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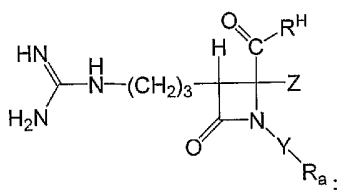
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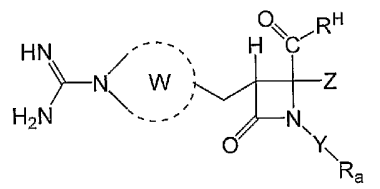
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(54) Title: SUBSTITUTED AZETIDINONES



(I)



(II)

(57) Abstract: Compounds are provided which have the structure of formula (1), wherein A, B, C, D, m, Y, Ra, Rc, Rd, and Rd' are as described herein, and which are useful as inhibitors of tryptase, thrombin, trypsin, Factor Xa, Factor Vila, Factor XIa, and urokinase-type plasminogen activator and may be employed in preventing and/or treating asthma, chronic asthma, allergic rhinitis, and thrombotic disorders.

WO 2006/108039 A2

PATENT APPLICATION

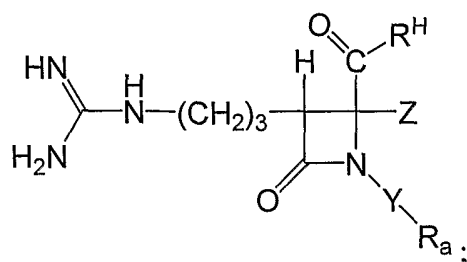
SUBSTITUTED AZETIDINONES

CROSS-REFERENCES TO RELATED APPLICATIONS

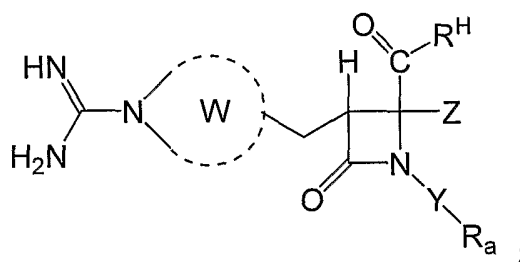
[0001] The present application claims priority to U.S. Provisional Patent Application No. 5 60/668,325, filed April 4, 2005 which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Bisacchi in U.S. Pat. No. 6,335,324 explicitly discloses 3 guanidinoalkyl-2-azetidinones which have one of the following two structures:

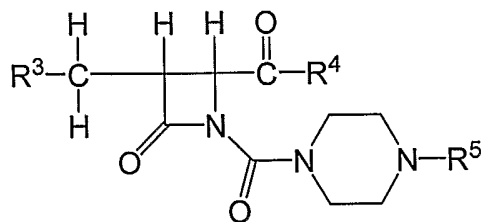


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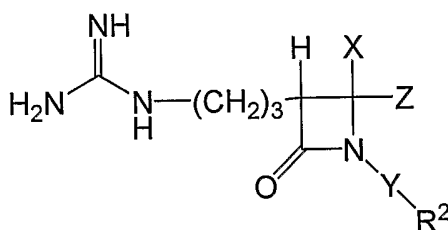
wherein W is an unsubstituted 4-8 membered cycloalkyl ring; Y is either C=O or SO₂; Z is either hydrogen or unsubstituted alkyl; R^H can be any substituent; and R² can be any substituent.

15 [0003] Bisacchi in U.S. Pat. Pub. No. 2004/0147502 A1 explicitly discloses 1-[piperazinecarbonyl]azetidinones of the formula:



wherein R^3 is any substituent, R^4 is OH, NH_2 , alkyl or heteroalkyl, and R^5 is any substituent.

[0004] Schumacher in U.S. Pat. Pub. No. 2004/0180855 A1 explicitly discloses methods of treating thrombosis in a mammal comprising administering a compound of the formula below
5 that is selective for inhibition of Factor XIa.



wherein X is COOH, COOR, CONR, unsubstituted alkyl and unsubstituted arylalkyl, Y is CO or SO₂, Z is H or unsubstituted alkyl, R² is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycloalkyl.

10 [0005] Thrombo-embolic disorders are the largest cause of mortality (myocardial infarction) and disability (stroke) in the industrialized world. Arterial thrombosis is initiated by atherosclerotic plaque rupture, exposure of tissue factor, and initiation of the coagulation vortex. A number of coagulation factors are present in the blood as precursors (e.g., Factors VII-XII), and when the coagulation system is triggered, these factors undergo a complicated,
15 ordered series of reactions that ultimately lead to thrombin production. Thrombin is a proteolytic enzyme that occupies a central position in the coagulation process. Thrombin catalyzes the conversion of fibrinogen to fibrin, is a key effector enzyme for blood clotting, and is also pivotal for other functions. High concentrations of thrombin inhibit fibrinolysis by activating the Thrombin Activated Fibrinolysis Inhibitor (TAFI), which can also be activated
20 by modest amounts of thrombin in the presence of soluble or membrane bound thrombomodulin. TAFIa removes the C-terminal lysine residues from fibrin, preventing the binding of t-PA and plasmin and thus, slowing fibrinolysis.

[0006] The complicated coagulation process is initiated by tissue factor (TF). Tissue factor binds and activates Factor VII (FVII), which is rapidly converted to activated Factor VIIa

(FVIIa) to form a TF:FVIIa complex. The TF:FVIIa complex activates Factors IX and X. Factor Xa generates small amounts of thrombin. The small amounts of thrombin activate Factor V, Factor VIII and platelets, accelerating thrombin production by Factors IXa and Xa. Activation of Factor V and FVIII accelerates catalytic activity of FVIIIa:FIXa and FVa:FXa, resulting in dramatically increased thrombin production. Another wave of thrombin generation occurs as a result of thrombin activation of Factor XIa. Factor XI activates more Factor IX. As the concentration of thrombin increases, more thrombin is generated, which in turn activates TAFI to then inhibit fibrinolysis.

[0007] This coagulation process involves an intrinsic pathway and an extrinsic pathway. In the intrinsic pathway, Factor XII (aka Hageman Factor) is converted from its inactive form (zymogen) to an active form, i.e., Factor XIIa. Activated Factor XII enzymatically activates Factor XI to Factor XIa. Activated Factor XI activates Factor IXa. Factor IXa then converts Factor X to Factor Xa. FXa activates prothombin to thrombin. Thrombin cleaves fibrinogen to form insoluble fibrin (the clot). In the extrinsic pathway, addition of thromboplastin (i.e., tissue factor) to plasma activates Factor VII. This complex, in the presence of calcium ions and phospholipids, activates Factor X to Factor Xa. Once Factor Xa is generated, the remainder of the cascade is similar to the intrinsic pathway. As can be seen, Factor XIa is involved only in the intrinsic pathway.

[0008] In vitro, the degree to which FXIa contributes to thrombin generation, platelet activation, and fibrin formation depends on the concentration of tissue factor. For example, in the absence of FXI (i.e., in FXIa deficient plasma), plasma stimulated with low levels of tissue factor (clot formation >10 minutes) showed a delay in the time required to generate thrombin and form clots. A FXI deficiency also decreased the amount of thrombin generated and platelet aggregation in whole blood. However, in blood or plasma stimulated by higher concentration of tissue factor (clot formation <5 minutes), a FXI deficiency had no effect on the thrombin generation or clot formation. Thus, a FXI deficiency will generally prolong thrombin generation but not in situations where the plasma is stimulated with high concentrations of tissue factor.

[0009] FXIa, via expanded thrombin generation, also plays a role in resisting fibrinolysis. Resistance of plasma clots to tPA and uPA-induced fibrinolysis depends on thrombin concentration (generated endogenously or added exogenously) in the plasma. The time required for clot lysis is proportional to the plasma TAFIa concentrations. However, clot lysis

can occur more rapidly, and the lysis made independent of plasma TAFI concentration, when blocking antibodies to FXIa are included in the assay.

[0010] Elevated levels of FXIa in the plasma and/or increased activation of FXIa is associated with various cardiovascular and other diseases. As an illustration, increased activation of FXIa occurs in patients with coronary artery disease and is related to the severity of the disease. Also, Factor IX activation peptide (a product of FXIa and TF:FVIIa cleavage of FIX) levels have been found to be significantly higher in patients with acute myocardial infarction and unstable angina compared with patients with stable angina. Concentrations of FXIa- α_1 AT (FXIa complexed to the serpin α_1 -antitrypsin) were also elevated in patients with recent myocardial infarction or unstable angina. Patients with high levels of Factor XI are at risk for deep venous thrombosis.

[0011] Proteins or peptides that reportedly inhibit Factor XIa are disclosed in WO 01/27079 to Entremed, Inc. There are advantages in using small organic compounds, however, in preparing pharmaceuticals, e.g., small compounds generally have better oral bioavailability and compatibility in making formulations to aid in delivery of the drug as compared with large proteins or peptides. Small organic compounds have been disclosed that reportedly inhibit coagulation factors besides Factor XIa. For example, compounds effective in inhibiting Factor Xa are described in U.S. Pat. Nos. 6,344,450 and 6,297,233, and WO 00/47563. Compounds effective in inhibiting Factors VIIa, Xa, as well as tryptase and urokinase are described in U.S. Pat. No. 6,335,324. Factor Xa inhibitors are disclosed in WO 98/57937 to the duPont Merck Pharmaceutical Co., and Factor VIIa inhibitors are disclosed in U.S. Pat. No. 6,358,960 to Ono Pharmaceuticals Inc., ("Ono"), and in WO 01/44172 to Axys Pharm. Inc.

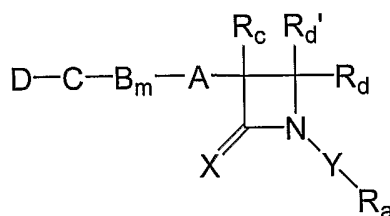
[0012] A possible adverse side effect associated with use of anti-thrombotic agents for treating cardiovascular diseases involves the risk of bleeding. For example, heparin is a known anti-thrombotic agent that has a highly-variable dose-related response, and its anticoagulant effects must be closely monitored to avoid a risk of serious bleeding. The erratic anticoagulant response of heparin is likely due to its propensity to bind non-specifically to plasma proteins. Aspirin also has been used as an anti-thrombotic agent but at high doses presents a risk of gastrointestinal bleeding. Thrombin inhibitors and their drawbacks are further discussed in WO 96/20689 to duPont Merck Pharmaceutical Co. Guanidine and beta lactam-containing compounds that are potent inhibitors of serine

proteases including thrombin and trypsin are described in U.S. Pat. No. 6,335,324, the entire contents of which is incorporated herein by reference.

SUMMARY OF THE INVENTION

[0013] This invention is directed to the novel β -lactam compounds of formula I shown
 5 below and to a method for the use of such compounds as inhibitors of various in vivo enzyme systems including trypsin, thrombin, trypsin, Factor Xa, Factor VIIa, Factor XIa, and urokinase-type plasminogen activator and their use in treating and/or preventing asthma and/or allergic rhinitis and/or thrombotic disorders.

[0014] In a first aspect, the invention provides a compound according to the following
 10 structure:



In this structure, A is a member selected from CR^1R^2 , NR^{1a} , O, S and SO_n . The symbol n is an integer selected from 0 to 2. Each R^{1a} is a member independently selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted
 15 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^5$, NR^3R^4 , OR^3 and SO_2R^5 . R^3 and R^4 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 20 unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^6$, and SO_2R^6 . R^6 is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^5 is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted
 25 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^3 and R^4 can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^1 is a member selected from H, substituted or unsubstituted alkyl,

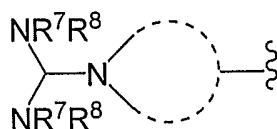
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, NR^7R^8 , SO_nR^9 , halogen, $\text{C}(\text{O})\text{R}^7$, CO_2R^7 , $\text{C}(\text{O})\text{NR}^7\text{R}^8$, and OR^7 . Each R^7 and each R^8 is a member independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $\text{C}(\text{O})\text{R}^{10}$, $\text{C}(\text{O})\text{OR}^{10}$, $\text{NR}^{10}\text{R}^{10a}$, OR^{10} , SO_2R^{10} and $\text{S}(\text{O})\text{R}^{10}$ wherein R^{10} and R^{10a} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^9 is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^7 and R^8 can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^2 is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and halogen. R^1 and R^2 can together represent an acyl group. R^1 and R^2 can be optionally joined together in a 3-8 membered ring. B is a member independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, carboxamido, NR^{11} , -S-, and -O-. R^{11} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $\text{C}(\text{O})\text{R}^{10}$, $\text{C}(\text{O})\text{OR}^{10}$, $\text{NR}^{10}\text{R}^{10a}$, OR^{10} , SO_2R^{10} and $\text{S}(\text{O})\text{R}^{10}$. The symbol m is an integer selected from 0 to 3. C is a member selected from a bond, C=O, SO_2 , N=C, -O- and -O- CR^5R^{10} -. R^5 and R^{10} can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. D is a member selected from substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted amidine, substituted or unsubstituted amidinohydrazone, substituted or unsubstituted guanidine, and substituted or unsubstituted amine. A and B can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. A and C can be

optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. A and D can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. B and C can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. B and D can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. C and D can be optionally joined, together with the atoms to which they are attached, to form a 3-8 membered ring. If m is greater than 2, each independently selected B can be optionally joined to form a 3-8 membered ring. X is a member selected from S, O, and NR⁷. Y is a member selected from a bond, C=Q, CR¹²R¹³, and SO_n. Q is a member selected from S, O, and NR⁷. R¹² is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, halogen. R¹³ is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl halogen. R¹² and R¹³ can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R_a is a member selected from NR⁷R⁸, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R⁷ and R⁸ can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R_c is a member selected from H, substituted or unsubstituted alkyl and halogen. R_d is a member selected from R¹⁶, (CR¹⁴R¹⁵)_pR¹⁶, C(R¹⁴)=CR¹⁶R²³ and CCR¹⁶. The symbol p is an integer selected from 0 to 3. R¹⁴ and R²³ are members independently selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R¹⁵ is a member selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R¹⁶ is a member selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C(O)R¹⁸, OR¹⁹, -OC(=Q)NR¹⁹R²¹, -NR¹⁹C(=Q)NR¹⁹R²¹, -NR²⁰SO₂R¹⁹, OSO₂R¹⁹, SO₂R²¹,

$S(O)R^{21}$, $SO_2NR^{19}R^{20}$, $NR^{19}R^{20}$ and CN. R^{18} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{21} , SR^{21} , $NR^{19}R^{20}$, and $-NR^{19}SO_2R^{20}$. R^{19} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{20} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^{22}$, SO_2R^{22} . R^{22} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{21} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{22}$ and $-SR^{22}$. R^{14} and R^{15} can be joined together in a 4-8 membered ring. R^{19} and R^{21} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^{14} and R^{23} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^{19} and R^{20} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R_d' is a member selected from H, substituted or unsubstituted alkyl and halogen. R_c and R_d can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R_c and R_d' can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring.

[0015] In an exemplary embodiment, the compound is subject to one or more of the following provisos. In an exemplary embodiment, the structure has the proviso that if

- a) Y is a member selected from C=O and SO_2 ;
 - ABC, in combination, form unsubstituted alkyl; and
 - D is substituted or unsubstituted guanidine; or
- b) Y is a member selected from C=O and SO_2 ;
 - AB, in combination, form unsubstituted alkyl; and
 - CD, in combination, form



wherein the dotted line represents carbon atoms necessary for the formation of one ring having 4 to 8 atoms;

then R_c cannot be a member selected from CH_3 , CH_2CH_3 , substituted alkyl, and unsubstituted alkyl; and R_d and R_d' cannot be members selected from CH_3 and CH_3 ; CH_2CH_3 and CH_2CH_3 ; CH_2CH_3 and CH_3 ; CH_3 and CH_2CH_3 ; substituted or unsubstituted alkyl and substituted or unsubstituted alkyl; H and substituted or unsubstituted alkyl; substituted or unsubstituted alkyl and H; H and COOH ; H and COOR^{1a} ; H and CONR^7R^8 ; unsubstituted alkyl and COOH ; unsubstituted alkyl and COOR^{1a} ; H and unsubstituted phenylalkyl; unsubstituted alkyl and unsubstituted phenylalkyl.

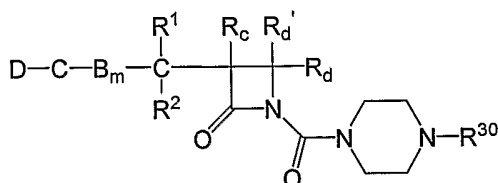
[0016] In another exemplary embodiment, part (a) of this proviso is

- a) Y is a member selected from $\text{C}=\text{O}$ and SO_2 ;
 ABC, in combination, form substituted alkyl; and
 D is substituted or unsubstituted guanidine.

[0017] In another exemplary embodiment, R_c of this proviso cannot be substituted alkyl. In another exemplary embodiment, R_c of this proviso cannot be unsubstituted alkyl.

[0018] In another exemplary embodiment, R_d and R_d' of this proviso cannot be members selected from CH_3 and CH_3 ; CH_2CH_3 and CH_2CH_3 ; CH_2CH_3 and CH_3 ; CH_3 and CH_2CH_3 ; H and COOH ; H and COOR^{1a} ; H and CONR^7R^8 ; unsubstituted alkyl and COOH ; unsubstituted alkyl and COOR^{1a} ; H and unsubstituted phenylalkyl; unsubstituted alkyl and unsubstituted phenylalkyl.

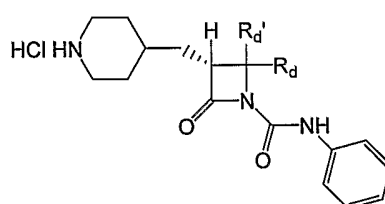
[0019] In another exemplary embodiment, the structure has the following proviso: if the compound has the following structure:



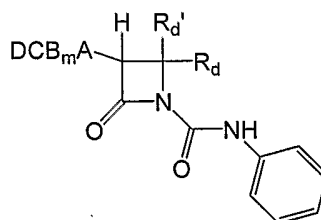
wherein R^{30} is a member selected from H, $\text{SO}_2\text{-R}^{31}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

- substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
 wherein R³¹ is unsubstituted alkyl, then at least one of R_d and R_d' does not
 comprise a carbonyl group which is directly attached, or alpha, to the
 azetidinone ring. In another exemplary embodiment, at least one of R_d and
 5 R_d' does not comprise a carbonyl group. In another exemplary embodiment,
 R³⁰ does not comprise a carbon atom.

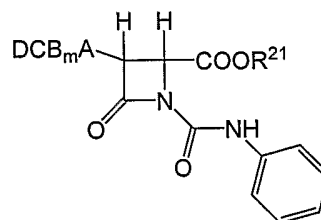
[0020] In another exemplary embodiment, the structure has the following proviso: the
 compound cannot have the following structure:



- 10 wherein at least one of R_d and R_d' comprise a carbonyl group which is directly attached, or
 alpha, to the azetidinone ring. In another exemplary embodiment, the compound cannot have
 the following structure:

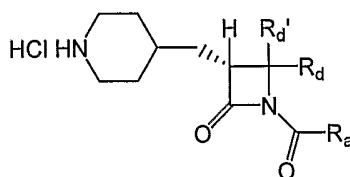


- 15 wherein DCB_mA comprises a piperidine ring or a salt thereof. In another exemplary
 embodiment, the compound cannot have the following structure:

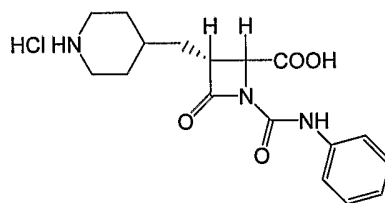


wherein DCB_mA comprises a piperidine ring or a salt thereof.

[0021] In another exemplary embodiment, the structure has the following proviso: the
 compound cannot have the following structure:



wherein R_a is NHR^8 , and R^8 includes a substituted or unsubstituted phenyl. In another exemplary embodiment, R^8 is unsubstituted phenyl. In yet another exemplary embodiment, R_a is $N(H)$ (unsubstituted phenyl). In another exemplary embodiment, the structure has the following proviso: the compound cannot have the following structure:

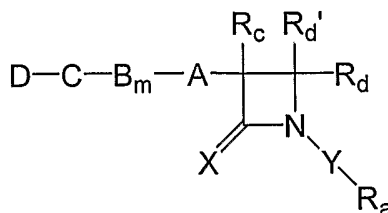


[0022] In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. No. 6,335,324. In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. Pub. No. 2004/0147502. In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. Pub. No. 2004/0180855.

[0023] In an exemplary embodiment, D is amidinohydrazone. In another exemplary embodiment, D is aminopyridine. In an exemplary embodiment, D is 2-aminopyridine. In an exemplary embodiment, D is 2-aminoaryl. In an exemplary embodiment, D is 2-aminophenyl. In an exemplary embodiment, A is S.

[0024] In an exemplary embodiment, at least one of said $R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{10a}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}$ and R^{23} is a member selected from substituted or unsubstituted arylalkyl and substituted or unsubstituted heteroarylalkyl. In another exemplary embodiment, D is a member selected from substituted or unsubstituted guanidine, substituted or unsubstituted amidinohydrazone, substituted or unsubstituted pyridine, substituted or unsubstituted aminopyridine.

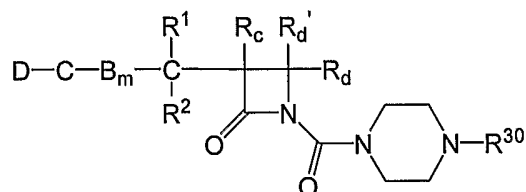
[0025] In a second aspect, the invention provides a compound according to the following structure:



In this structure, AB_mC , in combination, is a member selected from substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl. D is a member selected from substituted or unsubstituted guanidine, substituted or unsubstituted amidinohydrazone, substituted or unsubstituted pyridine, substituted or unsubstituted aminopyridine. R_c is a member selected from H and substituted or unsubstituted alkyl. R_d' is a member selected from H and substituted or unsubstituted alkyl. R_d is a member selected from R^{16} , $(CR^{14}R^{15})_pR^{16}$, $C(R^{14})=CR^{16}R^{23}$ and CCR^{16} . The symbol p is an integer selected from 0 to 3. R^{14} and R^{23} are members independently selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{15} is a member selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{16} is a member selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^{18}$, OR^{19} , $-OC(=Q)NR^{19}R^{21}$, $-NR^{19}C(=Q)NR^{19}R^{21}$, $-NR^{20}SO_2R^{19}$, OSO_2R^{19} , SO_2R^{21} , SOR^{21} , $SO_2NR^{19}R^{20}$, $NR^{19}R^{20}$, CN . R^{18} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{21} , $NR^{19}R^{20}$, and $-NR^{19}SO_2R^{20}$. R^{19} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{20} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,

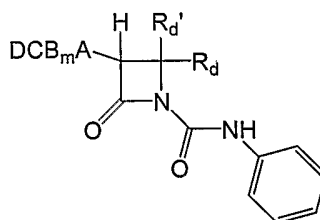
substituted or unsubstituted heteroaryl, $C(O)R^{22}$, SO_2R^{22} . R^{22} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{21} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{22}$. R^{14} and R^{15} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^{19} and R^{21} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^{14} and R^{23} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R^{19} and R^{20} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. X is a member selected from S, O, and NR^{35} . R^{35} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^{36}$, SO_2R^{36} . R^{36} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. Y is a member selected from a bond, $C=Q$, $CR^{12}R^{13}$, and SO_n . The symbol n is a member selected from 0 to 2. Q is a member selected from S, O, and NR^7 . R^{12} is a member selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{13} is a member selected from H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{12} and R^{13} can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring. R_a is a member selected from NR^7R^8 , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^7 and R^8 can be optionally joined, together with the atoms to which they are attached, to form a 4-8 membered ring.

[0026] In an exemplary embodiment, the compounds of the second aspect are subject to one or more of the following provisos. In an exemplary embodiment, the structure has the proviso that when D is unsubstituted guanidine, AB_mC cannot be unsubstituted alkyl. In an exemplary embodiment, the structure has the proviso that if the compound has the following structure:



in which R³⁰ is a member selected from H, SO₂-R³¹, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R³¹ is unsubstituted alkyl, then at least one of R_d and R_d' does not comprise a carbonyl group which is directly attached, or alpha, to the azetidinone ring.

[0027] In an exemplary embodiment, the second aspect has the proviso that the compound cannot have the following structure:



wherein DCB_mA comprises a piperidine ring or a salt thereof.

[0028] In an exemplary embodiment of one of the aspects of the invention, at least one of said R^{1a}, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R³⁵, R³⁶ and R_a is a member selected from substituted or unsubstituted arylalkyl and substituted or unsubstituted heteroarylalkyl.

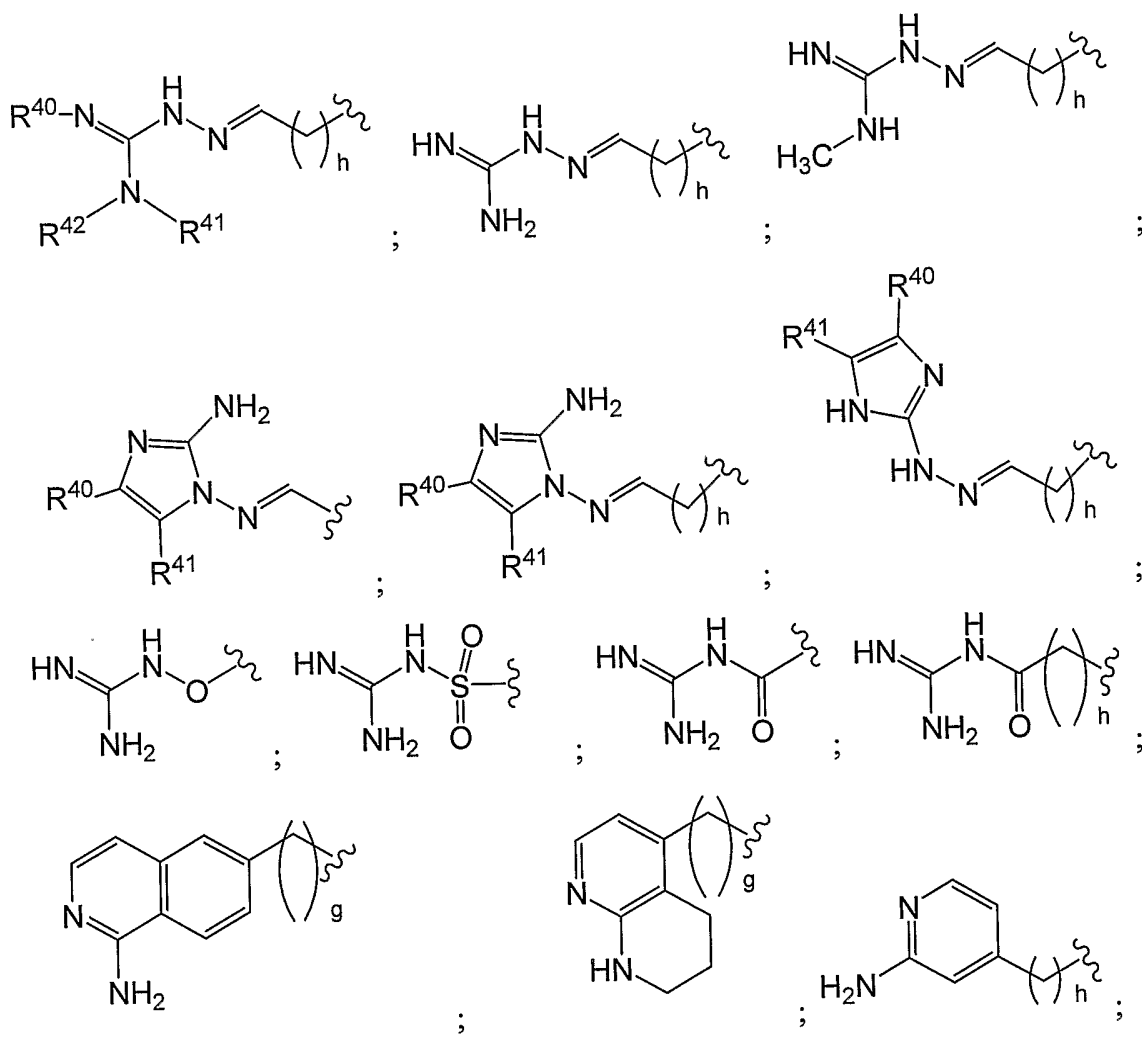
[0029] In an exemplary embodiment of one of the aspects of the invention, D is a member selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted amidine, substituted or unsubstituted amidinohydrazone, substituted or unsubstituted guanidine and substituted or unsubstituted amine.

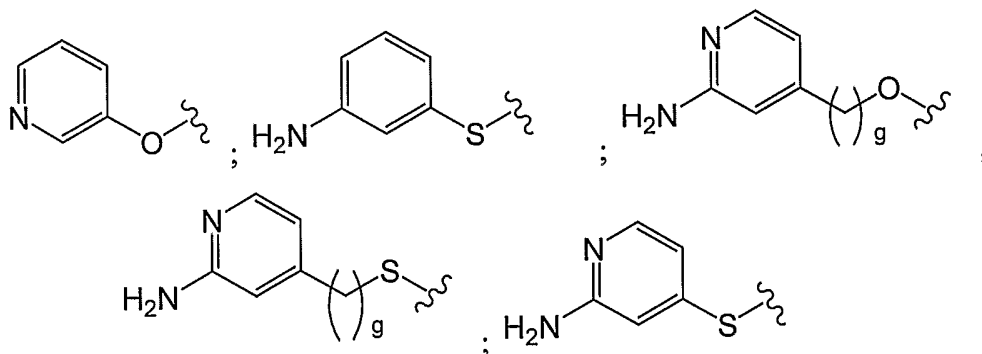
[0030] In an exemplary embodiment of one of the aspects of the invention, D is substituted or unsubstituted guanidine, and AB_mC, in combination, form a member selected from D-N=CR-Z⁵, D-O-Z⁵, D-SO₂Z⁵, -O-D, D-SO₂Z⁵, substituted or unsubstituted alkylene,

substituted or unsubstituted acylene, and substituted or unsubstituted heteroalkylene, and Z⁵ is a member selected from substituted or unsubstituted alkylene and substituted or unsubstituted acylene.

[0031] In an exemplary embodiment of one of the aspects of the invention, D is a member selected from substituted aryl and substituted or unsubstituted heteroaryl, and AB_mC, in combination, form a member selected from D-N=CR^{1a}-Z⁵, D-O-Z⁵, D-SO₂N, D-N=CR-, -O-D, -SO₂-D, substituted and substituted alkylene, substituted or unsubstituted acylene, and substituted or unsubstituted heteroalkylene, and Z⁵ is a member selected from substituted or unsubstituted alkylene and substituted and unsubstituted acylene.

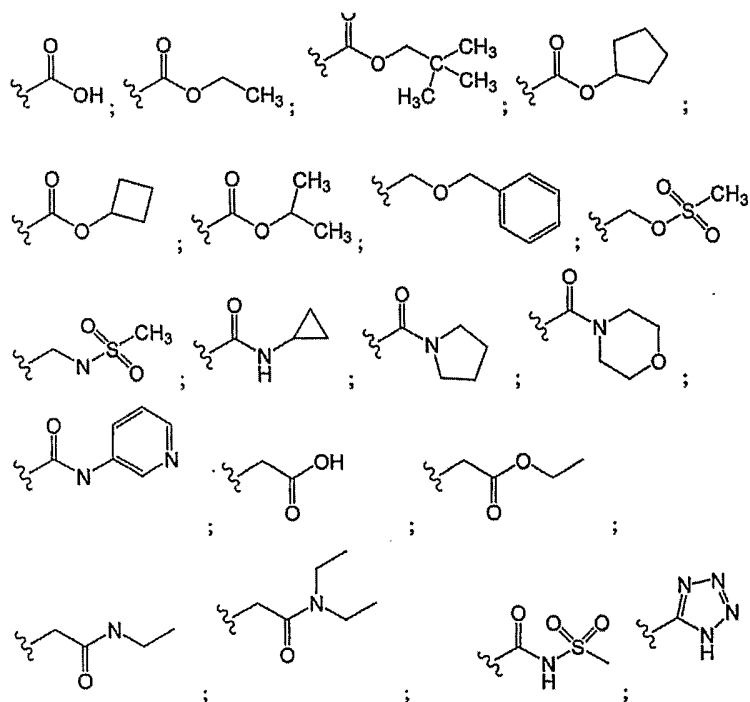
10 [0032] In an exemplary embodiment of one of the aspects of the invention, AB_mCD, in combination, form a member selected from





wherein the symbol g is an integer selected from 1 to 4. Each symbol h is an integer independently selected from 0 to 4. R⁴⁰, R⁴¹ and R⁴² are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

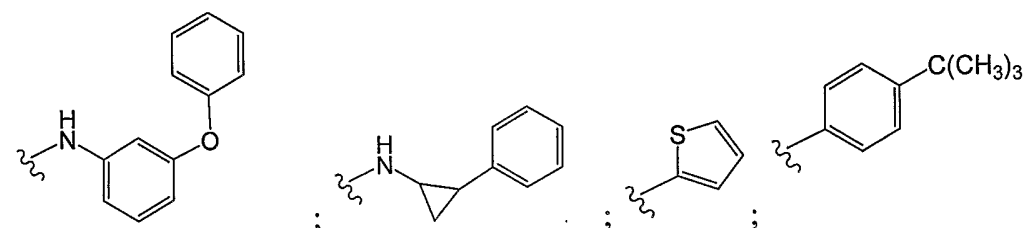
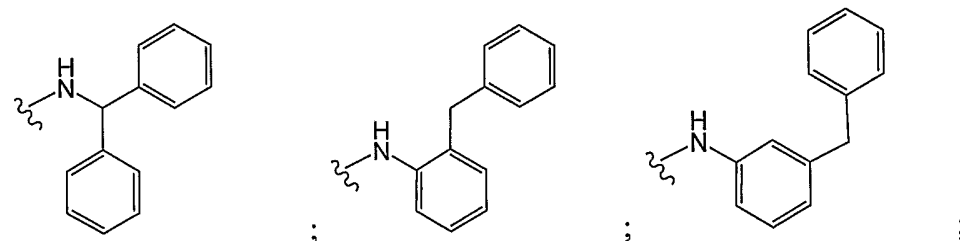
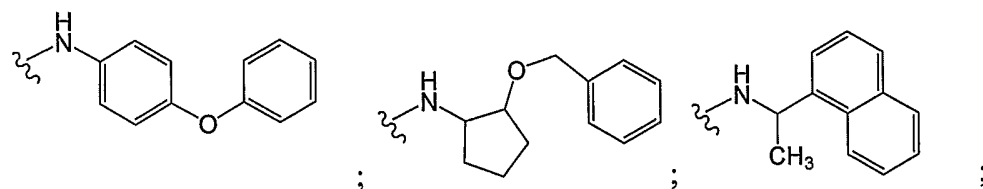
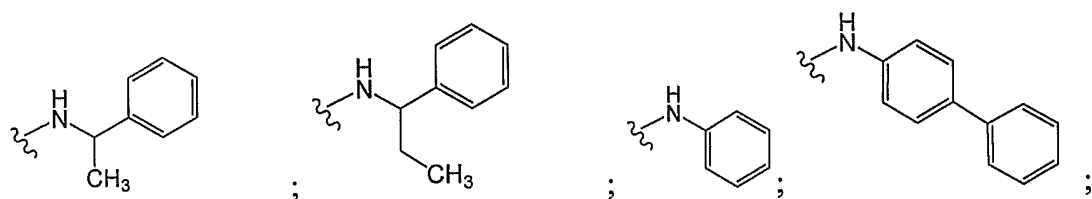
[0033] In an exemplary embodiment of one of the aspects of the invention, R_d is a member selected from



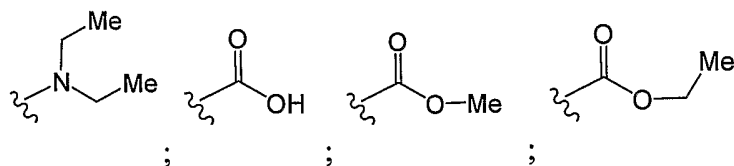
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and CF₃.

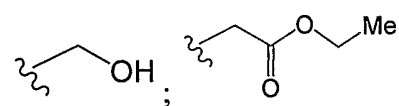
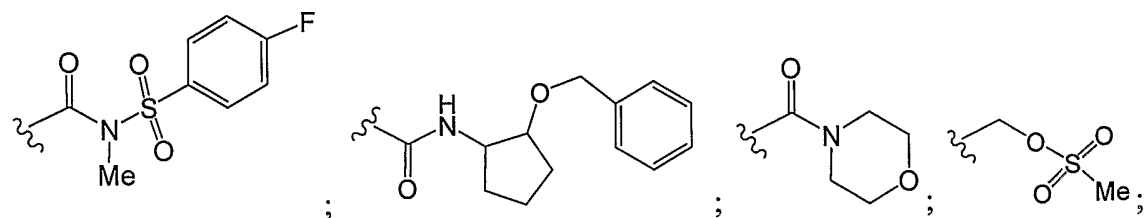
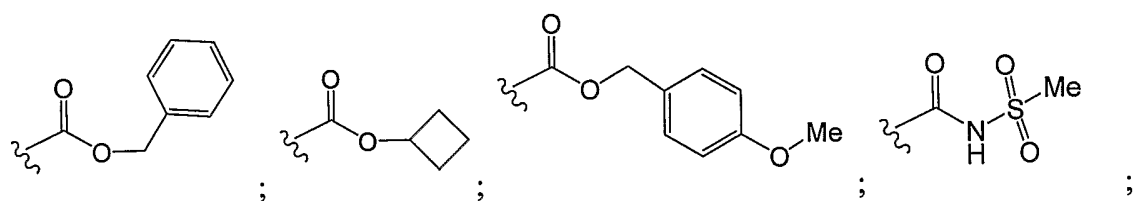
[0034] In an exemplary embodiment of one of the aspects of the invention, -Y-R_a, in combination, form a member selected from



. R₄ is

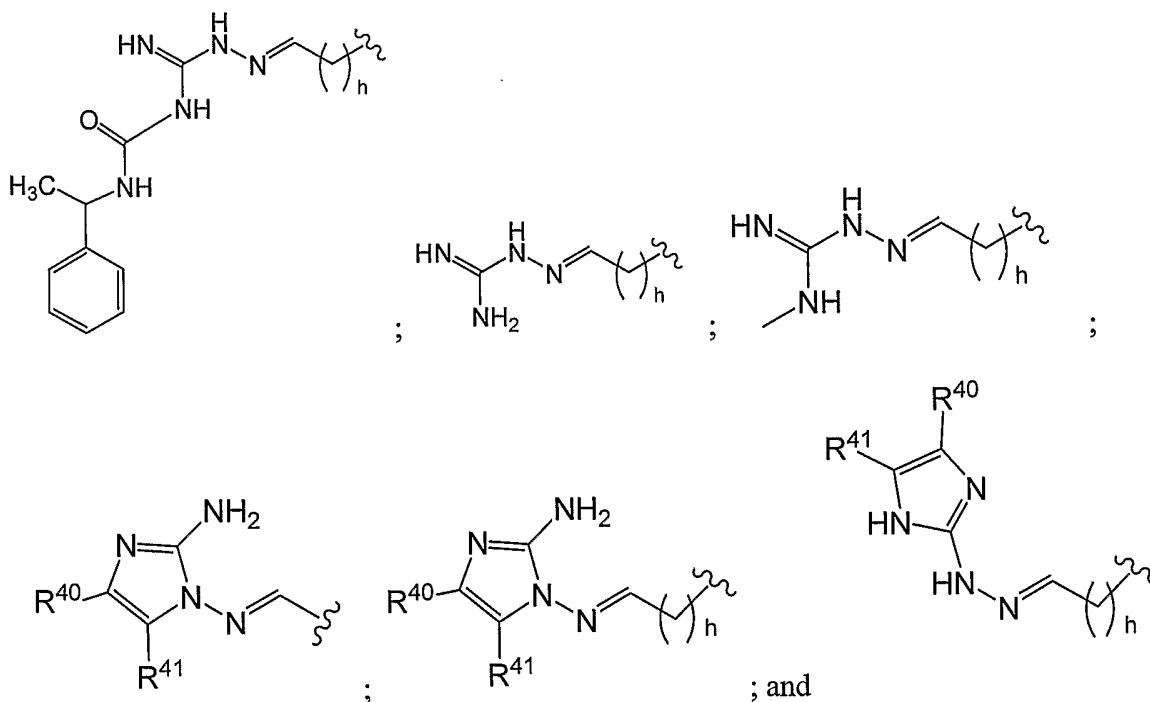


5 a member selected from



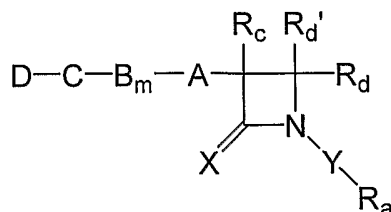
; and Y is a member selected from C(O) and S(O).

[0038] In another exemplary embodiment of one of the aspects of the invention, AB_mCD, in combination, form a member selected from



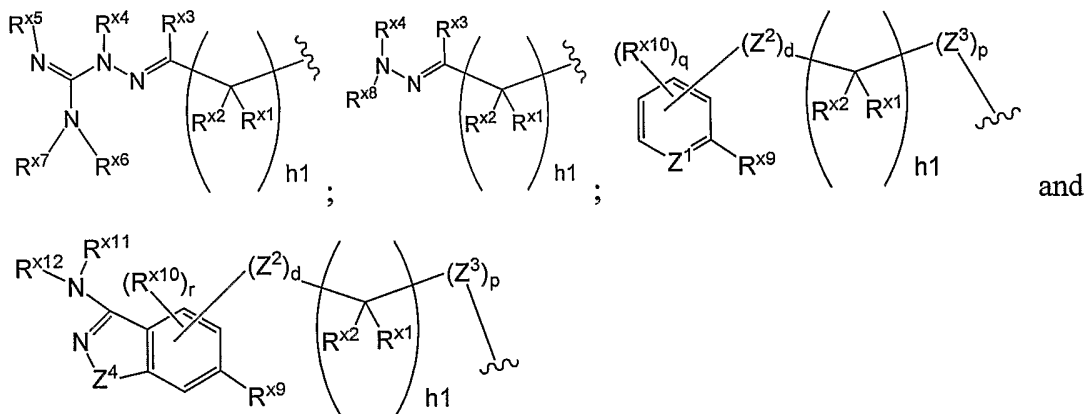
5 wherein h is an integer selected from 0 to 4.

[0039] In another aspect, the invention provides a compound according to the following structure:



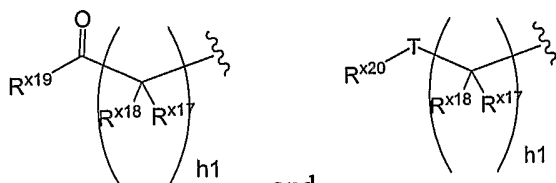
wherein

10 AB_mCD, in combination, is a member selected from:



in which the symbol h_1 is a member selected from 0 to 4. The symbol q is a member selected from 0 to 3. The symbol r is a member selected from 0 to 2. The symbols d and p are members independently selected from 0 and 1. The symbol Z^1 is member selected from CR^{x13} and N. The symbol Z^4 is a member selected from NR^7 and S. R^{x1} , R^{x2} , R^{x9} , R^{x10} and R^{x13} are members independently selected from H, OR^{y1} , $S(O)_nR^{y1}$, $NR^{y1}R^{y2}$, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x11} and R^{x12} are members independently selected from a positive charge, a salt counterion, H, $S(O)_nR^{y1}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The symbol n_1 is a member selected from 0 to 2. R^{y1} and R^{y2} are members independently selected from a charge (positive or negative), a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. Z^2 and Z^3 are members selected from $S(O)_n$, O, and NR^7 . The symbol n_1 is a member selected from 0 to 2. Each R^7 is a member selected from a positive charge, salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^{10}$, $C(O)OR^{10}$, $NR^{10}R^{10a}$, OR^{10} , SO_2R^{10} and $S(O)R^{10}$. Each R^{10} and each R^{10a} is a member independently selected from a positive charge, salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The symbol X is a member selected from O and S. The symbol Y is a member selected from C=Q. Q is a member selected from S and O. R_a is a member selected from R^{x14} and $NR^{x15}R^{x16}$. R^{x14} is a member selected from OR^{y3} , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x15} and R^{x16} are members independently selected from H, SO_2R^{y3} , $NR^{y3}R^{y4}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

R^{y3} and R^{y4} are members independently selected from a charge (either positive or negative), a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R_c is a member
 5 selected from H, substituted or unsubstituted alkyl and halogen. R_d is a member selected



from

and

. The symbol h1 is a member selected

from 0 to 4. T is a member selected from NR^{x23} and O. R^{x19} is a member selected from OR^{y5} , SR^{y5} , $NR^{y5}R^{y6}$, $NR^{x23}SO_2R^{x22}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x22} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x23} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x20} is a member selected from H, $C(O)R^{x24}$, SO_2R^{x24} , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x24} is a member selected from OR^{x22} , $NR^{x22}R^{x23}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{x17} and R^{x18} are members independently selected from H, OR^{y5} , $S(O)_{n1}R^{y5}$, $NR^{y5}R^{y6}$, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{y5} and R^{y6} are members independently selected from a charge (positive or negative), a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
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heteroaryl. R_d' is a member selected from H, substituted or unsubstituted alkyl and halogen. R_c and R_d can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R_c and R_d' can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x1} and R^{x2} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x2} and R^{x3} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x3} and R^{x4} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x4} and R^{x5} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x4} and R^{x6} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x5} and R^{x6} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x6} and R^{x7} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x4} and R^{x8} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x2} and R^{x9} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. two R^{x10} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x9} and R^{x10} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x12} and R^{x11} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x11} and R^{x10} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{y1} and R^{y2} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{y3} and R^{y4} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x15} and R^{x16} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring. R^{x22} and R^{x23} can be optionally joined, together with the atoms to which they are attached, to form a 5-8 membered ring.

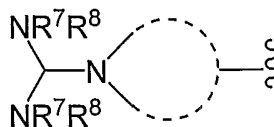
[0040] In an exemplary embodiment, the compound is subject to one or more of the provisos which are described herein. In an exemplary embodiment, the compound has the proviso that if

- a) Y is C=O;
ABC, in combination, form unsubstituted alkyl; and
D is substituted or unsubstituted guanidine; or

b) Y is C=O;

AB, in combination, form unsubstituted alkyl; and

CD, in combination, form



5

wherein

the dotted line represents carbon atoms necessary for the

formation of one ring having 4 to 8 atoms;

then R_c cannot be a member selected from CH₃ and CH₂CH₃; and R_d and R_d' cannot be

members selected from CH₃ and CH₃; CH₂CH₃ and CH₂CH₃; CH₂CH₃ and CH₃; CH₃ and

10 CH₂CH₃; H and COOH; H and COOR^{y5}; H and CONR¹⁰R^{10a}; unsubstituted alkyl and

COOH; unsubstituted alkyl and COOR^{y5}; H and unsubstituted phenylalkyl; unsubstituted

alkyl and unsubstituted phenylalkyl. In another exemplary embodiment, R_c cannot be a

member selected from CH₃, CH₂CH₃, substituted alkyl, and unsubstituted alkyl; and R_d and

R_d' cannot be members selected from CH₃ and CH₃; CH₂CH₃ and CH₂CH₃; CH₂CH₃ and

15 CH₃; CH₃ and CH₂CH₃; substituted or unsubstituted alkyl and substituted or unsubstituted

alkyl; H and substituted or unsubstituted alkyl; substituted or unsubstituted alkyl and H; H and

COOH; H and COOR^{y5}; H and CONR¹⁰R^{10a}; unsubstituted alkyl and COOH; unsubstituted

alkyl and COOR^{y5}; H and unsubstituted phenylalkyl; unsubstituted alkyl and unsubstituted

phenylalkyl.

20 [0041] In another exemplary embodiment, part (a) of this proviso is

a) Y is a member selected from C=O and SO₂;

ABC, in combination, form substituted alkyl; and

D is substituted or unsubstituted guanidine.

[0042] In another exemplary embodiment, R_c of this proviso cannot be substituted alkyl. In

25 another exemplary embodiment, R_c of this proviso cannot be unsubstituted alkyl.

[0043] In another exemplary embodiment, R_d and R_d' of this proviso cannot be members

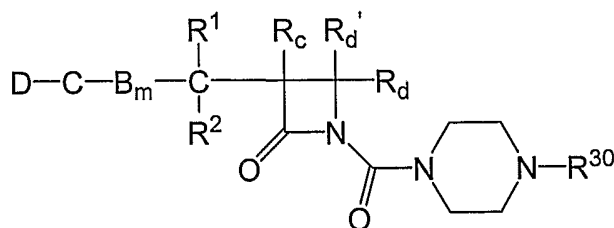
selected from CH₃ and CH₃; CH₂CH₃ and CH₂CH₃; CH₂CH₃ and CH₃; CH₃ and CH₂CH₃; H

and COOH; H and COOR^{y5}; H and CONR¹⁰R^{10a}; unsubstituted alkyl and COOH;

unsubstituted alkyl and COOR^{y5}; H and unsubstituted phenylalkyl; unsubstituted alkyl and

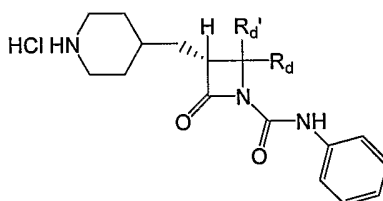
30 unsubstituted phenylalkyl.

[0044] In another exemplary embodiment, the structure has the following proviso: if the compound has the following structure:

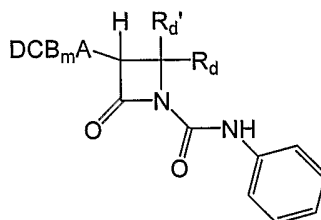


5 wherein R^{30} is a member selected from H, SO_2-R^{31} , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; wherein R^{31} is unsubstituted alkyl, then at least one of R_d and R_d' does not comprise a carbonyl group which is directly attached, or alpha, to the azetidinone ring.

