)—N(alkyl)—, alkyl-SO_2—, substituted alkyl-S_{20}—, aryl-SO_2—, cycloalkyl-SO_2—, cycloheteroalkyl-SO_2—, or heteroaryl-S_2. Also an available nitrogen or sulfur atom in the heteroaryl ring can be oxidized. Examples of heteroaryl rings include



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