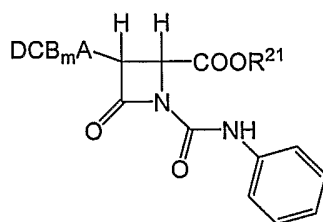
10 [0045] In another exemplary embodiment, the structure has the following proviso: the compound cannot have the following structure:



15 wherein at least one of R_d and R_d' comprise a carbonyl group which is directly attached, or alpha, to the azetidinone ring. In another exemplary embodiment, the compound cannot have the following structure:

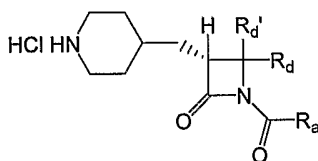


wherein DCB_mA comprises a piperidine ring or a salt thereof. In another exemplary embodiment, the compound cannot have the following structure:



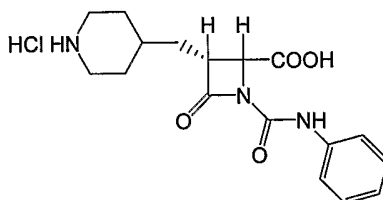
wherein DCB_mA comprises a piperidine ring or a salt thereof.

[0046] In another exemplary embodiment, the structure has the following proviso: the compound cannot have the following structure:



5

wherein R_a is NHR⁸, and R⁸ includes a substituted or unsubstituted phenyl. In another exemplary embodiment, R⁸ is unsubstituted phenyl. In yet another exemplary embodiment, R_a is N(H)(unsubstituted phenyl). In another exemplary embodiment, the structure has the following proviso: the compound cannot have the following structure:



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[0047] In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. No. 6,335,324. In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. Pub. No. 2004/0147502. In another exemplary embodiment, the structure has the following proviso: the compound cannot be a chemical compound which is explicitly disclosed (ie does not contain any variables) in U.S. Pat. Pub. No. 2004/0180855.

[0048] In another aspect, the invention provides a method of making one of the compounds of the invention. General and specific methods of synthesizing the compounds are provided herein.

5 [0049] In an exemplary embodiment, the invention provides a pharmaceutical composition comprising an effective amount of a compound of the invention including an inner salt or a pharmaceutically acceptable salt thereof, a hydrolysable ester thereof, or a solvate thereof and one or more pharmaceutically acceptable excipients. In an exemplary embodiment, the pharmaceutical composition is useful for enhancing thrombolysis or treating thrombosis, asthma, chronic asthma, or allergic rhinitis.

10 [0050] In an exemplary embodiment, the invention provides a pharmaceutical composition useful for treating asthma or allergic rhinitis comprising an effective amount of a compound of the invention including an inner salt or a pharmaceutically acceptable salt thereof, a hydrolysable ester thereof, or a solvate thereof and one or more pharmaceutically acceptable excipients.

15 [0051] In an exemplary embodiment, the invention provides a pharmaceutical composition useful for treating chronic asthma comprising an effective amount of a compound of the invention including an inner salt or a pharmaceutically acceptable salt thereof, a hydrolysable ester thereof, or a solvate thereof and one or more pharmaceutically acceptable excipients.

20 [0052] In an exemplary embodiment, the invention provides a method for treating asthma, chronic asthma or allergic rhinitis in a mammalian species comprising administering an effective amount of the composition of the invention.

[0053] In an exemplary embodiment, the invention provides a method for treating chronic asthma in a mammalian species comprising administering by inhalation to the bronchioles an effective amount of the composition of the invention.

25 [0054] In an exemplary embodiment, the invention provides a method of inhibiting tryptase in a mammal by administration of a compound according to the invention. In another exemplary embodiment, the invention provides a method of inhibiting factor XIa in a mammal by administration of a compound according to the invention. In yet another exemplary embodiment, the invention provides a method for enhancing thrombolysis or
30 inhibiting or preventing thrombosis in a mammalian species comprising administering an effective amount of the composition of the invention.

[0055] In an exemplary embodiment, the invention provides a method of treating thrombosis in a mammal comprising administering to the mammal a pharmaceutical composition that inhibits thrombosis in the mammal, wherein the pharmaceutical composition contains a therapeutically effective amount of a compound according to the invention that is selective for inhibiting Factor XIa.

[0056] In an exemplary embodiment, the invention provides a method of treating thrombosis in a mammal comprising administration of a compound according to the invention to the mammal having sufficient selectivity and potency for inhibition of Factor XIa, wherein the administration of the small molecule inhibits thrombosis in the mammal with no substantial effect on bleeding times in the mammal.

[0057] In an exemplary embodiment, the invention provides a method of inhibiting Factor XIa in a mammal by administration of a compound according to the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0058] FIG. 1 is a table displaying exemplary compounds of the invention.

[0059] FIG. 2 is a table displaying exemplary compounds of the invention and their IC₅₀ data for Factor XIa (FXIa) and tryptase. In this figure, (+++) represents an IC₅₀ value between 0.1 nM and 99.9 nM; (++) represents an IC₅₀ value between 100 nM and 9.99 μM; (+) represents an IC₅₀ value between 10 μM and 99.9 μM; and >(+) represents an IC₅₀ value greater than 99.9 μM.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

I. Definitions and Abbreviations

[0060] AcN-acetonitrile; AcOH acetic acid; Allyl Br allyl bromide; BH₃ borane; *t*-Boc *tert*-butoxycarbonyl; Boc₂O di-*tert*-butoxycarbonyl anhydride; BuLi butyl lithium; CAN ceric ammonium nitrate; CCl₄ carbon tetrachloride; CDI carbonyl diimidazole; DCC dicyclohexyl carbodiimide; DCM dichloromethane; DIEA diisopropylethylamine; DMAP dimethylaminopyridine; DMF dimethylformamide; EDC 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide; ESI-MS electrospray ionization mass spectrometry; EtOAc ethyl acetate; EtOH ethyl alcohol; HCl hydrochloric acid; HOBt 1-hydroxybenzotriazole; HPLC high pressure liquid chromatography; LC-MS liquid

chromatography mass spectrometry; LDA lithium diisopropylamide; LiHMDS lithium hexamethyldisilazide; MeOH methyl alcohol; MS mass spectrometry; NBS N-bromo succinimide; NMR nuclear magnetic resonance; Pd/C palladium on carbon; TBAF tetrabutylammonium fluoride; TBDMS *tert*-butyldimethylsilyl; TEA triethylamine; TFA trifluoroacetic acid; THF tetrahydrofuran; TIPS triisopropylsilyl; TLC thin layer chromatography; TMSCHN₂ trimethylsilyl diazomethane; TMSCl trimethylsilyl chloride.

[0061] "Reactive functional group," as used herein refers to groups including, but not limited to, olefins, acetylenes, alcohols, phenols, ethers, oxides, halides, aldehydes, ketones, carboxylic acids, esters, amides, cyanates, isocyanates, thiocyanates, isothiocyanates, amines, hydrazines, hydrazones, hydrazides, diazo, diazonium, nitro, nitriles, mercaptans, sulfides, disulfides, sulfoxides, sulfones, sulfonic acids, sulfinic acids, acetals, ketals, anhydrides, sulfates, sulfenic acids isonitriles, amidines, imides, imidates, nitrones, hydroxylamines, oximes, hydroxamic acids thiohydroxamic acids, allenes, ortho esters, sulfites, enamines, ynamines, ureas, pseudoureas, semicarbazides, carbodiimides, carbamates, imines, azides, azo compounds, azoxy compounds, and nitroso compounds. Reactive functional groups also include those used to prepare bioconjugates, *e.g.*, N-hydroxysuccinimide esters, maleimides and the like. Methods to prepare each of these functional groups are well known in the art and their application to or modification for a particular purpose is within the ability of one of skill in the art (*see*, for example, Sandler and Karo, eds. ORGANIC FUNCTIONAL GROUP PREPARATIONS, Academic Press, San Diego, 1989).

[0062] "Non-covalent protein binding groups" are moieties that interact with an intact or denatured polypeptide in an associative manner. The interaction may be either reversible or irreversible in a biological milieu. The incorporation of a "non-covalent protein binding group" into a chelating agent or complex of the invention provides the agent or complex with the ability to interact with a polypeptide in a non-covalent manner. Exemplary non-covalent interactions include hydrophobic-hydrophobic and electrostatic interactions. Exemplary "non-covalent protein binding groups" include anionic groups, *e.g.*, phosphate, thiophosphate, phosphonate, carboxylate, boronate, sulfate, sulfone, thiosulfate, and thiosulfonate.

[0063] As used herein, "linking member" refers to a covalent chemical bond that includes at least one heteroatom. Exemplary linking members include -C(O)NH-, -C(O)O-, -NH-, -S-, -O-, and the like.

[0064] The term "targeting group" is intended to mean a moiety that is: (1) able to actively direct the entity to which it is attached (*e.g.*, contrast agent) to a target region, *e.g.*, a tumor; or (2) is preferentially passively absorbed by or entrained within a target tissue, for example a tumor. The targeting group can be a small molecule, which is intended to include both non-peptides and peptides. The targeting group can also be a macromolecule, which includes, but is not limited to, saccharides, lectins, receptors, ligand for receptors, proteins such as BSA, antibodies, poly(ethers), dendrimers, poly(amino acids) and so forth.

[0065] The term "cleavable group" is intended to mean a moiety that allows for release of the chelate from the rest of the conjugate by cleaving a bond linking the chelate (or chelate linker arm construct) to the remainder of the conjugate. Such cleavage is either chemical in nature, or enzymatically mediated. Exemplary enzymatically cleavable groups include natural amino acids or peptide sequences that end with a natural amino acid.

[0066] In addition to enzymatically cleavable sites, it is within the scope of the present invention to include one or more sites that are cleaved by the action of an agent other than an enzyme. Exemplary non-enzymatic cleavage agents include, but are not limited to, acids, bases, light (*e.g.*, nitrobenzyl derivatives, phenacyl groups, benzoin esters), and heat. Many cleavable groups are known in the art. *See*, for example, Jung *et al.*, *Biochem. Biophys. Acta*, **761**: 152-162 (1983); Joshi *et al.*, *J. Biol. Chem.*, **265**: 14518-14525 (1990); Zarling *et al.*, *J. Immunol.*, **124**: 913-920 (1980); Bouiziar *et al.*, *Eur. J. Biochem.*, **155**: 141-147 (1986); Park *et al.*, *J. Biol. Chem.*, **261**: 205-210 (1986); Browning *et al.*, *J. Immunol.*, **143**: 1859-1867 (1989). Moreover a broad range of cleavable, bifunctional (both homo- and hetero-bifunctional) spacer arms are commercially available from suppliers such as Pierce.

[0067] The symbol \sim , whether utilized as a bond or displayed perpendicular to a bond indicates the point at which the displayed moiety is attached to the remainder of the molecule, solid support, etc.

[0068] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0069] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the present invention.

[0070] The compounds of the invention may be prepared as a single isomer (*e.g.*,
5 enantiomer, *cis-trans*, positional, diastereomer) or as a mixture of isomers. In a preferred embodiment, the compounds are prepared as substantially a single isomer. Methods of preparing substantially isomerically pure compounds are known in the art. For example, enantiomerically enriched mixtures and pure enantiomeric compounds can be prepared by using synthetic intermediates that are enantiomerically pure in combination with reactions
10 that either leave the stereochemistry at a chiral center unchanged or result in its complete inversion. Alternatively, the final product or intermediates along the synthetic route can be resolved into a single stereoisomer. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers are well known in the art and it is well within the ability of one of skill in the art to choose an appropriate
15 method for a particular situation. *See, generally, Furniss et al. (eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5TH ED., Longman Scientific and Technical Ltd., Essex, 1991, pp. 809-816; and Heller, Acc. Chem. Res. 23: 128 (1990).*

[0071] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example,
20 the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0072] Where substituent groups are specified by their conventional chemical formulae,
25 written from left to right, they equally encompass the chemically identical substituents, which would result from writing the structure from right to left, *e.g.*, -CH₂O- is intended to also recite -OCH₂-; --NHS(O)₂-- is also intended to represent --S(O)₂HN--; etc.

[0073] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof,
30 which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups

such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as "heteroalkyl." Alkyl groups that are limited to hydrocarbon groups are termed "homoalkyl".

10 [0074] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is
15 a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0075] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0076] The term "heteroalkyl," by itself or in combination with another term, means, unless
20 otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S and Si may be placed at any interior position of
25 the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$, $-\text{CH}_2-\text{O}-\text{SO}_2-$
30 $\text{O}-\text{CH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy,

alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'$ represents both $-C(O)_2R'$ and $-R'C(O)_2-$.

5 [0077] In general, the term "acyl" is also selected from the group set forth above. As used herein, the term "acyl" refers to groups attached to, and fulfilling the valence of a carbonyl carbon that is either directly or indirectly attached to the compounds of the present invention.

[0078] In general, the term "acylene" refers to an alkylene group which comprises an acyl group.

10 [0079] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0080] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0081] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl,

3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalanyl, 5-quinoxalanyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0082] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0083] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted or unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0084] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents," and they can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1-3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents,

one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0085] Similar to the substituents described for the alkyl radical, the aryl substituents and heteroaryl substituents are generally referred to as "aryl substituents" and "heteroaryl substituents," respectively and are varied and selected from, for example: halogen, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R''R''')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

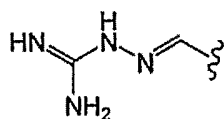
[0086] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula - (CRR')_s-X-(CR''R''')_d-, where s and d are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C₁-C₆)alkyl.

[0087] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), silicon (Si), phosphorus (P) and boron (B).

[0088] The symbol "R" is a general abbreviation that represents a substituent group that is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups.

[0089] The term "amidinohydrazone", as used herein, refers to a moiety according to the following structure:

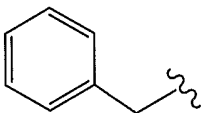
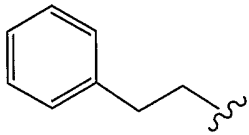


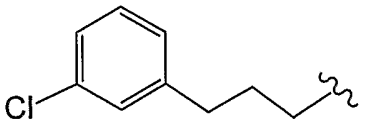
5 wherein one or more of the hydrogens in this structure can be replaced with an 'R' group.

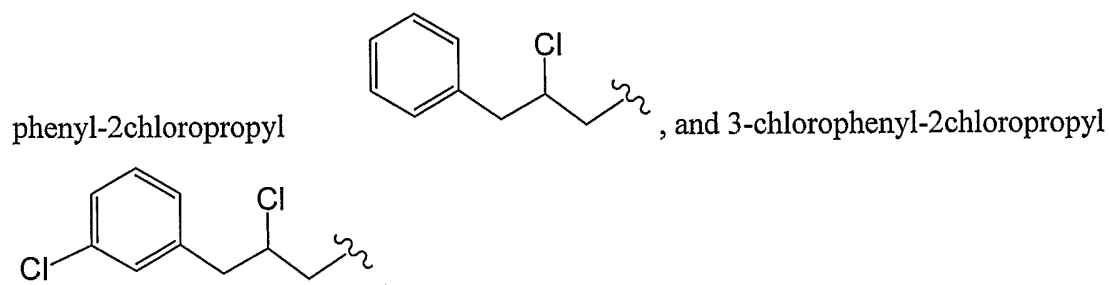
[0090] "Protecting group," as used herein refers to a portion of a substrate that is substantially stable under a particular reaction condition, but which is cleaved from the substrate under a different reaction condition. A protecting group can also be selected such that it participates in the direct oxidation of the aromatic ring component of the compounds of the invention. For examples of useful protecting groups, *see*, for example, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York, 1991.

[0091] "Ring" as used herein means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. A ring includes fused ring moieties. The number of atoms in a ring is typically defined by the number of members in the ring. For example, a "5- to 8-membered ring" means there are 5 to 8 atoms in the encircling arrangement. The ring optionally included a heteroatom. Thus, the term "5- to 8-membered ring" includes, for example pyridinyl and piperidinyl. The term "ring" further includes a ring system comprising more than one "ring", wherein each "ring" is independently defined as above.

[0092] The term, "phenylalkyl", as used herein, refers to a moiety in which the phenyl ring is connected to the rest of the molecule through an alkyl chain. Examples of phenylalkyl

moieties include phenylmethyl  and phenylethyl . Other

examples of substituted phenylalkyl is 3-chlorophenylpropyl .



[0093] The term “pharmaceutically acceptable salts” includes salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, trifluoroacetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., “Pharmaceutical Salts”, Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0094] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0095] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

III. Compounds

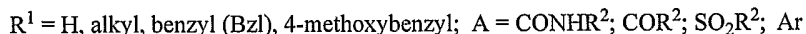
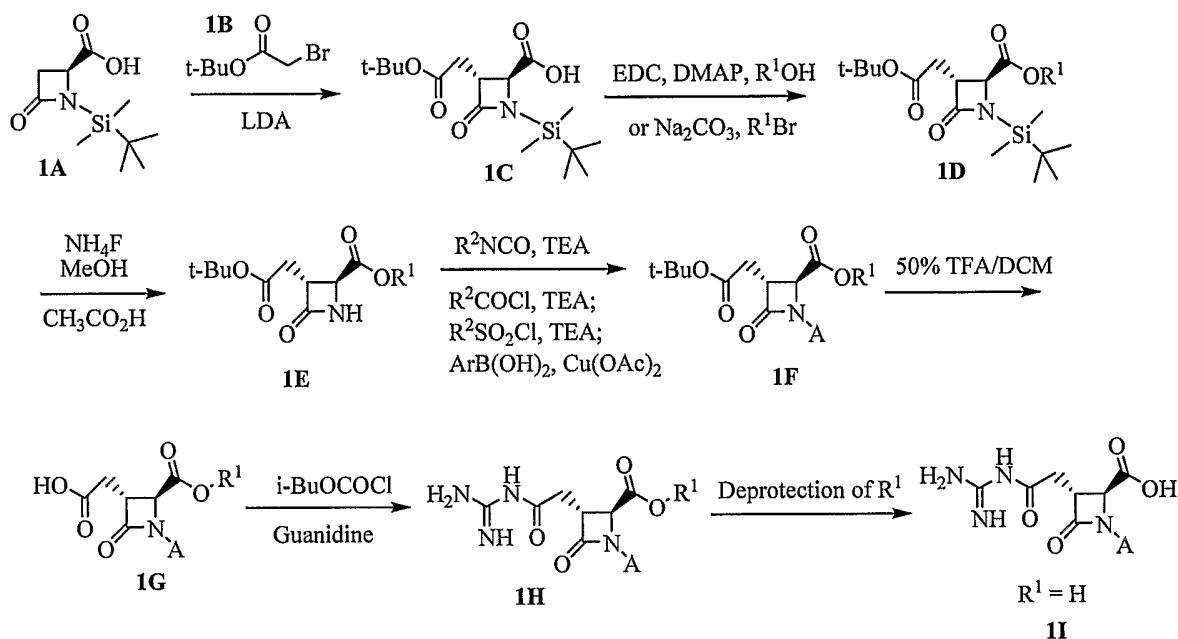
[0096] Representative compounds of the invention are provided in **FIG. 1** and **FIG. 2**.

10 IV. Synthesis and Purification of the Compounds

[0097] The compounds of the invention are synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention, it is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

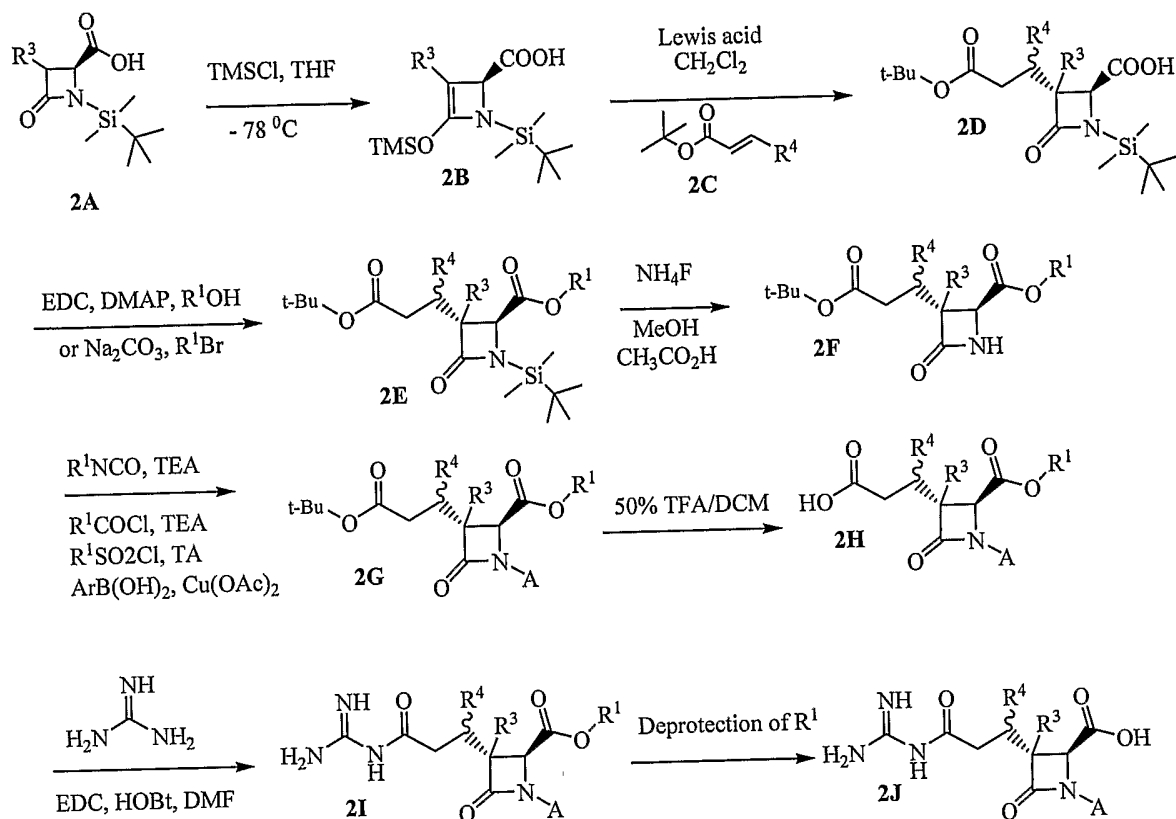
IV. a) 2-Guanidinyl 2-oxo ethylene

Scheme 1



[0098] One method of synthesizing compounds of the invention with 2-guanidinyl-2-oxo-
 5 ethylene substituents is shown in Scheme 1. In this Scheme, **1A** can be treated with
 bromomethyl t-butyl ester **1B** and lithium diisopropyl amide (“LDA”) in order to provide **1C**.
1C then undergoes esterification with an alcohol ($\text{R}^1\text{-OH}$), EDC, DMAP in order to provide
1D. **1C** can alternatively undergo esterification under alkylation conditions using a
 halogenated compound and sodium carbonate in order to provide **1D**. **1D** can be desilylated
 10 using a mixture of ammonium fluoride, methanol, and acetic acid in order to provide **1E**. **1E**
 can be treated with an isocyanate and TEA to produce **1F** with an urea moiety. **1E** can
 alternatively be treated with an acyl chloride and TEA to produce **1F** with an amide moiety.
1E can alternatively be treated with a sulfonyl chloride and TEA to produce **1F** with a
 sulfonamide moiety. **1E** can alternatively be treated with an aryl boronic acid and Cu(OAc)_2
 15 to produce **1F** with an aryl moiety. **1F** can be treated with TFA in order to remove the t-butyl
 group on **1F** to produce **1G**. **1G** can be treated with guanidine and isobutylchloroformate in
 order to produce **1H**. **1H** can be converted to the acid **1I** by treating with hydrogen and
 palladium on carbon in ethyl acetate when $\text{R}^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when R^1
 = 4-methoxybenzyl.

Scheme 2

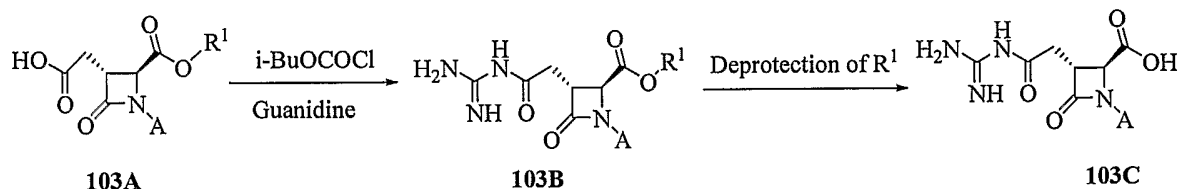


$\text{R}^1 = \text{H, alkyl, benzyl (Bzl), 4-methoxybenzyl}; \text{A} = \text{CONHR}^2; \text{COR}^2; \text{SO}_2\text{R}^2; \text{Ar, R}^3 = \text{H, Me}; \text{R}^4 = \text{Me, alkyl, aryl}$

[0099] A second method of synthesizing compounds of the invention with 2-guanidiny-2-oxo-ethylene substituents is shown in Scheme 2. In this Scheme, 2A can be treated with trimethylsilylchloride in THF in order to provide 2B. 2B can then be treated with an appropriate metal catalyst in order to provide 2D. 2D can then be treated with an alcohol (R¹-OH), EDC, DMAP in order to provide 2E. 2D can alternatively undergo esterification via alkylation using a halogenated compound and sodium carbonate in order to provide 2E. 2E can be then treated with a mixture of ammonium fluoride, methanol, and acetic acid in order to provide 2F. 2F can be treated with an isocyanate and TEA to produce 2G with a urea moiety. 2F can alternatively be treated with an acyl chloride and TEA to produce 2G with an amide moiety. 2F can alternatively be treated with a sulfonyl chloride and TEA to produce 2G with a sulfonamide moiety. 2F can alternatively be treated with an aryl boronic acid and Cu(OAc)₂ to produce 2G with a substituted or unsubstituted aryl moiety. A substituted or unsubstituted heteroaryl moiety may be used in place of the aryl moiety. 2G can be treated with TFA in order to deprotect the t-butyl group on 2G and to produce 2H. 2H can then be treated with guanidine under peptide coupling conditions (e.g. ethyl diisopropyl

carbodiimide (EDC) and hydroxybenzotriazole (HOBT) in order to product **2I**. **2I** can be converted to **2J** by treating with hydrogen and palladium on carbon in ethyl acetate when R^1 = benzyl, or trifluoroacetic acid (TFA) when R^1 = 4-methoxybenzyl.

Scheme 103

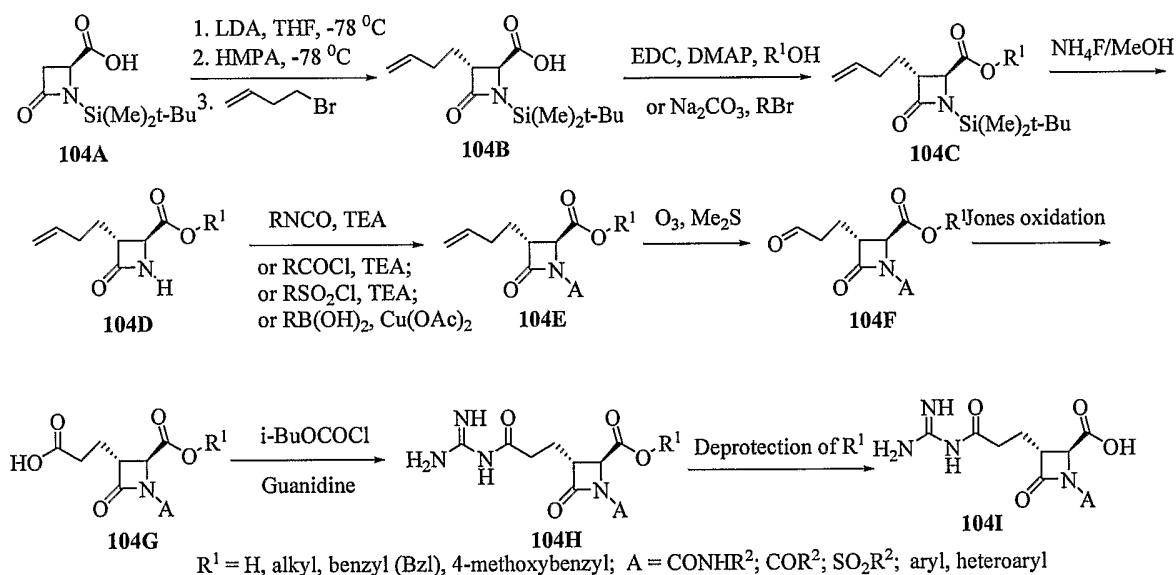


5

R^1 = H, alkyl, benzyl (Bzl), 4-methoxybenzyl; A = CONHR²; COR²; SO₂R²; aryl, heteroaryl

[0100] A method of synthesizing azetidinones bearing R₃ substituents containing an acylguanidine moiety is described in scheme 103. The preparation of **103A** is described in scheme 1. This compound may be coupled via an intermediate mixed anhydride with guanidine to provide **103B**. **103B** can be converted to the acid **103C** by treating with hydrogen and palladium on carbon in ethyl acetate when R^1 = benzyl, or trifluoroacetic acid (TFA) when R^1 = 4-methoxybenzyl.

Scheme 104

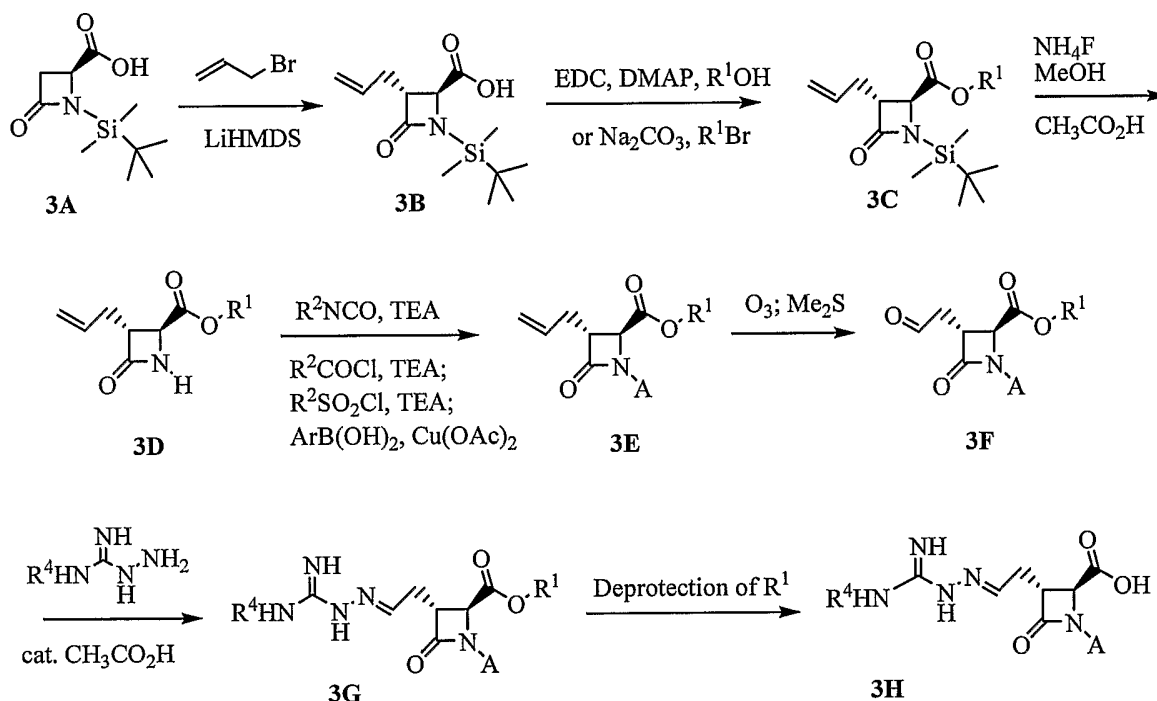


[0101] A method of synthesizing azetidinones bearing R₃ substituents containing an acylguanidine moiety is described in scheme 104. Alkylation of the dianion of acid **104A** using homoallyl bromide provides **104B**. Esterification can provide **104C**. Desilylation affords **104D**. **104D** can then be treated with an isocyanate and TEA to produce **104E** with a urea functionality. **104D** can alternatively be treated with an acyl chloride and TEA to

produce **104E** with an amide functionality. **104D** can alternatively be treated with a sulfonyl chloride and TEA to produce **104E** with a sulfonamide functionality. **104D** can alternatively be treated with an aryl boronic acid and $\text{Cu}(\text{OAc})_2$ to produce **104E** with an aryl functionality. Ozonolysis provides aldehyde **104F**. Oxidation can provide **104G**. Coupling with guanidine via an active ester provides **104H**. **104H** can be converted to the acid **104I** by treating with hydrogen and palladium on carbon in ethyl acetate when $\text{R}^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when $\text{R}^1 = 4\text{-methoxybenzyl}$.

IV. b) N-guanidinyl 2-iminyl ethylene

Scheme 3



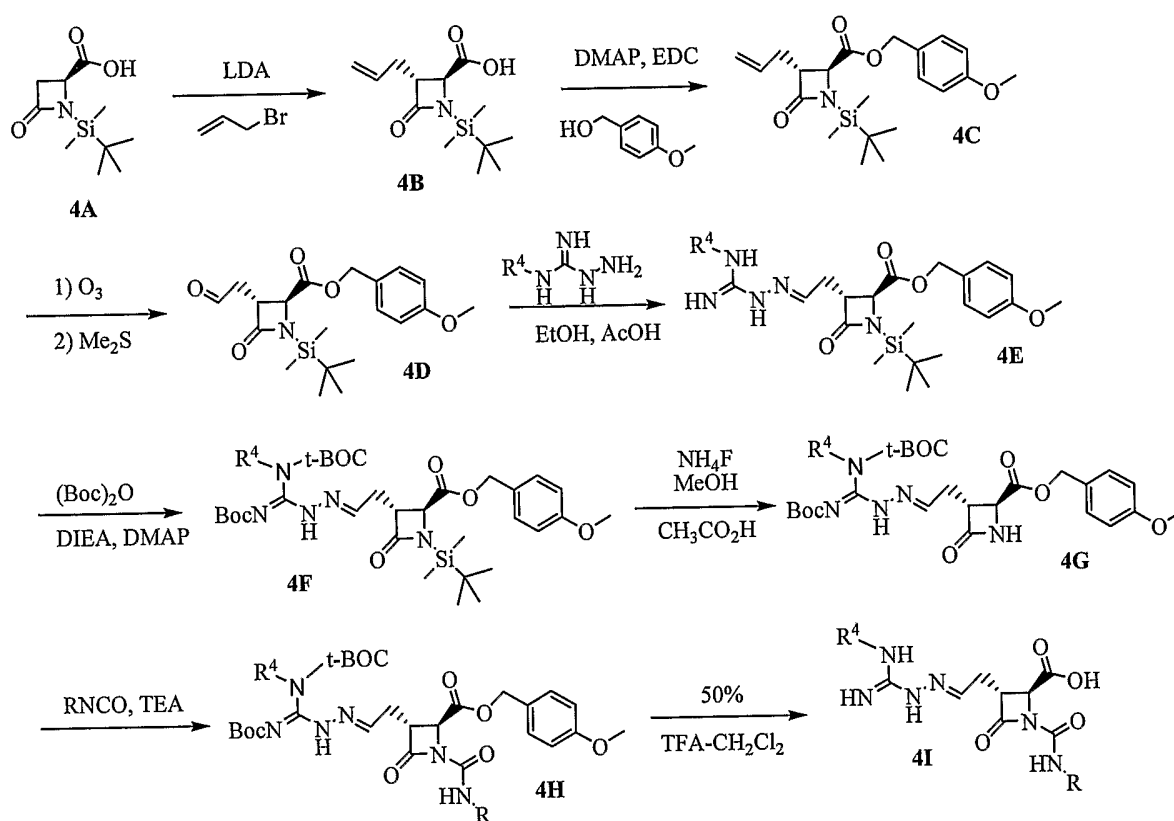
$\text{R}^1 = \text{H, alkyl, benzyl (Bzl), 4-methoxybenzyl}$; $\text{A} = \text{CONHR}^2; \text{COR}^2; \text{SO}_2\text{R}^2$; Ar
 $\text{R}^4 = \text{H, alkyl, Bzl}$

10

[0102] One method of synthesizing compounds of the invention with N-guanidinyl-2-iminyl-ethylene substituents is shown in Scheme 3. In this Scheme, **3A** can be treated with lithium hexamethyldisilazide (LiHMDS) and 2-propenyl bromide to produce **3B**. **3B** can be treated with an alcohol ($\text{R}^1\text{-OH}$), EDC, DMAP in order to produce **3C**. **3B** can alternatively be treated with a halogenated compound and sodium carbonate in order to provide **3C**. **3C** can then be treated with a mixture of ammonium fluoride, methanol, and acetic acid in order to provide **3D**. **3D** can then be treated with an isocyanate and TEA to produce **3E** with an urea moiety. **3D** can alternatively be treated with an acyl chloride and TEA to produce **3E**

with an amide moiety. **3D** can alternatively be treated with a sulfonyl chloride and TEA to produce **3E** with a sulfonamide moiety. **3D** can alternatively be treated with an aryl boronic acid and $\text{Cu}(\text{OAc})_2$ to produce **3E** with a substituted or unsubstituted aryl moiety. A substituted or unsubstituted heteroaryl moiety may be used in place of the aryl moiety. **3E** can be subjected to ozonolysis to produce **3F**. **3F** can be treated with substituted or unsubstituted aminoguanidine and a catalytic amount of an organic acid in order to produce **3G**. Finally, **3G** can be converted to **3H** by treating with hydrogen and palladium on carbon in ethyl acetate when $\text{R}^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when $\text{R}^1 = 4\text{-methoxybenzyl}$.

Scheme 4



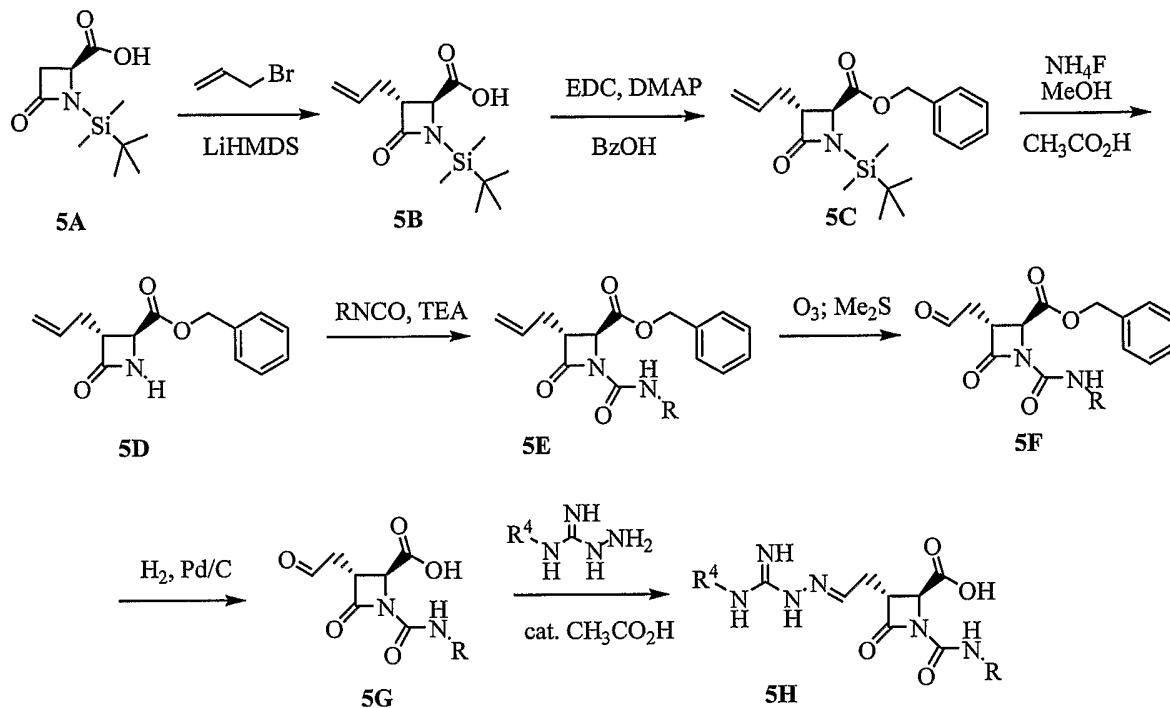
10

[0103] Another method of synthesizing compounds of the invention with N-guanidiny-2-iminyl-ethylene substituents is shown in Scheme 4. In this Scheme, **4A** can be treated with LDA and allyl bromide to produce **4B**. **4B** can be then treated with 4-methoxybenzyl alcohol, EDC and DMAP in order to produce **4C**. **4C** can be subjected to ozonolysis to produce **4D**. **4D** can be treated with substituted or unsubstituted aminoguanidine ($\text{R}^4 = \text{H}$, alkyl) and a catalytic amount of an organic acid in order to produce **4E**. **4E** can then be treated with $(\text{Boc})_2\text{O}$, DIEA and DMAP in order to produce **4F**. **4F** can then be treated with a mixture of ammonium fluoride, methanol, and acetic acid in order to provide **4G**. **4G** can

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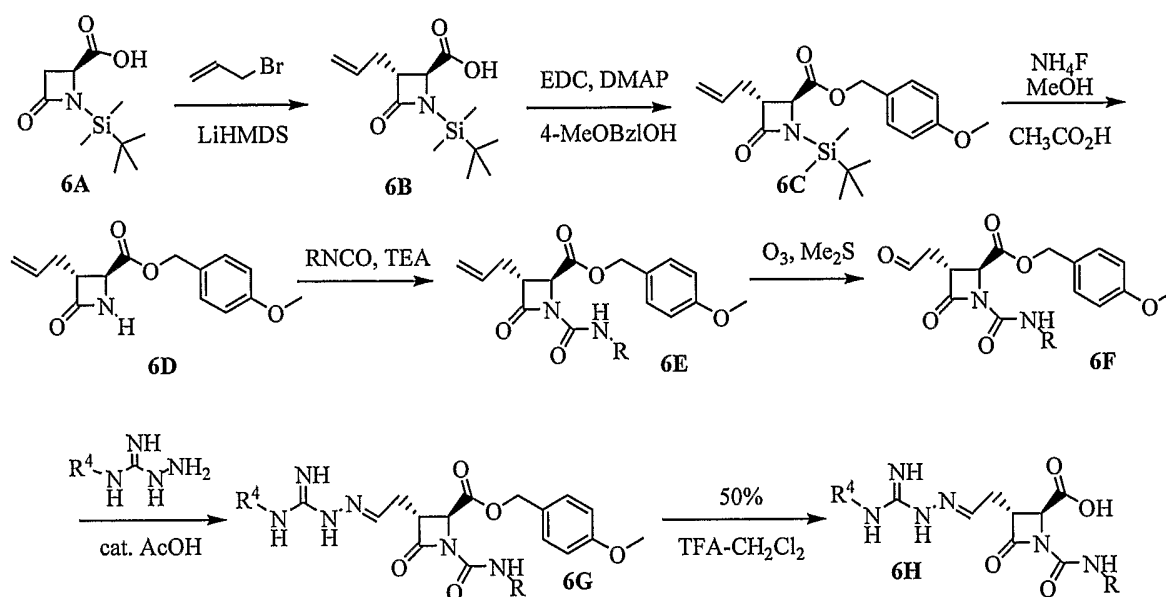
then be treated with an isocyanate and TEA to produce **4H** with an urea moiety. **4H** can then be treated with TFA in order to produce **4I**.

Scheme 5



- 5 **[0104]** Another method of synthesizing compounds of the invention with N-guanidinyl-2-iminyl-ethylene substituents is shown in Scheme 5. In this Scheme, **5A** can be treated with LiHMDS and 2-propenyl bromide to produce **5B**. **5B** can be treated with benzyl alcohol, EDC, DMAP in order to produce **5C**. **5C** can be treated with a mixture of ammonium fluoride and methanol in order to provide **5D**. **5D** can be treated with an isocyanate and TEA
- 10 to produce **5E** with an urea moiety. **5E** can be subjected to ozonolysis to produce **5F**. **5F** can be subjected to hydrogenolysis in order to produce **5G**. **5G** can be treated with substituted or unsubstituted aminoguanidine and a catalytic amount of an organic acid in order to produce **5H**.

Scheme 6

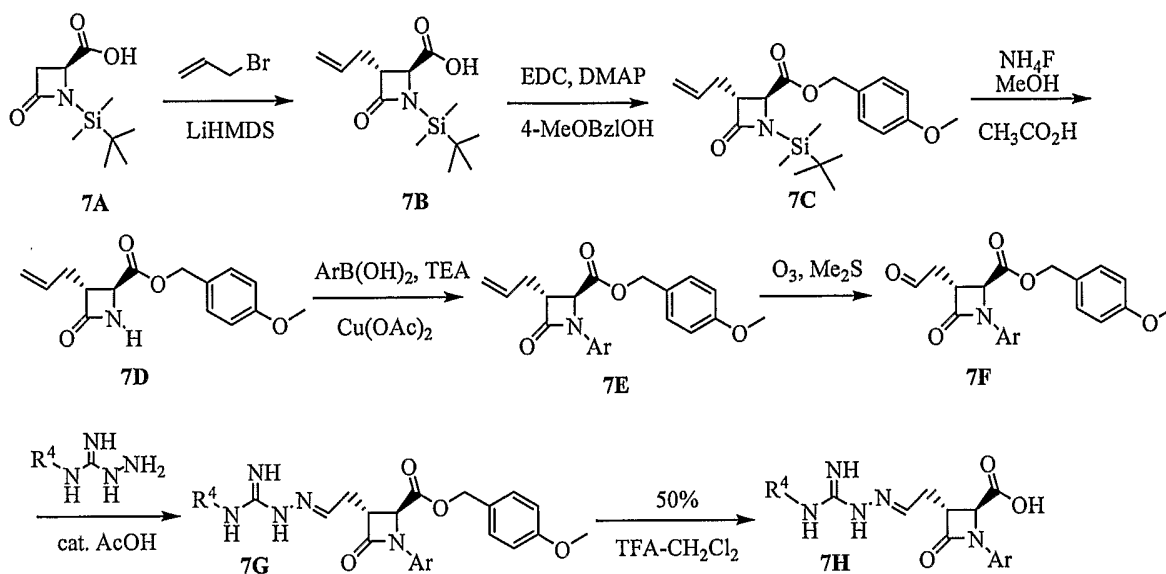


[0105] Another method of synthesizing compounds of the invention with N-guanidinylyl-2-iminyl-ethylene substituents is shown in Scheme 6. In this Scheme, **6A** can be treated with

5 LiHMDS and 2-propenyl bromide to produce **6B**. **6B** can be treated with 4-methoxybenzyl alcohol, EDC, DMAP in order to produce **6C**. **6C** can be treated with a mixture of ammonium fluoride, methanol, and acetic acid in order to provide **6D**. **6D** can be treated with an isocyanate and TEA to produce **6E** with an urea moiety. **6E** can be subjected to ozonolysis to produce **6F**. **6F** can be treated with substituted or unsubstituted

10 aminoguanidine and a catalytic amount of an organic acid in order to produce **6G**. **6G** can then be treated with TFA in order to produce **6H**.

Scheme 7

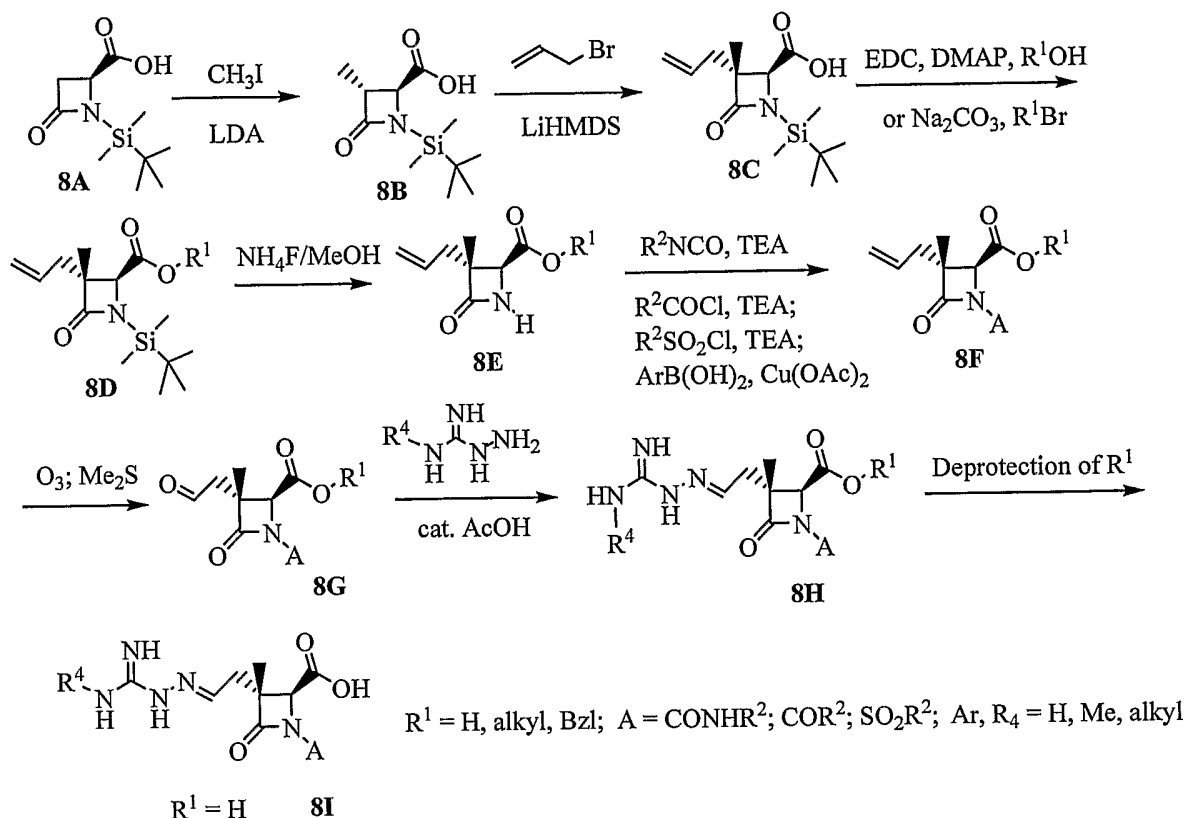


[0106] Another method of synthesizing compounds of the invention with N-guanidinyl-2-iminyl-ethylene substituents is shown in Scheme 7. In this Scheme, 7A can be treated with

5 LiHMDS and 2-propenyl bromide to produce 7B. 7B can be treated with 4-methoxybenzyl alcohol, EDC, DMAP in order to produce 7C. 7C can be treated with ammonium fluoride, methanol, and acetic acid in order to provide 7D. 7D can be treated with an aryl boronic acid and Cu(OAc)₂ to produce 7E with a substituted or unsubstituted aryl moiety. A substituted or unsubstituted heteroaryl moiety may be used in place of the aryl moiety. 7E can be subjected

10 to ozonolysis to produce 7F. 7F can be treated with substituted or unsubstituted guanidine and a catalytic amount of an organic acid in order to produce 7G. 7G can be treated with TFA in order to produce 7H.

Scheme 8



[0107] Another method of synthesizing compounds of the invention with N-guanidinyl-2-iminyl-ethylene substituents is shown in Scheme 8. In this Scheme, **8A** can be treated with

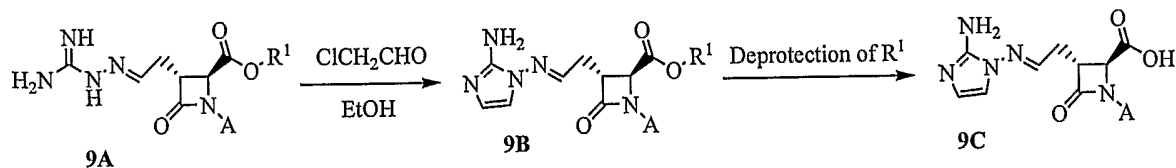
5 LDA and methyl iodide to produce **8B**. **8B** can be treated with LiHMDS and 2-propenyl bromide to produce **8C**. **8C** can be treated with an alcohol ($\text{R}^1\text{-OH}$), EDC, DMAP in order to produce **8D**. **8C** can alternatively be treated with a halogenated compound and sodium carbonate in order to provide **8D**. **8D** can be treated with ammonium fluoride and methanol

10 in order to provide **8E**. **8E** can be treated with an isocyanate and TEA to produce **8F** with a urea moiety. **8E** can alternatively be treated with an acyl chloride and TEA to produce **8F** with an amide moiety. **8E** can alternatively be treated with a sulfonyl chloride and TEA to produce **8F** with a sulfonamide moiety. **8E** can alternatively be treated with an aryl boronic acid and $\text{Cu}(\text{OAc})_2$ to produce **8F** with a substituted or unsubstituted aryl moiety. A substituted or unsubstituted heteroaryl moiety may be used in place of the aryl moiety. **8F** can

15 be subjected to ozonolysis to produce **8G**. **8G** can be treated with substituted or unsubstituted aminoguanidine and a catalytic amount of an organic acid in order to produce **8H**. **8H** can then be deprotected in order to produce **8I** by treating with hydrogen and palladium on carbon in ethyl acetate when $\text{R}^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when $\text{R}^1 = 4\text{-methoxybenzyl}$.

IV. c) *N1-ethylidene-1H-imidazole-1,2-diamine*

Scheme 9

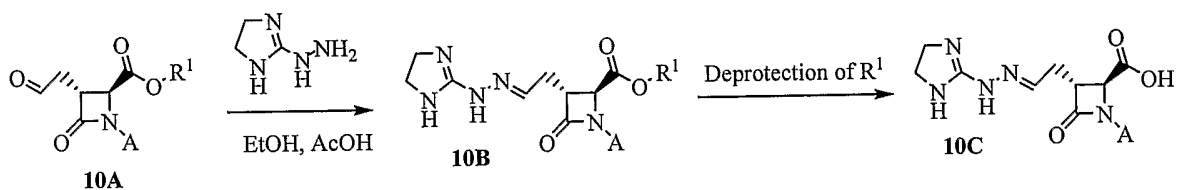


$R^1 = \text{H, alkyl, Bzl, 4-methoxybenzyl}; A = \text{CONHR}^2; \text{COR}^2; \text{SO}_2\text{R}^2; \text{aryl, substituted aryl, heteroaryl}$

[0108] One method of synthesizing compounds of the invention with N-[2-amino-
 5 pyrazinyl] 2-iminyl ethylene substituents is shown in Scheme 9. **9A** is a compound that can be produced by the methods described in Schemes 3-8. **9A** can be treated with ClCH_2CHO in ethanol in order to produce **9B**. **9B** can be used to produce **9C** by treating with hydrogen and palladium on carbon in ethyl acetate when $R^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when $R^1 = \text{4-methoxybenzyl}$.

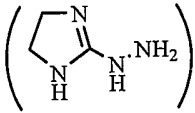
10 IV. d) *1-(4,5-dihydro-1H-imidazol-2-yl)-2-propylidenehydrazine*

Scheme 10



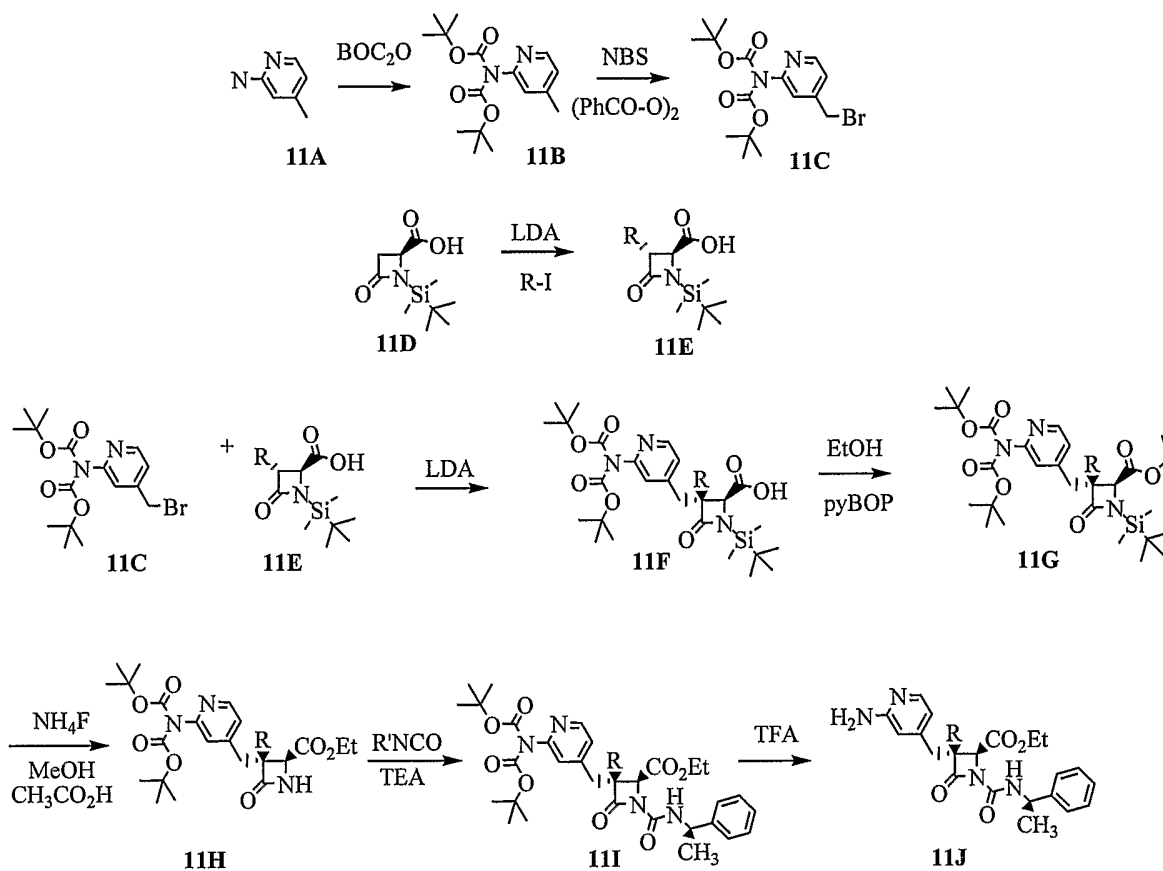
$R^1 = \text{H, alkyl, Bzl, 4-methoxybenzyl}; A = \text{CONHR}^2; \text{COR}^2; \text{SO}_2\text{R}^2; \text{aryl, substituted aryl, heteroaryl}$

[0109] One method of synthesizing compounds of the invention with N-[dihydroimidazolyl]
 2-hydrazinylimino ethylene substituents is shown in Scheme 10. **10A** is a compound that can
 15 be produced by the methods described in Schemes 3-8 (See **3F**, **5F**, **6F**, **7F**, **8G**). **10A** can be

treated with 1-(4,5-dihydro-1H-imidazol-2-yl)hydrazine  in ethanol and acetic acid in order to produce **10B**. **10B** can be converted to **10C** by treating with hydrogen and palladium on carbon in ethyl acetate when $R^1 = \text{benzyl}$, or trifluoroacetic acid (TFA) when $R^1 = \text{4-methoxybenzyl}$.

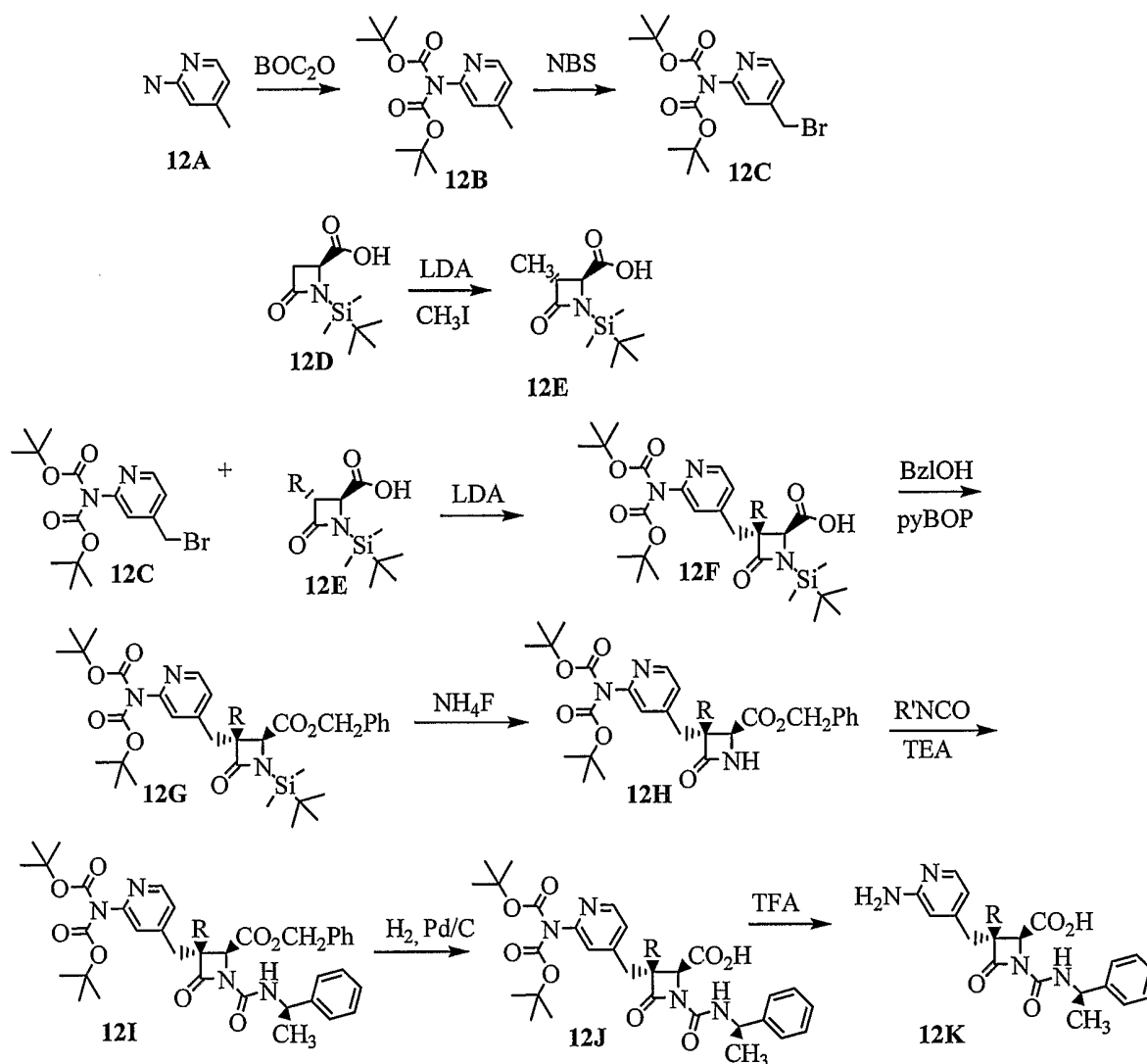
IV. e) Heteroarylmethyl

Scheme 11



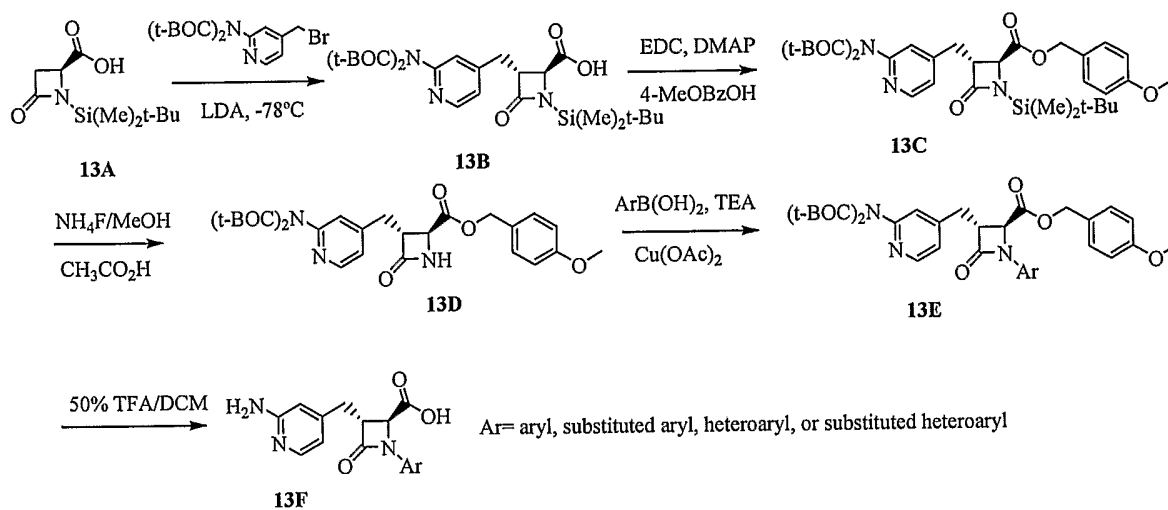
- [0110] An alternative method of synthesizing heteroarylmethyl substituents is shown in
- 5 Scheme 11. Bis-BOC protection of **11A** and bromination provides **11C**. **11C** can be used in the LDA-mediated alkylation of **11E**. **11E** can in turn prepared from **11D** by LDA-mediated alkylation with iodomethane, where R = Me. The alkylated product **11F** can be converted to **11G** using ethanol and a peptide coupling agent such as pyBOP. **11G** can be desilylated to **11H** using ammonium fluoride, converted to urea **11I** using and an appropriate isocyanate and triethylamine, and deprotected with TFA to provide **11J**.
- 10

Scheme 12



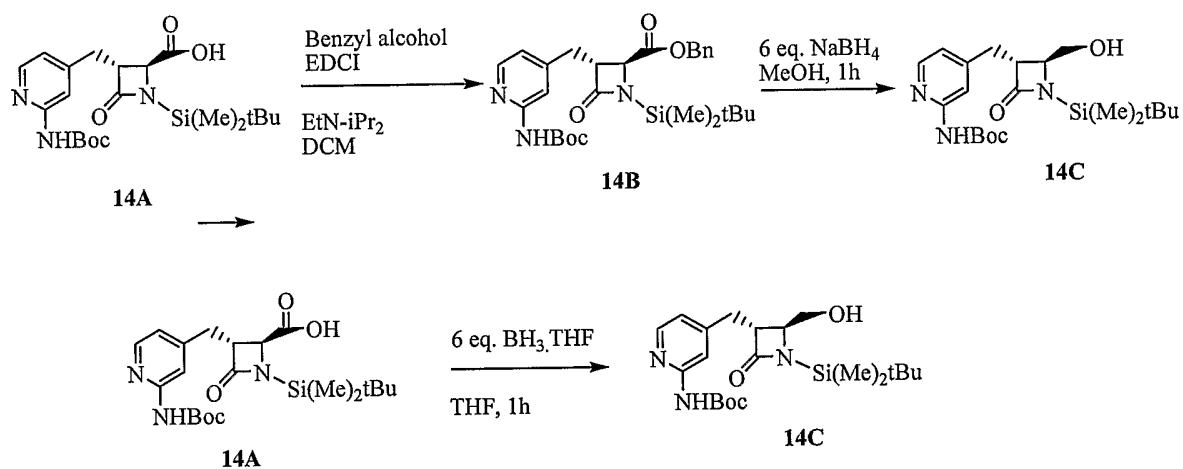
- [0111] An alternative method of synthesizing heteroarylmethyl substituents is shown in Scheme 12. Compound 12F was described in scheme 11 (compound 11F with R = H). A benzyl ester 12G can be prepared from 12F using benzyl alcohol and a peptide coupling agent such as pyBOP. 12G can be desilylated with ammonium fluoride to provide 12H. Treatment with an appropriate isocyanate can provide 12I. Hydrogenolysis can provide 12J, and BOC removal using TFA can provide 12K.

Scheme 13



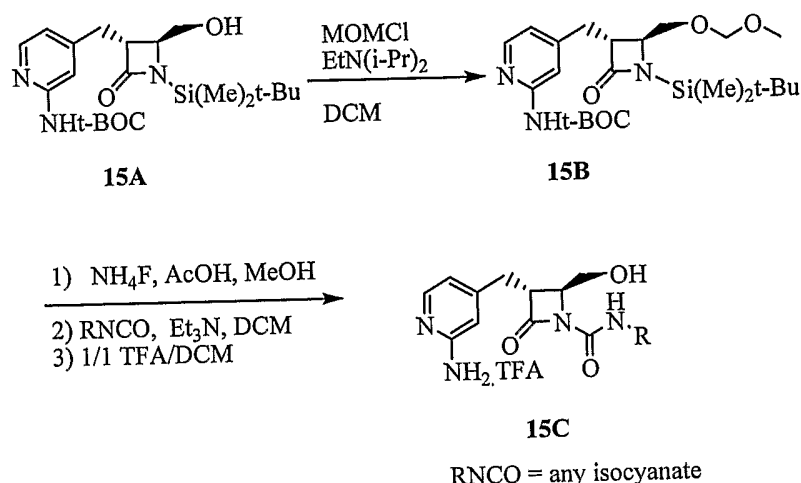
[0112] An alternative method of synthesizing heteroarylmethyl substituents is shown in Scheme 13. **13D** is prepared in an analogous fashion to **12G** (with R=H) in scheme 12. **13D** can be treated with an aryl boronic acid to provide **13E**, and the aryl moiety may be substituted aryl, aryl, or heteroaryl. **13B** can be treated with TFA to give acid **13F**.

Scheme 14



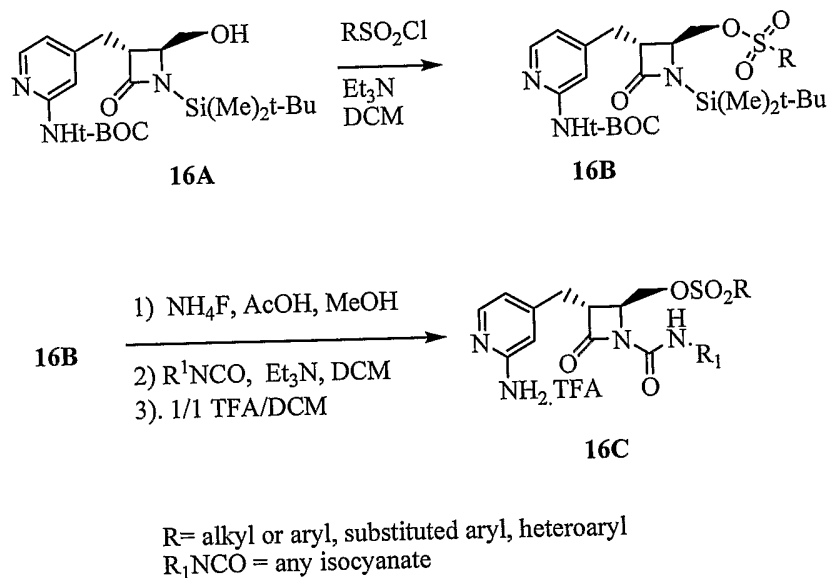
[0113] A precursor for the synthesis of many heteroarylmethyl variants can be prepared according to Scheme 14. **14A** can be treated with a mixture of benzyl alcohol, EDC, and diisopropylethylamine in DCM to produce **14B**. **14B** can be treated with excess sodium borohydride in order to produce **14C**. **14A** can alternatively be directly converted to **14C** through reduction with BH_3 in THF.

Scheme 15



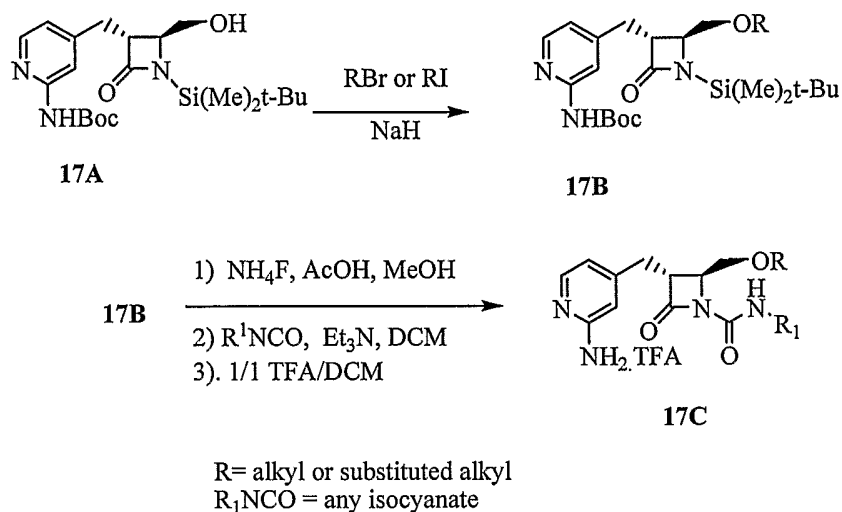
[0114] Compound **15A** from Scheme 14 can be used to produce **15B** by alkylation with chloromethyl methyl ether. **15B** can be readily converted to **15C** as shown in scheme 15, by ammonium fluoride mediated desilylation, isocyanate acylation, and TFA-mediated BOC deprotection.

Scheme 16



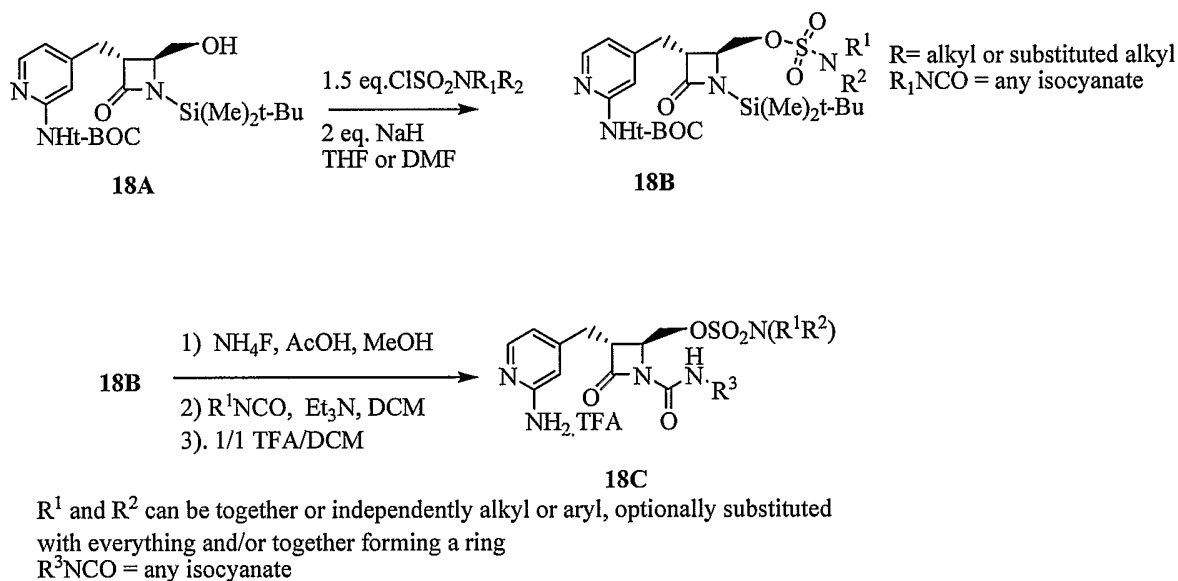
[0115] **16A** from scheme 14 can be used to produce **16B** by base-mediated sulfonylation. **16B** can be readily converted to **16C** by 3 steps that include ammonium fluoride mediated desilylation, isocyanate acylation, and BOC deprotection with TFA.

Scheme 17



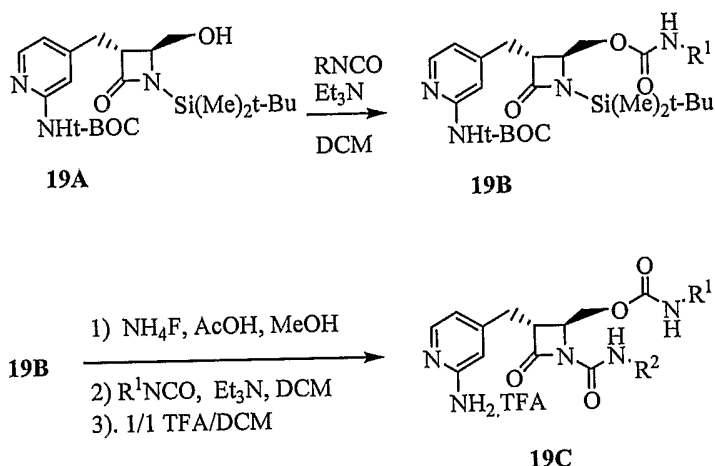
[0116] The precursor from Scheme 14 (17A) can be used to produce 17B by base-mediated alkylation. 17B can be readily converted to 17C by 3 steps that include ammonium fluoride mediated desilylation, isocyanate acylation, and BOC deprotection with TFA.

Scheme 18



[0117] The precursor from Scheme 14 (18A) can be used to produce 18B by base-mediated reaction with a sulfamoyl chloride. 18B can be readily converted to 18C by 3 steps that include ammonium fluoride mediated desilylation, isocyanate acylation, and BOC deprotection with TFA.

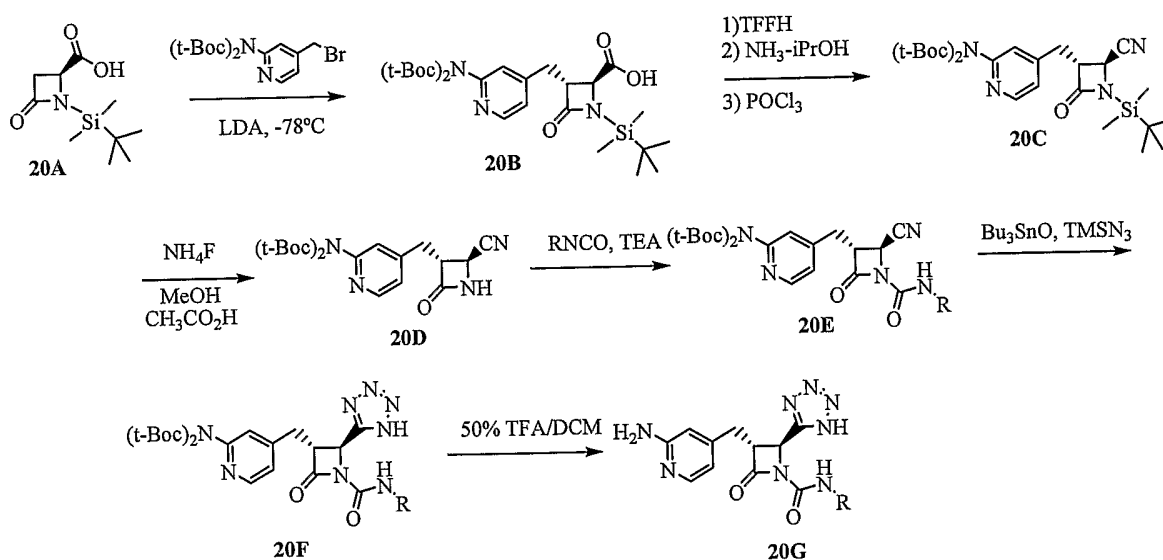
Scheme 19



R^1NCO and R^2NCO = alkyl, aryl, heteroaryl, and substituted variants thereof

[0118] The precursor from Scheme 14 (**19A**) can be used to produce carbamate **19B** by base-mediated reaction with an isocyanate. **19B** can be readily converted to **19C** by 3 steps that include ammonium fluoride mediated desilylation, isocyanate acylation, and BOC deprotection with TFA.

Scheme 20

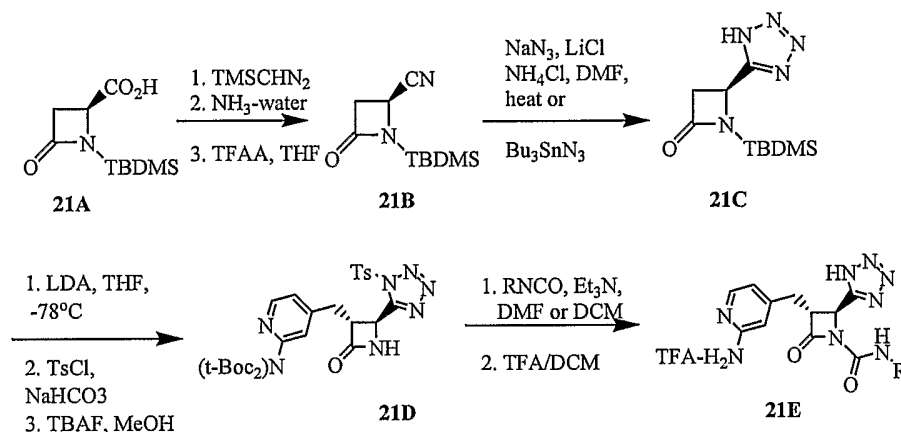


RNCO = alkyl, substituted alkyl, aryl, or heteroaryl isocyanate

[0119] One method of synthesizing compounds of the invention with tetrazole is shown in Scheme 20. LDA-mediated alkylation of **20A** can provide acid **20B**. **20B** can be converted to the nitrile **20C** by coupling via an acyl halide, reaction with ammonia to form a primary amide, and finally dehydration. **20C** can be desilylated with ammonium fluoride to form **20D**. Treatment of **20D** with an isocyanate provides urea **20E**. The nitrile can be used to

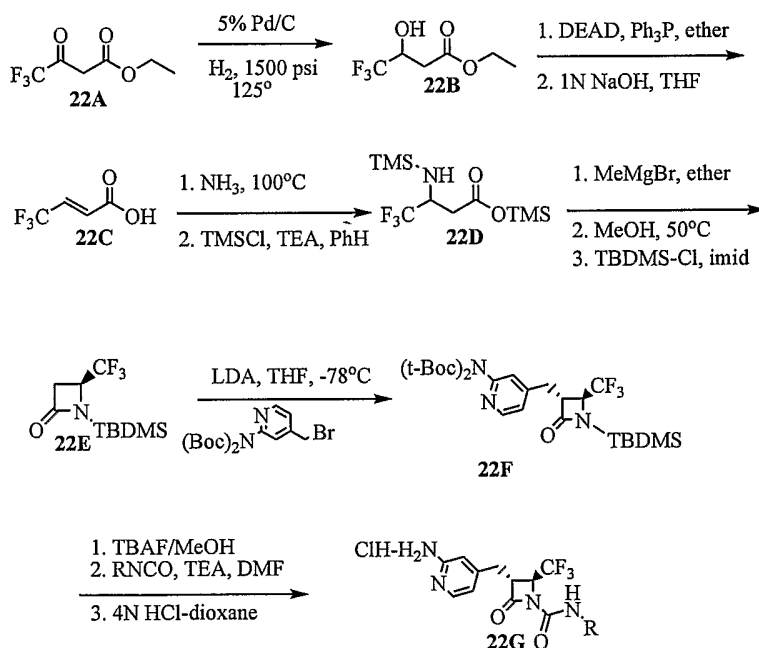
form tetrazole **20F** using TMS azide and a tin oxide reagent. TFA-mediated BOC deprotection provides urea **20G**.

Scheme 21



- 5 **[0120]** One method of synthesizing compounds of the invention with tetrazole is shown in Scheme 21. **21A** can be treated with TMSCHN₂, aqueous ammonia and then TFAA in order to produce **21B**. **21B** can be treated with sodium azide in the presence of LiCl, NH₄Cl and DMF in order to produce **21C**. **21C** can also be obtained by reacting **21B** with azidotributylstannane. **21C** can then be alkylated with LDA and the Boc-protected bromo-aminopyridine, protected with tosyl chloride and finally subjected to TBDMS removal under TBAF conditions to produce **21D**. **21D** can then be acylated with an isocyanate and all protecting groups removed with TFA to produce desired tetrazoles **21E**.
- 10

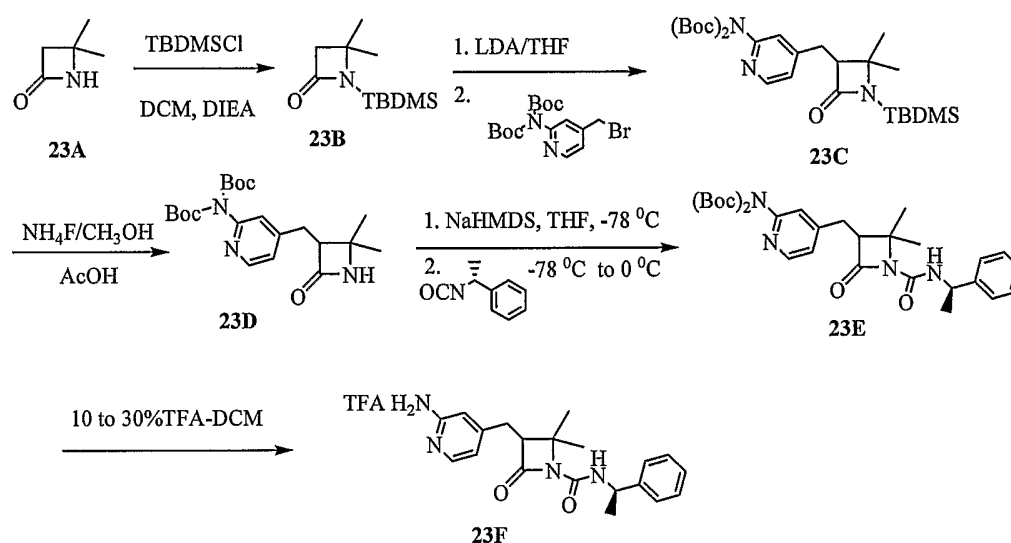
Scheme 22



[0121] One method of synthesizing compounds of the invention with trifluoromethyl is shown in Scheme 22. **22A** can be hydrogenated to provide ketone **22B**. Ketone **22B** can then be subjected to Mitsunobu conditions followed by elimination to form **22C**. **22C** can be transformed by Michael addition of ammonia and protection of the amine to give **22D**.

- 5 Treatment of **22D** with methylmagnesium bromide to cyclize to the β -lactam followed by methanolysis and TBDMS protection to give **22E**. **22E** can then be alkylated to give **22F**. **22F** can be treated with TBAF to remove the TBDMS group, acylated and then all protecting groups removed with TFA to produce desired CF_3 compounds of the invention **22G**.

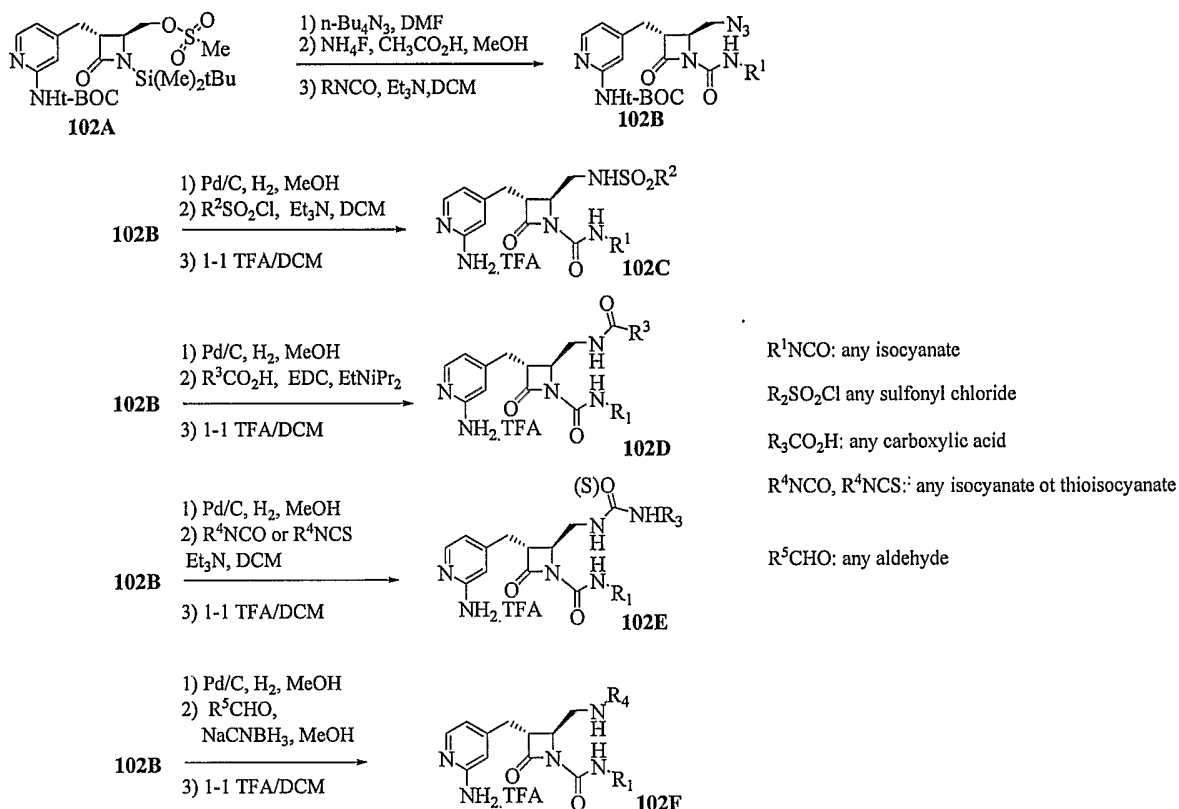
Scheme 23



[0122] One method of synthesizing compounds of the invention with geminally substituted methyl groups is shown in Scheme 23. **23A** can be treated with TBDMSCl and TEA to produce **23B**. **23B** can be treated with LDA and then Bis-BOC protected 4-(bromomethyl)pyridin-2-amine in order to produce **23C**. **23C** can be treated with ammonium fluoride in methanol in order to produce **23D**. **23D** can be treated with NaHMDS and then an isocyanate in order to produce **23E**. **23E** can be treated with TFA in dichloromethane in order to produce **23F**.

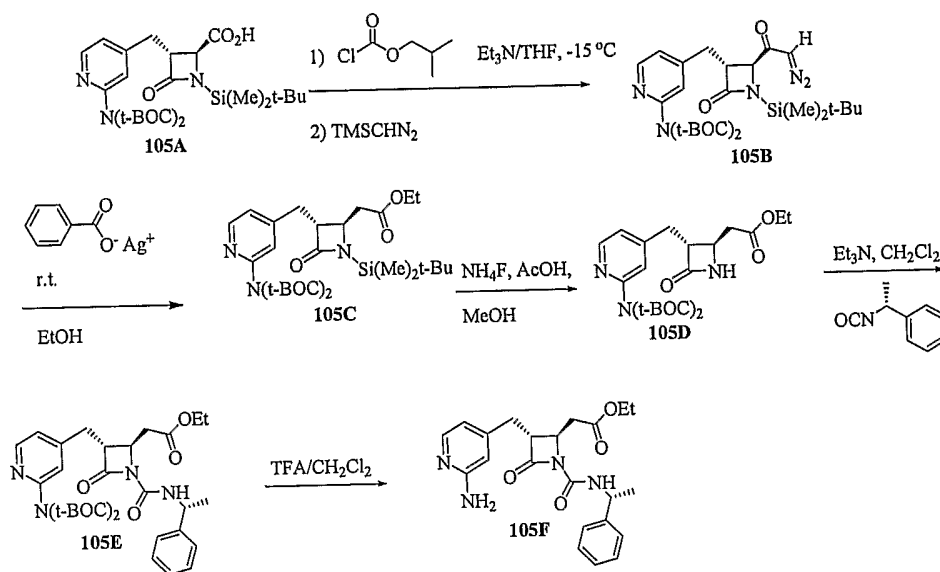
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Scheme 102



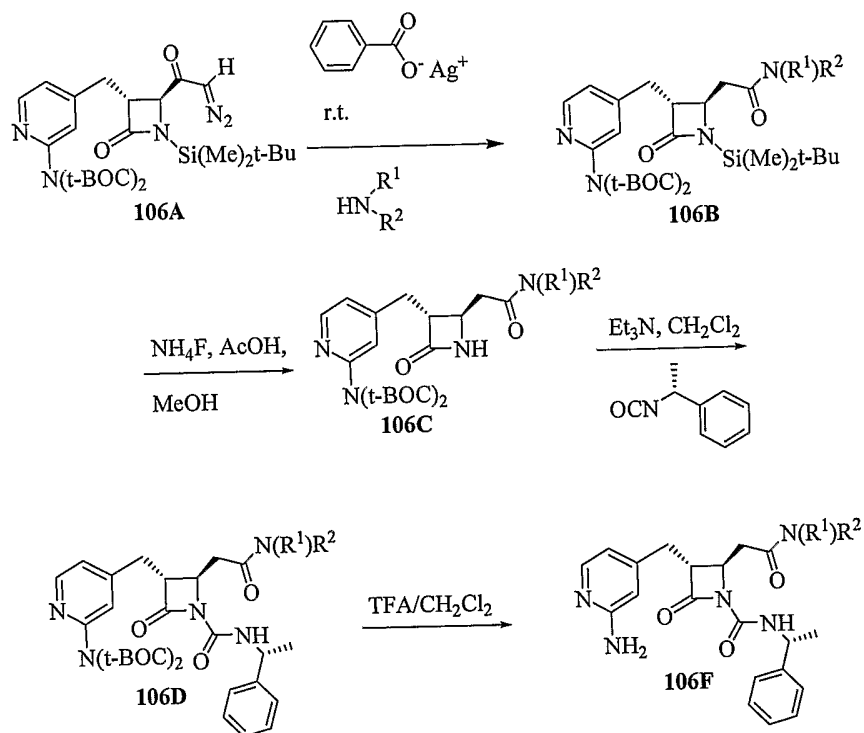
[0123] A method of synthesizing azetidinones bearing R_4 substituents containing sulfonamide, amides, urea, thiourea, and amino groups is shown in Scheme 102. Compound **102A** is described in scheme 16. **102A** can be converted to **102B** by a three step sequence including displacement of the mesylate with azide, desilylation, and acylation with an appropriate isocyanate. **102B** can be converted to sulfonamide **102C** by a sequence involving reduction, sulfonylation, and BOC deprotection with TFA. Additionally, **102B** can be converted to amide **102D** by a sequence involving reduction, coupling with a carboxylic acid, and BOC deprotection with TFA. Additionally, **102B** can be converted to urea **102E** by a sequence involving reduction, acylation with an isocyanate, and BOC deprotection with TFA. Additionally, **102B** can be converted to amine **102F** by a sequence involving reduction, reductive amination with an aldehyde, and BOC deprotection with TFA.

Scheme 105



[0124] A method of synthesizing azetidinones bearing R_4 substituents bearing a methylene (CH₂) group attached to the azetidinone is shown in scheme 105. Acid **105A** (scheme 11) can be converted to diazoketone **105B** via the reaction of its mixed anhydride with TMS diazomethane. Silver promoted rearrangement provides **105C**. Desilylation can provide **105D**. Acylation with an appropriate isocyanate can provide **105E**. TFA deprotection can provide **105F**.

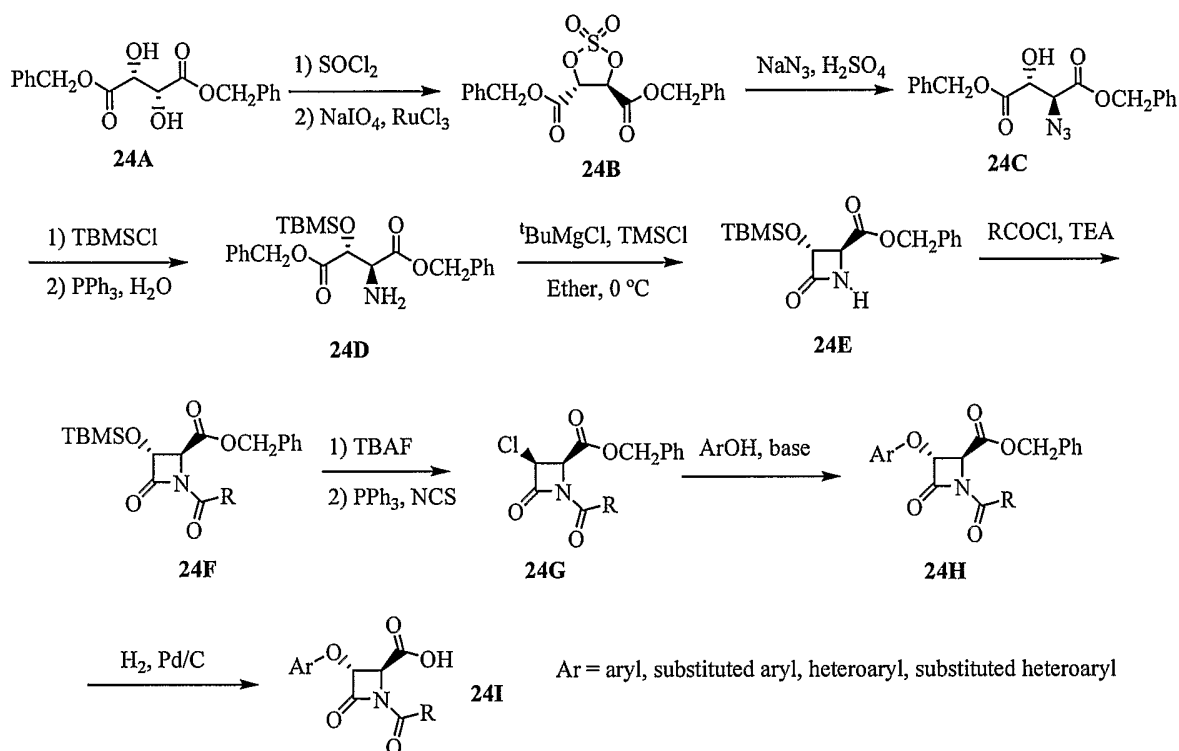
Scheme 106



[0125] A method of synthesizing azetidinones bearing R₄ substituents bearing a methylene (CH₂) group attached to the azetidinone is shown in scheme 106. Diazoketone **106A** (scheme 105) can undergo silver promoted rearrangement in the presence of an amine to provide **106B**. Desilylation can provides **106C**. Acylation with an appropriate isocyanate can provide **106D**. TFA deprotection can provide **106E**.

IV. f) Aryloxy

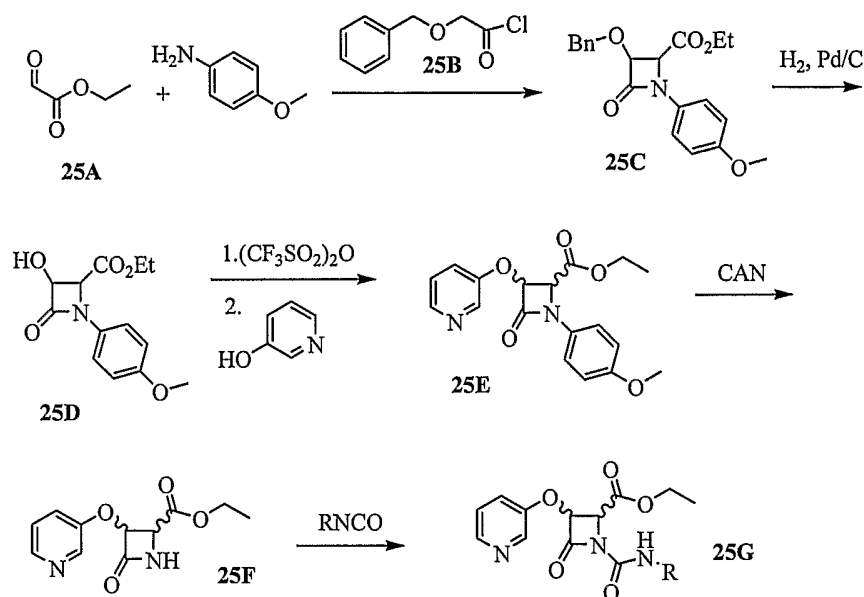
Scheme 24



[0126] One method of synthesizing compounds of the invention with aryloxy substituents is shown in Scheme 24. **24A** can be treated with thionyl chloride and then sodium periodate and ruthenium trichloride in order to produce **24B**. **24B** can be treated with sodium nitrate in sulfuric acid in order to produce **24C**. **24C** can be treated with TBMSCl and then triphenylphosphine in water in order to produce **24D**. **24D** can be treated with t-BuMgCl and TMSCl in ether in order to produce **24E**. **24E** can be treated with an acyl chloride in order to produce **24F**. **24F** can then be treated with TBAF and then triphenylphosphine and isothiocyanate in order to produce **24G**. **24G** can be treated with an aryl alcohol (or alternatively a substituted aryl, heteroaryl, or substituted heteroaryl alcohol) and base in order to produce **24H**. **24H** can be subjected to hydrogenation conditions in order to produce **24I**.

IV. g) Heteroaryloxy [pyridinyloxy]

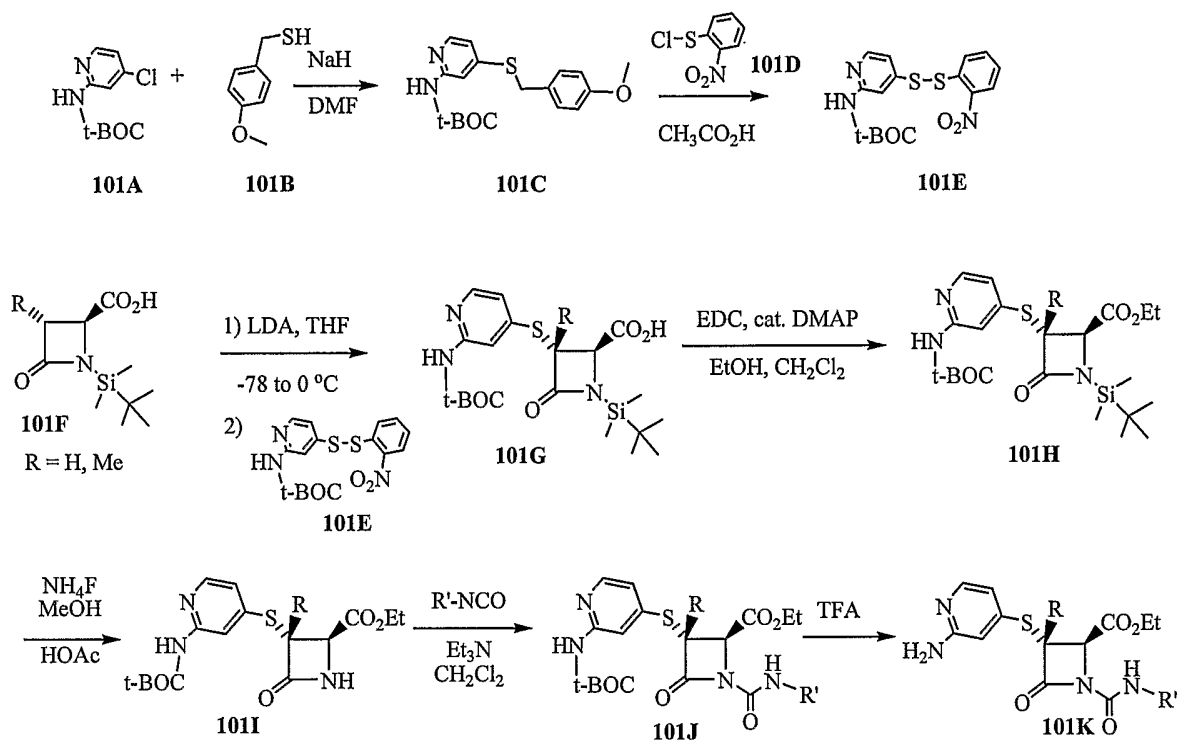
Scheme 25



[0127] N-Heteroaryloxy substituents on azetidinone compounds can be synthesized as shown in Scheme 25. **25A** and **25B** can be treated with 4-methoxyaniline under dehydrating conditions to produce an intermediate imine, which is treated with 2-benzyloxyacetylchloride to form compound **25C**. **25C** can be subjected to catalytic hydrogenation conditions in order to produce **25D**. The secondary alcohol of **25D** can be activated with $(\text{CF}_3\text{SO}_2)_2\text{O}$ and addition of 3-hydroxypyridine can provide **25E**. An alternative path to **25E** can be through a Mitsunobu reaction of **25D** and 3-hydroxypyridine in the presence of triphenylphosphine and DEAD. **25E** can be treated with ceric ammonium nitrate (CAN) in order to produce **25F**. **25F** can be treated with various isocyanates in order to produce **25G**.

IV. h) *Heteroarylthio*

Scheme 101

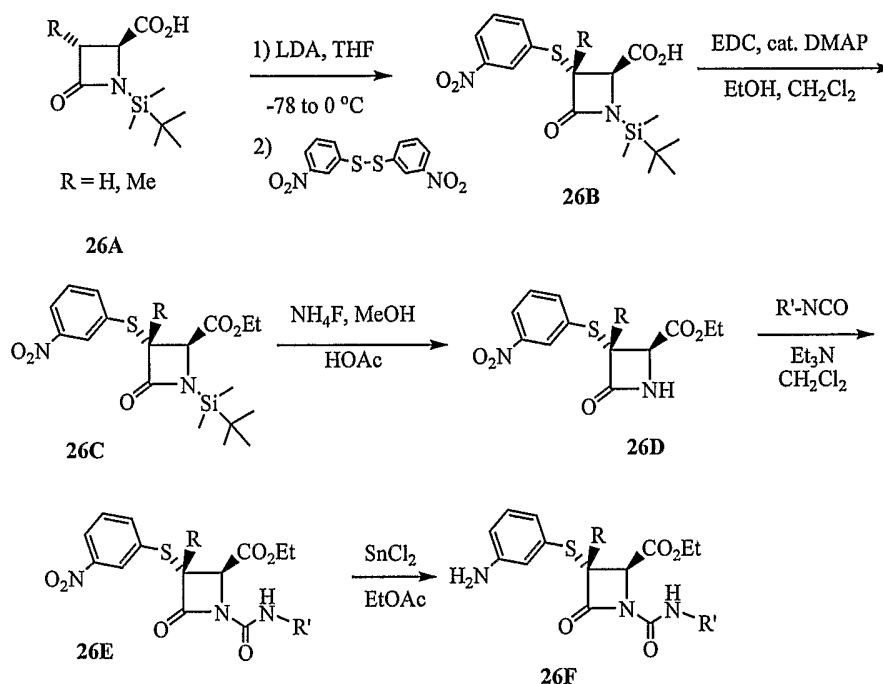


[0128] A method of synthesizing heteroarylthio substituents is shown in Scheme 101.

- 5 Compound **101A** can be treated with sulfide **101B** to provide thioether **101C**. **101C** can be treated with sulfenyl chloride **101D** to form disulfide **101E**. This disulfide can be used to functionalize the dianion of **101F**, forming thioether **101G**. Esterification with a mixture of ethanol, DMAP, and EDC can provide **101H**. The TBDMS group can deprotected using a mixture of ammonium fluoride, acetic acid, and methanol to form **101I**. **101I** can be treated
- 10 with various isocyanates in the presence of triethylamine to provide **101J**. BOC deprotection with TFA can provide **101K**.

IV. i) Arylthio

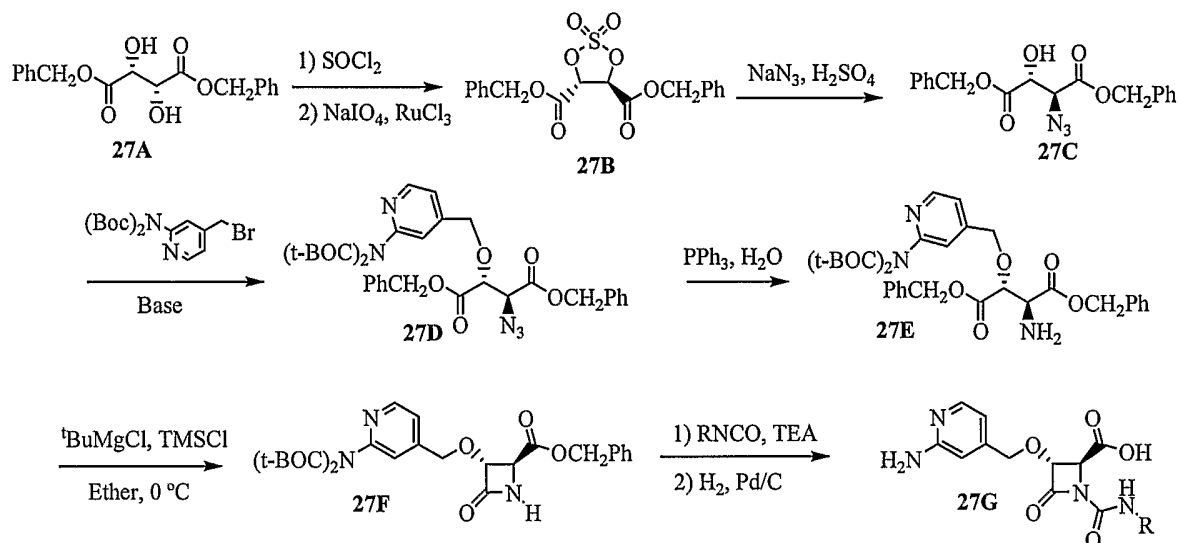
Scheme 26



[0129] A method of synthesizing arylthio substituents is shown in Scheme 26. Compound 5 **26A** can be treated with LDA to form the lithium dianion. Addition of bis-3-nitrophenyldisulfide provides **26B**. The carboxylate of **26B** can be converted to the ethyl ester using ethanol, DMAP, and EDC. The TBDMS group in the resulting ester **26C** can be deprotected using ammonium fluoride in methanol. **26D** can be treated with various isocyanates in the presence of triethylamine to provide **26E**. The nitro group can be reduced 10 using tin (II) chloride to give the aromatic amine **26F**.

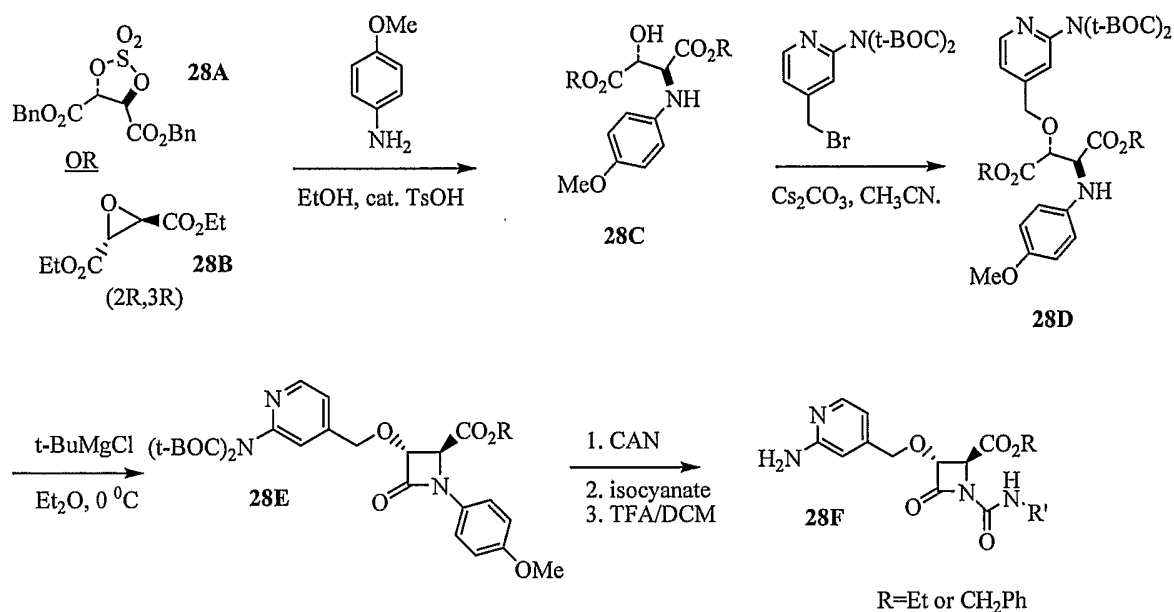
IV. j) Heteroarylalkoxy

Scheme 27



[0130] One method of synthesizing compounds of the invention with [2-amino-4-azabenyloxy] substituents is shown in Scheme 27. Dibenzyltartaric acid **27A** can be treated with thionyl chloride and then sodium periodate in the presence of ruthenium trichloride in order to produce **27B**. **27B** can be treated with sodium azide in sulfuric acid in order to produce **27C**. Bis-BOC protected-2-amino-4-bromomethyl pyridine can be treated with **27C** in the presence of a base in order to produce **27D**. The azide group of **27D** can be reduced with triphenylphosphine (Staudinger reaction) in the presence of water in order to produce **27E**. **27E** can be treated with $t\text{-BuMgCl}$ and TMSCl in ether to produce **27F**. **27F** can be treated with an isocyanate and TEA, and then subjected to hydrogenation conditions in order to produce **27G**.

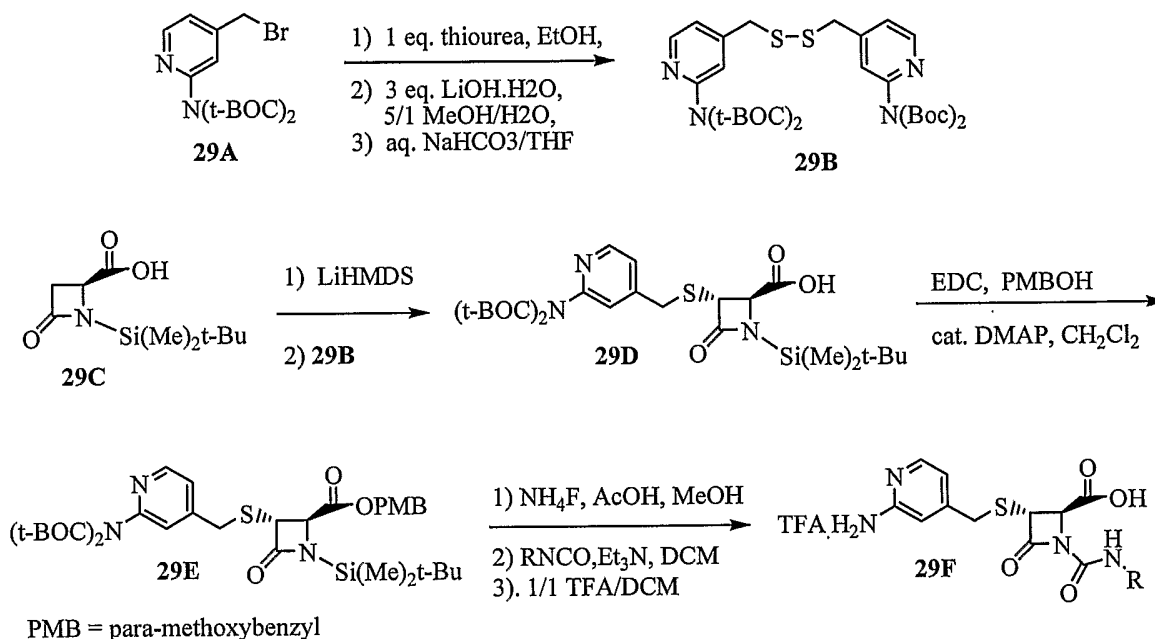
Scheme 28



- [0131] A method of synthesizing compounds of the invention with [2-amino-pyridinyl] methoxy substituents is shown in Scheme 28. **28A** or **28B** can be treated with 4-
- 5 methoxyaniline in ethanol with a catalytic amount of an organic acid in order to produce **28C**. **28C** can be treated with Bis-BOC protected-2-amino-4-bromomethylpyridine in order to produce **28D**. **28D** can be treated with t-butylMgCl in ether in order to produce **28E**. Deprotection of the 4-methoxyphenyl using CAN followed by reaction with various isocyanates, followed by BOC removal in TFA/DCM produces **28F**.

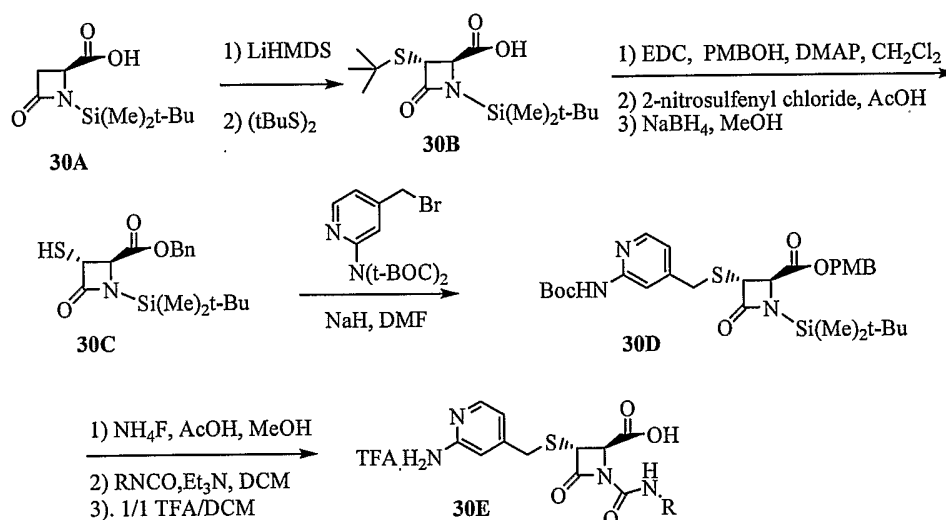
IV. k) Heteroarylalkylthio

Scheme 29



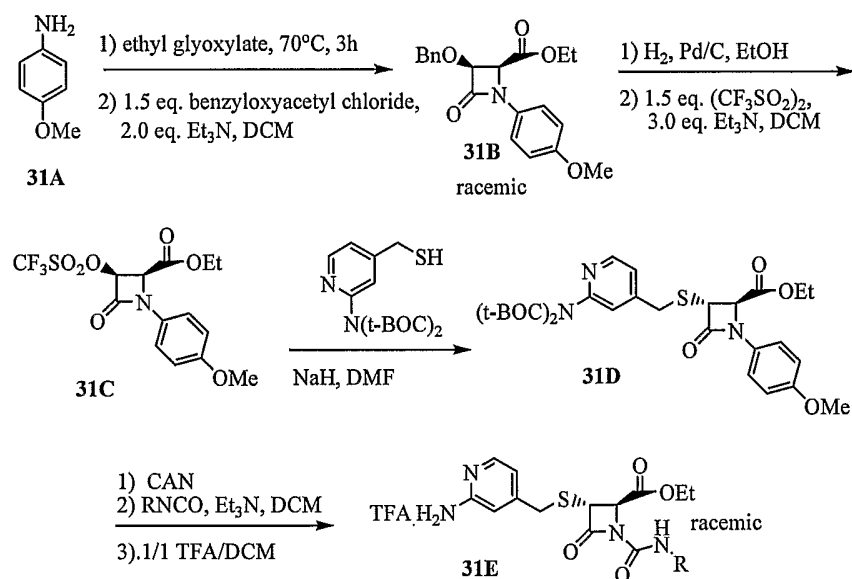
[0132] Heteroarylthio substituents can be synthesized on azetidinone compounds as shown in Scheme 29. **29A** can be treated with an equivalent of thiourea, then three equivalents of lithium hydroxide, and then sodium bicarbonate in order to produce **29B**. The lithium dianion of **29C** can be treated with **29B** to provide compound **29E**. The carboxylic acid of **29D** can be protected as the para-methoxybenzyl ester using para-methoxybenzylalcohol in the presences of EDC and DMAP in order to produce **29E**. Deprotection of the TBDMS group of **29E** followed by urea formation with isocyanate, and finally TFA deprotection of the BOC groups can produce **29F**.

Scheme 30



[0133] An alternative method of synthesizing heteroarylthio substituents is shown in Scheme 30. **30A** can be treated with 2.4 eq. of a lithium reagent to provide the dianion of **30A** and then 1.2 eq. of (t-BuS)₂ in order to produce **30B**. **30B** can be treated with EDC and DMAP in order to produce the benzyl ester **30C**. **30C** can be treated with Bis-BOC protected-2-amino-4-bromomethylpyridine and sodium hydride in DMF in order to produce **30D**. **30D** can be treated with ammonium fluoride, then isocyanate and finally TFA in order to produce **30E**.

Scheme 31



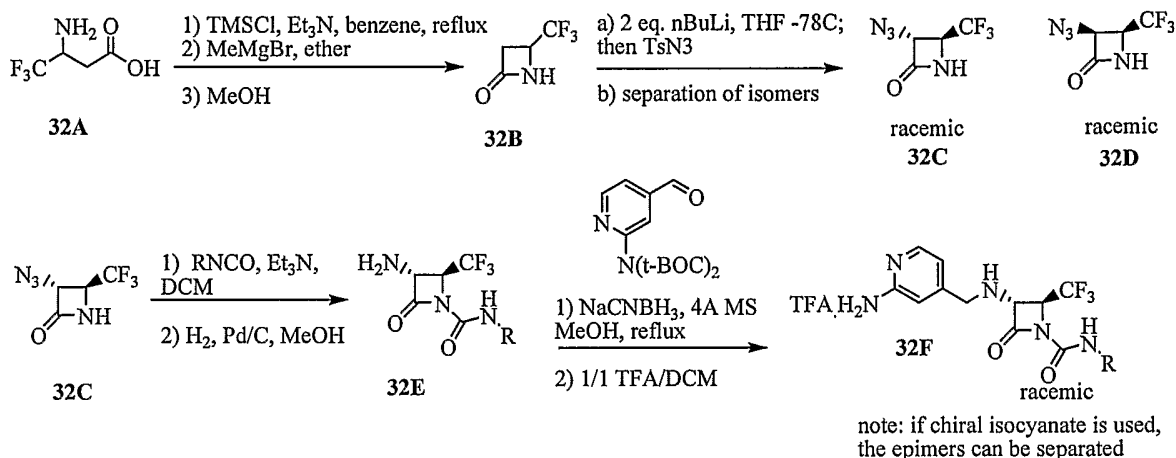
Note: if a chiral isocyanate is used, the two epimers can then be separated

10 [0134] An alternative method of synthesizing heteroarylthio substituents is shown in Scheme 31. **31A** can be condensed with ethyl glyoxylate, and the resulting imine can be acylated with an appropriate acid chloride and cyclized to provide **31B**. Hydrogenolysis and treatment with triflic anhydride can provide **31C**. Displacement of the triflate with an appropriate mercaptan can provide thio ether **31D**. Removal of the aryl group with CAN, treatment with an appropriate isocyanate, and deprotection can provide **31E**.

15

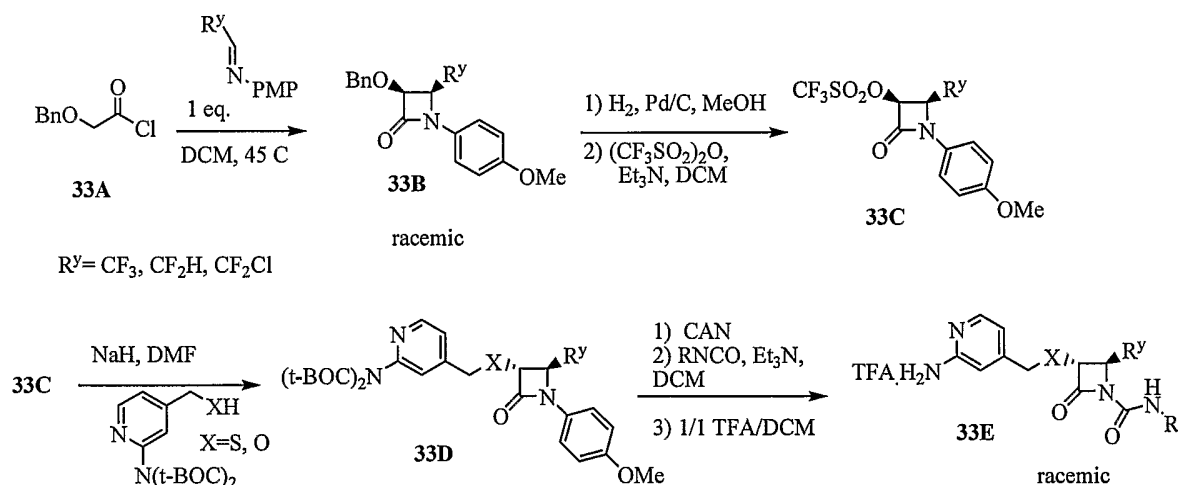
IV. 1) Heteroarylalkylamino

Scheme 32



[0135] A method of synthesizing compounds with 4-trifluoromethyl substituents is shown in Scheme 32. **32A** can be treated with TMS-chloride followed by deprotonation with a Grignard reagent to form **32B**. The resulting beta-lactam **32B** can be treated with 2 equiv. of n-butyl lithium to provide the dianion with after quenching with tosyl azide to give a mixture of **32C** and **32D**. Separation of the mixture followed by urea formation and reduction of the azide can provide **32E**. **32E** can undergo reductive amination with an appropriate aldehyde in the presence of a reducing agent such as NaCNBH₃ to provide, after deprotection of the BOC groups with TFA, **32F**.

Scheme 33

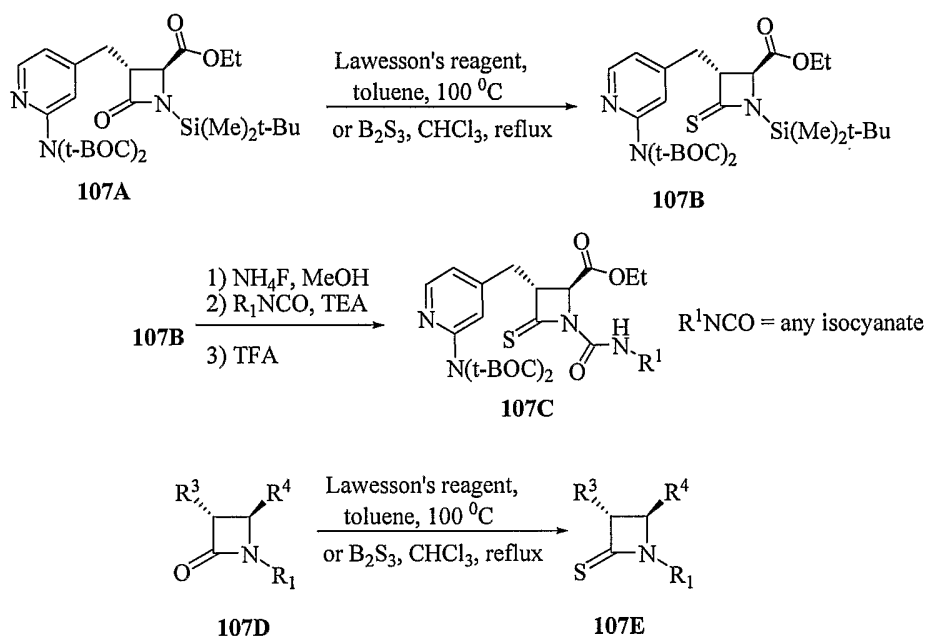


[0136] A method of synthesizing compounds with halomethyl substituents is shown in Scheme 33. **33B** can be prepared by heterocyclization of **33A** with various imines. The

resulting beta-lactam **33B** can be hydrogenolyzed to give the intermediate alcohol with is subsequently activated using trifluoromethanesulfonyl anhydride to give triflate **33C**. Displacement of the trifluoromethanesulfonate with S or O nucleophiles can provide **33D**. Deprotection of the para-methoxyphenyl with CAN, urea formation using various
5 isocyanates, and deprotection of the BOC groups with TFA can provide **33E**.

IV. m) Thio- β -lactams

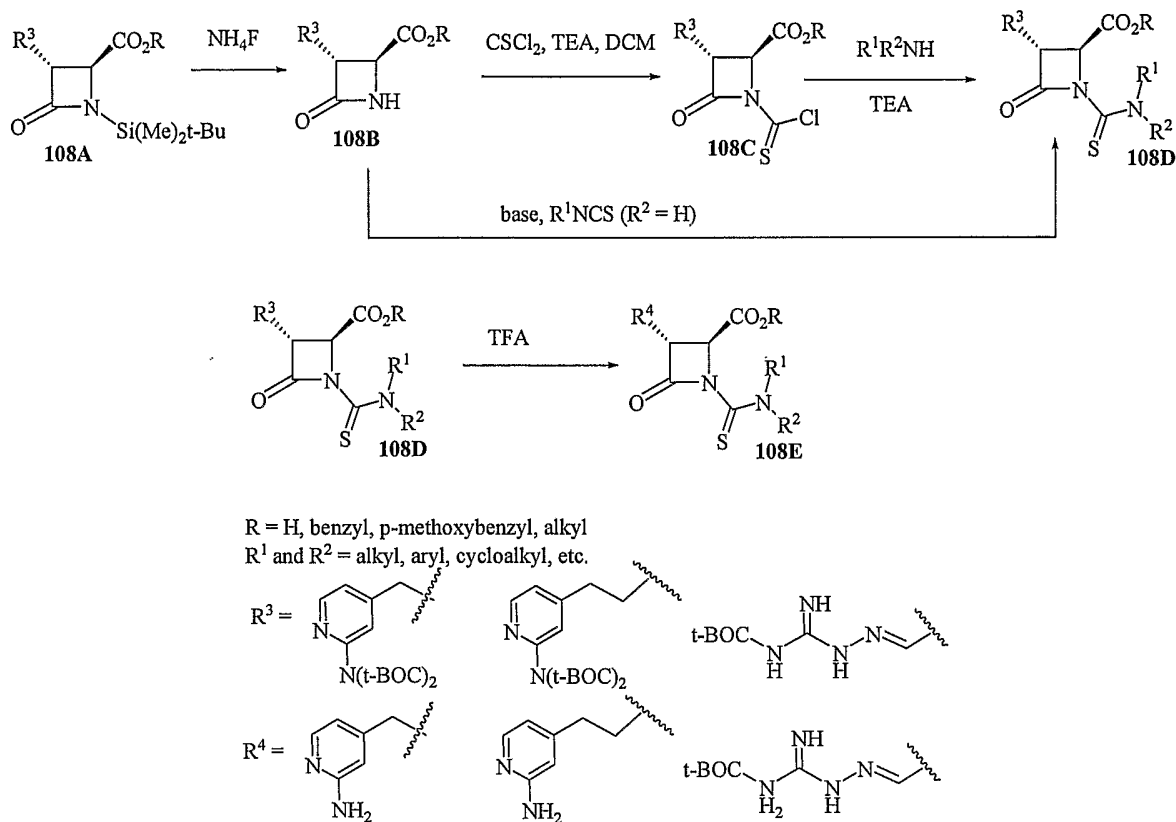
Scheme 107



[0137] A method of synthesizing thioazetidinones is shown in scheme 107. Beta lactam
10 **107A** can be converted to its thio analog **107B**. Desilylation, acylation with an appropriate isocyanate, and TFA deprotection can provide **107E**. This chemistry may be applied to other beta lactams **107D** of this invention to provide thio analogs **107E**.

IV. n) *Thiourea*

Scheme 108



[0138] A method of synthesizing azetidinone thioureas is shown in scheme 108. An

5 appropriate ester **108A** (see schemes 7 and 11) can be desilylated to provide **108B**. **108B** can be converted either directed to **108D** via a thioisocyanate acylation or in a two step procedure involving intermediate chloride **108C**. TFA deprotection can provide **108E**.

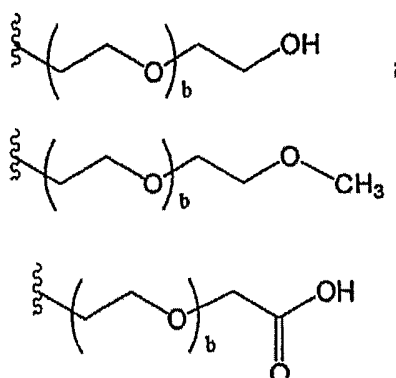
IV. o) *Additional Exemplary Moieties*

[0139] In another exemplary embodiment, the compounds of the invention comprise a

10 moiety that increases the water-solubility of the parent compound. This moiety can be covalently attached, directly or indirectly, to the 1, 2, 3 or 4 position on the azetidinone ring. Exemplary moieties of use for increasing a compound's water solubility include ethers and polyethers, *e.g.*, a member selected from ethylene glycol, and ethylene glycol oligomers, having a molecular weight of from about 60 daltons to about 10,000 daltons, and more

15 preferably of from about 100 daltons to about 1,000 daltons.

[0140] Representative polyether-based substituents include, but are not limited to, the following structures:



in which b is preferably a number from 1 to 100, inclusive. Other functionalized polyethers
 5 are known to those of skill in the art, and many are commercially available from, for example, Shearwater Polymers, Inc. (Alabama).

[0141] In another exemplary embodiment, the compounds of the invention comprise a moiety that includes a reactive functional group for conjugating the compound to another molecule or to a surface. This moiety can be attached, directly or indirectly, to the 1, 2, 3 or
 10 4 position on the azetidinone ring. The linkers of use in the compounds of the invention can also include a cleaveable group. In an exemplary embodiment, the cleaveable group is interposed between the azetidinone core and a targeting agent or macromolecular backbone. Representative useful reactive groups are discussed in greater detail in succeeding sections. Additional information on useful reactive groups is known to those of skill in the art. *See*, for
 15 example, Hermanson, BIOCONJUGATE TECHNIQUES, Academic Press, San Diego, 1996.

Reactive Functional Groups

[0142] As discussed above, the azetidinone core of the compounds of the invention are optionally tethered to other species by means of bonds formed between a reactive functional group on the azetidinone or a linker attached to the azetidinone, and a reactive functional
 20 group of complementary reactivity on the other species. For clarity of illustration the succeeding discussion focuses on the conjugation of representative azetidinones of the invention to polymers, including poly(ethers) and dendrimers, and to targeting agents useful for translocating the azetidinone-targeting agent conjugate across a membrane. The focus exemplifies selected embodiments of the invention from which others are readily inferred by
 25 one of skill in the art. No limitation of the invention is implied, by focusing the discussion on the representative embodiments.

[0143] Exemplary azetidinones of the invention bear a reactive functional group, which is generally located on the azetidinone ring or on a substituted or unsubstituted alkyl or heteroalkyl chain attached to the ring, allowing their facile attachment to another species. A convenient location for the reactive group is the terminal position of an alkyl or heteroalkyl substituent of the azetidinone core.

[0144] Reactive groups and classes of reactions useful in practicing the present invention are generally those that are well known in the art of bioconjugate chemistry. Currently favored classes of reactions available with reactive analogues are those proceeding under relatively mild conditions. These include, but are not limited to nucleophilic substitutions (*e.g.*, reactions of amines and alcohols with acyl halides, active esters), electrophilic substitutions (*e.g.*, enamine reactions) and additions to carbon-carbon and carbon-heteroatom multiple bonds (*e.g.*, Michael reaction, Diels-Alder addition). These and other useful reactions are discussed in, for example, March, *ADVANCED ORGANIC CHEMISTRY*, 3rd Ed., John Wiley & Sons, New York, 1985; Hermanson, *BIOCONJUGATE TECHNIQUES*, Academic Press, San Diego, 1996; and Feeney *et al.*, *MODIFICATION OF PROTEINS*; *Advances in Chemistry Series*, Vol. 198, American Chemical Society, Washington, D.C., 1982.

[0145] Exemplary reaction types include the reaction of carboxyl groups and various derivatives thereof including, but not limited to, N-hydroxysuccinimide esters, N-hydroxybenzotriazole esters, acid halides, acyl imidazoles, thioesters, p-nitrophenyl esters, alkyl, alkenyl, alkynyl and aromatic esters. Hydroxyl groups can be converted to esters, ethers, aldehydes, *etc.* Haloalkyl groups are converted to new species by reaction with, for example, an amine, a carboxylate anion, thiol anion, carbanion, or an alkoxide ion. Dienophile (*e.g.*, maleimide) groups participate in Diels-Alder. Aldehyde or ketone groups can be converted to imines, hydrazones, semicarbazones or oximes, or reacted via such mechanisms as Grignard addition or alkyllithium addition. Sulfonyl halides react readily with amines, for example, to form sulfonamides. Amine or sulfhydryl groups are, for example, acylated, alkylated or oxidized. Alkenes can be converted to an array of new species using cycloadditions, acylation, Michael addition, *etc.* Epoxides react readily with amines and hydroxyl compounds.

[0146] Exemplary combinations of reactive functional groups found on a ligand of the invention and on a targeting moiety (or polymer or linker) are set forth in Table 1.

TABLE 1

Chemical Functionality 1	Chemical Functionality 2	Linkage
Hydroxy	Carboxy	Ester
	Hydroxy	Carbonate
	Amine	Carbamate
	SO ₃	Sulfate
	PO ₃	Phosphate
	Carboxy	Acyloxyalkyl
	Ketone	Ketal
	Aldehyde	Acetal
	Hydroxy	Anhydride
	Mercapto	Mercapto
Carboxy		Acyloxyalkyl Thioether
Carboxy		Thioester
Carboxy		Amino amide
Mercapto		Thioester
Carboxy		Acyloxyalkyl ester
Carboxy		Acyloxyalkyl amide
Amino		Acyloxyalkoxy carbonyl
Carboxy		Anhydride
Carboxy		N-acylamide
Amino	Hydroxy	Ester
	Hydroxy	Hydroxymethyl ketone ester
	Hydroxy	Alkoxy carbonyl oxyalkyl
	Carboxy	Acyloxyalkylamine
	Carboxy	Acyloxyalkylamide
	Amino	Urea
	Carboxy	Amide
	Carboxy	Acyloxyalkoxycarbonyl
	Amide	N-Mannich base
	Carboxy	Acyloxyalkyl carbamate
Phosphate oxygen ester	Hydroxy	Phosphate
	Amine	Phosphoramidate
	Mercapto	Thiophosphate ester
Ketone Sulfonamide	Carboxy	Enol ester
	Carboxy	Acyloxyalkyl sulfonamide
	Ester	N-sulfonyl- imidate

[0147] One skilled in the art will readily appreciate that many of these linkages may be produced in a variety of ways and using a variety of conditions. For the preparation of esters,

see, e.g., March *supra* at 1157; for thioesters, *see*, March, *supra* at 362-363, 491, 720-722, 829, 941, and 1172; for carbonates, *see*, March, *supra* at 346-347; for carbanates, *see* March, *supra* at 1156-57; for amides, *see*, March *supra* at 1152; for ureas and thioureas, *see*, March *supra* at 1174; for acetals and ketals, *see*, Greene *et al. supra* 178-210 and March *supra* at 1146; for acyloxyalkyl derivatives, *see*, PRODRUGS: TOPICAL AND OCULAR DRUG DELIVERY, K. B. Sloan, ed., Marcel Dekker, Inc., New York, 1992; for enol esters, *see*, March *supra* at 1160; for N-sulfonylimidates, *see*, Bundgaard *et al.*, *J. Med. Chem.*, **31**:2066 (1988); for anhydrides, *see*, March *supra* at 355-56, 636-37, 990-91, and 1154; for N-acylamides, *see*, March *supra* at 379; for N-Mannich bases, *see*, March *supra* at 800-02, and 828; for hydroxymethyl ketone esters, *see*, Petracek *et al. Annals NY Acad. Sci.*, **507**:353-54 (1987); for disulfides, *see*, March *supra* at 1160; and for phosphonate esters and phosphonamidates.

[0148] The reactive functional groups can be chosen such that they do not participate in, or interfere with, the reactions necessary to assemble the reactive ligand analogue.

Alternatively, a reactive functional group can be protected from participating in the reaction by the presence of a protecting group. Those of skill in the art will understand how to protect a particular functional group from interfering with a chosen set of reaction conditions. For examples of useful protecting groups, *see* Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York, 1991.

[0149] Generally, prior to forming the linkage between the ligand and the targeting (or other) agent, and optionally, the linker group, at least one of the chemical functionalities is activated. One skilled in the art will appreciate that a variety of chemical functionalities, including hydroxy, amino, and carboxy groups, can be activated using a variety of standard methods and conditions. For example, a hydroxyl group of the ligand (or targeting agent) can be activated through treatment with phosgene to form the corresponding chloroformate, or p-nitrophenylchloroformate to form the corresponding carbonate.

[0150] In an exemplary embodiment, the invention makes use of a targeting agent that includes a carboxyl functionality. Carboxyl groups may be activated by, for example, conversion to the corresponding acyl halide or active ester. This reaction may be performed under a variety of conditions as illustrated in March, *supra* pp. 388-89. In an exemplary embodiment, the acyl halide is prepared through the reaction of the carboxyl-containing group with oxalyl chloride. The activated agent is combined with a ligand or ligand-linker arm combination to form a conjugate of the invention. Those of skill in the art will

appreciate that the use of carboxyl-containing targeting agents is merely illustrative, and that agents having many other functional groups can be conjugated to the ligands of the invention.

Targeting Groups

5 [0151] The compounds of the invention may also be conjugated to an agent that targets the compound to a specific tissue or region of disease. The compound of the invention can be targeted for specific delivery to the cells to be treated by conjugation of the compounds to a targeting agent. The term "targeting agent" refers to a species that serves to deliver the compound of the invention to a specific site. Targeting agents include, for example, molecules that specifically bind molecules present on a cell surface. Such targeting agents
10 useful in the invention include anti-cell surface antigen antibodies; cytokines, including interleukins, factors such as epidermal growth factor (EGF), and the like, are also specific targeting agents known to bind cells expressing high levels of their receptors. Targeting agents include species that are taken up by cells using either active or passive mechanisms.

[0152] Particularly useful targeting agents for targeting the compounds of the invention to
15 cells for therapeutic activity include those ligands that bind antigens or receptors present on virus-infected cells to be treated. For example, antigens present on T-cells, such as CD48, can be targeted with antibodies. Antibody fragments, including single chain fragments, can also be used. Other such ligand-receptor binding pairs are known in the scientific literature for targeting anti-viral treatments to target cells. Methods for producing conjugates of the
20 compounds of the invention and the targeting moieties are known.

[0153] Membrane translocation polypeptides are another exemplary targeting agent. Membrane translocation polypeptides" have amphiphilic or hydrophobic amino acid subsequences that have the ability to act as membrane-translocating carriers. In one embodiment, homeodomain proteins have the ability to translocate across cell membranes.
25 The shortest internalizable peptide of a homeodomain protein, Antennapedia, was found to be the third helix of the protein, from amino acid position 43 to 58 (*see, e.g., Prochiantz, Current Opinion in Neurobiology* 6:629-634 (1996)). Another subsequence, the h (hydrophobic) domain of signal peptides, was found to have similar cell membrane translocation characteristics (*see, e.g., Lin et al., J. Biol. Chem.* 270: 14255-14258 (1995)).

30 [0154] Examples of peptide sequences include, but are not limited to: an 11 amino acid peptide of the tat protein of HIV; a 20 residue peptide sequence which corresponds to amino acids 84-103 of the p16 protein (*see Fahraeus et al., Current Biology* 6:84 (1996)); the third

helix of the 60-amino acid long homeodomain of Antennapedia (Derossi *et al.*, *J. Biol. Chem.* 269:10444 (1994)); the h region of a signal peptide such as the Kaposi fibroblast growth factor (K-FGF) h region (Lin *et al.*, *supra*); or the VP22 translocation domain from HSV (Elliot & O'Hare, *Cell* 88:223-233 (1997)). Other suitable chemical moieties that provide enhanced cellular uptake may also be chemically linked to the compounds of the invention.

[0155] Such subsequences can be used to translocate compounds of the invention across a cell membrane. Compounds of the invention can be conveniently fused to or derivatized with such sequences. Typically, the translocation sequence is provided as part of a fusion protein. Optionally, a linker as described herein can be used to link the compound of the invention and the translocation sequence. Any suitable linker can be used, *e.g.*, a peptide linker or other chemical linkers.

[0156] Toxin molecules also have the ability to transport compounds across cell membranes. Often, such molecules are composed of at least two parts (called "binary toxins"): a translocation or binding domain or polypeptide and a separate toxin domain or polypeptide. Typically, the translocation domain or polypeptide binds to a cellular receptor, and then the toxin is transported into the cell. Several bacterial toxins, including *Clostridium perfringens* iota toxin, diphtheria toxin (DT), *Pseudomonas* exotoxin A (PE), pertussis toxin (PT), *Bacillus anthracis* toxin, and pertussis adenylate cyclase (CYA), have been used in attempts to deliver peptides to the cell cytosol as internal or amino-terminal fusions (Arora *et al.*, *J. Biol. Chem.*, 268: 3334-3341 (1993); Perelle *et al.*, *Infect. Immun.*, 61: 5147-5156 (1993); Stenmark *et al.*, *J. Cell Biol.* 113: 1025-1032 (1991); Donnelly *et al.*, *PNAS U.S.A.* 90: 3530-3534 (1993); Carbonetti *et al.*, *Abstr. Annu. Meet. Am. Soc. Microbiol.* 95: 295 (1995); Sebo *et al.*, *Infect. Immun.* 63:3851-3857 (1995); Klimpel *et al.*, *PNAS U.S.A.* 89:10277-10281 (1992); and Novak *et al.*, *J. Biol. Chem.* 267:17186-17193 (1992)).

[0157] Non-covalent protein binding groups are also of use to target the compounds of the invention to specific regions of the body and to increase the half-life of the agent through protein binding.

Macromolecular Conjugates

[0158] In an exemplary embodiment, the invention provides a macromolecular, *i.e.*, MW > 1000 D, conjugate between the azetidinone core and a macromolecular species. In one embodiment, a macromolecular conjugate of the invention is formed by covalently conjugating an azetidinone to a macromolecule via a reactive functional group. In another

embodiment, the macromolecular conjugate is formed by a non-covalent interaction between a azetidinone derivative and a macromolecule, *e.g.*, a serum protein.

[0159] In the following discussion, the invention is described by reference to specific macromolecules of use for forming conjugates with the novel azetidinone cores of the invention. Those of skill in the art will appreciate that the focus of the discussion is for clarity of illustration and does not limit the scope of the invention. The invention provides macromolecular conjugates that include components derived from biomolecules and synthetic molecules. Exemplary biomolecules include polypeptides (*e.g.*, antibodies, enzymes, receptors, antigens, immunogens such as KLH (keyhole limpet hemocyanin), BSA (bovine serum albumin) and HSA (human serum albumin); polysaccharides (*e.g.*, starches, inulin, dextran); lectins, nonpeptide antigens and the like. Exemplary synthetic polymers include poly(acrylic acid), poly(lysine), poly(glutamic acid), poly(ethylene imine), *etc.*

Covalent Conjugation

[0160] Selection of an appropriate reactive functional group on an azetidinone core of the invention to form a desired macromolecular species is well within the abilities of one of skill in the art. Exemplary reactive functional groups of use in forming the covalent conjugates of the invention are discussed above. It is well within the abilities of one of skill to select and prepare an azetidinone core of the invention having an appropriate reactive functional group of complementary reactivity to a reactive group on its conjugation partner.

[0161] In one embodiment, the bond formed between reactive functional groups of the macromolecule and that of the azetidinone attaches the azetidinone to the macromolecule essentially irreversibly via a “stable bond” between the components. A “stable bond”, as used herein, is a bond, which maintains its chemical integrity over a wide range of conditions (*e.g.*, amide, carbamate, carbon-carbon, ether, *etc.*). In another embodiment, a “cleaveable bond” links the macromolecule and the azetidinone. A “cleaveable bond”, as used herein, is a bond that undergoes scission under selected conditions. Cleaveable bonds include, but are not limited to, disulfide, imine, carbonate and ester bonds. As discussed in the preceding sections, the reactive functional group can be located at one or more positions of the azetidinone.

Polysaccharides

[0162] In an exemplary embodiment, the present invention provides conjugates between an azetidinone core and saccharides, *e.g.*, polysaccharides. In an exemplary embodiment, the

invention provides a conjugate between a azetidinone and inulin. Inulin is a naturally occurring polysaccharide, which has been previously investigated as a carrier for diagnostic moieties (Rongved, P. K., *J. Carbohydr. Res.* **1991**, 214, 315; Corsi, D. M. V. E. *et al.*, *Chem. Eur. J.* **2001**, 7, 64). The structure of inulin can be described as a mixture of linear β -(2 \rightarrow 1)-linked α -D-fructofuranosyl chains with a α -D-glucopyranosyl unit at the terminal end. Inulin is commercially available in a variety of molecular weights and the degree of polymerization varies from 10 to 30, resulting in a molecular weight distribution of 1500 to 5000 Da. The high hydrophilicity, pH stability, low solution viscosity and biocompatibility of inulin ensure that its conjugates have favorable pharmacological properties.

10 ***Dendrimer-Based Agents***

[0163] In another aspect, the present invention provides a azetidinone as set forth above, which is attached to a dendrimer via a reactive functional group. Similar to the polymeric group discussed above, the dendrimer has at least two reactive functional groups. In one embodiment, one or more formed azetidinone is attached to the dendrimer. Alternatively, the azetidinone is formed directly on the dendrimer.

[0164] In an exemplary embodiment, a water-soluble and bio-adapted polyester (polypropionate) class of dendrimers has been designed to provide favorable pharmacokinetic properties. See., for example, Ihre, H. *et al.*, *Macromolecules* **1998**, 31, 4061; Ihre, H. *et al.*, *J. Am. Chem. Soc.* **1996**, 118, 6388; Anders, H., Ihre, H., Patent W0/9900440 (Sweden)). In an exemplary embodiment, the termini of the dendrimers are conjugated to a azetidinone core of the invention.

Poly(ethylene glycol)-based Agents

[0165] In another exemplary embodiment, the invention provides a conjugate between a azetidinone core of the invention and poly(ethylene glycol). Poly(ethylene glycol) (PEG) is used in biotechnology and biomedical applications. The use of this agent has been reviewed (POLY(ETHYLENE GLYCOL) CHEMISTRY: BIOTECHNICAL AND BIOMEDICAL APPLICATIONS, J. M. Harris, Ed., Plenum Press, New York, 1992). Modification of enzymes (Chiu *et al.*, *J. Bioconjugate Chem.*, **4**: 290-295 (1993)), RGD peptides (Braatz *et al.*, *Bioconjugate Chem.*, **4**: 262-267 (1993)), liposomes (Zalipsky, *S. Bioconjugate Chem.*, **4**: 296-299 (1993)), and CD4-IgG glycoprotein (Chamow *et al.*, *Bioconjugate Chem.*, **4**: 133-140 (1993)) are some of the recent advances in the use of polyethylene glycol. Surfaces treated with PEG

have been shown to resist protein deposition and have improved resistance to thrombogenicity when coated on blood contacting biomaterials (Merrill, "Poly(ethylene oxide) and Blood Contact: A Chronicle of One Laboratory," in POLY(ETHYLENE GLYCOL) CHEMISTRY: BIOTECHNICAL AND BIOMEDICAL APPLICATIONS, Harris, Ed., Plenum Press, New York, (1992), pp. 199-220).

[0166] Many routes are available for attaching an azetidinone core of the invention onto a polymeric or oligomeric species. See, for example, Dunn, R.L., *et al.*, Eds. POLYMERIC DRUGS AND DRUG DELIVERY SYSTEMS, ACS Symposium Series Vol. 469, American Chemical Society, Washington, D.C. 1991; Herren *et al.*, *J. Colloid and Interfacial Science* **115**: 46-55 (1987); Nashabeh *et al.*, *J. Chromatography* **559**: 367-383 (1991); Balachandar *et al.*, *Langmuir* **6**: 1621-1627 (1990); and Burns *et al.*, *Biomaterials* **19**: 423-440 (1998).

[0167] Many activated derivatives of poly(ethyleneglycol) are available commercially and in the literature. It is well within the abilities of one of skill to choose, and synthesize if necessary, an appropriate activated PEG derivative with which to prepare a conjugate useful in the present invention. See, Abuchowski *et al.* *Cancer Biochem. Biophys.*, **7**: 175-186 (1984); Abuchowski *et al.*, *J. Biol. Chem.*, **252**: 3582-3586 (1977); Jackson *et al.*, *Anal. Biochem.*, **165**: 114-127 (1987); Koide *et al.*, *Biochem Biophys. Res. Commun.*, **111**: 659-667 (1983), tresylate (Nilsson *et al.*, *Methods Enzymol.*, **104**: 56-69 (1984); Delgado *et al.*, *Biotechnol. Appl. Biochem.*, **12**: 119-128 (1990)); N-hydroxysuccinimide derived active esters (Buckmann *et al.*, *Makromol. Chem.*, **182**: 1379-1384 (1981); Joppich *et al.*, *Makromol. Chem.*, **180**: 1381-1384 (1979); Abuchowski *et al.*, *Cancer Biochem. Biophys.*, **7**: 175-186 (1984); Katre *et al.* *Proc. Natl. Acad. Sci. U.S.A.*, **84**: 1487-1491 (1987); Kitamura *et al.*, *Cancer Res.*, **51**: 4310-4315 (1991); Boccu *et al.*, *Z. Naturforsch.*, **38C**: 94-99 (1983), carbonates (Zalipsky *et al.*, POLY(ETHYLENE GLYCOL) CHEMISTRY: BIOTECHNICAL AND BIOMEDICAL APPLICATIONS, Harris, Ed., Plenum Press, New York, 1992, pp. 347-370; Zalipsky *et al.*, *Biotechnol. Appl. Biochem.*, **15**: 100-114 (1992); Veronese *et al.*, *Appl. Biochem. Biotech.*, **11**: 141-152 (1985)), imidazolyl formates (Beauchamp *et al.*, *Anal. Biochem.*, **131**: 25-33 (1983); Berger *et al.*, *Blood*, **71**: 1641-1647 (1988)), 4-dithiopyridines (Woghiren *et al.*, *Bioconjugate Chem.*, **4**: 314-318 (1993)), isocyanates (Byun *et al.*, *ASAIO Journal*, M649-M-653 (1992)) and epoxides (U.S. Pat. No. 4,806,595, issued to Noishiki *et al.*, (1989). Other linking groups include the urethane linkage between amino groups and activated PEG. See, Veronese, *et al.*, *Appl. Biochem. Biotechnol.*, **11**: 141-152 (1985).

V. Pharmaceutical Compositions and Methods of Treatment

[0168] The pharmaceutical compositions, or pharmaceutical formulations, of the invention can take a variety of forms adapted to the chosen route of administration. In general, they include a compound of the invention and at least one pharmaceutical excipient. Those skilled
5 in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutical formulations incorporating the compounds described herein. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, propylene glycol, mineral oil, vegetable oil and dimethylsulfoxide (DMSO).

10 [0169] The compositions of the invention may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It is further understood that the best method of administration may be a combination of methods. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is
15 particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques.

[0170] The pharmaceutical formulations containing compounds of the invention are preferably in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous
20 or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0171] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical formulations, and such compositions may contain one or more agents selected from the group consisting of sweetening agents,
25 flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and
30 disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay

disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

5 [0172] Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and 10 lubricants such as those known in the art. The inventive compounds may be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl 15 methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ); and agents to control release such as polyacrylic copolymer (e.g., CARBOPOL 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

20 [0173] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0174] Aqueous suspensions contain the active materials in admixture with excipients 25 suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; and dispersing or wetting agents, which may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty 30 acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more
5 flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0175] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and
10 flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0176] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or
15 wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0177] Pharmaceutical formulations of the invention may also be in the form of oil-in-water emulsions and water-in-oil emulsions. The oily phase may be a vegetable oil, for example
20 olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth; naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol; anhydrides, for example sorbitan monooleate; and condensation products of the said partial esters with ethylene oxide, for
25 example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0178] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical formulations may be in
30 the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may

also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or
5 suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0179] The composition of the invention may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared
10 by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0180] Alternatively, the compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be
15 suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0181] For administration to non-human animals, the composition containing the therapeutic compound may be added to the animal's feed or drinking water. Also, it will be convenient to formulate animal feed and drinking water products so that the animal takes in
20 an appropriate quantity of the compound in its diet. It will further be convenient to present the compound in a composition as a premix for addition to the feed or drinking water. The composition can also added as a food or drink supplement for humans.

[0182] Dosage levels of the order of from about 5 mg to about 250 mg per kilogram of body weight per day and more preferably from about 25 mg to about 150 mg per kilogram of body
25 weight per day, are useful in the treatment of the above-indicated conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the condition being treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

30 [0183] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. It will be understood, however, that the specific dose level for

any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

- 5 [0184] Preferred compounds of the invention will have desirable pharmacological properties that include, but are not limited to, oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.
- 10 [0185] Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of laboratory animals that receive the compound
- 15 intravenously.
- [0186] Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcova, et al. (*Journal of Chromatography B* (1996) volume 677, pages 1-27).
- [0187] Compound half-life is inversely proportional to the frequency of dosage of a
- 20 compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition*, (1998) volume 26, pages 1120-1127).
- [0188] The amount of the composition required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the
- 25 condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician.
- [0189] Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing
- 30 or dispersing agents such as those known in the art.

[0190] Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

[0191] Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

[0192] The novel compounds of the invention possess tryptase inhibitory activity. As a result of this tryptase activity, the compounds of the invention as well as an inner salt thereof, a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof, are useful as antiinflammatory agents particularly in the treatment of chronic asthma and may also be useful in treating or preventing allergic rhinitis, inflammatory bowel disease, psoriasis, conjunctivitis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, and other chronic inflammatory joint diseases, or diseases of joint cartilage destruction. Additionally, these compounds may be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture. Additionally, these compounds may be useful for treating or preventing diabetic retinopathy, tumor growth and other consequences of angiogenesis. Additionally, these compounds may be useful for treating or preventing fibrotic conditions, for example, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and hypertrophic scars.

[0193] The compounds of the invention are also inhibitors of Factor Xa and/or Factor VIIa. As a result, the compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may also be useful in the treatment or prevention of thrombotic events associated with coronary artery and cerebrovascular disease, venous or arterial thrombosis, coagulation syndromes, ischemia and angina (stable and unstable), deep vein thrombosis (DVT), disseminated intravascular coagulopathy, Kasacach-Merritt syndrome, pulmonary embolism, myocardial infarction, cerebral infarction, cerebral thrombosis, transient ischemic attacks, atrial fibrillation, cerebral embolism, thromboembolic complications of surgery (such as hip or knee replacement, introduction of artificial heart valves and endarterectomy) and peripheral arterial occlusion and may also be useful in treating or preventing myocardial infarction, stroke, angina and

other consequences of atherosclerotic plaque rupture. The compounds of the invention possessing Factor Xa and/or Factor VIIa inhibition activity may also be useful as inhibitors of blood coagulation such as during the preparation, storage and fractionation of whole blood.

5 [0194] The compounds of the invention are also inhibitors of urokinase-type plasminogen activator. As a result, the compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may be useful in the treatment or prevention of restenosis and aneurysms, in the treatment or prevention of myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture, and may also be useful in the treatment of malignancies, prevention of
10 metastases, prevention of prothrombotic complications of cancer, and as an adjunct to chemotherapy.

[0195] The compounds of the invention also possess thrombin and trypsin inhibitory activity. As a result, the compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof
15 may be useful in treating or preventing pancreatitis, in the treatment or prevention of thrombotic events as described above, and may also be useful as inhibitors of blood coagulation such as during the preparation, storage, and fractionation of whole blood.

[0196] The compounds of the invention are also inhibitors of Factor XIa. As a result, the compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt
20 thereof, a hydrolyzable ester thereof, or a solvate thereof may also be useful in the treatment or prevention of thrombotic events associated with coronary artery and cerebrovascular disease, venous or arterial thrombosis, coagulation syndromes, ischemia and angina (stable and unstable), deep vein thrombosis (DVT), disseminated intravascular coagulopathy, Kasacach-Merritt syndrome, pulmonary embolism, myocardial infarction, cerebral infarction,
25 cerebral thrombosis, transient ischemic attacks, atrial fibrillation, cerebral embolism, thromboembolic complications of surgery (such as hip or knee replacement, introduction of artificial heart valves and endarterectomy) and peripheral arterial occlusion and may also be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture. The compounds of the invention possessing Factor XIa
30 inhibition activity may also be useful as inhibitors of blood coagulation such as during the preparation, storage and fractionation of whole blood.

- 5 [0197] The compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may be administered orally, topically, rectally or parenterally or may be administered by inhalation into the bronchioles or nasal passages. The method of administration will, of course, vary upon the type of disease being treated. The amount of active compound administered will also vary according to the method of administration and the disease being treated. An effective amount will be within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg per day in a single or multiple doses administered at appropriate intervals throughout the day.
- 10 [0198] The pharmaceutical composition used in these therapies can be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms such as tablets, pills, powders, liquid solutions or suspensions, liposomes, injectable and infusible solutions. Such compositions can include pharmaceutically acceptable excipients, preservatives, stabilizers, and other agents conventionally employed in the pharmaceutical industry.
- 15 [0199] When the compounds of the invention as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof are employed to treat asthma or allergic rhinitis they will may be formulated as aerosols. The term "aerosol" includes any gas-borne suspended phase of the active compound which is capable of being inhaled into the bronchioles or nasal passage. Aerosol formulations include a gas-borne suspension of droplets of the active compound as produced in a metered dose inhaler or nebulizer or in a mist sprayer. Aerosol formulations also include a dry powder composition suspended in air or other carrier gas. The solutions of the active compounds of the invention used to make the aerosol formulation will be in a concentration of from about 0.1 to about 100 mg/ml, more preferably 0.1 to about 30 mg/ml, and most preferably from about 1 to about 10 mg/ml. The solution will usually include a pharmaceutically acceptable buffer such as a phosphate or bicarbonate to give a pH of from about 5 to 9, preferably 6.5 to 7.8, and more preferably 7.0 to 7.6. Preservatives and other agents can be included according to conventional pharmaceutical practice.
- 20 25 30 [0200] Other pharmaceutically active agents can be employed in combination with the compounds of the invention depending upon the disease being treated. For example, in the treatment of asthma, β -adrenergic agonists such as albuterol, terbutaline, formoterol, fenoterol or prenaline can be included as can anticholinergics such as ipratropium bromide,

anti-inflammatory corticosteroids such as beclomethasone, triamcinolone, flurisolide or dexamethasone, and anti-inflammatory agents such as cromolyn and nedocromil.

5 [0201] In addition to the novel compounds of the invention and the methods of use for the compounds of the invention, this invention is also directed to novel intermediates and novel synthetic routes employed in the preparation of such compounds.

10 [0202] FXIa inhibition according to the invention represents a more effective and safer method of inhibiting thrombosis compared to inhibiting other coagulation serine proteases such as thrombin or Factor Xa. Administration of a small molecule FXIa inhibitor should have the effect of inhibiting thrombin generation and clot formation with no or substantially no effect on bleeding times and little or no impairment of haemostasis. These results differ substantially from that of other "direct acting" coagulation protease inhibitors (*e.g.* active-site inhibitors of thrombin and Factor Xa), which demonstrate prolongation of bleeding time and less separation between antithrombotic efficacy and bleeding time prolongation. A preferred method according to the invention comprises administering to a mammal a pharmaceutical composition containing at least one compound of the invention.

15 [0203] The methods of the present invention are useful for treating or preventing those conditions which involve the action of Factor XIa. Accordingly, the methods of the present invention are useful in treating consequences of atherosclerotic plaque rupture including cardiovascular diseases associated with the activation of the coagulation cascade in thrombotic or thrombophilic states. As used herein, the terms "treating" or "treatment" encompass responsive and/or prophylaxis measures, *e.g.*, measures designed to inhibit or delay the onset of the disease, achieve a full or partial reduction of the symptoms or disease state, and/or to alleviate, lessen, or cure the disease or disorder and/or its symptoms.

20 [0204] More particularly, the methods of the present invention may be used to treat acute coronary syndromes such as coronary artery disease, myocardial infarction, unstable angina (including crescendo angina), ischemia (*e.g.*, ischemia resulting from vascular occlusion), and cerebral infarction. The methods of the present invention further may be useful in treating stroke and related cerebral vascular diseases (including cerebrovascular accident and transient ischemic attack); venous thrombosis and thrombo-embolism, such as deep vein thrombosis (DVT) and pulmonary embolism; thrombosis associated with atrial fibrillation, ventricular enlargement, dilated cardiac myopathy, or heart failure; peripheral arterial disease and intermittent claudication; the formation of atherosclerotic plaques and transplant

atherosclerosis; restenosis following arterial injury induced endogenously (by rupture of an atherosclerotic plaque), or exogenously (by invasive cardiological procedures such as vessel wall injury resulting from angioplasty); disseminated intravascular coagulopathy, Kasabach-Merritt syndrome, cerebral thrombosis, cerebral embolism, and disseminated intravascular
5 coagulopathy.

[0205] Additionally, the methods of the present invention may be useful in treating thrombo-embolic consequences or complications associated with surgery (such as hip replacement, endarterectomy, introduction of artificial heart valves, vascular grafts, mechanical organs, and implantation or transplantation of organ, tissue or cells); medications
10 (such as oral contraceptives, hormone replacement, and heparin, e.g., for treating heparin-induced thrombocytopenia); and pregnancy or childbirth. The methods of the present invention may be used to treat thrombosis due to confinement (i.e. immobilization, hospitalization, bed rest, limb immobilization, e.g., with immobilizing casts, etc.).

[0206] The methods of the present invention also may be useful in preventing thrombosis and complications in patients genetically predisposed to arterial thrombosis or venous
15 thrombosis (including activated protein C resistance, FVleiden, Prothrombin 20210, elevated coagulation factors FVII, FVIII, FIX, FX, FXI, prothrombin, TAFI and fibrinogen), elevated levels of homocystine, and deficient levels of antithrombin, protein C, and protein S. The inventive methods may be used for treating heparin-intolerant patients, including those with
20 congenital and acquired antithrombin III deficiencies, heparin-induced thrombocytopenia, and those with high levels of polymorphonuclear granulocyte elastase. The methods of this invention may be used to treat all forms of thrombophilia.

[0207] The methods of the present invention may also be used to maintain blood vessel potency, for example, in patients undergoing transluminal coronary angioplasty, or in
25 connection with vascular surgery such as bypass grafting, arterial reconstruction, atherectomy, vascular grafts, stent patency, and organ, tissue or cell implantation and transplantation. The inventive methods may be used to inhibit blood coagulation in connection with the preparation, storage, fractionation, or use of whole blood. For example, the inventive methods may be used in maintaining whole and fractionated blood in the fluid
30 phase such as required for analytical and biological testing, e.g., for ex vivo platelet and other cell function studies, bioanalytical procedures, and quantitation of blood-containing components, or for maintaining extracorporeal blood circuits, as in dialysis or surgery (e.g., coronary artery bypass surgery).

[0208] In addition, the methods of the present invention may be useful in treating and preventing the prothrombotic complications of cancer. The methods may be useful in treating tumor growth, as an adjunct to chemotherapy, for preventing angiogenesis, and for treating cancer, more particularly, cancer of the lung, prostate, colon, breast, ovaries, and bone.

5 [0209] The methods of the present invention also may be used to treat diabetes mellitus, hypertension, or hypercholesterolemia.

[0210] In carrying out the methods of the present invention, it may be desired to administer the compounds of the invention (Factor XIa inhibitors) in combination with each other and one or more other agents for achieving a therapeutic benefit such as antithrombotic or
10 anticoagulant agents, anti-hypertensive agents, anti-ischemic agents, anti-arrhythmic agents, platelet function inhibitors, and so forth. More particularly, the inventive methods may be carried out by administering the small molecule Factor XIa inhibitors in combination with aspirin, clopidogrel, ticlopidine or CS-747, warfarin, low molecular weight heparins (such as LOVENOX), GPIIb/GPIIIa blockers, PAI-1 inhibitors such as XR-330 and T-686, P2Y1 and
15 P2Y12 receptor antagonists; thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, thromboxane A synthetase inhibitors (such as picotamide), serotonin-2-receptor antagonists (such as ketanserin); compounds that inhibit other coagulation factors such as FVII, FVIII, FIX, FX, prothrombin, TAFI, and fibrinogen, and/or other compounds that inhibit FXI; fibrinolytics such as TPA, streptokinase, PAI-1 inhibitors, and inhibitors of
20 α -2-antiplasmin such as anti- α -2-antiplasmin antibody fibrinogen receptor antagonists, hypolipidemic agents, such as HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, AZ4522, and itavastatin), and microsomal triglyceride transport protein inhibitors (such as disclosed in U.S. Pat. Nos. 5,739,135, 5,712,279 and 5,760,246); antihypertensive agents such as angiotensin-converting enzyme inhibitors (e.g.,
25 captopril, lisinopril or fosinopril); angiotensin-II receptor antagonists (e.g., irbesartan, losartan or valsartan); ACE/NEP inhibitors (e.g., omapatrilat and gemopatrilat); and/or β -blockers (such as propranolol, nadolol and carvedilol). The inventive methods may be carried out by administering the small molecule Factor XIa inhibitors in combination with anti-arrhythmic agents such as for atrial fibrillation, for example, amiodarone or dofetilide.

30 [0211] In carrying out the methods of the present invention, it may be desired to administer the compounds of the invention (Factor XIa inhibitors) in combination with agents that increase the levels of cAMP or cGMP in cells for a therapeutic benefit. For example, the compounds of the invention may have advantageous effects when used in combination with

phosphodiesterase inhibitors, including PDE1 inhibitors (such as those described in Journal of Medicinal Chemistry, Vol. 40, pp. 2196-2210 [1997]), PDE2 inhibitors, PDE3 inhibitors (such as revizinone, pimobendan, or olprinone), PDE4 inhibitors (such as rolipram, cilomilast, or piclamilast), PDE7 inhibitors, or other PDE inhibitors such as dipyridamole, cilostazol, sildenafil, denbutyline, theophylline (1,2-dimethylxanthine), ARIFLO™ (i.e., cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid), arofyline, roflumilast, C-11294A, CDC-801, BAY-19-8004, cipamfylline, SCH351591, YM-976, PD-189659, mesiopram, pumafentrine, CDC-998, IC-485, and KW-4490.

5
10 [0212] The inventive methods may be carried out by administering the compounds of the invention in combination with prothrombolytic agents, such as tissue plasminogen activator (natural or recombinant), streptokinase, reteplase, activase, lanoteplase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, and the like.

15 [0213] The inventive methods may be carried out by administering the compounds of the invention in combination with β -adrenergic agonists such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, or fenoterol; anticholinergics such as ipratropium bromide; anti-inflammatory corticosteroids such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide or dexamethasone; and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, monteleukast and
20 pranleukast.

[0214] The small molecule Factor XIa inhibitors may act synergistically with one or more of the above agents. Thus, reduced doses of thrombolytic agent(s) may be used, therefore obtaining the benefits of administering these compounds while minimizing potential hemorrhagic and other side effects.

25 [0215] The effective amount of a small molecule Factor XIa inhibitor administered according to the present invention may be determined by one of ordinary skill in the art. The specific dose level and frequency of dosage for any particular subject may vary and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of
30 excretion, drug combination, and severity of the particular condition. An exemplary effective amount of compounds of the invention may be within the dosage range of about 0.1 to about

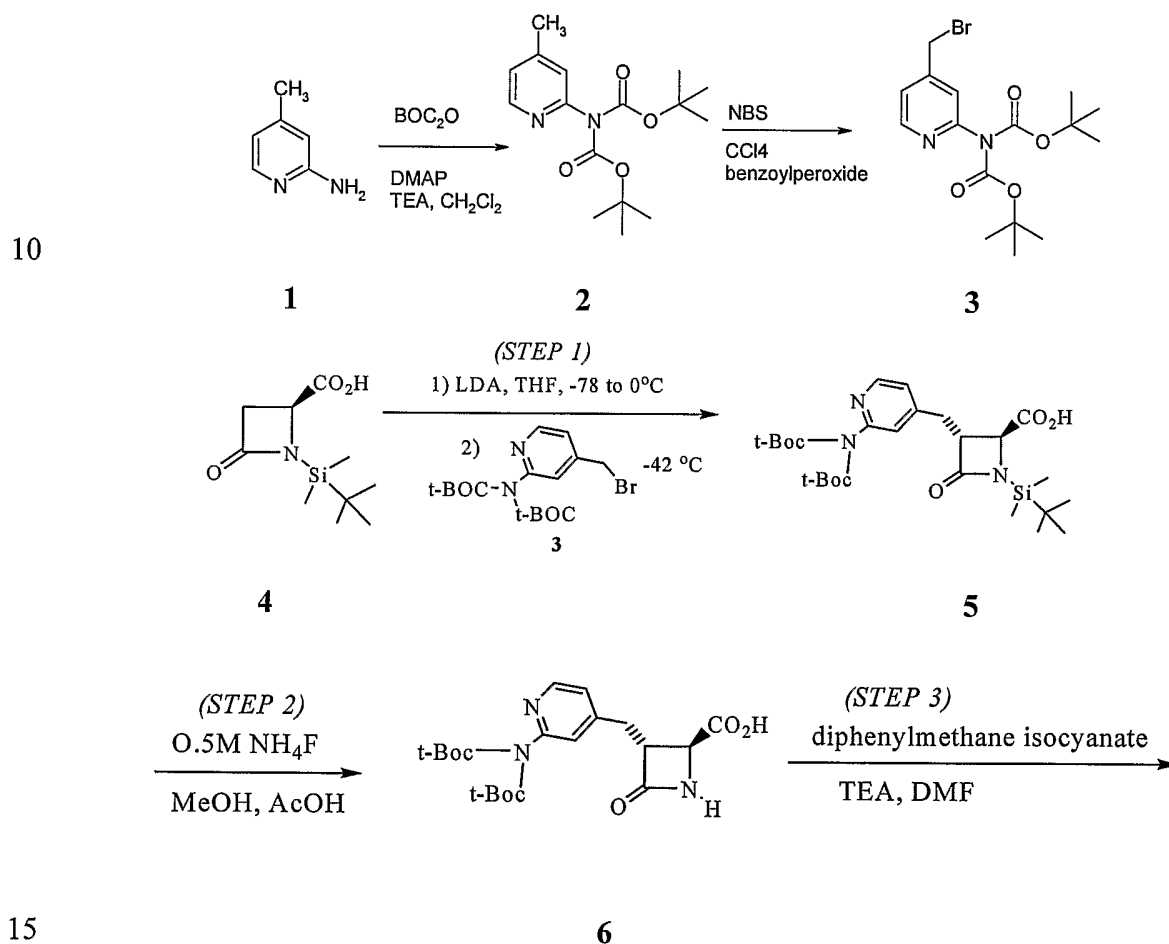
100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

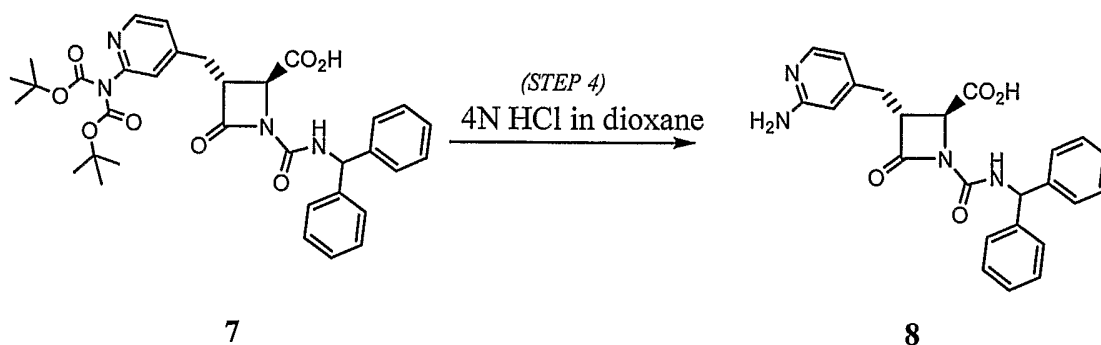
EXAMPLES

- 5 [0216] Proton NMR are recorded on Varian AS 300 spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Micromass Quattro II.

EXAMPLE 1

General method A for the preparation of 3-aminopyridyl beta-lactam acids.





[0217] **4-Methyl-2-bis(Boc)-aminopyridine (2):** Under argon, in a 1-L, 3-necked flask was placed a solution of 2-aminopicoline (16.23 g, 150.1 mmol, 1.0 equiv), triethylamine (41.8 mL, 30.04 g, 300.2 mmol, 2.0 equiv), dimethylaminopyridine (DMAP) (18.3 g, 150 mmol, 1.0 equiv), and CH₂Cl₂ (300 mL). The mixture was cooled to 5-7°C in an ice-water bath with magnetic stirring. A solution of Boc-anhydride (100g, 458.2 mmol, 3.1 equiv) in CH₂Cl₂ (100 mL) was added dropwise over a period of 30 min. The ice bath was removed and the reaction allowed to warm to room temperature with stirring for 4h. The reaction mixture was worked up by washing the CH₂Cl₂ solution with sat. NH₄Cl (2 x 400 mL) followed by sat. NaHCO₃ (2 x 400 mL), and then passing the solution through silica gel (350 mL fritted glass funnel) (elution with CH₂Cl₂, 500 mL). Rotary-evaporation of the solvent and tert-butanol at 5 mm Hg, 70°C, 18 h provided the crude product as a semi-crystalline straw-colored oil. This material was further purified by silica gel chromatography on a 330 g Combi-flash pre-packed cartridge, gradient elution with 100% hexanes to 20% ethyl acetate in hexanes. Fractions containing product were pooled and evaporated to provide 27.6 g, 60% yield of an oil. The oil was transformed into a solid by first dissolving it in CH₂Cl₂, then adding hexane and concentrating *in vacuo* at 25°C for 30min, followed by high vacuum produced a free-flowing powder **2**. TLC: hexanes/EtOAc [2:1] R_f ~ 0.6.

[0218] **4-Bromomethyl-2-bis-Boc-aminopyridine (3):** To a solution of 4-methyl-2-bis(boc)aminopyridine **2** (26.0g, 84.4 mmol, 1.0 equiv) in CCl₄ (421 mL) was added N-bromosuccinimide (15.0g, 84.4 mmol, 1.0 equiv) and dibenzoylperoxide (97%) (204 mg, 0.84 mmol, 0.01 equiv). The reaction mixture was quickly heated to reflux (hot plate with assistance from a heat gun) and the reaction was illuminated with a 500-watt halogen work light and two, 175-watt incandescent spotlights (Home Depot). The reaction was monitored at 210nm and when the reaction had reached completion (1hr at reflux), the reaction mixture was cooled to room temperature, filtered through celite/fritted glass to remove much of the succinimide. The volatiles were removed to give a crude material which was purified by silica gel chromatography (330 gram Combiflash silica gel) using gradient elution from 1%

acetone in CH₂Cl₂ to 8% acetone in CH₂Cl₂. Fractions containing pure product from each of the four chromatography runs were pooled and evaporated to provide 10g (31%) of **3** as a yellow foam.

[0219] **(2S,3R)-1-(tert-butyldimethylsilyl)-3-((2-(di-t-butyloxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (5)**: Commercially available beta-lactam **4** (15.31 mmol, 3.51g, 1.0 eq.) was dissolved in 40 mL dry THF at room temperature with magnetic stirring, in an oven-dried flask with dry stir bar under dry argon. The solution was cooled to -78°C and the LDA solution (2.05 eq., 31.38 mmol, 17.4 mL 1.8M solution from Aldrich) was added slowly over 5 minutes by syringe to the cooled stirring solution. The solution was kept at -78°C for 15 minutes and warmed to 0 °C with an ice bath. The solution was kept at 0°C for 45 minutes, and then cooled to -42°C (dry ice-acetonitrile). Bromide **3** (5.34g, 13.78 mmol, 0.9 eq.) was dissolved in 20 mL of dry THF and cooled to -42°C (dry ice-acetonitrile). The resulting bromide solution was added dropwise via a dry narrow bore cannula to the enolate solution using balloon pressure, with both vessels cooled to -42°C during the 30 minute addition. A deep dark blue-black color forms immediately. After the addition was complete, the vial that contained the bromide solution was rinsed with two 2 mL portions of dry THF, which was cooled to -42°C and added to the enolate solution. The reaction vessel was kept at -42°C for 4 hours. A quench solution was prepared by adding 50g of ice to 150 mL of 5% aqueous KHSO₄ solution in an Erlenmeyer. The reaction mixture was poured into the quench solution, and the vessel was rinsed with 5 X 20 mL aliquots of ethyl acetate, which were poured into the quench solution. The two layers were poured into a separatory funnel. The pH of the aqueous layer was 2-3. The organic layer was separated, the organic layer extracted with 3 portions of ethyl acetate, and the combined organic layers were washed with brine and concentrated *in vacuo*. The residue was dissolved in minimal methylene chloride and put on a 120g pre-packed ISCO Combiflash silica column. The column was eluted with a dual solvent system: solvent A = hexane, solvent B = 2% acetic acid in ethyl acetate. The gradient applied was 0-30% B over 3 minutes, 30% B for 10 minutes, ramped 30 to 50% B over 10 minutes, 50% B for 15 minutes, 50 to 80% B over 10 minutes, 80% for 10 minutes. Product **5** eluted in the 50% B fractions and all pure fractions containing **5** were concentrated *in vacuo* to yield **5** (4.76g, 64%) as a crunchy yellow foam. TLC (3:2 EtOAc/hexanes/1% AcOH) R_f=0.2.

[0220] **(2S,3R)-3-((2-(di-t-butyloxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (6)**: To a solution of pyridyl beta-lactam acid **5** (0.4g, 1.0

eq.) in 3.4 mL methanol and 0.12 mL acetic acid was added 0.5M ammonium fluoride in methanol (1.5mL, 1.0 eq.). The solution was stirred for 3 hours until disappearance of all starting material. The reaction was then concentrated *in vacuo* and put under high vacuum overnight to yield a yellow solid which was taken on to the next step without further purification.

[0221] (2S,3R)-1-(benzhydrylcarbamoyl)-3-((2-(di-*t*-butyloxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (7): To a solution of beta-lactam acid **6** (50 mg, 1.0 eq) in dimethylformamide (1.2 mL) was added diphenylmethylisocyanate (100 uL, 4.45 eq.), triethylamine (80 uL, 4.8 eq.). The reaction was stirred at room temperature for 23 hours and then concentrated *in vacuo*. The crude material was purified by preparative TLC eluting with 9:1:0.2 ethyl acetate:methanol:acetic acid to yield **7** (42 mg, 56%) as a yellow foam.

[0222] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(benzhydrylcarbamoyl)-4-oxoazetidine-2-carboxylic acid (8): To solid **7** (42 mg) was added 4N HCl-dioxane (1.0 mL). The reaction was capped and stirred at room temperature for 5.5 hrs (or until reaction is complete) and then triturated with diethyl ether to yield a crude solid which was further purified via preparative HPLC (C18, acetonitrile/water, 0.1% TFA) to give **8** (10.6 mg, 35%) as a white powder.

[0223] (2S,3R)-1-(((1S,2S)-2-(benzyloxy)cyclopentyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (9): Compound **9** was synthesized by general method A using (1R,2R)-benzyloxycyclopentyl isocyanate (step 3).

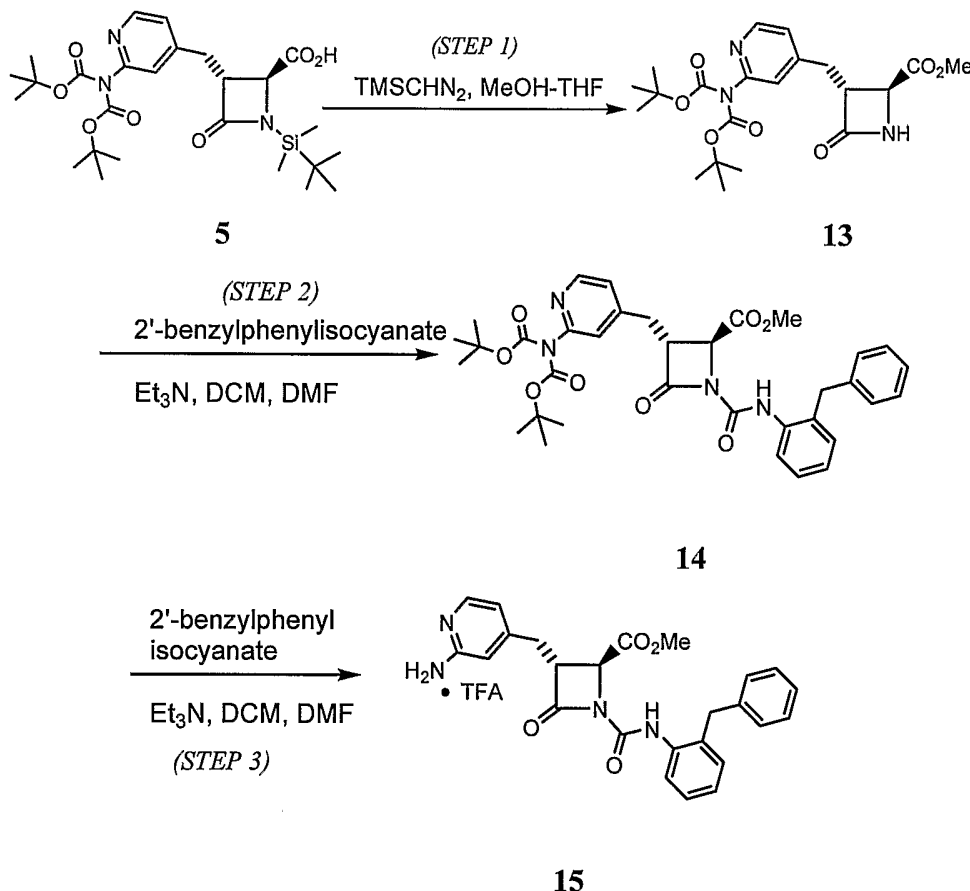
[0224] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N1,N2-bis((1S,2S)-2-(benzyloxy)cyclopentyl)-4-oxoazetidine-1,2-dicarboxamide (10): Compound **10** was synthesized by general method A using (1R,2R)-benzyloxycyclopentyl isocyanate (step 3). Note: This compound was a byproduct from step 3 which was independently isolated via the same preparative TLC conditions and deprotected using the same conditions in step 4 (4N HCl-dioxane).

[0225] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N1,N2-bis(3-benzylphenyl)-4-oxoazetidine-1,2-dicarboxamide (11): Compound **11** was synthesized by general method A using 3-benzylphenylisocyanate (step 3). Note: This compound was a byproduct from step 3 which was independently isolated via the same preparative TLC conditions and deprotected using the same conditions in step 4 (4N HCl-dioxane).

[0226] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-N1,N2-bis(3-phenoxyphenyl)azetidine-1,2-dicarboxamide (12): Compound 12 was synthesized by general method A using 3-phenoxyphenylisocyanate (step 3). Note: This compound was a byproduct from step 7 which was independently isolated via the same preparative TLC conditions and deprotected using the same conditions in step 4 (4N HCl-dioxane).

EXAMPLE 2

General method B for the preparation of 3-aminopyridyl beta-lactam methyl esters.



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[0227] (2S,3R)-methyl 3-((2-(di-*t*-butyloxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (13): To a solution of pyridyl beta-lactam acid 5 (0.1g, 1.0 eq.) in 3 mL methanol and 1.0 mL tetrahydrofuran was added 2.0M trimethylsilyldiazomethane in hexanes (558 μ L, 6.0 eq.). After disappearance of all starting material, the reaction was concentrated in vacuo. The crude material was purified by reverse phase HPLC (C18, acetonitrile/water with 0.1% TFA) to yield 13 (45.5 mg, 56%) as a clear oil.

[0228] (2S,3R)-methyl 1-((2-benzylphenyl)carbamoyl)-3-((2-(di-*t*-butyloxycarbonylamino) pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (14): To a

solution of beta-lactam ester **13** (11 mg, 1.0 eq) in dichloromethane (0.75 mL) was added 2'-benzylphenyl isocyanate (10 uL, 2.0 eq.), triethylamine (11 uL, 3.0 eq.) and a few drops of DMF to solubilize any undissolved material. The reaction was stirred at room temperature for 21 hours and then concentrated *in vacuo*. The crude material was taken on to the next step without further purification.

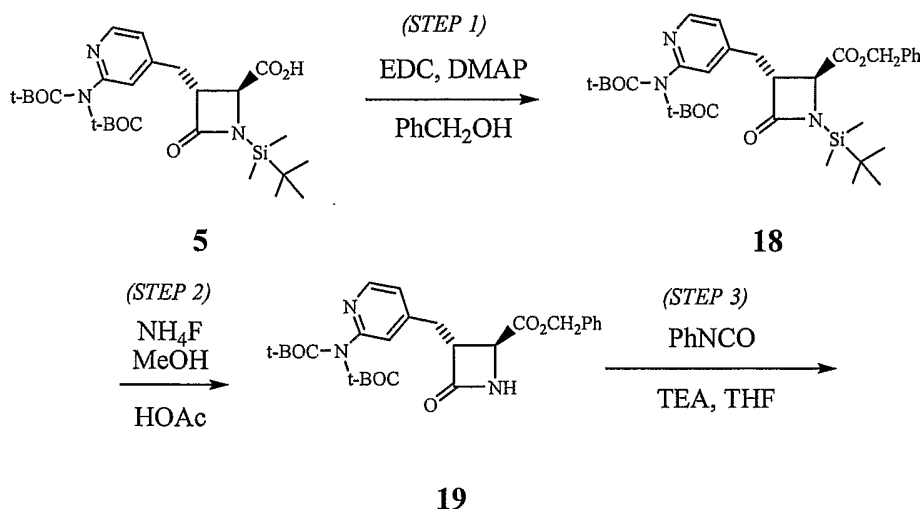
[0229] (2S,3R)-methyl 3-((2-aminopyridin-4-yl)methyl)-1-((2-benzylphenyl)carbamoyl)-4-oxoazetidine-2-carboxylate (15): To crude acylated beta-lactam ester **14** was added 4N HCl in dioxane (2 mL). The reaction was capped and stirred for 4 hours and then concentrated *in vacuo*. The crude material was purified via reverse phase HPLC (C18, acetonitrile/water with 0.1% TFA) to yield **15** (3.6 mg) as a white solid.

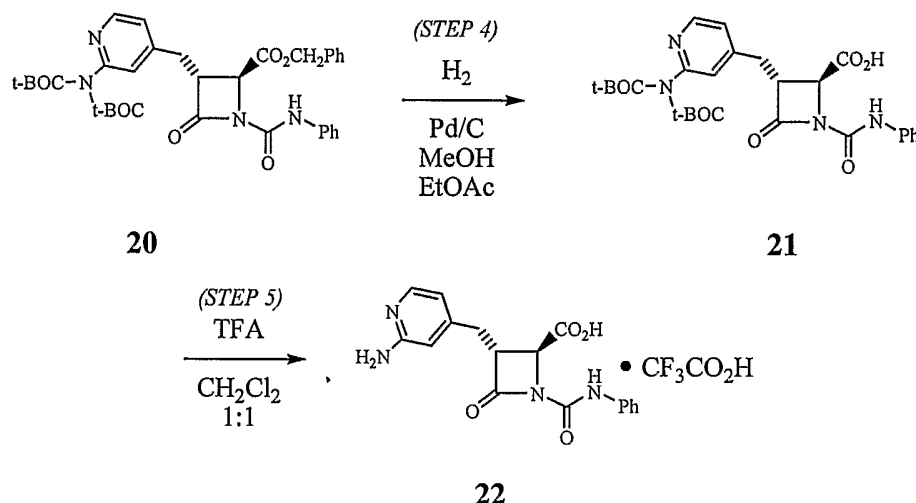
[0230] (2S,3R)-methyl 1-(((1S,2R)-2-phenylcyclopropyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate trifluoroacetate (16): Compound **16** was synthesized by general method B using trans-2-phenyl-cyclopropyl isocyanate (step 3) to yield **16** (3.9 mg) as a white solid.

[0231] (2S,3R)-methyl 1-(((1R,2R)-2-(benzyloxy)cyclopentyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate trifluoroacetate (17): Compound **17** was synthesized by general method B using (1S,2S)-2-benzyloxycyclopentyl isocyanate (step 3) to yield **17** (5.0 mg) as a white solid.

EXAMPLE 3

20 General method C for the preparation of 3-aminopyridyl beta-lactam esters and amides.





5 [0232] **(2S,3R)-benzyl 1-(tert-butyldimethylsilyl)-3-((2-(di-
 butoxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (18)**: The beta-
 lactam acid **5** (136 mg, 0.254 mmol) was dissolved in 4 mL dry dichloromethane at room
 temperature. EDC (73 mg, 3 equiv.), benzyl alcohol (33 mg, 32 μ L, 1.2 equiv), and catalytic
 DMAP (3 mg) were added sequentially. The reaction was stirred overnight under argon,
 10 diluted with 20 mL ethyl acetate and 25 mL water. The water layer was washed with 3
 portions of ethyl acetate, and the combined organic layers were dried over sodium sulfate,
 filtered, and concentrated *in vacuo*. The residue was purified by column chromatography
 using a gradient of 10 to 30% ethyl acetate in hexane, yielding **18** (72%). MS: 626.3
 [M+H]⁺.

15 [0233] **(2S,3R)-benzyl 3-((2-(di-*t*-butoxycarbonylamino)pyridin-4-yl)methyl)-4-
 oxoazetidine-2-carboxylate (19)**: Ester **18** (127 mg, 0.20 mmol) was dissolved in 1 mL dry
 methanol at room temperature. 1 mL of a 0.5 M solution of ammonium fluoride in methanol
 (0.5 mmol, 2.5 equiv.) was added, then 60 mg acetic acid (1 mmol, 5 equiv). The reaction
 was stirred overnight under argon, diluted with 20 mL ethyl acetate and 20 mL saturated
 20 sodium bicarbonate solution. The water layer was washed with 3 portions of ethyl acetate,
 and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in
 vacuo*. The residue was purified by column chromatography eluting with 3:1 methylene
 chloride/ethyl acetate to yield **19** (72 mg, 69%). MS: 611.2 [M+H]⁺.

25 [0234] **(2S,3R)-benzyl 3-((2-(di-*t*-butoxycarbonylamino)pyridin-4-yl)methyl)-4-oxo-1-
 (phenylcarbamoyl)azetidine-2-carboxylate (20)**: Deprotected lactam **19** (72 mg, 0.14
 mmol) was dissolved in 4 mL dry THF at room temperature. Triethylamine (71 mg, 5 equiv.)
 was added, then 42 mg (2.5 equiv.) of the isocyanate. The reaction was stirred overnight

under argon and concentrated *in vacuo*. The residue was purified by column chromatography eluting with methylene chloride to yield **20** (75 mg, 85%). MS: 631.3. $[M+H]^+$.

[0235] (2S,3R)-3-((2-(di-*t*-butoxycarbonylamino)pyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (21): Acylated lactam ester **20** (56 mg,

5 0.089 mmol) was dissolved in 2 mL of 1:1 methanol-ethyl acetate in a 20 mL glass vial. 10% palladium on carbon catalyst (10 mg) was added, and the solution was stirred under an atmosphere of hydrogen at room temperature overnight under argon, filtered, and then concentrated *in vacuo*. The residue was pure by HPLC/MS and was taken to the next step without purification. MS: 541.1 $[M+H]^+$.

10 **[0236] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid trifluoroacetate (22):** Acylated lactam acid **21** (from the previous step) was dissolved in 2 mL of 1:1 TFA-methylene chloride in a 20 mL glass vial. The solution was stirred for 1 hour at room temperature under argon and then concentrated *in vacuo*. The residue was purified by preparative HPLC using a C18 column and a gradient of 20-60%

15 water in acetonitrile. All fractions containing the desired product were pooled and concentrated *in vacuo*. Freeze-drying from 1:1 water:acetonitrile gave **22** (25 mg, 62% for 2 steps). MS: 341.1 $[M+H]^+$.

[0237] (2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid trifluoroacetate (23): Compound **23** was synthesized by

20 general method C using α -methylbenzylamine isocyanate (step 3).

[0238] (2S,3R)-1-(((R)-1-(naphthalen-1-yl)ethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid trifluoroacetate (24): Compound **24** was synthesized by general method C using α -methylnaphthyl isocyanate (step 3).

[0239] (2S,3R)-ethyl 1-(((R)-1-(naphthalen-1-yl)ethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate trifluoroacetate (25): Compound **25** was synthesized by general method C using ethyl alcohol (step 1) and α -methylnaphthyl isocyanate (step 3).

[0240] (2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate trifluoroacetate (26): Compound **26** was synthesized by general method C using ethyl alcohol (step 1) and phenyl isocyanate (step 3).

30

[0241] **(2S,3R)-benzyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate trifluoroacetate (27):** Compound 27 was synthesized by general method C using benzyl alcohol (step 1) and phenyl isocyanate (step 3).

5 [0242] **(2S,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate trifluoroacetate (28):** Compound 28 was synthesized by general method C using ethyl alcohol (step 1) and α -methylbenzylamine isocyanate (step 3).

10 [0243] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2,N2-diethyl-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide trifluoroacetate (29):** Compound 29 was synthesized by general method C using dimethylamine (step 1) and α -methylbenzylamine isocyanate (step 3).

15 [0244] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-ethyl-N2-methyl-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide trifluoroacetate (30):** Compound 30 was synthesized by general method C using N-methyl-N-ethylamine (step 1) and α -methylbenzylamine isocyanate (step 3).

[0245] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(morpholine-4-carbonyl)-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide trifluoroacetate (31):** Compound 31 was synthesized by general method C using morpholine (step 1) and α -methylbenzylamine isocyanate (step 3).

20 [0246] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-N1-((R)-1-phenylethyl)-N2-(pyridin-3-yl)azetidine-1,2-dicarboxamide trifluoroacetate (32):** Compound 32 was synthesized by general method C using 3-aminopyridine (step 1) and α -methylbenzylamine isocyanate (step 3).

25 [0247] **(2S,3R)-benzyl 3-(benzofuran-5-ylmethyl)-4-oxoazetidine-2-carboxylate (33) and (2S,3R)-3-(benzofuran-5-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (34):** Compounds 33 and 34 were synthesized by general method A (step 1) using 5-(bromomethyl)benzofuran as the electrophile instead of 4-bromomethyl-2-bis-Boc-aminopyridine and then the synthesis was completed by following general method C. The compounds were separated via silica gel chromatography eluting with 10-40% ethyl acetate
30 in hexanes. Yield of 33: 56 mg.

[0248] (2S,3R)-3-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-oxo-1-

(phenylcarbamoyl)azetidione-2-carboxylic acid (35): Compound **35** was synthesized by general method A (step 1) using 5-(2-bromoethyl)benzo[d][1,3] dioxole as the electrophile instead of 4-bromomethyl-2-bis-Boc-aminopyridine. The starting 5-

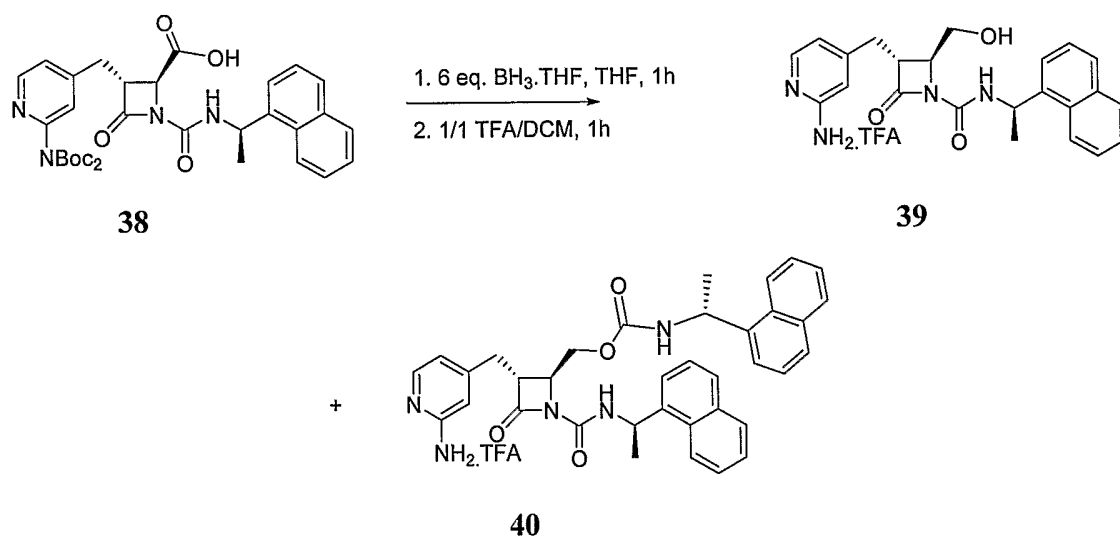
5 (bromomethyl)benzo[d][1,3]dioxole was made by standard treatment of benzo[d][1,3]dioxol-5-ylmethanol with carbon tetrabromide and triphenylphosphine in toluene. The synthesis was then completed by following general method C.

[0249] (2S,3R)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-4-oxo-1-

(phenylcarbamoyl)azetidione-2-carboxylic acid (36): Compound **36** was synthesized by general method A (step 1) using 5-(bromomethyl)benzo[d][1,3] dioxole as the electrophile instead of 4-bromomethyl-2-bis-Boc-aminopyridine. The synthesis was then completed by following general method C.

[0250] (2S,3R)-3-(3-chlorobenzyl)-4-oxo-1-(phenylcarbamoyl)azetidione-2-carboxylic acid (37):

Compound **37** was synthesized by general method A (step 1) by using 1-(bromomethyl)-3-chlorobenzene as the electrophile instead of 4-bromomethyl-2-bis-Boc-aminopyridine. The completion of the synthesis then followed general method C using 4-methoxybenzyl alcohol (step 1). Removal of the PMB group was accomplished by treatment with TFA/DCM at room temperature for one hour to yield the desired acid **37** (45 mg, 100%).

EXAMPLE 4**20 General method D for the preparation of 3-aminopyridyl beta-lactam alcohols.**

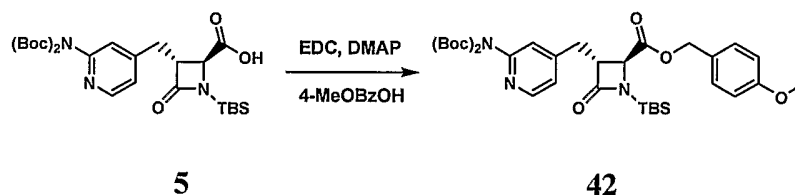
[0251] (2S,3R)-1-(((R)-1-(naphthalen-1-yl)ethyl)carbamoyl)-3-((2-(di-*t*-butoxy carbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (**38**): Compound **38** was synthesized by general method C using α -ethylnaphthyl isocyanate.

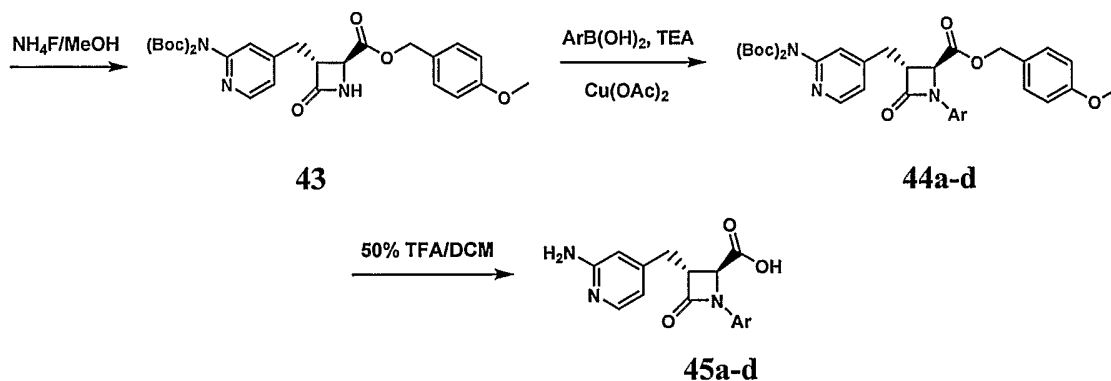
[0252] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(hydroxymethyl)-N-((R)-1-(naphthalen-1-yl)ethyl)-4-oxoazetidine-1-carboxamide trifluoroacetate (**39**) and ((2S,3R)-1-(((R)-1-(naphthalen-1-yl)ethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidin-2-yl)methyl (R)-1-(naphthalen-1-yl)ethylcarbamate trifluoroacetate (**40**): To a solution of compound **38** (0.03 g, 0.048 mmol) in 1 ml anhydrous THF was added 1M borane in THF (0.29 ml, 0.29 mmol) dropwise and the reaction mixture was stirred at room temperature for 1 h. Then the reaction was slowly quenched with water, acidified to pH 1 with 1 N HCl, and then neutralized with sodium bicarbonate solution. The reaction mixture was extracted twice with ethyl acetate and the organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The desired product was purified by silica gel chromatography (12 g pre-packed Si column, hexane /ethyl acetate eluents) to yield the Boc protected alcohol (0.008 g, 27% yield; LS/MS M+H 605.1, calc. 605.48). The alcohol (0.008 g, 0.013 mmol) was treated with 1 ml 1/1 TFA/DCM for 1 h at room temperature. Afterwards, the reaction mixture was concentrated *in vacuo* and the solid washed with ethyl ether (three times) to give the **39** as a TFA salt (2.2 mg). LS/MS M+H 405.12, calc. 405.5 and **40** as a TFA salt (2.5 mg).

[0253] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(hydroxymethyl)-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide (TFA salt) (**41**): Compound **41** was synthesized by general method C using α -ethylnaphthyl isocyanate (step 3) and finished following general method D (2.5 mg, white powder) LC/MS M+H 355.2, calc. 355.17.

EXAMPLE 5

25 General method E for the preparation of N-aryl 3-aminopyridyl beta-lactams.





5 [0254] **(2S,3R)-4-methoxybenzyl-1-(tert-butyldimethylsilyl)-3-((2-(di-*t*-butoxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (42)**: A mixture of 534 mg of crude compound **5** (1.0 mmol), EDC hydrochloride salt (403 mg, 2.1 mmol), DMAP (24 mg, 0.2 mmol) and 4-methoxybenzyl alcohol (416 mg, 3.0 mmol) in dichloromethane (5 ml) was stirred at room temperature overnight. The solvent was removed
 10 in *vacuo*. The residue was dissolved with ethyl acetate, washed with 5% aqueous KHSO₄, water and brine. The organic layer was dried over Na₂SO₄, then concentrated to yield a crude material which was purified by ISCO silica gel column using 0-20% ethyl acetate in hexanes to afford **42** (463 mg, 71%): Anal. C₃₄H₄₉N₃O₈Si, Mol. Wt.: 655.85, Found: ESI-MS: 656.0 (M+H)⁺.

15 [0255] **(2S,3R)-4-methoxybenzyl-3-((2-(di-*t*-butoxycarbonylamino)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (43)**: A solution of 1.7 ml of 0.5 M ammonium fluoride in methanol (0.85 mmol) was added to a mixture of compound **42** (463 mg, 0.71 mmol), acetic acid (140 μ l, 2.45 mmol) and methanol (7 ml). The mixture was stirred at room temperature for 3 h. The solvent was removed and the residue was taken up in toluene
 20 (2-3 ml) to assist removal of AcOH. After solvent was removed, the residue was taken up in DCM. The resulting white solids were filtered off. Concentration of the filtrate gave **43** (0.44 g), which was ready for next step reaction without further purification. Anal. C₂₈H₃₅N₃O₈, Mol. Wt.: 541.59, Found: ESI-MS: 541.8 (M+H)⁺.

[0256] **Compounds (44a-d)**: A mixture of β -lactam **43** (30 mg, 0.055 mmol), aryl boronic acid (0.11 mmol), copper acetate (20 mg, 0.11 mmol), triethylamine (31 μ l, 0.22 mmol) and activated 4A molecular sieves (56 mg) in dichloromethane (1.3 ml) was stirred at room
 25 temperature overnight. The reaction mixture was filtered through celite and the filtrate was concentrated. Preparative TLC (20% EtOAc/Hexanes) of the residue gave the desired products **44a-d** in 27-78% yield.

[0257] **Compounds (45a-d):** The crude esters **44a-d** were treated with 30% TFA in DCM (3 ml). After two hours, LC-MS analyses indicated completion of the reactions. The solvent was removed and the residue was purified by preparative HPLC (Vydac reverse phase C-18 column, 22 x 250 mm ID). Mobile phase: A = 0.1% TFA in water, B = 0.1% TFA in
 5 acetonitrile. The flow rate was 12 ml / min. The gradient time was 5% B to 55 % B or 10% B to 60% B over 30 min. The desired products were thus obtained:

[0258] **(2S,3R)-1-(4-((4-fluorophenyl)carbamoyl)phenyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (45a):** Yield 2.5 mg.

[0259] **(2S,3R)-1-(3-((4-fluorophenyl)carbamoyl)phenyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (45b):** Yield 3.2 mg.
 10

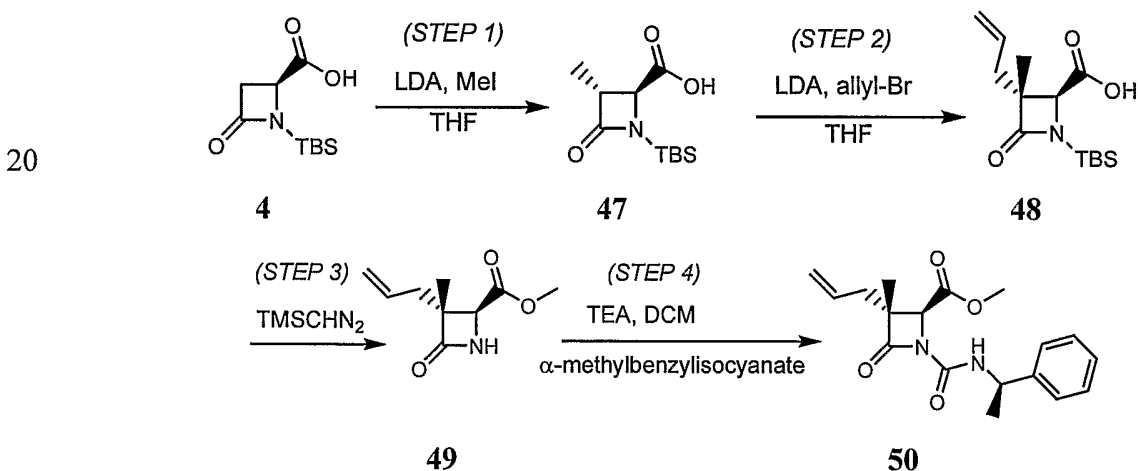
[0260] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(3-(benzyloxy)phenyl)-4-oxoazetidine-2-carboxylic acid (45c):** Yield 2.0 mg.

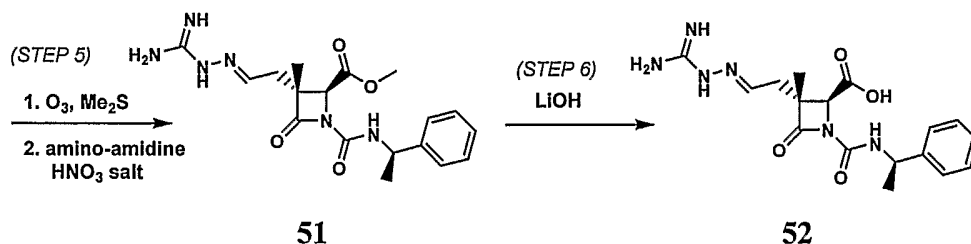
[0261] **(2S,3R)-4-methoxybenzyl 3-((2-aminopyridin-4-yl)methyl)-1-(benzofuran-2-yl)-4-oxoazetidine-2-carboxylate (45d):** Yield 1.7 mg.

[0262] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(4-(benzyloxy)-2-fluorophenyl)-4-oxoazetidine-2-carboxylic acid (46):** Compound **46** was synthesized by general method E using 4-(benzyloxy)-2-fluorophenylboronic acid.
 15

EXAMPLE 6

General method F for synthesis of 3,3-alkyl, methyl beta-lactams





[0263] **(2S,3R)-1-(tert-butyldimethylsilyl)-3-methyl-4-oxoazetidine-2-carboxylic acid (47)**: To a solution of (S)-1-(tert-butyldimethylsilyl)-4-oxoazetidine-2-carboxylic acid **4** (2.00 g, 8.73 mmol.) in THF (30 ml) at -78°C was added LDA (19 ml, 2.0 eq.). After the solution was stirred for 20 min. at -78°C , it was warmed to 0°C for 5 min. The solution was re-cooled to -78°C and methyl iodide (3.10 g, 2.5 eq.) in THF (5 ml) was added. The reaction solution was warmed up to room temperature, quenched with aqueous KHSO_4 solution (10%, 30 ml), extracted with ethyl acetate (3 X). The combined organic layers were washed with brine twice and dried with MgSO_4 . After concentrating *in vacuo*, **47** was obtained. ^1H NMR (CDCl_3): 0.15, 0.35 (s, 6H), 1.14 (s, 9H), 1.35 (d, 3H), 3.71 (d, 1H), 4.14 (m, 1H). $\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Si}$, Mol. Wt.: 243.37, found: 244 (M+1).

[0264] **(2S,3R)-3-allyl-1-(tert-butyldimethylsilyl)-3-methyl-4-oxoazetidine-2-carboxylic acid (48)**: To a solution of compound **47** (0.200 g, 0.823 mmol) in THF (5 ml) at -78°C was added a solution of LDA (1.10 ml, 2.4 eq.). The reaction solution was stirred for 20 min. at that temperature, warmed to -20°C and allyl bromide (0.138 ml, 2.0 eq.) was added slowly. Reaction mixture was warmed to 0°C for 30 min. and quenched with KHSO_4 (20 ml, 10%), extracted with ethyl acetate (3 X). Combined organic layers were washed with brine twice and dried over MgSO_4 . After concentrating *in vacuo*, compound **48** was obtained. ^1H NMR (CDCl_3): 0.15, 0.37 (s, 6H), 1.16 (s, 9H), 1.33 (s, 3H), 2.50 (m, 2H), 3.98 (s, 1H), 5.22 (m, 2H), 5.88 (m, 1H). $\text{C}_{14}\text{H}_{25}\text{NO}_3\text{Si}$, Mol. Wt.: 283.44. Found: 284 (M+1).

[0265] **(2S,3R)-methyl 3-allyl-3-methyl-4-oxoazetidine-2-carboxylate (49)**: TMS diazomethane (1.23 ml, 3.0 eq. 2 M in THF) was added to a solution of the acid compound **48** (260 mg, 0.82 mmol) in methanol (5 ml) at 0°C and stirred at room temperature overnight to yield the deprotected product **46**. ^1H NMR (CDCl_3): 1.30 (s, 3H), 2.50 (m, 2H), 3.80 (s, 3H), 4.08 (s, 3H), 5.30 (m, 2H), 5.85 (m, 1H), 5.92 (s, b, 1H). $\text{C}_9\text{H}_{13}\text{NO}_3$, Mol. Wt.: 183.2. Found: 184 (M+1).

[0266] **(2S,3R)-methyl 1-(((R)-1-phenylethyl)carbamoyl)-3-allyl-3-methyl-4-oxoazetidine-2-carboxylate (50)**: To a solution of **49** (120 mg, 0.66 mmol) in methylene chloride (15 ml) was added triethylamine (0.27 ml, 3.0 eq.), DMAP (8.0 mg, 10% mmol)

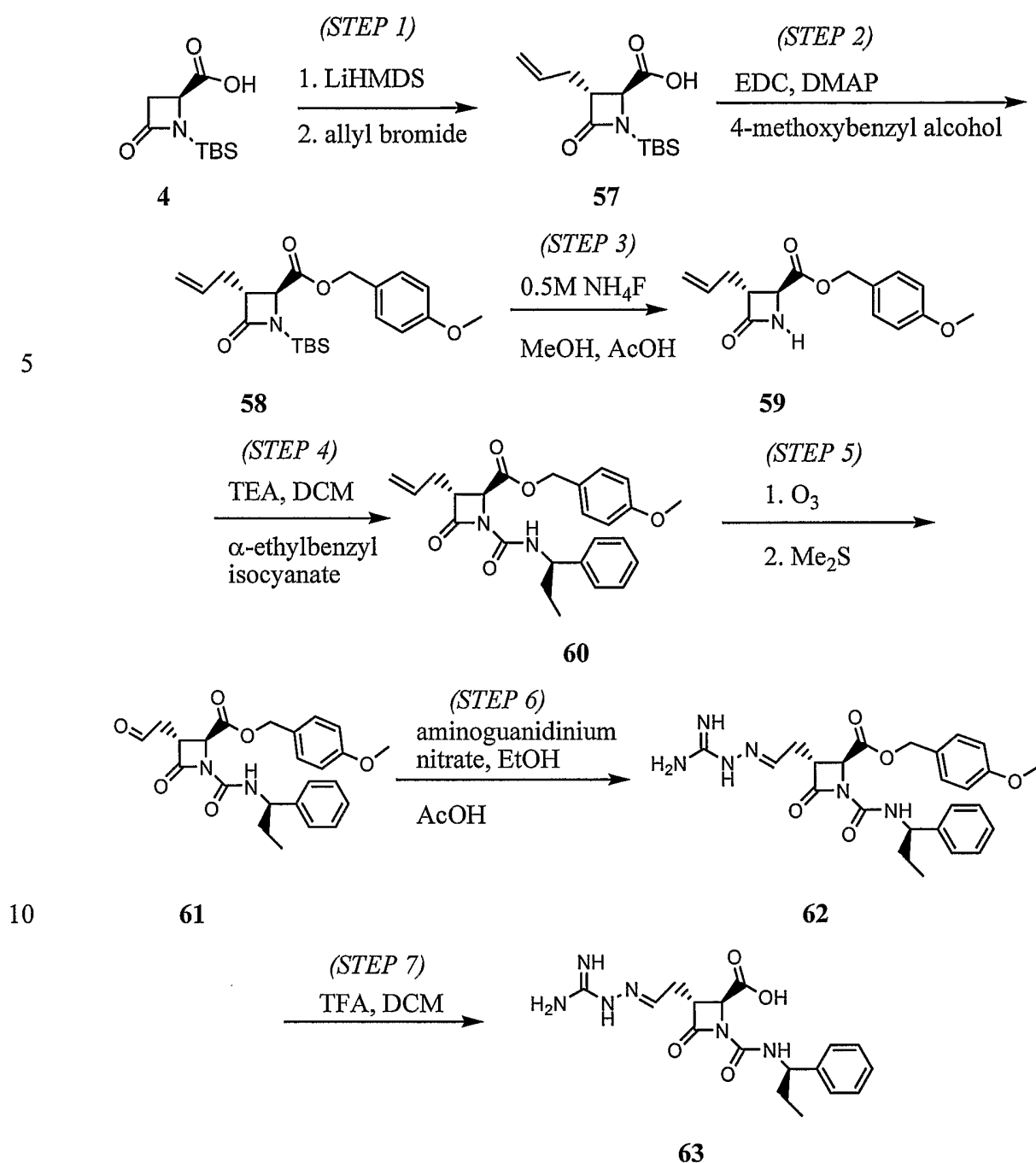
and α -methyl-benzyl isocyanate (146 mg, 1.5 eq.). The reaction was stirred overnight and concentrated *in vacuo* to yield a crude material, which was extracted with ethyl acetate and aqueous NH_4Cl . Combined organic layers were washed with brine purified via silica gel chromatography to yield compound **47**. $^1\text{H NMR}$ (CDCl_3): 1.35 (s, 3H), 1.60 (d, 3H), 2.50 (m, 2H), 3.82 (s, 3H), 4.44 (s, 1H), 5.50 (m, 1H), 5.25 (m, 2H), 5.83 (m, 1H), 6.74 (d, b, 1H), 7.40 (m, 5H). $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$, Mol. Wt.: 330.38. Found: 331 (M+1).

[0267] **(2S,3R)-methyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-iminoguanidinoethyl)-3-methyl-4-oxoazetidine-2-carboxylate (51)**: To a solution of **50** (135 mg) in methylene chloride (5 mL) at -78°C was bubbled O_3 until a blue color was seen. The reaction was quenched with dimethylsulfide. Removal of solvents gave the desired aldehyde product, which was used in the next step without further purification. To a solution of the freshly prepared aldehyde compound (118 mg, 0.36 mmol) in ethanol (0.75 mL) was added amino amidine (HNO_3 salt, 98 mg, 2.0 eq.) and acetic acid (30 μL , 3.0 eq.). The mixture was stirred for 1.5 h and residual after removal of solvent was purified via reverse-phase HPLC to yield compound **51** (41 mg). $\text{C}_{18}\text{H}_{24}\text{N}_6\text{O}_4$, Mol. Wt.: 388.42. Found: 389 (M+1).

[0268] **(2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-(2-iminoguanidinoethyl)-3-methyl-4-oxoazetidine-2-carboxylic acid (52)**: To a solution of compound **51** (10 mg) in 1:1:1 THF:methanol:water (1.5 mL total) was added solid LiOH (3.5 eq.). The reaction was stirred at room temperature for 30 min. LCMS showed formation of the desired acid and disappearance of the starting methyl ester. The crude material was purified via reverse-phase HPLC to yield pure **52**. $\text{C}_{17}\text{H}_{22}\text{N}_6\text{O}_4$, Mol. Wt.: 374.39. Found: 375 (M+1).

[0269] **(2S,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-((6-aminopyridin-3-yl)methyl)-3-methyl-4-oxoazetidine-2-carboxylate (53) and (2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-((6-aminopyridin-3-yl)methyl)-3-methyl-4-oxoazetidine-2-carboxylic acid (54)**: Compounds **53** and **54** were synthesized by general method F using 4-bromomethyl-2-bis-boc-aminopyridine as the alkylating agent in step 2 and forming the ethyl ester (step 3) analogous to the ester synthesis in general method C.

EXAMPLE 7

General method G for the preparation of N-alkyl amidinohydrazone beta-lactams.

[0270] (2*S*,3*R*)-3-Allyl-1-(tert-butyl-dimethyl-silanyl)-4-oxo-azetidine-2-carboxylic acid (57): To a solution of (*S*)-1-(tert-butyl-dimethyl-silyl)-4-oxoazetidine-2-carboxylic acid (4) (2.00 g, 8.73 mmol.) in anhydrous THF (20 mL) at -78°C was added 1.0 M solution of LiHMDS (20 ml, 20.1 mmol, 2.3 eq.) in THF. After the solution was stirred for 30 min. at -78°C, it was warmed to 0°C for 10 min. The solution was recooled to -78°C and allyl bromide (1.28 g, 10.5 mmol, 1.2 eq.) was added slowly. The reaction solution was stirred at -78°C for

1h, then warmed up to room temperature and stirred for another hour. The reaction mixture was quenched with aqueous 10 % KHSO₄ solution (30 ml) and extracted with ethyl acetate (40 mL x 3). The combined organic layers were washed with brine twice and dried over Na₂SO₄. After removal of solvent, compound **57** was obtained as crystalline solid (2.0 g, 85%); 78 % purity by LCMS, ¹HNMR (300 MHz, CDCl₃): 0.12 (s, 3H), 0.30 (s, 3H), 0.95 (s, 9H), 2.55 (m, 2H), 3.41 (m, 1H), 3.80 (d, J= 2.61 Hz, 1H), 5.16 (m, 2H), 5.72 (m, 1H). Anal. C₁₃H₂₃NO₃Si, Mol. Wt.: 269.41, Found: ESI-MS: 270.0 (M+H)⁺.

[0271] (2S,3R)-3-Allyl-1-(tert-butyl-dimethyl-silanyl)-4-oxo-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (58): A mixture of 900 mg of crude compound **57** (3.34

10 mmol) above, EDC hydrochloride salt (1.34 g, 7.01 mmol), DMAP (83 mg, 0.67 mmol) and 4-methoxybenzyl alcohol (1.40 g, 10.1 mmol) in dichloromethane (9 mL) was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved with ethyl acetate, washed with 5% aqueous KHSO₄, water (x2) and brine (x1). The organic layer was dried over Na₂SO₄, then concentrated to yield the crude **58** with LC purity: 60%.

15 Purification by ISCO silica gel column using 0-20% AcOEt in Hexanes afforded 630 mg of compound **58** (49% yield, 81 % purity): ¹HNMR (300 MHz, CDCl₃): 0.13 (s, 3H), 0.32 (s, 3H), 0.95 (s, 9H), 2.56 (m, 2H), 3.43 (m, 1H), 3.81 (d, J= 2.60 Hz, 1H), 3.82 (s, 3H), 4.67 (s, 2H), 5.17 (m, 2H), 5.72 (m, 1H), 6.94 (d, 2H), 7.34 (d, 2H). Anal. C₂₁H₃₁NO₄Si, Mol. Wt.: 389.56, Found: ESI-MS: 390.0 (M+H)⁺.

20 **[0272] (2S,3R)-3-Allyl-4-oxo-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (59):**

A solution of 6.2 mL of 0.5 M ammonium fluoride in methanol (3.1 mmol) was added to a mixture of compound **58** (1.0g, 2.57 mmol), acetic acid (530 uL, 9.0 mmol) and methanol (25 mL). The mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was taken up in toluene (2~3 mL) to assist removal of AcOH. After solvent was

25 removed, the residue was taken up in DCM. The resulting white solids were filtered off. Concentration of the filtrate gave 0.70 g of the crude **59** with purity: 91.1%, ¹HNMR (300 MHz, CDCl₃): 2.60 (m, 2H), 3.38 (m, 1H), 3.87 (s, 3H), 3.98 (d, 1H), 5.22 (m, 4H), 5.83 (m, 1H), 6.15 (b, s, 1H), 6.90 (d, 2H), 7.35 (d, 2H). Anal. C₁₅H₁₇NO₄, Mol. Wt.: 275.3, Found: ESI-MS: 275.8 (M+H)⁺.

30 **[0273] (2S,3R)-3-Allyl-4-oxo-1-(1-phenyl-propylcarbamoyl)-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (60):** A mixture of compound **59** (41 mg, 0.15 mmol),

triethylamine (83 uL, 0.60 mmol), α -ethyl-benzyl isocyanate (29 mg, 0.18 mmol) in

methylene chloride (1.2 mL) was stirred overnight. TLC analysis indicated the completion the reaction. Removal of solvents gave the crude material, which was purified by preparative TLC plate (15% EtOAc in hexanes), yielding 38.2 mg of compound **60** (59%): LC-MS purity: 98.1%; ¹HNMR (300 MHz, CDCl₃): 0.95 (t, 3H), 1.92 (m, 2H), 2.69 (m, 2H), 3.30 (m, 1H), 3.83 (s, 3H), 4.22 (d, 1H), 4.85 (q, 1H), 5.18 (m, 4H), 5.80 (m, 1H), 6.85 (br, d, 1H), 7.45 (m, 9H). Anal. C₂₅H₂₈N₂O₅, Mol. Wt.: 436.5, Found: ESI-MS: 437.1 (M+H)⁺.

[0274] (3S,4R)-4-Oxo-3-(2-oxo-ethyl)-1-(1-phenyl-propylcarbamoyl)-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (61): Ozone was bubbled through a solution of **60** (38.1 mg, 0.087 mmol) in dry methylene chloride (6 mL) at -78 °C until a faint blue color persisted. The reaction mixture was quenched with dimethylsulfide (200 uL) at -78 °C, then the cooling bath was removed. After the solvent was concentrated, the residue was taken up in EtOAc. Removal of solvents gave the desired aldehyde product **61**, which was sufficiently pure for next step without further purification. Anal. C₂₄H₂₆N₂O₆, Mol. Wt.: 338.47, Found: ESI-MS: 439.0 (M+H)⁺, 461.0 (M+Na)⁺.

[0275] (2S,3R)-4-Oxo-3-(3-amindinohydrozone-ethyl)-1-(1-phenyl-propylcarbamoyl)-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (62): To a solution of the freshly prepared aldehyde **61** (29 mg, 0.066 mmol) in ethanol (0.5 mL) was added aminoguanidinium nitrate (18 mg, 0.13 mmol) and acetic acid (11 uL, 0.20 mmol). The mixture was stirred at room temperature for 2 h. Concentration of solvent gave the crude desired product **62**. Anal. C₂₅H₃₀N₆O₅, Mol. Wt.: 494.54. Found: ESI-MS: 495.0 (M+H)⁺.

[0276] (2S,3R)-4-Oxo-3-(3-amindinohydrozone-ethyl)-1-(1-phenyl-propylcarbamoyl)-azetidine-2-carboxylic acid (63): The crude ester **62** was treated with a mixture of TFA/DCM (1.5 mL/2 mL). After one and half hours, LC-MS analysis indicated that no ester was present. The solvent was removed and the residue was purified by preparative HPLC (Vydac reverse phase C-18 column, 22 x 250 mm ID). Mobil phase: A = 0.1% TFA in water; B = 0.1% TFA in acetonitrile. The flow rate was 12 mL/min. The gradient time was 5% B to 55 % B over 50 min. The peak of interest was eluted at around 27 minutes to give 3.5 mg of the desired product, **63** as a white solid with 95.6 % purity. ¹HNMR (300 MHz, CDCl₃): 0.84 (t, 3H), 1.80 (m, 2H), 2.83 (m, 2H), 3.70 (dt, 1H), 4.25 (d, 1H), 4.61 (q, 1H), 6.58 (br s, 1H), 7.15-7.65 (m, 9H), 11.65(s 1H), 13.10 (br s, 1H); Anal. C₁₇H₂₄N₆O₄, Mol. Wt.: 374.39, Found: ESI-MS: 375.0 (M+H)⁺.

[0277] **(2S,3R)-cyclobutyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
iminoguanidinoethyl)-4-oxoazetidine-2-carboxylate (64):** Compound 64 was synthesized
by general method G using cyclobutyl alcohol (step 2) and α -methylbenzylisocyanate (step
4). Yield: 72.5 mg (48%). Mol. Wt.: 414.46. Found: ESI-MS: 415.0 (M+H)⁺.

5 [0278] **(2S,3R)-methyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
iminoguanidinoethyl)-4-
oxoazetidine-2-carboxylate (65):** Compound 65 was synthesized by general method G with
step 2 esterification accomplished via TMSCHN₂ in hexanes and using α -
methylbenzylisocyanate in step 4.

[0279] **(2S,3R)-N2,N2-diethyl-3-(2-
iminoguanidinoethyl)-4-oxo-N1-((R)-1-
phenylethyl)azetidine-1,2-dicarboxamide (66):** Compound 66 was synthesized by general
10 method G, using diethylamine in step 2 and α -methylbenzylisocyanate in step 4, to yield 4.1
mg (35%). Mol. Wt.: 415.49. Found: ESI-MS: 416.0 (M+H)⁺.

[0280] **(2S,3R)-3-(2-
iminoguanidinoethyl)-4-oxo-1-(biphenylcarbamoyl)azetidine-2-
carboxylic acid (67):** Compound 67 was synthesized by general method G using 4-
15 biphenylisocyanate (step 4). Yield: 1.1 mg (6.8% over 2 steps). Mol. Wt.: 408.41. Found:
ESI-MS: 409.0 (M+H)⁺.

[0281] **(2S,3R)-methyl 3-(2-
iminoguanidinoethyl)-4-oxo-1-
(phenylcarbamoyl)azetidine-2-carboxylate (68):** Compound 68 was synthesized by
20 general method G with step 2 esterification accomplished via TMSCHN₂ in hexanes and
using phenylisocyanate in step 4.

[0282] **(2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
iminoguanidinoethyl)-4-
oxoazetidine-2-carboxylic acid (69), (2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-(2- (R)-
1-phenylethyl)carbamoyl)-iminoguanidinoethyl)-4-oxoazetidine-2-carboxylic acid (70)
and (2S,3R)-3-(2-(R)-1-phenylethyl)carbamoyl)-iminoguanidinoethyl)-4-oxoazetidine-2-
25 carboxylic acid (71):** Compounds 69-71 were synthesized by general method G using α -
methylbenzylisocyanate (step 4). The compounds were separated via reverse phase HPLC
(acetonitrile/water) with 0.1% TFA added to the mobile phase.

[0283] **(2S,3R)-3-(2-
iminoguanidinoethyl)-4-oxo-1-((4-
phenoxyphenyl)carbamoyl)azetidine-2-carboxylic acid (72):** Compound 72 was
30 synthesized by general method G using 4-phenoxyphenyl isocyanate (step 4).

[0284] **(2S,3R)-3-(2-iminoguanidinoethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (73):** Compound 73 was synthesized by general method G using phenyl isocyanate (step 4).

5 [0285] **(2S,3R)-cyclobutyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
imino(methylguanidino) ethyl)-4-oxoazetidine-2-carboxylate (74):** Compound 74 was synthesized by general method G using cyclobutyl alcohol (step 2), α -methylbenzyl isocyanate (step 4) and N-methylpimagedine (step 6).

10 [0286] **(2S,3R)-benzyl 3-(2-iminoguanidinoethyl)-4-oxo-1-
(biphenylcarbamoyl)azetidine-2-carboxylate (75):** Compound 75 was synthesized by general method G using benzyl alcohol (step 2) and 4-biphenylisocyanate (step 4).

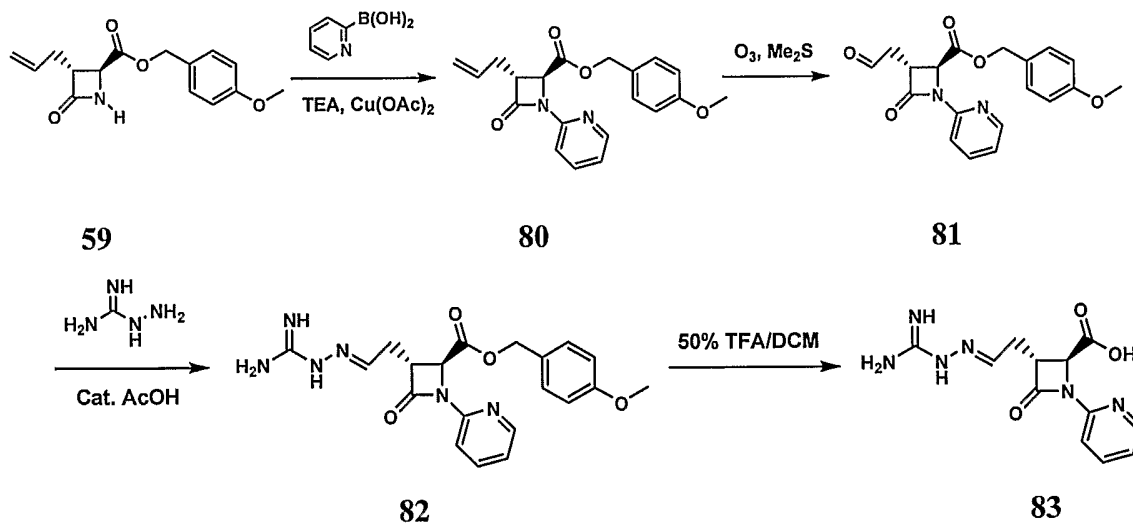
[0287] **(2S,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
imino(methylguanidino)ethyl)-4-oxoazetidine-2-carboxylate (76):** Compound 76 was synthesized by general method G using ethyl alcohol (step 2), α -methylbenzylisocyanate (step 4) and N-methyl pimagedine (step 6).

15 [0288] **(2S,3R)-1-(((R)-1-phenylpropyl)carbamoyl)-3-(2-
imino(methylguanidino)ethyl)-4-oxoazetidine-2-carboxylic acid (77):** Compound 77 was synthesized by general method G using α -ethylbenzylisocyanate (step 4) and N-methyl pimagedine (step 6).

20 [0289] **(2S,3R)-4-methoxybenzyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(2-
iminoguanidino ethyl)-4-oxoazetidine-2-carboxylate (78):** Compound 78 was synthesized by general method G using α -methylbenzylisocyanate (step 4).

25 [0290] **(2S,3R)-1-(((R)-1-phenylpropyl)carbamoyl)-3-((E)-2-(2-(4,5-dihydro-1H-
imidazol-2-amine)imino)ethyl)-4-oxoazetidine-2-carboxylic acid:** Compound 79 was synthesized by general method G using α -ethylbenzylisocyanate (step 4) and 1-(4,5-dihydro-1H-imidazol-2-yl)hydrazine in step 6 (2.7 mg, 88%).

EXAMPLE 8

General method H for the preparation of N-aryl amidinohydrazone beta-lactams.

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[0291] 3-Allyl-4-oxo-1-pyridin-2-yl-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (80): A mixture of β -lactam **59** (60 mg, 0.22 mmol), Pyridin-2-boronic acid (81 mg, 0.66 mmol), copper acetate (120 mg, 0.66 mmol), triethylamine (0.153 mL, 1.1 mmol) and activated 4A molecular sieves (270 mg) in dichloromethane (5 mL) was stirred at room temperature for 2 days. The reaction mixture was filtered through celite and the filtrate was concentrated. Preparative TLC (20% EtOAc/Hexanes) of the residue gave the desired product **80** (19.2 mg, 24.8%) ^1H NMR (300 MHz, CDCl_3): 2.60 (m, 2H), 3.49 (m, 1H), 3.81 (s, 3H), 4.41 (d, $J = 2.61$ Hz, 1H), 5.11-5.21 (m, 4H), 5.82 (m, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.01 (m, 1H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.66-7.72 (m, 2H); 8.19 (d, $J = 4.7$ Hz, 1H) Anal. $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$, Mol. Wt.: 352.38. Found: ESI-MS: 352.9 ($\text{M}+\text{H}$) $^+$.

20

[0292] 4-Oxo-3-(2-oxo-ethyl)-1-pyridin-2-yl-azetidine-2-carboxylic acid 4-methoxy-benzyl ester (81): Ozone was bubbled through a solution of **80** (24.0 mg) in dry methylene chloride (7 mL) at -78°C until a faint blue color persisted (about 10 min). The reaction mixture was quenched with dimethylsulfide (200 μL) at -78°C , then the cooling bath was removed. After the solvent was concentrated, the residue was taken up in EtOAc. Removal of solvents gave the desired aldehyde product **81**, which was sufficiently pure to carry on to the next step without further purification. Anal. $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$, Mol. Wt.: 354.36. Found: ESI-MS: 354.9 ($\text{M}+\text{H}$) $^+$.

25

[0293] (2S,3R)-4-methoxybenzyl-3-(2-guanidinoiminoethyl)-4-oxo-1-(pyridin-2-yl)azetidine-2-carboxylate (82): To a solution of the freshly prepared aldehyde **81** (32.2 mg,

0.068 mmol) in ethanol (0.85 mL) was added aminoguanidinium nitrate (19 mg, 0.14 mmol) and acetic acid (12 μ L, 0.20 mmol). The mixture was stirred at room temperature for 3 h. Concentration of solvent gave the crude desired product **82**. Anal. $C_{20}H_{30}N_6O_4$, Mol. Wt.: 410.43. Found: ESI-MS: 411.0 (M+H)⁺.

- 5 **[0294] (2S,3R)-3-(2-guanidinoiminoethyl)-4-oxo-1-(pyridin-2-yl)azetidine-2-carboxylic acid (83):** The crude ester **82** was treated with TFA/DCM (0.75 mL/1 mL). After one and half hours, LC-MS analysis indicated completion of the reaction. The solvent was removed and the residue was purified by preparative HPLC (Vydac reverse phase C-18 column, 22 x 250 mm ID). Mobil phase: A = 0.1% TFA in water, B = 0.1% TFA in
10 acetonitrile. The flow rate was 12 mL/min. The gradient time was 5% B to 50 % B over 45 min. The desired product, **83**, was obtained as a white solid (5.5 mg). Anal. $C_{19}H_{24}N_6O_4$, Mol. Wt.: 290.28, Found: ESI-MS: 291.0 (M+H)⁺.

Synthesis of **86** and **87**

- 15 **[0295] (2R,3R)-1-(isopropylidimethylsilyl)-3-(3-nitrophenylthio)-4-oxoazetidine-2-carboxylic acid (84):** Using glassware, starting materials, and THF that are each rigorously dry is essential for successful alkylation, as well as keeping the reaction mixture under dry argon. Commercially available beta-lactam acid **4** (15.31 mmol, 3.51 g) was dissolved in 40 mL dry THF at room temperature with magnetic stirring, in an oven-dried flask with dry stir bar under dry argon. The solution was cooled to -78°C and the LDA solution (2.05
20 equivalent relative to acid, 31.38 mmol, 17.4 mL 1.8M solution from Aldrich) was added slowly over 5 minutes by syringe to the cooled stirring solution. The solution was kept at -78°C for 15 minutes and warmed to 0°C with an ice bath. The solution was kept at 0°C for 45 minutes, and then cooled to -42°C (dry ice-acetonitrile). The disulfide was dissolved in 20 mL of dry THF and cooled to -42°C (dry ice-acetonitrile). The disulfide solution was added
25 dropwise via a dry narrow bore cannula to the enolate solution using balloon pressure, with both vessels cooled to -42°C during the 30 minute addition. After the addition was complete, the vial was rinsed with two 2 mL portions of dry THF, which was cooled to -42°C and added to the enolate solution also. The reaction vessel was kept at -42°C for 4 hours and then warmed to 0°C . A quench solution was prepared by adding 50g of ice to 150 mL of 5%
30 aqueous KHSO_4 solution in an Erlenmeyer. The reaction mixture was poured into the quench solution, and the vessel was rinsed with 5 x 20 mL aliquots of ethyl acetate, which were poured into the quench solution. The two layers were poured into a separatory funnel. The pH of the aqueous layer was 2-3. The organic layer was separated, the aqueous layer was

extracted with 3 portions of ethyl acetate, and the combined organic layers were washed with brine and concentrated *in vacuo*. The solution was warmed to 0°C and after 4 hours worked up in the standard way (KHSO₄ quench). The desired product **84** was purified by column chromatography on silica gel using 50:50:1 hexane: ethyl acetate: acetic acid as eluent.

5 Product MS: 383.1 [M+H]⁺.

[0296] **(2R,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(3-nitrophenylthio)-4-oxoazetidine-2-carboxylate (85a) and (2R,3S)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(3-nitrophenylthio)-4-oxoazetidine-2-carboxylate (85b)**. The completion of the synthesis of **85a-b** was accomplished by following general method C using ethyl alcohol (step 1), and
10 α -methylbenzylisocyanate (step 3).

[0297] **(2R,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(3-aminophenylthio)-4-oxoazetidine-2-carboxylate (86)**: To a solution of compound **85a** (18 mg, 41 μ mol) in ethyl acetate (1 mL) was added tin chloride monohydrate (2.5 eq.) and the solution was heated to 50°C. After 1 h the solution was concentrated *in vacuo*. The residue was purified by column
15 chromatography using a gradient of hexane/ethyl acetate 20-100% as eluent to yield **86** (12 mg, 72%). Product MS: 414.1 (M+1).

[0298] **(2R,3S)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(3-aminophenylthio)-4-oxoazetidine-2-carboxylate (87)**: To a solution of **85b** (17 mg, 38 μ mol) in ethyl acetate (1 mL) at room temperature was added tin chloride monohydrate (2.5 eq.) and the solution was
20 heated to 50°C. After 1 h the solution was concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane/ethyl acetate 20-100% as eluent to yield **87** (10 mg, 63%). Product MS: 414.1 (M+1).

Synthesis of 90

[0299] **(2S)-ethyl 1-(((R)-1-phenylethyl)carbamothioyl)-3-((2-(tert-butoxycarbonyl)pyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (89)**: Compound **88**
25 was prepared by general method C using ethyl alcohol (step 1). To the solution of **88** (23 mg) in THF was added LiHMDS (0.14 mL, 1M solution in THF) at -78 °C. The reaction mixture was warmed up to 0°C for 5 h and then was quenched with 5% KHSO₄ to pH~5. After extraction with ethyl acetate, the organic layer was washed with brine, dried over
30 Na₂SO₄ and concentrated *in vacuo* to yield **89** LC/MS (ESI) *m/z* 512.8.

[0300] **(2S)-ethyl 1-(((R)-1-phenylethyl)carbamothioyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (90)**: Compound **89** (crude) was treated with 50%

TFA-DCM at 0°C. LCMS was used to monitor the reaction until it was completed. The reaction mixture was condensed and the residue was purified by preparative HPLC with 5-70% acetonitrile-water (with 0.1%TFA) as mobile phase and gradient time 40 min to afford **90** (9 mg, 26% yield). ¹H NMR (DMSO) δ 8.44 (d, 1H), 7.70 (d, 1H), 7.37-7.27 (m, 5H), 7.26 (s, 2H), 6.72 (s, 1H), 6.66 (d, 1H), 5.51 (m, 1H), 4.38 (d, 1H), 4.22 (dd, 2H), 3.40 (d, 1H), 3.14 (m, 2H), 1.62 (d, 3H), 1.22 (t, 3H), LC/MS (ESI) *m/z* 413.1.

Synthesis of 93

[0301] **(2S)-4-Methoxybenzyl 3-((2-bis(tert-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (91)**: Compound **91** was prepared by general method C using 4-methoxybenzyl alcohol (step 1).

[0302] **(2S)-4-Methoxybenzyl 1-(((R)-1-phenylethyl)carbamoithiyl)-3-((2-bis(tert-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylate (92)**: Compound **92** was prepared analogously to the synthesis of **89** and the crude sample was taken on without further purification. LC/MS (ESI) *m/z* 705.0.

[0303] **(2S)-1-(((R)-1-phenylethyl)carbamoithiyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetidine-2-carboxylic acid (93)**: Compound **93** was prepared analogously to the synthesis of **90**. The crude sample was purified by preparative HPLC with 0-70% acetonitrile-water (with 0.1%TFA) as mobile phase and gradient time 40 min to afford **93** (5.6 mg, 16%). HPLC purity, >96%, ¹H NMR (DMSO) δ 9.04 (d, 1H), 8.00 (br, 2H), 7.90 (d, 1H), 7.41-7.27 (m, 5H), 6.90 (m, 2H), 5.44 (m, 1H), 4.33 (d, 1H), 3.69 (m, 1H), 3.2 (m, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), LC/MS (ESI) *m/z* 385.1.

Synthesis of 96

[0304] **(2S,3R)-3-((2-bis(tert-butoxylcarbonyl)aminopyridin-4-yl)methyl)-N-(methylsulfonyl)-4-oxoazetidine-2-carboxamide (94)**: Compound **5** was prepared by general method A. To a solution of **5** (40 mg, 1 eq.) in dichloromethane (1 mL) was added EDC-HCl (17 mg, 1.2 eq.), HOBt (12 mg, 1.2 eq.), DIEA (16 uL, 1.2 eq.) and methanesulfonamide (9 mg, 1.2 eq.). The reaction was stirred at room temperature for 12 hrs and then concentrated *in vacuo*. The crude material was redissolved in dichloromethane and washed with saturated NaHCO₃ and water, dried over sodium sulfate and concentrated *in vacuo* to give 22 mg of crude **94** as a tan oil which was taken on to the next step without further purification.

[0305] **(2S,3R)-3-((2-bis(*tert*-butoxycarbonyl)aminopyridin-4-yl)methyl)-N2-(methylsulfonyl)-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide (95):** To a solution of crude **94** in THF (1 mL) was added DIEA (8 uL, 1.5 eq.) and (R)-(+)- α -methylbenzylisocyanate. The reaction was stirred for 12 hours at room temperature. Ethyl acetate was added to the reaction mixture and washed with water. The organic layer was concentrated *in vacuo*. The crude product was purified using a silica gel column and a gradient elution from 10% EtOAc/hexanes to 100% EtOAc followed by 10% MeOH in DCM to elute **95**. Product fractions were concentrated *in vacuo* to give 20 mg of compound **95**.

[0306] **(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-(methylsulfonyl)-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide (96):** To a solution of **95** in 1 mL dichloromethane was added 300 uL of TFA. The reaction was stirred for 1 hour and then concentrated *in vacuo*. The crude material was purified via reverse phase HPLC (C18, acetonitrile/water with 0.1% TFA) to yield 0.75 mg of **96**. MS $[M+H]^+ = 446.0$

Synthesis of 101

[0307] **(2S,3R)-3-((2-bis(*tert*-butoxycarbonyl)aminopyridin-4-yl)methyl)-1-(*tert*-butyldimethylsilyl)-N-(4-fluorophenylsulfonyl)-4-oxoazetidine-2-carboxamide (97):** Compound **5** was prepared by general method A. To a solution of **5** (50.6 mg, 1.0 eq.) in THF (1 mL) was added carbonyldiimidazole (CDI, 23 mg, 1.5 eq.) and DMAP (17 mg, 1.5 eq.). The reaction was stirred for 1 hour at room temperature. Then 4-fluorobenzenesulfonamide (20 mg, 1.2 eq.) and DBU (15 uL, 1.05 eq.) were added and the capped vial was allowed to stir for 16 hours. The reaction was then concentrated *in vacuo* to yield crude **97**.

[0308] **(2S,3R)-3-((2-bis(*tert*-butoxycarbonyl)aminopyridin-4-yl)methyl)-N-(4-fluorophenylsulfonyl)-4-oxoazetidine-2-carboxamide (98):** To a solution of crude **97** from above in MeOH:AcOH (900 uL: 100 uL) was added 0.5M NH_4F in MeOH (190 uL, 1.0 eq.). After 2 hours and 20 minutes the reaction was concentrated *in vacuo* and triturated with dichloromethane to yield **98** as a yellow foam which was taken on to the next step without further purification.

[0309] **(2S,3R)-3-((2-bis(*tert*-butoxycarbonyl)aminopyridin-4-yl)methyl)-N-(4-fluorophenylsulfonyl)-N-methyl-4-oxoazetidine-2-carboxamide (99):** To a solution of **98** (18 mg, 1.0 eq.) in MeOH: THF (1 mL: 300 uL) was added 2.0M TMSCHN_2 in hexanes (266 uL, 17 eq.). After 15 minutes, TLC showed complete conversion of starting material. The

reaction was poured into ethyl acetate and then washed with 0.2N HCl, 1N NaHCO₃ and brine. The organic layer was then dried over sodium sulfate and concentrated *in vacuo*. The product was then purified via reverse phase HPLC (C18, acetonitrile/water with 0.1% TFA) to yield **99** (11.9 mg, 65%) as a clear oil.

5 **[0310] (2S,3R)-3-((2-bis(*tert*-butoxycarbonyl)aminopyridin-4-yl)methyl)-N2-(4-fluorophenylsulfonyl)-N2-methyl-4-oxo-N1-((R)-1-phenylethyl)azetidione-1,2-dicarboxamide (100):** To a solution of **99** in DMF (0.75 mL) was added (R)- α -methylbenzylisocyanate (6 μ L, 2.0 eq.) and TEA (8.5 μ L, 3.0 eq.). The reaction was stirred under an atmosphere of argon for 20 hours. The reaction was then concentrated *in vacuo* and
10 taken on to the next step without further purification.

[0311] (2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-(4-fluorophenylsulfonyl)-N2-methyl-4-oxo-N1-((R)-1-phenylethyl)azetidione-1,2-dicarboxamide (101): To crude **100** from above was added 4N HCl in dioxane (2 mL). The reaction was capped, stirred for 4 hours, concentrated *in vacuo* and triturated with diethyl ether. The crude product was
15 dissolved in acetonitrile/methanol, filtered and purified via reverse phase HPLC (C18, acetonitrile/water with 0.1% TFA) to yield **101** (1.7 mg).

Synthesis of **106**

[0312] (2S,3R)-benzyl 3-((2-(bis-N,N-*t*-butoxycarbonyl)aminopyridin-4-yl)methyl)-1-(tert-butyldimethylsilyl)-4-oxoazetidione-2-carboxylate (102): Compound **102** was
20 synthesized by general method C using α -methylbenzyl isocyanate (step 3).

[0313] (3R,4S)-3-((2-(bis-N,N-*t*-butoxycarbonyl)aminopyridin-4-yl)methyl)-1-(tert-butyldimethylsilyl)-4-(hydroxymethyl)azetidione-2-one (103): To a solution of compound **102** (0.35 g, 0.56 mmol) in 10 ml anhydrous methanol was added sodium borohydride (0.128g, 3.36 mmol) in several batches. The reaction was stirred at room temperature for 2
25 hr, then slowly quenched with water and acidified with 1N HCl. The reaction mixture was extracted with ethyl acetate (three times), dried over magnesium sulfate and concentrated *in vacuo*. The viscous oil was triturated with ether to give the alcohol **103** as a white solid (0.184 g, 63%). LS/MS M+H 522.3, calc. 522.29.

[0314] ((2S,3R)-3-((2-(bis-N,N-*t*-butoxycarbonyl)aminopyridin-4-yl)methyl)-1-(tert-butyldimethylsilyl)-4-oxoazetidione-2-yl)methyl methanesulfonate (104): To a solution of alcohol **103** (0.047 mmol) in 2 ml of dichloromethane was added methanesulfonyl chloride (0.071 mmol) and triethylamine (0.141 mmol) dropwise and the reaction was stirred at room
30

temperature overnight. Afterwards, it was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give compound **104** as a yellow oil (85%). LS/MS M+H 600.3, calc. 600.22.

5 **[0315] ((2S,3R)-3-((2-(bis-N,N-*t*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4-oxoazetid-2-yl)methyl methanesulfonate (105):** To a solution of compound **104** (0.04 mmol) in 1 ml anhydrous methanol were added ammonium fluoride (0.048 mmol, 0.5 M in methanol) and acetic acid (0.144 mmol) and the reaction was stirred at room temperature for 2 h. Afterwards, it was concentrated *in vacuo* and the residual acetic acid was azeotroped
10 with toluene. The solid was diluted with dichloromethane and was filtered through a syringe filter. The solution was concentrated *in vacuo* to give compound **105** as a clear oil (quantitative yield) LS/MS M+H 486.5, calc. 486.13.

[0316] ((2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetid-2-yl)methyl methanesulfonate TFA salt (106): To a solution of compound **105**
15 (0.04 mmol) in 2 ml anhydrous methylene chloride was added isocyanate (0.06 mmol) and triethyl amine (0.12 mmol) dropwise and the reaction mixture was stirred at room temperature for 5 h. Afterwards, the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Column
20 chromatography purification (silica, hexane/ethyl acetate) gave the product in 70 % yield. (LS/MS M+H 633.4, calc. 633.2). The product was treated with 1 ml TFA:dichloromethane for 1 h at room temperature. Afterwards, it was concentrated *in vacuo* and washed with ethyl ether (five times). Compound **106** was obtained as a white solid (76%). LS/MS M+H 433.3, calc. 433.15.

25 **Synthesis of 112**

[0317] (2S,3S)-ethyl 3-(benzyloxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (108): To a solution of p-anisidine (**107**, 5.4 mmol) in 10 ml anhydrous dichloromethane and 2 ml toluene were added ethyl glyoxylate (8.0 mmol, 50% solution in toluene) and anhydrous magnesium sulfate (3.0 g). The reaction mixture was heated at 70°C for 3 h. Afterwards, the
30 mixture was filtered and cooled to 0°C with an ice/water bath. Triethylamine (10.8 mmol) and benzyloxyacetyl chloride (8.1 mmol) were added dropwise and the reaction mixture was stirred at room temperature for 18 h. Afterwards, it was concentrated *in vacuo* and triturated

with ethyl ether and hexane to give compound **108** as a tan solid (69 % yield). LS/MS M+H 356.2, calc. 356.12.

[0318] (2S,3S)-ethyl 1-(4-methoxyphenyl)-4-oxo-3-

(trifluoromethylsulfonyloxy)azetidine-2-carboxylate (109): Palladium hydroxide (0.186

5 mmol, 20% on carbon, wet) was added to a round bottom flask. The flask was evacuated and backfilled with hydrogen (three times). Afterwards a solution of compound **108** (3.72 mmol) in anhydrous methanol (30 ml) was added to the flask and the reaction was stirred for 18 h at room temperature under a positive atmosphere of hydrogen. Afterwards, the mixture was filtered through celite and concentrated *in vacuo* to give the free alcohol as a white solid. To
10 a cold (0°C) solution of the alcohol (0.377 mmol) in anhydrous dichloromethane (2 ml) were added triethylamine (1.13 mmol) and trifluoromethanesulfonyl chloride (0.57 mmol) dropwise and the reaction was stirred at 0°C for 30 min. Afterwards, it was diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Compound **109** was
15 obtained as an orange solid (quant. yield). LS/MS M+H 398.5, calc. 398.3.

[0319] (2R,3R)-ethyl 3-mercapto-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate

(110): To a solution of triisopropylsilane thiol (0.91 mmol) in anhydrous THF (2 ml) was added sodium hydride (0.68 mmol, 60% in mineral oil) and the reaction mixture was stirred at room temperature for 15 min. Afterwards, compound **109** (0.45 mmol, dissolved in 2 ml

20 THF) was added to the reaction and the mixture was stirred at room temperature for 1 h. Then it was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography purification (12 g pre-packed silica column, hexane/ethyl acetate) afforded the protected thiol. The thiol (0.126 mmol) was
25 then diluted with anhydrous methanol (2ml) and ammonium fluoride (0.15 mmol, 0.5 M in methanol) and acetic acid (0.454 mmol) were added to the reaction and the mixture was stirred at room temperature for 2 h. Afterwards, it was concentrated *in vacuo* and the residual acetic acid was azeotroped with toluene. The solid was diluted with dichloromethane and was filtered through a syringe filter. The solution was concentrated *in vacuo* to give
30 compound **110** as a clear oil (23% yield for both steps). LS/MS M+H 282.3, calc. 282.1.

[0320] (2R,3R)-ethyl 3-((2-bis(butoxycarbonyl)aminopyridin-4-yl)methylthio)-4-oxoazetidine-2-carboxylate (111): To a solution of compound **110** (0.05 mmol) in

anhydrous THF (2 ml) was added sodium hydride (0.07 mmol, 60% in mineral oil) and the reaction mixture was stirred at room temperature for 15 min. Afterwards, bromide A was added (0.08 mmol) and the reaction was stirred at room temperature for 1 h. Then it was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography purification (4 g pre-packed silica column, hexane/ethyl acetate) afforded the product as a yellow oil (48 % yield). The product was then diluted with acetonitrile (1ml) and water (0.5 ml) and cooled to 0°C with an ice water bath. Ceric ammonium nitrate (0.08 mmol) dissolved in water (0.5 ml) was added and the reaction was stirred at 0 °C for 30 min. Afterwards, the reaction was concentrated *in vacuo* and diluted with ethyl acetate and sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (three times), dried over magnesium sulfate and concentrated *in vacuo*. Compound 111 was obtained as a clear oil (96 % yield). LS/MS M+H 482.3, calc. 482.2.

[0321] (2R,3R)-ethyl 1-(((R)-1-phenylethyl)carbamoyl)-3-((2-aminopyridin-4-yl)methylthio)-4-oxoazetidine-2-carboxylate (112): To a solution of compound 111 (0.025 mmol) in 2 ml anhydrous methylene chloride were added isocyanate B (0.038 mmol) and triethylamine (0.075 mmol) dropwise and the reaction mixture was stirred at room temperature for 5 h. Afterwards, the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product was treated with 1 ml TFA/dichloromethane for 1 h at room temperature. Afterwards, it was concentrated *in vacuo* and washed with ethyl ether. The two diastereomers were separated on reverse phase HPLC (acetonitrile/ water as eluents). Compound 112 was obtained as a white solid (0.001 mg). LS/MS M+H 429.62, calc. 429.5

[0322] (2R,3R)-ethyl 3-((2-aminopyridin-4-yl)methylthio)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (113) and (2R,3S)-ethyl 3-((2-aminopyridin-4-yl)methylthio)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (114): Compound 113 and 114 were synthesized by the same method used to synthesis 112 with the omission of the NH₄F/AcOH/MeOH deprotection step. The final TFA deprotection yielded the mixture of the 113 and 114. The isomers were separated via reverse phase HPLC (acetonitrile/water) with 0.1% TFA added to the mobile phase.

Synthesis of 119

[0323] (3R,4S)-3-((2-bis(*t*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-1-(*tert*-butyldimethylsilyl)-4-(2-diazoacetyl)azetid-2-one (115): To a solution of compound **5** (100 mg, 0.186 mmol) in THF (1 mL) at -15°C was added triethylamine (27.8 uL, 0.2 mmol) and ethyl chloroformate (20 uL, 0.2 mmol). The reaction mixture was then stirred at -15°C for 30 minutes and the ppt was then filtered off under an atmosphere of argon. To the crude anhydride was then added acetonitrile (1 mL) and 2.0M TMSCHN₂ in hexanes (0.2 mL, 0.4 mmol). The reaction was stirred at 4°C for 48 h, at which point LCMS showed complete conversion of starting material. Diethyl ether (25 mL) was added to the reaction and washed with 10% NaHSO₄ (25 mL), saturated NaHCO₃ (25 mL) and brine (25 mL). The crude material was purified by Combiflash silica gel chromatography (0-3 min: 100% hexanes, 3-10 min: 40% EtOAc in hexanes) to yield **115** (32 mg). Exact mass. 559.28. Found ES MS [M+H]⁺ 559.9.

[0324] (3R,4S)-3-((2-bis(*t*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4-(2-diazoacetyl)azetid-2-one (116): To a solution of **115** (50 mg, 0.089 mmol) in methanol (1 mL) at room temperature was added 0.5 M ammonium fluoride (178 uL, 0.089 mmol) and acetic acid (14 uL, 0.257 mmol). The reaction was stirred for 16 hours and then purified with Combiflash silica gel chromatography (0-10 min: 100% ethyl acetate) to yield **116** (39 mg).

[0325] (2S,3R)-3-((2-bis(*t*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-2-(2-diazoacetyl)-4-oxo-N-((R)-1-phenylethyl)azetid-1-carboxamide (117): To a solution of **116** (39 mg, 0.089 mmol) in anhydrous DCM (2 mL) was added (R)-(+)-methylbenzylamine (30 mg, 2 eq.) and triethylamine (36 uL, 3 eq.). The reaction was stirred for 16 hours and the crude mixture was purified via preparative TLC (70% EtOAc in hexanes) to yield **117** (43.4 mg).

[0326] Ethyl 2-((2R,3R)-1-(((R)-1-phenylethyl)carbonyl)-3-((2-bis(*t*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4-oxoazetid-2-yl)acetate (118): To a solution of **117** (10 mg, 0.016 mmol) in ethanol (2 mL) was added silver benzoate (1 mg, 10% w/w) and the mixture was stirred at room temperature for 16 hours. The crude material was then purified by preparative TLC (70% EtOAc in hexanes) to yield **118** (4 mg). Exact mass. 610.3. Found ES MS [M+H]⁺ 610.9.

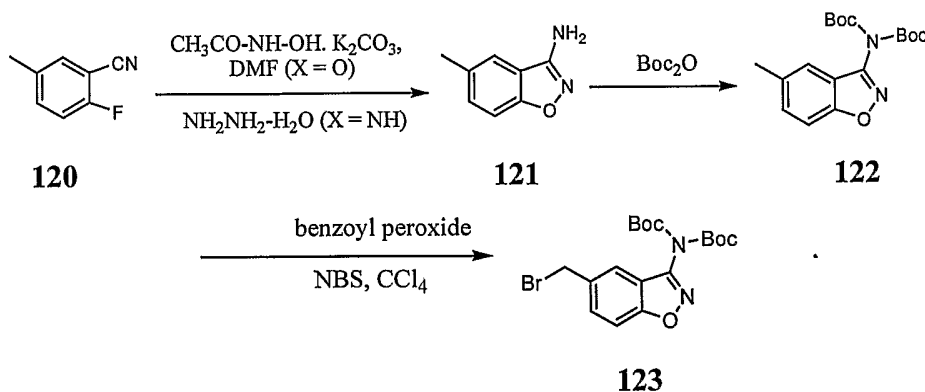
[0327] Ethyl 2-((2R,3R)-1-(((R)-1-phenylethyl)carbonyl)-3-((2-aminopyridin-4-yl)methyl)-4-oxoazetid-2-yl)acetate (119): Compound **118** was dissolved in 1:1

TFA:DCM (2 mL) and the reaction stirred for 2 hours and then concentrated *in vacuo* to yield a crude material which was purified by reverse phase HPLC (acetonitrile/water with 0.1% TFA) to yield **119** (1.2 mg).

Synthesis of **123**

5

Alkylating agent synthesis



10 **[0328] 5-Methyl-benzo[d]isoxazol-3-ylamine (121)** Acetohydroxamic acid (1.69 g, 22.5 mmol) in DMF (45 mL) was stirred with K_2CO_3 and several drops of water at RT for 30 min, the 2-fluoro-5-methylbenzonitrile (**120**) (1.35 g, 10 mmol) in DMF (5 mL) was added and the reaction mixture was stirred at RT for 3 days. The reaction was diluted with water and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and
 15 concentrated *in vacuo* to provide **121** (878 mg, 60%). LC-MS (ESI) m/z 149.2.

[0329] Benzo[d]isoxazol-3-bis(N,N-t-butoxycarbonyl)amine (122): To a solution of **121** (148 mg, 1 mmol) in DCM (2 mL) was added di-*t*-butyldicarbonate (546 mg, 2.5 mmol), DIEA (0.348 mL, 2 mmol), and DMAP (22.2 mg, 1 mmol) at 0°C . The reaction was warmed up to RT and stirred for 4 hr and then diluted with ethyl acetate and treated with aqueous
 20 ammonium chloride to pH 6. The organic layer was separated and washed with brine and concentrated *in vacuo*. The residue purified by silica gel chromatography using 100% hexane as the eluent to yield **122** (347 mg, 100%), LC-MS (ESI) m/z 348.8.

[0330] 5-(Bromomethyl)benzo[d]isoxazol-3-(bis(*t*-butoxycarbonyl))amine (123): To a solution of **122** (1.37g, 3.9mmol) in CCl_4 was added N-bromosuccinimide (700 mg, 1 eq.)
 25 and benzoyl peroxide (54 mg, 0.04 eq.). The mixture was heated to 85°C for 4 hours and then filtered after cooling to room temperature. The filtrate was concentrated *in vacuo* and purified via silica gel chromatography eluting with 0-10% EtOAc in hexanes to provide **123** (630 mg).

Synthesis of 129

[0331] **(S)-benzyl 4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate (125)** A solution of aniline (**124**) (0.186 mL, 2 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (5 mL) was dropped into a phosgene solution (1.27 mL, 20% in toluene) at 0°C and stirred for 30 min. Then (S)-benzyl 4-oxoazetidine-2-carboxylate (531 mg, 2.6 mmol) in THF (5 mL) was added. The resultant reaction mixture was stored in a refrigerator overnight and then filtered. The filtrate was condensed and the residue was purified by medium pressure chromatography (silica gel column) with dichloromethane as the eluent to provide **125** (474 mg, 73%). ¹H NMR (CDCl₃) δ 8.28 (br, 1H), 7.48-7.29 (m, 9H), 7.14-7.09 (m, 1H), 5.25 (s, 2H), 4.62-4.57 (m, 1H), 3.43-3.35 (m, 1H), 3.12-3.05 (m, 1H), LC-MS (ESI) *m/z* 324.0.

[0332] **(S)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate acid (126)** Compound **125** was dissolved in a methanol-ethanol solution and 10% Pd-C catalyst was added. The reaction vessel was then evacuated and flushed with hydrogen. The reaction was stirred under an atmosphere of hydrogen until all the starting material was consumed as evidenced by LCMS to yield **126** (quantitative yield). ¹H NMR (MeOD) δ 7.63-7.46 (m, 2H), 7.34-7.29 (m, 2H), 7.13-7.08 (m, 1H), 4.54-4.51 (m, 1H), 3.48 (dd, J = 6.4, 15.8 Hz, 1H), 3.09 (dd, J = 2.3, 16.8 Hz, 1H), LC-MS (ESI) *m/z* 234.9.

[0333] **(2S,3R)-3-((3-di-Boc-aminobenzo[d]isoxazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (128)** A solution of **126** (41 mg, 0.174 mmol) in THF was added to 1.0M LiHMDS in THF(0.635 mL) at -78°C and the reaction mixture was stirred for 30 min and then slowly warmed up to room temperature over 1 h. The reaction mixture was cooled back to -78°C followed by addition of compound **127** (44 mg, 0.103 mmol) dissolved in THF. After 30 min, the reaction mixture was warmed up to 0°C for one hour and then to room temperature for another hour. The reaction was quenched with aqueous ammonia chloride and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC to afford **128** (32 mg, 54%), LC/MS (ESI) *m/z* 581.0.

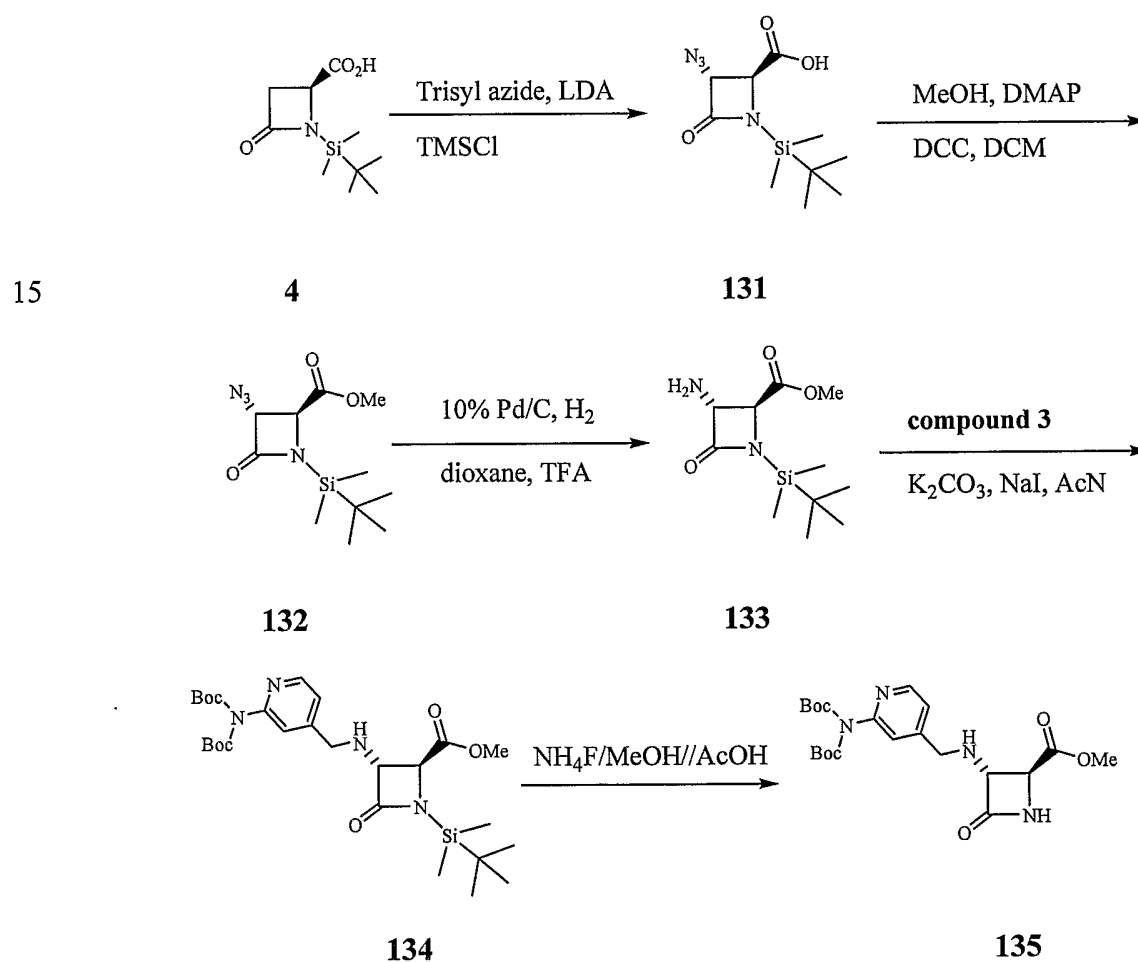
[0334] **(2S,3R)-3-((3-aminobenzo[d]isoxazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (129)**: Compound **128** (32 mg) was treated with 20% TFA-DCM for 20 min at room temperature. The reaction was concentrated *in vacuo* and the residue was purified by preparative HPLC (Vydac, Protein & Peptide C18 column, 0-60%

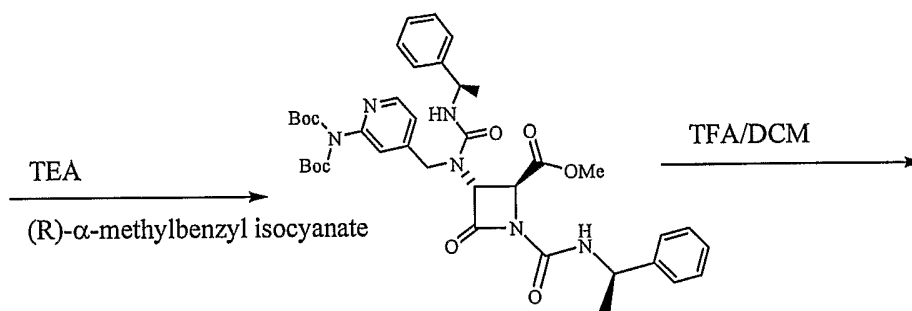
H₂O-acetonitrile w/0.1% TFA, gradient change in 50 min) to afford **129** (7.2 mg, 26%), ¹H NMR (DMSO) δ 8.95 (s, 1H), 7.77 (s, 1H), 7.55 (d, J = 8.3 Hz, 3H), 7.43 (d, J = 8.55 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 4.35 (d, J = 2.8 Hz, 1H), 3.76 (m, 1H), 3.27 (d, J = 7.7 Hz, 2H), LC-MS (ESI) *m/z* 381.1.

- 5 **[0335] (2S,3R)-3-((3-amino-1H-indazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (130):** Compound **130** was prepared analogously to **129** using hydrazine instead of acetohydroxamic acid in the synthesis of the alkylating agent. Yield 2.3 mg. ¹H NMR (DMSO) δ 11.60 (br, 1H), 8.90 (s, 1H), 7.63 (s, 1H), 7.51 (d, J = 6.0 Hz, 2H), 7.35-7.20 (m, 5H), 7.09 (t, J = 6.9 Hz, 1H), 6.45 (br, 2H), 4.28
10 (d, J = 2.7 Hz, 1H), 3.69 (dt, J = 2.7, 7.3 Hz, 1H), 3.17 (d, J = 7.4 Hz, 2H), LC-MS (ESI) *m/z* 380.1.

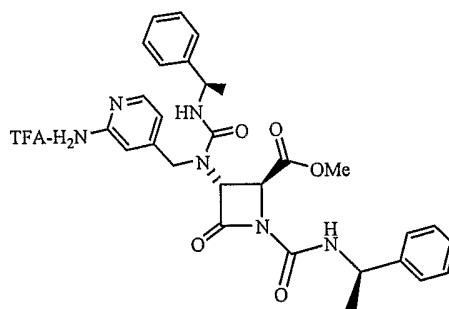
EXAMPLE 9

General method J for the synthesis of 3-substituted-amino beta-lactams.





136



137

5 [0336] **(2S,3R)-3-azido-1-(tert-butyldimethylsilyl)-4-oxoazetidine-2-carboxylic acid (131)**: To LDA (1.8M, 4.99 mL) and THF (10 mL) at -78°C was added dropwise (*S*)-1-*t*-butyldimethylsilyl-4-oxo-2-azetidinecarboxylic acid (**4**, 1.0g) in THF (15 mL). The resulting solution was warmed to -30°C or -10°C for 30 min. If a slurry formed, additional THF was added to solublize the azetidine. After 30 min., the solution was cooled to -78°C . A pre-cooled solution (-10°C) of trisyl azide (1.61 g) in THF (10 mL) was added slowly. The

10 reaction mixture was stirred for one hour before quenching with TMSCl (0.82 mL). The cold bath was then removed and the solution allowed to stir for an additional hour. Saturated sodium bicarbonate (100 mL) was added and the aqueous layer was extracted with diethyl ether (2 x 100 mL). The organic extracts were discarded. The aqueous layer was then

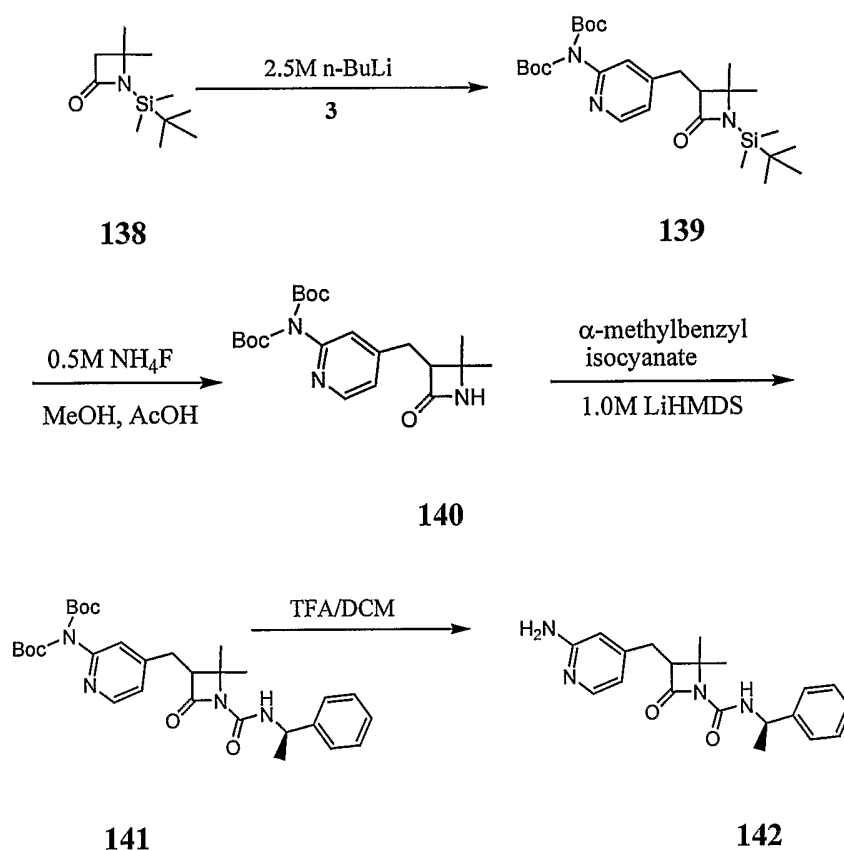
15 brought to pH=7 by slow addition of 1N HCl and extracted with Et₂O (2 x 100 mL) and the organic layers were discarded. The aqueous layer was then brought to pH=3 by slow addition of 1N HCl and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to yield **131** which was taken on to the next step without further purification.

20 [0337] **(2S,3R)-methyl 3-azido-1-(tert-butyldimethylsilyl)-4-oxoazetidine-2-carboxylate (132)**: To a solution of crude **131** (1.58g) in CH₂Cl₂ (25mL) was added methanol (0.26 mL, 6.43 mmol). DCC (1.45g, 7.02 mmol) and catalytic DMAP. The

solution was stirred at room temperature overnight. The solution was then filtered through Celite and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 20% EtOAc in hexanes, to yield pure **132**.

- [0338] (2S,3R)-methyl 3-amino-1-(tert-butyldimethylsilyl)-4-oxoazetidine-2-carboxylate (133):** To a solution of **132** (5.85mmol) in 3:1 methanol: dioxane (25 mL) was added a few drops of TFA and 10% Pd/C (10 wt%). The reaction was stirred under atmospheric hydrogen for one hour and then filtered through Celite. The solvent was removed and the residue triturated with diethyl ether to afford **133**, which was used in the next step without further purification.
- [0339] (2S,3R)-methyl 1-(tert-butyldimethylsilyl)-3-((2-(di-(*t*-butoxycarbonyl)-amino)pyridin-4-yl)methylamino)-4-oxoazetidine-2-carboxylate (134):** To a solution of **133** and **3** in acetonitrile was added potassium carbonate and catalytic NaI. The resultant solution was heated at reflux until complete by TLC (~1-2h.) The solution was then cooled and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate and the organic layer was washed with water (2 x X mL) and brine (x mL.). The organic layer was then dried over MgSO₄, and concentrated *in vacuo*. The product was then purified by silica gel chromatography, eluting with 50-100% ethyl acetate in hexanes, to yield pure **134**.
- [0340] (2S,3R)-methyl 3-((2-(di-(*t*-butoxycarbonyl)-amino)pyridin-4-yl)methylamino)-4-oxoazetidine-2-carboxylate (135):** Compound **135** was synthesized following the procedure outlined in steps 2 of General method C.
- [0341] (2S,3R)-methyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(1-((2-(di-(*t*-butoxycarbonyl)-amino)pyridin-4-yl)methyl)-3-((R)-1-phenylethyl)ureido)-4-oxoazetidine-2-carboxylate (136):** Compound **136** was synthesized following the procedure outlined in steps 3 of General method C.
- [0342] (2S,3R)-methyl 1-(((R)-1-phenylethyl)carbamoyl)-3-(1-((2-aminopyridin-4-yl)methyl)-3-((R)-1-phenylethyl)ureido)-4-oxoazetidine-2-carboxylate (137), TFA salt:** Compound **137** was synthesized following the procedure outlined in steps 5 of General method C.

EXAMPLE 10

General method K for the preparation of geminal dimethyl beta-lactams.

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[0343] 1-(*Tert*-butyldimethylsilyl)-3-(3-chloropropyl)-4,4-dimethylazetidin-2-one (138): 4,4-dimethylazetidin-2-one was prepared as described in *J. Medicinal Chemistry* 1994, 37, 897-906 and then as described in US 6,335,324.

[0344] 3-((2-(*N,N*-bis-*tert*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-1-(*tert*-butyldimethylsilyl)-4,4-dimethylazetidin-2-one (139): The alkylation procedure from patent US 6,335,324, p.22 except a) 3, 4-bromomethyl-2-bis-Boc-aminopyridine, was used as the alkylating agent instead of 3-chloropropyl iodide and b) the reaction was allowed to warm up to room temperature after the addition of the 3.

[0345] 3-((2-(*N,N*-bis-*tert*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-4,4-dimethylazetidin-2-one (140): To 139 (31 mg) was added 0.5M NH₄F in methanol (143 uL) and acetic acid (11 uL) and stirred until disappearance of the starting material. The reaction was concentrated *in vacuo* and re-dissolved in DCM. After 2 hr, the precipitate was filtered and the filtrate purified via preparative TLC (50% ethyl acetate in hexanes) to yield 140 (20 mg, 84%).

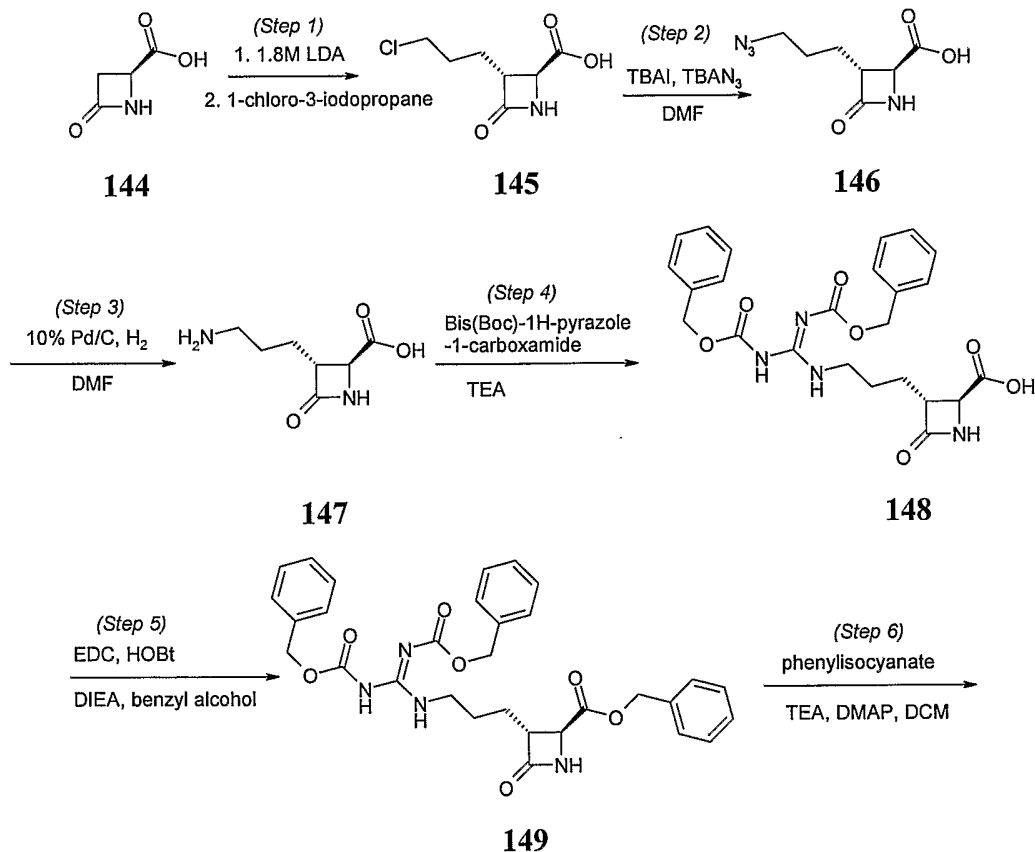
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[0346] **3-((2--(N,N-bis-*tert*-butoxycarbonyl)-aminopyridin-4-yl)methyl)-2,2-dimethyl-4-oxo-N-((R)-1-phenylethyl)azetidione-1-carboxamide (141):** To a solution of **140** (0.03 mmol) in anhydrous THF (1 mL) was cooled to -78°C and then 1.0 M LiHMDS (1.2 eq) was added slowly via syringe. After stirring for 30 minutes at -78°C , α -methylbenzyl isocyanate (1.2 eq.) was added via syringe. The reaction was then allowed to warm up to 0°C over 30 minutes (or until LCMS showed no starting material). The reaction was then quenched with saturated ammonium chloride, extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. The reaction was concentrated *in vacuo* and taken on without further purification.

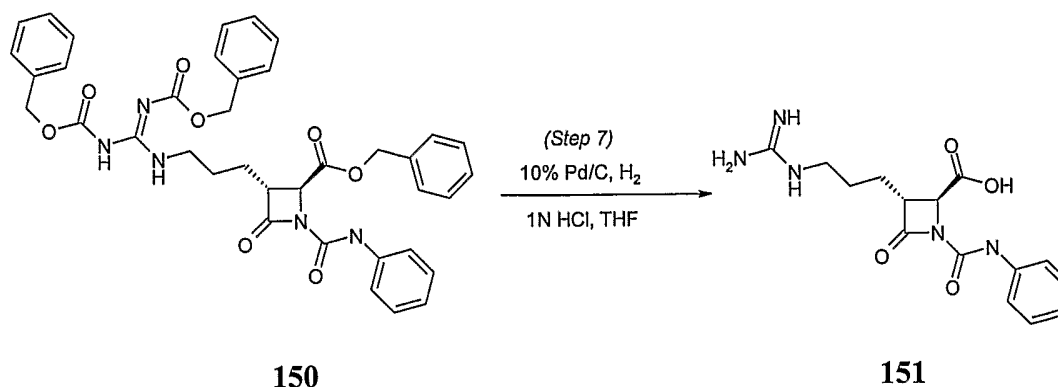
10 [0347] **3-((2-aminopyridin-4-yl)methyl)-2,2-dimethyl-4-oxo-N-((R)-1-phenylethyl)azetidione-1-carboxamide (142):** A solution of crude **141** in DCM (1 mL) was cooled to 0°C and then TFA (200 μL) was added. After 4 hr, the reaction was concentrated *in vacuo* and the crude material purified via reverse phase HPLC (acetonitrile/water) with 0.1% TFA to yield **142** (13.3 mg) as the TFA salt.

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EXAMPLE 11

General method L for the preparation of 3-propylguanidine beta-lactams.

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[0348] 4(2S,3R)-3-(3-chloropropyl)-4-oxoazetidine-2-carboxylic acid (145):

Commercially available beta-lactam acid **144** (1g, 1.0 eq.) was dissolved in anhydrous THF (15 mL) and the solution was cooled to -78°C under an atmosphere of argon. 1.8M LDA in heptane/THF/ethylbenzene (5.9 mL, 2.4 eq.) was added slowly to the cooled solution via syringe. The reaction was stirred for 20 minutes at -78°C and then 1-chloro-3-iodopropane (0.6 mL, 1.2 eq.) was slowly added to the cooled solution. The reaction was stirred a further hour at -78°C , warmed to room temperature and poured into 1:1 cold 1N HCl: brine (75 mL). The aqueous phase was extracted with ethyl acetate (2 x 75 mL) and the organic layers were combined and washed with saturated NaHCO_3 (2 x 25 mL). The basic layer was then washed again with ethyl acetate (75 mL). The basic aqueous layer was then acidified with 1N HCl-brine and extracted with ethyl acetate (2 x 50 mL) and the organic layers were combined and dried over sodium sulfate. Concentration *in vacuo* yielded **145** (0.88g) as a dark yellow oil.

[0349] (2S,3R)-3-(3-azidopropyl)-4-oxoazetidine-2-carboxylic acid (146): To a solution of **145** (1.0g, 1.0 eq.) in anhydrous DMF (5 mL) was added tetrabutylammonium iodide (60 mg, 0.05 eq.) and tetrabutylammonium azide (1.1g, 1.2 eq.). The reaction was stirred at room temperature for 72 hours and the poured into 1N HCl-brine and extracted with ethyl acetate (2 x 20 mL). Then the organic layers were extracted with saturated NaHCO_3 (3 x 15 mL). The combined basic aqueous layers were then acidified with 1N-HCl:brine and then the acidic solution was extracted with ethyl acetate (3 x 20 mL). These last organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield **146** (0.59g) as a brown oil.

[0350] (2S,3R)-3-(3-aminopropyl)-4-oxoazetidine-2-carboxylic acid (147): To a solution of **146** (0.59g, 1.0 eq.) in DMF (5 mL) and acetic acid (1 mL) was added 10% Pd/C (300 mg). The flask was evacuated and flushed with hydrogen. The reaction was then stirred at room temperature under an atmosphere of hydrogen for 16 hours. The reaction was then

filtered through Celite and crude amine **147** was immediately used in the next step as a solution in DMF.

[0351] (2S,3R,E)-3-(3-(2,3-bis(3-phenylpropanoyl)guanidino)propyl)-4-oxoazetidine-2-carboxylic acid (148): To the DMF solution of amine **147** (330mg of amine) was added
5 N,N'-bis(benzyloxycarbonyl)-1H-pyrazole-1-carboxamide (718 mg, 1.0 eq.) and DIEA (1.5 mL). The reaction was stirred at room temperature for 6 hours and then poured into 1N HCl:brine and extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and extracted with saturated NaHCO₃ (2 x 25 mL). The basic aqueous layers were then acidified with 1N HCl:brine and extracted with ethyl acetate (2 x 25 mL). These last organic
10 layers were dried over sodium sulfate and concentration *in vacuo* yielded a crude material (200 mg) as a colorless oil. The crude material was purified via silica gel chromatography eluting with a gradient elution from ethyl acetate to 1% acetic acid in EtOAc to give **148** (74mg).

[0352] (2S,3R,E)-benzyl 3-(3-(2,3-bis(3-phenylpropanoyl)guanidino)propyl)-4-oxoazetidine-2-carboxylate (149): To a solution of **148** (74 mg, 1.0 eq.) in DMF (1.5 mL)
15 was added benzyl alcohol (19 μ L, 1.2 eq.), EDC-HCl (35 mg, 1.2 eq.), HOBt (24 mg, 1.2 eq.) and DIEA (60 μ L, 2.4 eq.). The reaction was stirred at room temperature for 16 hours and then diluted with ethyl acetate and washed with 1N HCl. The aqueous layer was then washed with ethyl acetate (2 x 10 mL). The combined organics were then washed with saturated
20 NaHCO₃ (2 x 10 mL), water (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the crude product (55 mg) as a colorless oil. The product was purified by silica gel chromatography using a gradient elution from 20% EtOAc in hexanes to 50% EtOAc in hexanes to yield **149** (50 mg).

[0353] (2S,3R,E)-benzyl 3-(3-(2,3-bis(3-phenylpropanoyl)guanidino)propyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate (150): To a solution of **149** (50 mg, 1.0 eq.) in
25 DCM (2 mL) was added phenylisocyanate (29 μ L, 3.0 eq.), triethylamine (12 μ L, 1 eq.) and DMAP (1 mg). The reaction was stirred for 18 hours at room temperature and then diluted with dichloromethane and washed with 1N HCl and water. The organic layer was then concentrated *in vacuo* and purified via silica gel chromatography eluting with 15% EtOAc in
30 hexanes to give **150** (10 mg).

[0354] (2S,3R)-3-(3-guanidinopropyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid (151): To a solution of **150** (10 mg, 1.0 eq.) in THF (3 mL) and 1N HCl

(0.5 mL) was added 10% Pd/C (20 mg). The reaction flask was then evacuated and flushed with hydrogen and stirred under an atmosphere of hydrogen for 18 hours. The reaction was then filtered through Celite and concentrated *in vacuo*. The crude material was purified via HPLC (C18, acetonitrile/water, 0.1% TFA) to yield **151** (0.5 mg).

5 **[0355] (2S,3R)-Ethyl 3-(3-guanidinopropyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate (152):** Compound **152** was synthesized by general method L using ethyl alcohol (step 5) and phenyl isocyanate (step 6) to yield **152**.

[0356] (2S,3R)-1-((4-Methoxybenzyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (153): Compound **153** was synthesized by general method
10 L using 4-methoxybenzylisocyanate (step 6) to yield **153** (6.8 mg).

[0357] (2S,3R)-1-((4-Methoxyphenethyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (154): Compound **154** was synthesized by general method L using 4-methoxyphenethylisocyanate (step 6) to yield **154** (23 mg).

[0358] (2S,3R)-1-(((R)-1-(Naphthalen-1-yl)ethyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (155): Compound **155** was synthesized by general method
15 L using (R)-1-naphthylethylisocyanate (step 6) to yield **155** (31.1 mg, 66%).

[0359] (2S,3R)-1-((3-Ethylphenyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (156): Compound **156** was synthesized by general method L using 4-ethylphenylisocyanate (step 6) to yield **156** (25.1 mg, 61%).

20 **[0360] (2S,3R)-1-(((S)-1-Phenylethyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (157):** Compound **157** was synthesized by general method L using (S)-1-methylbenzylisocyanate (step 6) to yield **157**.

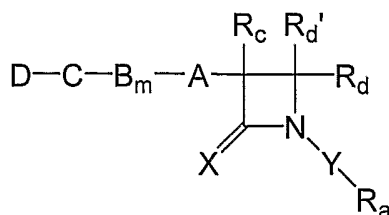
[0361] (2S,3R)-1-(((S)-1-(naphthalen-1-yl)ethyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (158): Compound **158** was synthesized by general method
25 L using (S)-1-naphthylethylisocyanate (step 6) to yield **158** (25.3 mg, 77%).

[0362] (2S,3R)-1-((4-ethylphenyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (159): Compound **159** was synthesized by general method L using 4-ethylphenylisocyanate (step 6) to yield **159** (24.8 mg, 63%).

[0363] **(2S,3R)-1-(((R)-1-phenylethyl)carbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid (160)**: Compound **160** was synthesized by general method L using (R)-1-methylbenzylisocyanate (step 6) to yield **160**.

WHAT IS CLAIMED IS:

1 1. A compound according to the following structure:



2

3 wherein

4 A is a member selected from CR^1R^2 , NR^{1a} , O, S and SO_n

5 wherein

6 n is an integer selected from 0 to 2;

7 each R^{1a} is a member independently selected from a negative charge, a salt
 8 counterion, H, substituted or unsubstituted alkyl, substituted or
 9 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
 10 substituted or unsubstituted heterocycloalkyl, substituted or
 11 unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(O)R^5$,
 12 NR^3R^4 , OR^3 , SO_2R^5 and $S(O)R^5$

13

wherein

14

R^3 and R^4 are members independently selected from a positive
 15 charge, a salt counterion, H, substituted or unsubstituted
 16 alkyl, substituted or unsubstituted heteroalkyl, substituted
 17 or unsubstituted cycloalkyl, substituted or unsubstituted
 18 heterocycloalkyl, substituted or unsubstituted aryl,
 19 substituted or unsubstituted heteroaryl, $C(O)R^6$ and SO_2R^6

20

wherein

21

R^6 is a member selected from substituted or unsubstituted
 22 alkyl, substituted or unsubstituted heteroalkyl,
 23 substituted or unsubstituted cycloalkyl, substituted
 24 or unsubstituted heterocycloalkyl, substituted or
 25 unsubstituted aryl, substituted or unsubstituted
 26 heteroaryl;

27

R^5 is a member selected from substituted or unsubstituted alkyl,
 28 substituted or unsubstituted heteroalkyl, substituted or

28

29 unsubstituted cycloalkyl, substituted or unsubstituted
30 heterocycloalkyl, substituted or unsubstituted aryl,
31 substituted or unsubstituted heteroaryl

32 wherein

33 R^3 and R^4 can be optionally joined, together with the atoms
34 to which they are attached, to form a 4-8 membered
35 ring

36 R^1 is a member selected from H, substituted or unsubstituted alkyl,
37 substituted or unsubstituted heteroalkyl, substituted or
38 unsubstituted cycloalkyl, substituted or unsubstituted
39 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
40 unsubstituted heteroaryl, NR^7R^8 , SO_nR^9 , halogen, $C(O)R^7$, CO_2R^7 ,
41 $C(O)NR^7R^8$, and OR^7

42 wherein

43 each R^7 and each R^8 is a member independently selected from H,
44 substituted or unsubstituted alkyl, substituted or
45 unsubstituted heteroalkyl, substituted or unsubstituted
46 cycloalkyl, substituted or unsubstituted heterocycloalkyl,
47 substituted or unsubstituted aryl, substituted or
48 unsubstituted heteroaryl, $C(O)R^{10}$, $C(O)OR^{10}$, $NR^{10}R^{10a}$,
49 OR^{10} , SO_2R^{10} and $S(O)R^{10}$

50 wherein

51 R^{10} and R^{10a} are members independently selected from H,
52 substituted or unsubstituted alkyl, substituted or
53 unsubstituted heteroalkyl, substituted or
54 unsubstituted cycloalkyl, substituted or
55 unsubstituted heterocycloalkyl, substituted or
56 unsubstituted aryl, substituted or unsubstituted
57 heteroaryl

58 R^9 is a member selected from substituted or unsubstituted alkyl,
59 substituted or unsubstituted heteroalkyl, substituted or
60 unsubstituted cycloalkyl, substituted or unsubstituted
61 heterocycloalkyl, substituted or unsubstituted aryl,
62 substituted or unsubstituted heteroaryl

- 63 wherein
- 64 R^7 and R^8 can be optionally joined, together with the atoms
- 65 to which they are attached, to form a 4-8 membered
- 66 ring;
- 67 R^2 is a member selected from H, substituted or unsubstituted alkyl,
- 68 substituted or unsubstituted heteroalkyl, substituted or
- 69 unsubstituted cycloalkyl, substituted or unsubstituted
- 70 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
- 71 unsubstituted heteroaryl, and halogen
- 72 wherein
- 73 R^1 and R^2 can together represent an acyl group;
- 74 R^1 and R^2 can be optionally joined together in a 3-8 membered ring;
- 75 B is a member independently selected from substituted or unsubstituted alkyl,
- 76 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
- 77 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
- 78 unsubstituted aryl, substituted or unsubstituted heteroaryl, carboxamido,
- 79 NR^{11} , -S-, and -O-
- 80 wherein
- 81 R^{11} is a member selected from H, substituted or unsubstituted alkyl,
- 82 substituted or unsubstituted heteroalkyl, substituted or
- 83 unsubstituted cycloalkyl, substituted or unsubstituted
- 84 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
- 85 unsubstituted heteroaryl, $C(O)R^{10}$, SO_2R^{10} ;
- 86 m is an integer selected from 0 to 3;
- 87 C is a member selected from a bond, C=O, SO_2 , N=C, -O- and -O-CR⁵R¹⁰-
- 88 wherein
- 89 R^5 and R^{10} can be optionally joined, together with the atoms to which they
- 90 are attached, to form a 3-8 membered ring;
- 91 D is a member selected from substituted or unsubstituted cycloalkyl, substituted or
- 92 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
- 93 substituted or unsubstituted heteroaryl, substituted or unsubstituted
- 94 amidine, substituted or unsubstituted amidinohydrazone, substituted or
- 95 unsubstituted guanidine, and substituted or unsubstituted amine
- 96 wherein

97 A and B can be optionally joined, together with the atoms to which they
98 are attached, to form a 3-8 membered ring;
99 A and C can be optionally joined, together with the atoms to which they
100 are attached, to form a 3-8 membered ring;
101 A and D can be optionally joined, together with the atoms to which they
102 are attached, to form a 3-8 membered ring;
103 B and C can be optionally joined, together with the atoms to which they
104 are attached, to form a 3-8 membered ring;
105 B and D can be optionally joined, together with the atoms to which they
106 are attached, to form a 3-8 membered ring;
107 C and D can be optionally joined, together with the atoms to which they
108 are attached, to form a 3-8 membered ring
109 if m is greater than 2, each independently selected B can be optionally
110 joined to form a 3-8 membered ring;
111 X is a member selected from S, O, and NR^7 ;
112 Y is a member selected from a bond, $\text{C}=\text{Q}$, $\text{CR}^{12}\text{R}^{13}$, and SO_n
113 wherein
114 Q is a member selected from S, O, and NR^7
115 R^{12} is a member selected from H, substituted or unsubstituted alkyl,
116 substituted or unsubstituted heteroalkyl, substituted or
117 unsubstituted cycloalkyl, substituted or unsubstituted
118 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
119 unsubstituted heteroaryl, and halogen;
120 R^{13} is a member selected from H, substituted or unsubstituted alkyl,
121 substituted or unsubstituted heteroalkyl, substituted or
122 unsubstituted cycloalkyl, substituted or unsubstituted
123 heterocycloalkyl, substituted or unsubstituted aryl, and substituted
124 or unsubstituted heteroaryl halogen;
125 wherein R^{12} and R^{13} can be optionally joined, together with the atoms to
126 which they are attached, to form a 4-8 membered ring; and
127 R_a is a member selected from NR^7R^8 , substituted or unsubstituted alkyl,
128 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
129 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
130 unsubstituted aryl, and substituted or unsubstituted heteroaryl

- 131 wherein
- 132 R^7 and R^8 can be optionally joined, together with the atoms to which they
- 133 are attached, to form a 4-8 membered ring;
- 134 R_c is a member selected from H, substituted or unsubstituted alkyl and halogen;
- 135 R_d is a member selected from R^{16} , $(CR^{14}R^{15})_pR^{16}$, $C(R^{14})=CR^{16}R^{23}$ and CCR^{16}
- 136 wherein
- 137 p is an integer selected from 0 to 3;
- 138 R^{14} and R^{23} are members independently selected from H, halogen,
- 139 substituted or unsubstituted alkyl, substituted or unsubstituted
- 140 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
- 141 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
- 142 substituted or unsubstituted heteroaryl;
- 143 R^{15} is a member selected from H, halogen, substituted or unsubstituted
- 144 alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 145 unsubstituted cycloalkyl, substituted or unsubstituted
- 146 heterocycloalkyl, substituted or unsubstituted aryl
- 147 wherein
- 148 R^{16} is a member selected from halogen, substituted or unsubstituted alkyl,
- 149 substituted or unsubstituted heteroalkyl, substituted or
- 150 unsubstituted cycloalkyl, substituted or unsubstituted
- 151 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
- 152 unsubstituted heteroaryl, $C(O)R^{18}$, OR^{19} , $-OC(=Q)NR^{19}R^{21}$,
- 153 $-NR^{19}C(=Q)NR^{19}R^{21}$, $-NR^{20}SO_2R^{19}$, OSO_2R^{19} , SO_2R^{21} , $S(O)R^{21}$,
- 154 $SO_2NR^{19}R^{20}$, $NR^{19}R^{20}$, CN
- 155 wherein
- 156 R^{18} is a member selected from substituted or unsubstituted alkyl,
- 157 substituted or unsubstituted heteroalkyl, substituted or
- 158 unsubstituted cycloalkyl, substituted or unsubstituted
- 159 heterocycloalkyl, substituted or unsubstituted aryl,
- 160 substituted or unsubstituted heteroaryl, OR^{21} , SR^{21} ,
- 161 $NR^{19}R^{20}$, and $-NR^{19}SO_2R^{20}$
- 162 wherein
- 163 R^{21} is a member selected from a negative charge, a salt
- 164 counterion, H, substituted or unsubstituted alkyl,

165 substituted or unsubstituted heteroalkyl,
166 substituted or unsubstituted cycloalkyl, substituted
167 or unsubstituted heterocycloalkyl, substituted or
168 unsubstituted aryl, substituted or unsubstituted
169 heteroaryl, -OR²² and -SR²²;

170 R¹⁹ is a member selected from H, substituted or unsubstituted alkyl,
171 substituted or unsubstituted heteroalkyl, substituted or
172 unsubstituted cycloalkyl, substituted or unsubstituted
173 heterocycloalkyl, substituted or unsubstituted aryl,
174 substituted or unsubstituted heteroaryl;

175 R²⁰ is a member selected from H, substituted or unsubstituted alkyl,
176 substituted or unsubstituted heteroalkyl, substituted or
177 unsubstituted cycloalkyl, substituted or unsubstituted
178 heterocycloalkyl, substituted or unsubstituted aryl,
179 substituted or unsubstituted heteroaryl, C(O)R²², SO₂R²²

180 wherein

181 R²² is a member selected from substituted or unsubstituted
182 alkyl, substituted or unsubstituted heteroalkyl,
183 substituted or unsubstituted cycloalkyl, substituted
184 or unsubstituted heterocycloalkyl, substituted or
185 unsubstituted aryl, substituted or unsubstituted
186 heteroaryl;

187 wherein

188 R¹⁴ and R¹⁵ can be optionally joined, together with the atoms to
189 which they are attached, to form a 4-8 membered ring

190 R¹⁹ and R²¹ can be optionally joined, together with the atoms to
191 which they are attached, to form a 4-8 membered ring

192 R¹⁴ and R²³ can be optionally joined, together with the atoms to
193 which they are attached, to form a 4-8 membered ring

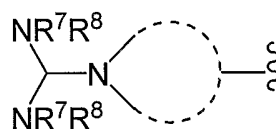
194 R¹⁹ and R²⁰ can be optionally joined, together with the atoms to
195 which they are attached, to form a 4-8 membered ring

196 R_d' is a member selected from H, substituted or unsubstituted alkyl and halogen;

197 wherein

198 R_c and R_d can be optionally joined, together with the atoms to which they
 199 are attached, to form a 5-8 membered ring; and
 200 R_c and R_d' can be optionally joined, together with the atoms to which they
 201 are attached, to form a 5-8 membered ring;
 202 with the proviso for the compound, or salts thereof, that if:

- 203 a) Y is a member selected from C=O and SO₂;
 204 ABC, in combination, form unsubstituted alkyl; and
 205 D is substituted or unsubstituted guanidine; or
 206 b) Y is a member selected from C=O and SO₂;
 207 AB, in combination, form unsubstituted alkyl; and
 208 CD, in combination, form



209

210

wherein

211

the dotted line represents carbon atoms necessary for the

212

formation of one ring having 4 to 8 atoms;

213

then R_c cannot be a member selected from CH₃ and CH₂CH₃; and R_d and

214

 R_d' cannot be members selected from CH₃ and CH₃; CH₂CH₃ and

215

CH₂CH₃; CH₂CH₃ and CH₃; CH₃ and CH₂CH₃; H and COOH; H

216

and COOR^{1a}; H and CONR⁷R⁸; unsubstituted alkyl and COOH;

217

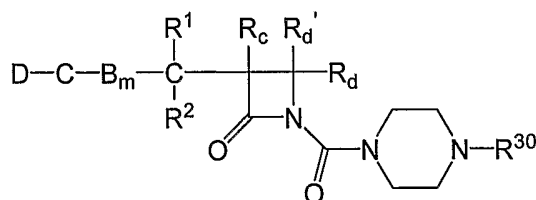
unsubstituted alkyl and COOR^{1a}; H and unsubstituted phenylalkyl;

218

unsubstituted alkyl and unsubstituted phenylalkyl;

219

and with the further proviso that if the compound has the following structure:



220

221

wherein

222

 R^{30} is a member selected from H, SO₂-R³¹, substituted or

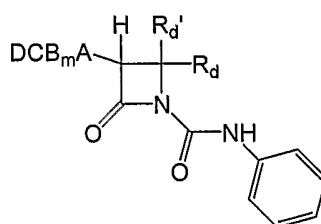
223

unsubstituted alkyl, substituted or unsubstituted

224

heteroalkyl, substituted or unsubstituted cycloalkyl,

225 substituted or unsubstituted heterocycloalkyl,
 226 substituted or unsubstituted aryl, and substituted or
 227 unsubstituted heteroaryl
 228 wherein
 229 R^{31} is unsubstituted alkyl
 230 then at least one of R_d and R_d' does not comprise a carbonyl group which
 231 is directly attached, or alpha, to the azetidinone ring
 232 and with the proviso that the compound cannot have the following structure:

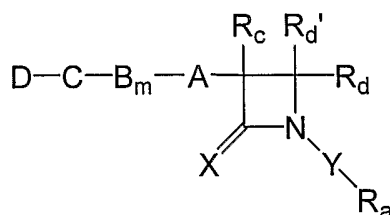


233

234 wherein DCB_mA comprises a piperidine ring or a salt thereof.

1 2. The compound according to claim 1, wherein at least one of said R ,
 2 $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{10a}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}$
 3 R^{22} and R^{23} is a member selected from substituted or unsubstituted arylalkyl and
 4 substituted or unsubstituted heteroarylalkyl.

1 3. A compound according to the following structure:



2

3 wherein

4 AB_mC , in combination, is a member selected from substituted or unsubstituted
 5 alkyl and substituted or unsubstituted heteroalkyl;

6 D is a member selected from

7 substituted or unsubstituted guanidine;
 8 substituted or unsubstituted amidinohydrazone;
 9 substituted or unsubstituted pyridine
 10 substituted or unsubstituted aminopyridine;

11 R_c is a member selected from H and substituted or unsubstituted alkyl;
 12 R_d' is a member selected from H and substituted or unsubstituted alkyl;
 13 R_d is a member selected from R^{16} , $(CR^{14}R^{15})_pR^{16}$ and $C(R^{14})=CR^{16}R^{23}$, CCR^{16}
 14 wherein

15 p is an integer selected from 0 to 3;
 16 R^{14} and R^{23} are members independently selected from H, halogen,
 17 substituted or unsubstituted alkyl, substituted or unsubstituted
 18 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 19 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
 20 substituted or unsubstituted heteroaryl;
 21 R^{15} is a member selected from H, halogen, substituted or unsubstituted
 22 alkyl, substituted or unsubstituted heteroalkyl, substituted or
 23 unsubstituted cycloalkyl, substituted or unsubstituted
 24 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
 25 unsubstituted heteroaryl

26 wherein

27 R^{16} is a member selected from halogen, substituted or unsubstituted
 28 alkyl, substituted or unsubstituted heteroalkyl, substituted or
 29 unsubstituted cycloalkyl, substituted or unsubstituted
 30 heterocycloalkyl, substituted or unsubstituted aryl,
 31 substituted or unsubstituted heteroaryl, $C(O)R^{18}$, OR^{19} , -
 32 $OC(=Q)NR^{19}R^{21}$, $-NR^{19}C(=Q)NR^{19}R^{21}$, $-NR^{20}SO_2R^{19}$,
 33 OSO_2R^{19} , SO_2R^{21} , SOR^{21} , $SO_2NR^{19}R^{20}$, $NR^{19}R^{20}$, CN

34 wherein

35 R^{18} is a member selected from substituted or unsubstituted
 36 alkyl, substituted or unsubstituted heteroalkyl,
 37 substituted or unsubstituted cycloalkyl, substituted
 38 or unsubstituted heterocycloalkyl, substituted or
 39 unsubstituted aryl, substituted or unsubstituted
 40 heteroaryl, OR^{21} , $NR^{19}R^{20}$, and $-NR^{19}SO_2R^{20}$;

41 R^{19} is a member selected from H, substituted or
 42 unsubstituted alkyl, substituted or unsubstituted
 43 heteroalkyl, substituted or unsubstituted cycloalkyl,
 44 substituted or unsubstituted heterocycloalkyl,

45 substituted or unsubstituted aryl, substituted or
46 unsubstituted heteroaryl;
47 R^{20} is a member selected from H, substituted or
48 unsubstituted alkyl, substituted or unsubstituted
49 heteroalkyl, substituted or unsubstituted cycloalkyl,
50 substituted or unsubstituted heterocycloalkyl,
51 substituted or unsubstituted aryl, substituted or
52 unsubstituted heteroaryl, $C(O)R^{22}$, SO_2R^{22}

53 wherein

54 R^{22} is a member selected from substituted or
55 unsubstituted alkyl, substituted or
56 unsubstituted heteroalkyl, substituted or
57 unsubstituted cycloalkyl, substituted or
58 unsubstituted heterocycloalkyl, substituted or
59 unsubstituted aryl, substituted or
60 unsubstituted heteroaryl;

61 R^{21} is a member selected from substituted or unsubstituted
62 alkyl, substituted or unsubstituted heteroalkyl,
63 substituted or unsubstituted cycloalkyl, substituted
64 or unsubstituted heterocycloalkyl, substituted or
65 unsubstituted aryl, substituted or unsubstituted
66 heteroaryl and $-OR^{22}$

67 wherein

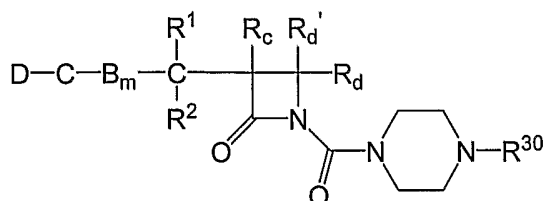
68 R^{14} and R^{15} can be optionally joined, together with the atoms to
69 which they are attached, to form a 4-8 membered ring
70 R^{19} and R^{21} can be optionally joined, together with the atoms to
71 which they are attached, to form a 4-8 membered ring
72 R^{14} and R^{23} can be optionally joined, together with the atoms to
73 which they are attached, to form a 4-8 membered ring
74 R^{19} and R^{20} can be optionally joined, together with the atoms to
75 which they are attached, to form a 4-8 membered ring

76 X is a member selected from S, O, and NR^{35}

77 wherein

78 R^{35} is a member selected from H, substituted or unsubstituted alkyl,
79 substituted or unsubstituted heteroalkyl, substituted or
80 unsubstituted cycloalkyl, substituted or unsubstituted
81 heterocycloalkyl, substituted or unsubstituted aryl, substituted or
82 unsubstituted heteroaryl, $C(O)R^{36}$, SO_2R^{36}
83 wherein
84 R^{36} is a member selected from substituted or unsubstituted
85 alkyl, substituted or unsubstituted heteroalkyl,
86 substituted or unsubstituted cycloalkyl, substituted
87 or unsubstituted heterocycloalkyl, substituted or
88 unsubstituted aryl, substituted or unsubstituted
89 heteroaryl;
90 Y is a member selected from a bond, $C=Q$, $CR^{12}R^{13}$, and SO_n
91 wherein
92 n is a member selected from 0 to 2;
93 Q is a member selected from S, O, and NR^7
94 R^{12} is a member selected from H, halogen, substituted or unsubstituted
95 alkyl, substituted or unsubstituted heteroalkyl, substituted or
96 unsubstituted cycloalkyl, substituted or unsubstituted
97 heterocycloalkyl, substituted or unsubstituted aryl, and substituted
98 or unsubstituted heteroaryl
99 R^{13} is a member selected from H, substituted or unsubstituted alkyl,
100 substituted or unsubstituted heteroalkyl, substituted or
101 unsubstituted cycloalkyl, substituted or unsubstituted
102 heterocycloalkyl, substituted or unsubstituted aryl, and substituted
103 or unsubstituted heteroaryl;
104 wherein R^{12} and R^{13} can be optionally joined, together with the atoms to
105 which they are attached, to form a 4-8 membered ring; and
106 R_a is a member selected from NR^7R^8 , substituted or unsubstituted alkyl,
107 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
108 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
109 unsubstituted aryl, and substituted or unsubstituted heteroaryl
110 wherein

111 R^7 and R^8 can be optionally joined, together with the atoms to which they
 112 are attached, to form a 4-8 membered ring;
 113 with the proviso that when D is unsubstituted guanidine, AB_mC cannot be unsubstituted
 114 alkyl
 115 and with the further proviso that if the compound has the following structure:



116
 117 wherein
 118 R^{30} is a member selected from H, SO_2-R^{31} , substituted or
 119 unsubstituted alkyl, substituted or unsubstituted
 120 heteroalkyl, substituted or unsubstituted cycloalkyl,
 121 substituted or unsubstituted heterocycloalkyl,
 122 substituted or unsubstituted aryl, and substituted or
 123 unsubstituted heteroaryl
 124 wherein
 125 R^{31} is unsubstituted alkyl
 126 then at least one of R_d and $R_{d'}$ does not comprise a carbonyl group which
 127 is directly attached, or alpha, to the azetidinone ring.

1 4. The compound according to claim 2, where at least one of said R^{1a} ,
 2 R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{35} , R^{36} and R_a is a member selected
 3 from substituted or unsubstituted arylalkyl and substituted or unsubstituted
 4 heteroarylalkyl.

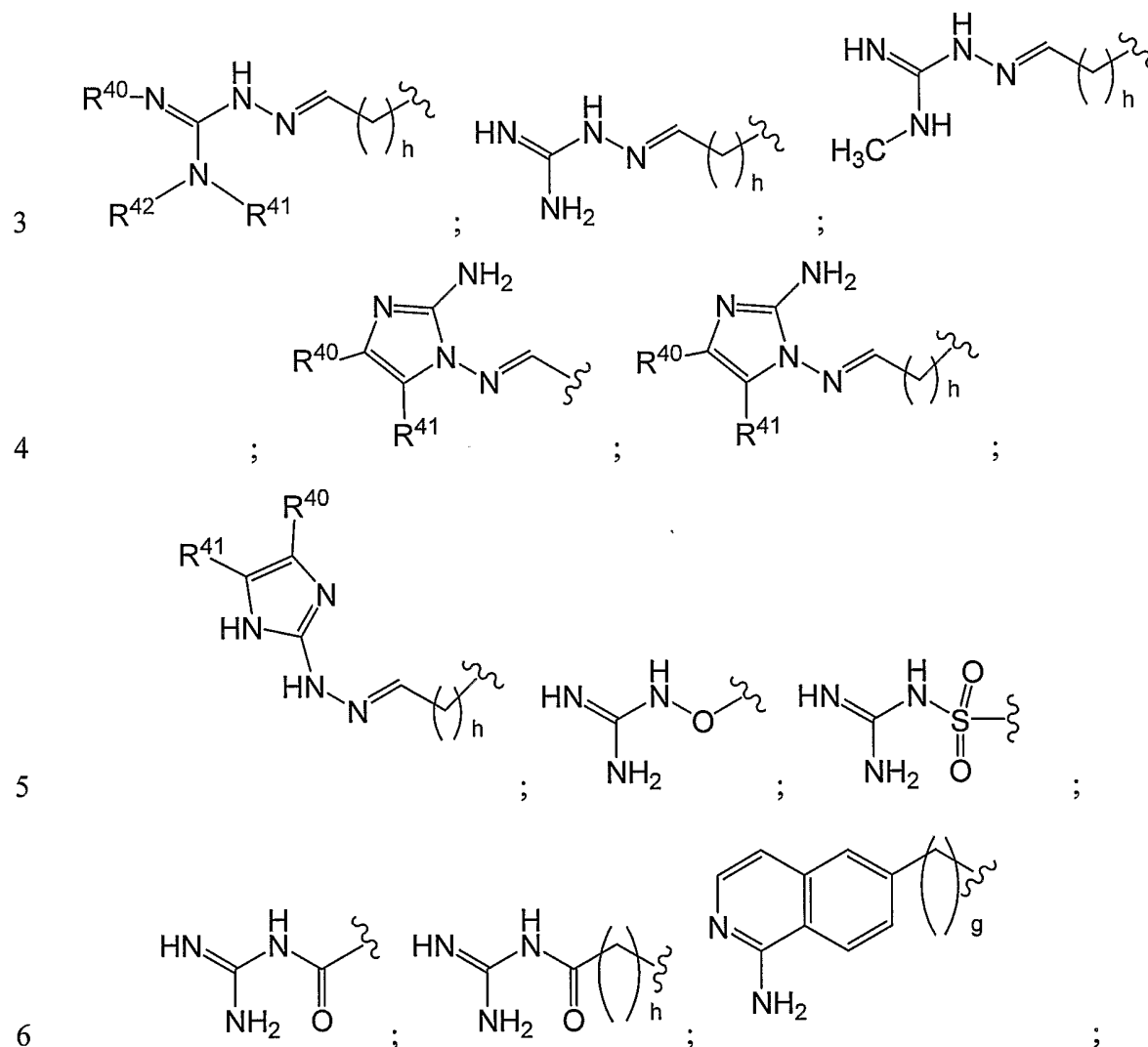
1 5. The compound according to claim 1, wherein D is a member
 2 selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,
 3 substituted or unsubstituted amidine, substituted or unsubstituted amidinohydrazone,
 4 substituted or unsubstituted guanidine, and substituted or unsubstituted amine.

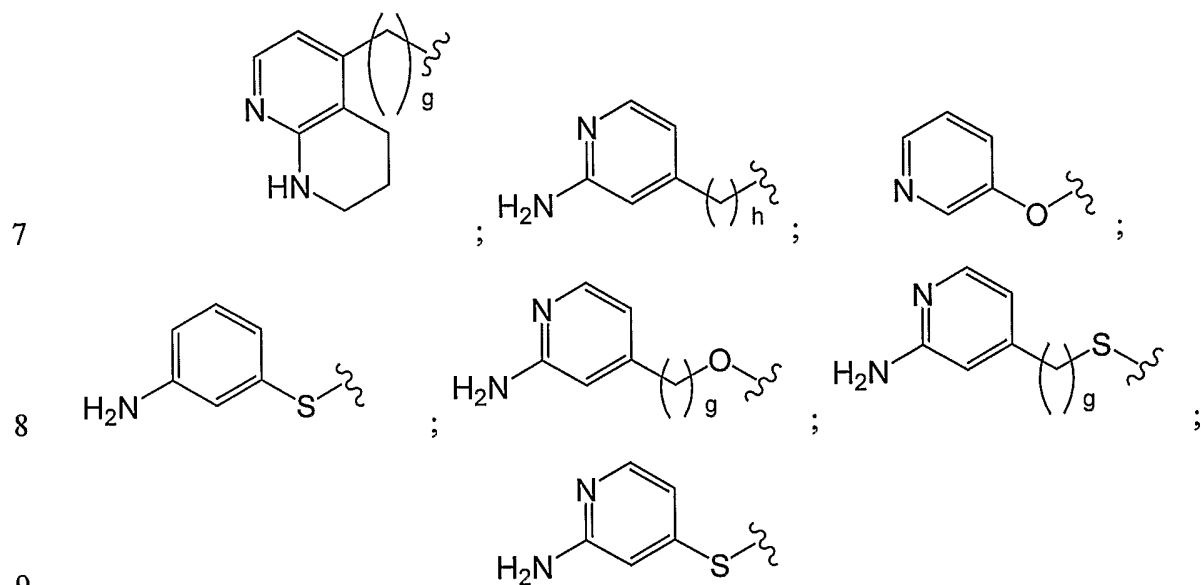
1 6. The compound according to claim 3, wherein D is substituted or
 2 unsubstituted guanidine, and AB_mC , in combination, form a member selected from D-

3 N=CR-, -O-D, -SO₂-D, substituted or unsubstituted alkylene, substituted or unsubstituted
 4 acylene, and substituted or unsubstituted heteroalkylene.

1 7. The compound according to claim 3, wherein D is a member
 2 selected from substituted aryl and substituted or unsubstituted heteroaryl, and AB_mC, in
 3 combination, form a member selected from D-N=CR-, -O-D, -SO₂-D, substituted or
 4 unsubstituted alkylene, substituted or unsubstituted acylene, and substituted or
 5 unsubstituted heteroalkylene.

1 8. The compound according to claims 1 or 2, wherein AB_mCD, in
 2 combination, form a member selected from





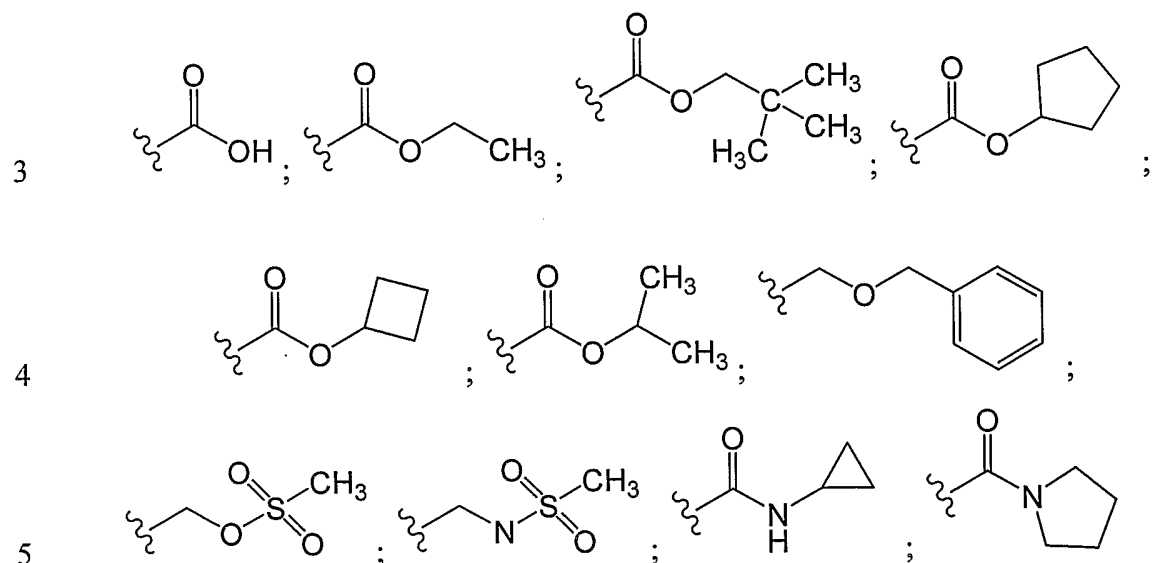
10 wherein

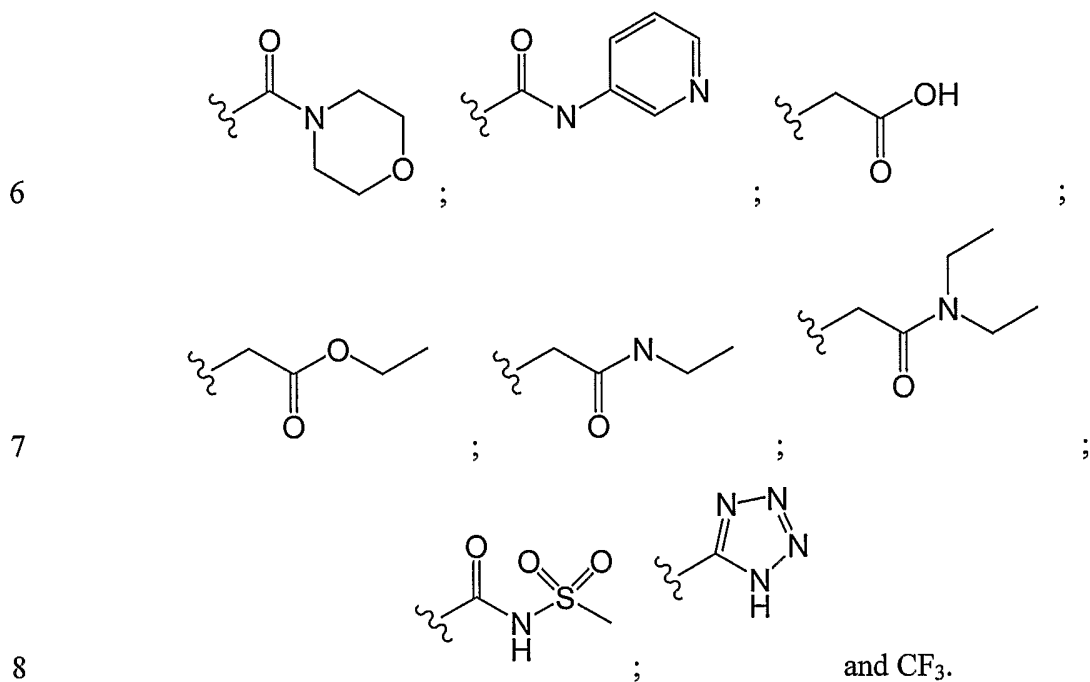
11 g is an integer selected from 1 to 4;

12 h is an integer selected from 0 to 4

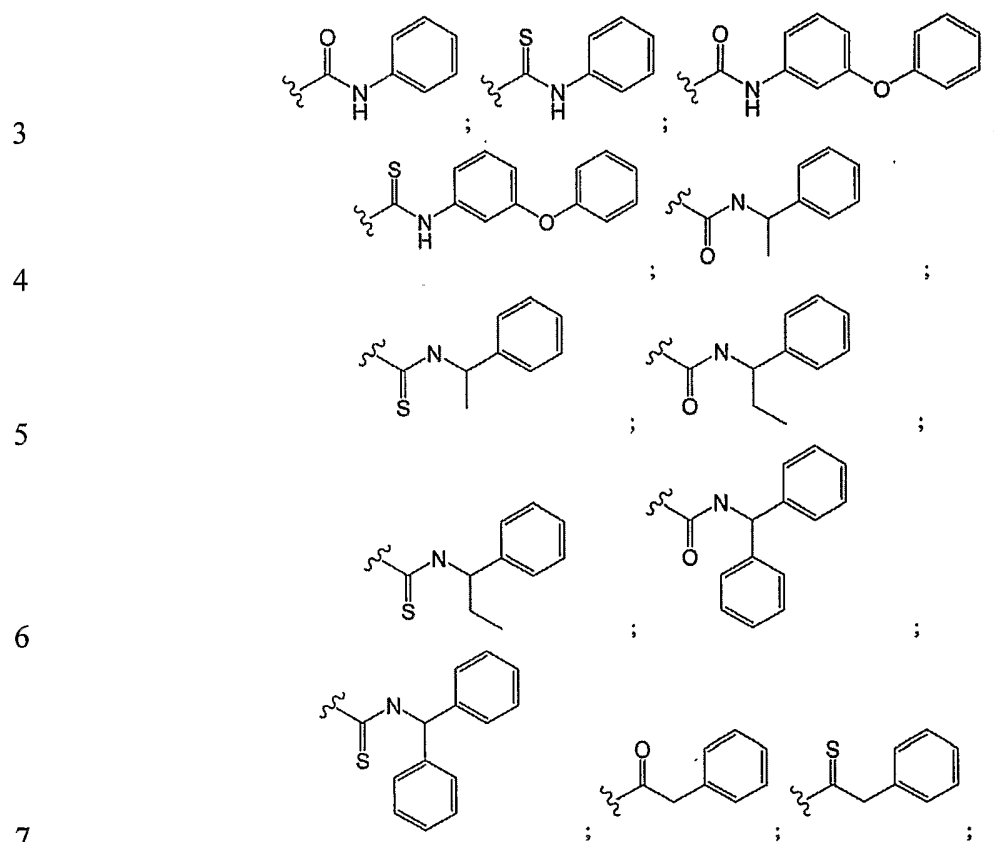
13 R^{40} , R^{41} and R^{42} are members independently selected from H, substituted or
 14 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 15 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
 16 substituted or unsubstituted aryl, and substituted or unsubstituted
 17 heteroaryl.

1 9. The compound according to claims 1 or 2, wherein R_d is a member
 2 selected from

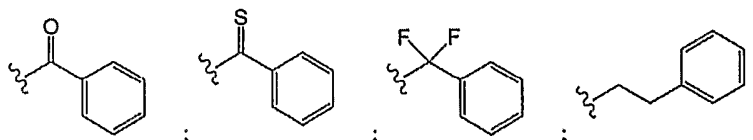




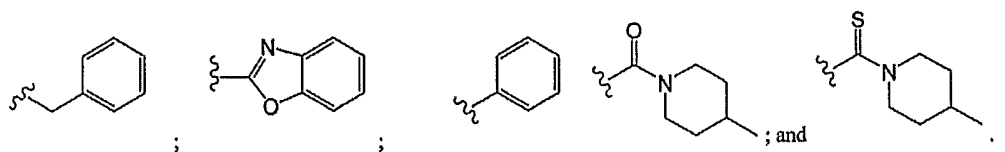
1 **10.** The compound according to claims 1 or 2, wherein -Y-R_a, in
 2 combination, form a member selected from



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9



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11. The compound according to claims 1 or 3, wherein R_c is a member selected from H, methyl and ethyl.

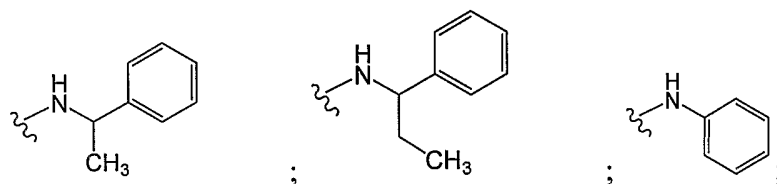
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12. The compound according to claims 1 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11, wherein X is S.

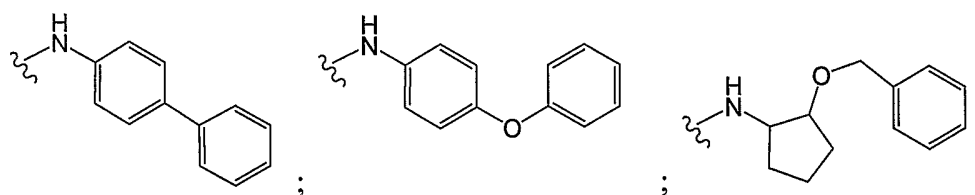
1

13. The compound according to claim 1, wherein R_a is a member

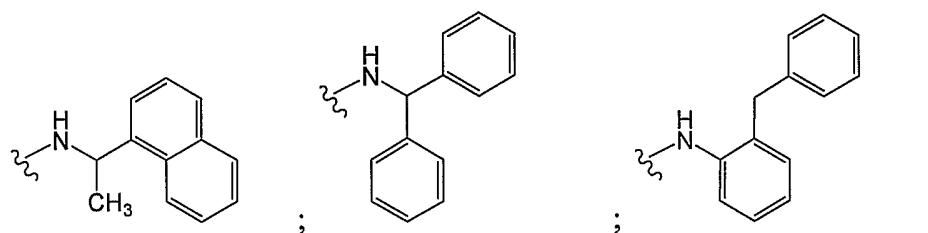
2 selected from

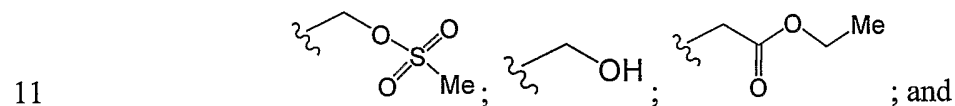
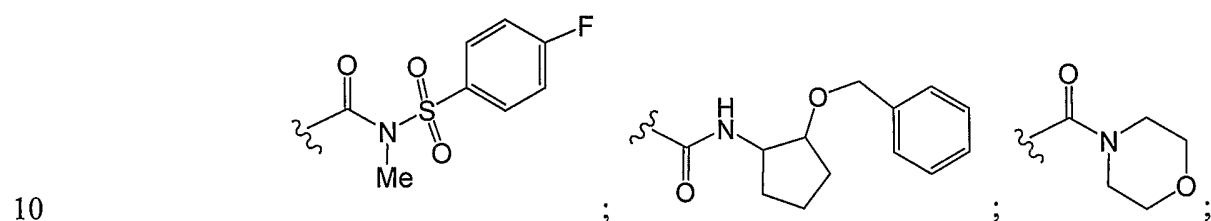
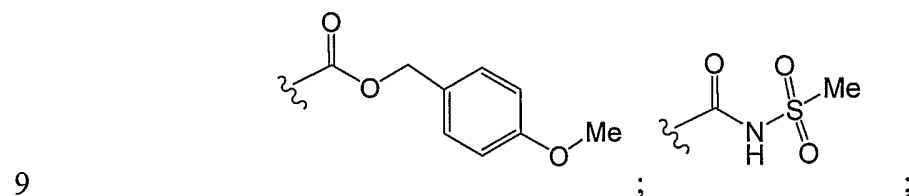
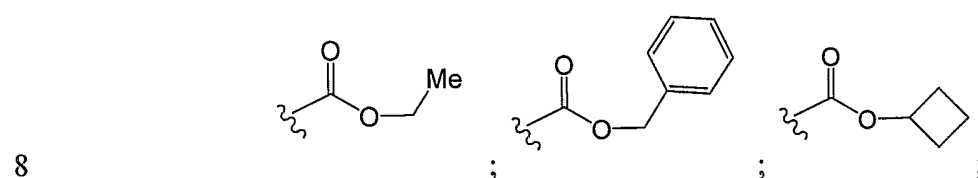
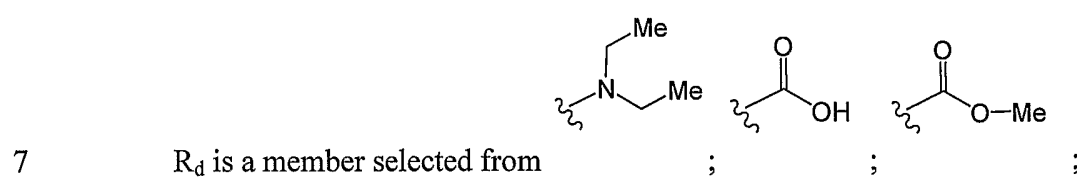
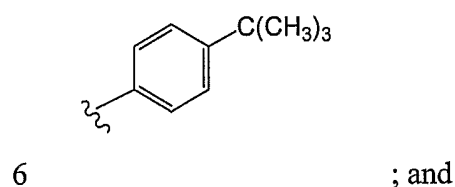
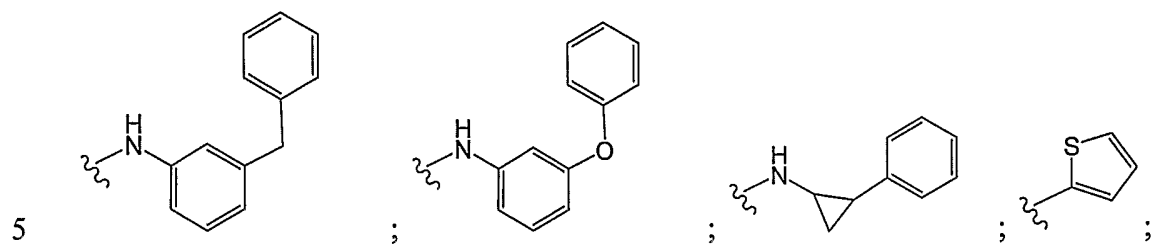


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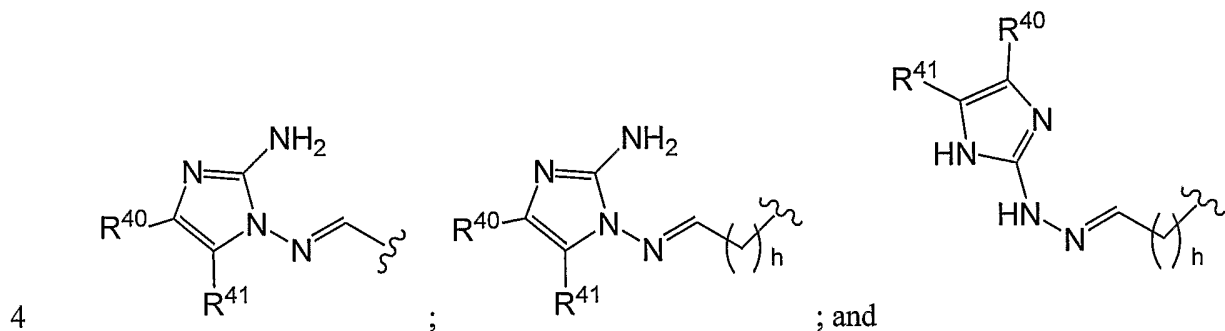
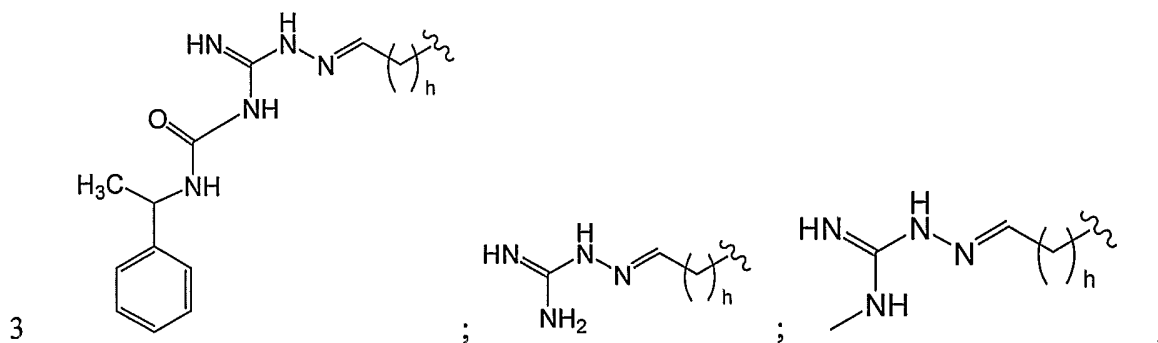




12 Y is a member selected from C(O) and S(O).

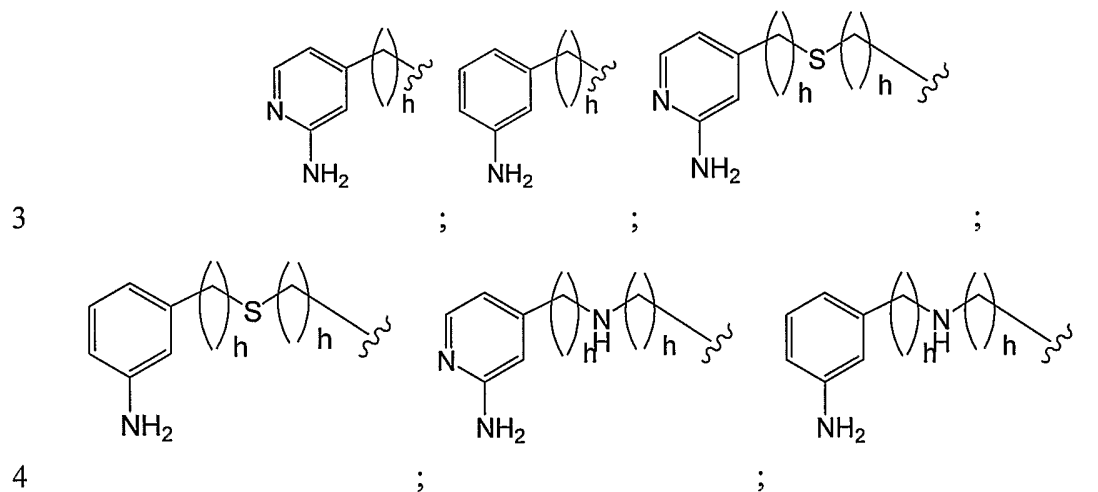
1 14. The compound according to claim 13, wherein

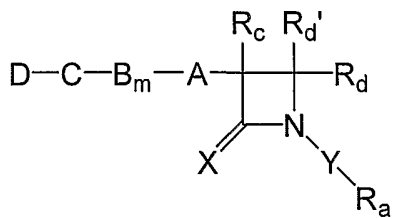
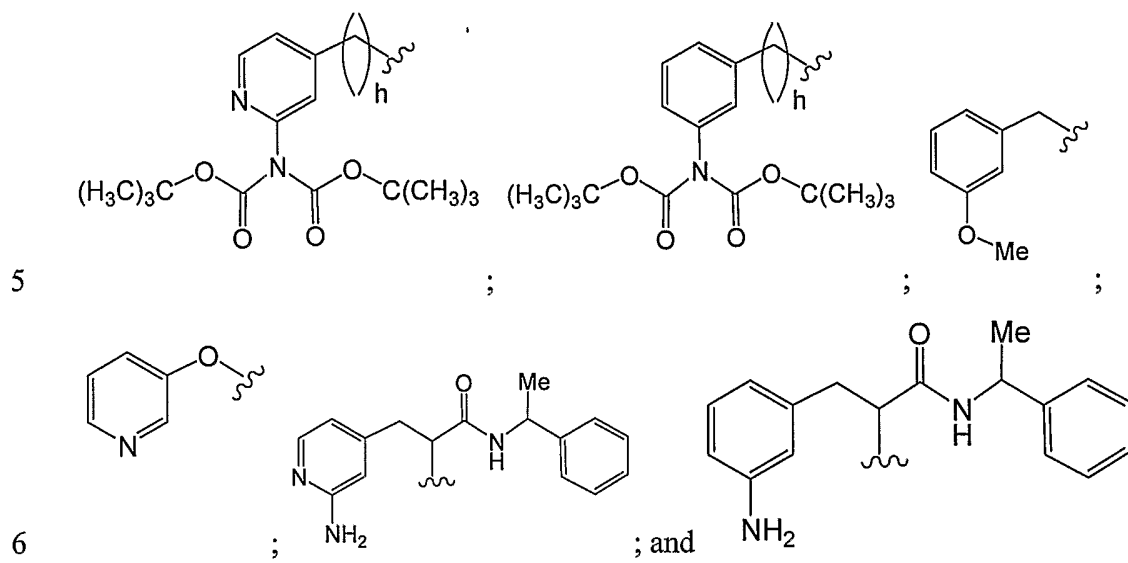
2 AB_mCD , in combination, form a member selected from



wherein h is an integer selected from 0 to 4.

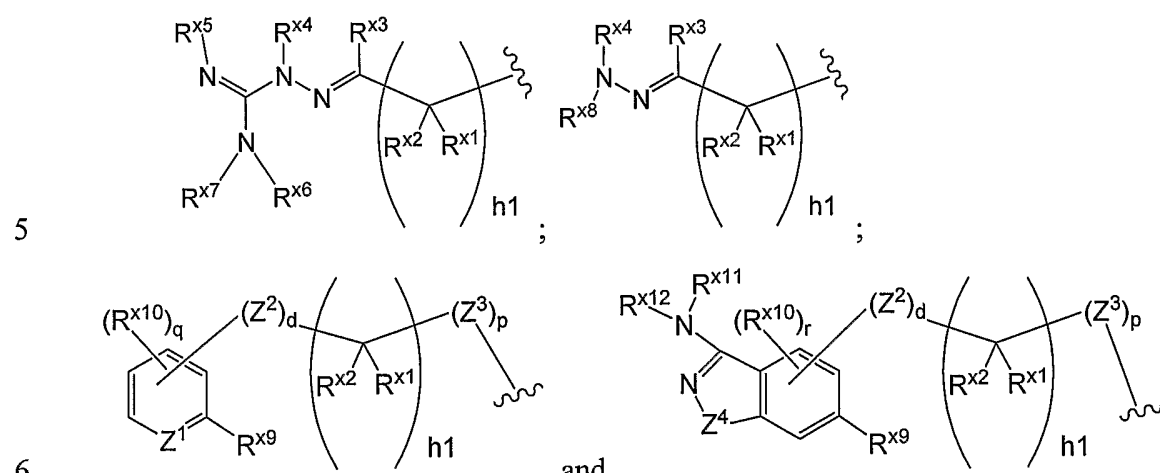
1 **15.** The compound according to claim 13, wherein
 2 AB_mCD, in combination, form a member selected from





2
3 wherein

4 AB_mCD, in combination, is a member selected from:



7 wherein

8 h1 is a member selected from 0 to 4;

9 q is a member selected from 0 to 3;

10 r is a member selected from 0 to 2;

11 d and p are members independently selected from 0 and 1;

12 Z¹ is member selected from CR^{x13} and N;

13 Z^4 is a member selected from NR^7 and S;
 14 R^{x1} , R^{x2} , R^{x9} , R^{x10} and R^{x13} are members independently selected from H, OR^{y1} ,
 15 $S(O)_{n1}R^{y1}$, $NR^{y1}R^{y2}$, halogen, substituted or unsubstituted alkyl,
 16 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 17 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 18 unsubstituted aryl, and substituted or unsubstituted heteroaryl;
 19 R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x11} and R^{x12} are members independently selected
 20 from a positive charge, a salt counterion, H, $S(O)_{n1}R^{y1}$, substituted or
 21 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 22 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
 23 substituted or unsubstituted aryl, and substituted or unsubstituted
 24 heteroaryl

25 wherein

26 $n1$ is a member selected from 0 to 2;
 27 R^{y1} and R^{y2} are members independently selected from a charge (positive or
 28 negative), a salt counterion, H, substituted or unsubstituted alkyl,
 29 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 30 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted
 31 or unsubstituted aryl, substituted or unsubstituted heteroaryl;

32 Z^2 and Z^3 are members selected from $S(O)_{n1}$, O, and NR^7 ;

33 wherein

34 $n1$ is a member selected from 0 to 2
 35 each R^7 is a member selected from a positive charge, salt counterion, H,
 36 substituted or unsubstituted alkyl, substituted or unsubstituted
 37 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 38 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
 39 substituted or unsubstituted heteroaryl, $C(O)R^{10}$, $C(O)OR^{10}$,
 40 $NR^{10}R^{10a}$, OR^{10} , SO_2R^{10} and $S(O)R^{10}$

41 wherein

42 each R^{10} and each R^{10a} is a member independently selected from a
 43 positive charge, salt counterion, H, substituted or
 44 unsubstituted alkyl, substituted or unsubstituted
 45 heteroalkyl, substituted or unsubstituted cycloalkyl,
 46 substituted or unsubstituted heterocycloalkyl, substituted

47 or unsubstituted aryl, and substituted or unsubstituted
48 heteroaryl

49 X is a member selected from O and S;

50 Y is a member selected from C=Q

51 wherein

52 Q is a member selected from S and O

53 R_a is a member selected from R^{x14} and $NR^{x15}R^{x16}$

54 wherein

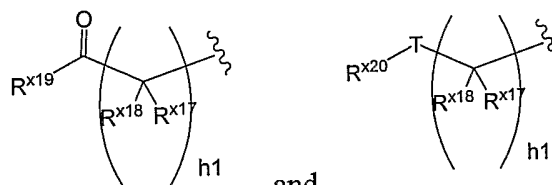
55 R^{x14} is a member selected from OR^{y3} , substituted or unsubstituted alkyl,
56 substituted or unsubstituted heteroalkyl, substituted or
57 unsubstituted cycloalkyl, substituted or unsubstituted
58 heterocycloalkyl, substituted or unsubstituted aryl, and substituted
59 or unsubstituted heteroaryl

60 R^{x15} and R^{x16} are members independently selected from H, SO_2R^{y3} ,
61 $NR^{y3}R^{y4}$, substituted or unsubstituted alkyl, substituted or
62 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
63 substituted or unsubstituted heterocycloalkyl, substituted or
64 unsubstituted aryl and substituted or unsubstituted heteroaryl

65 wherein

66 R^{y3} and R^{y4} are members independently selected from a charge
67 (either positive or negative), a salt counterion, H, substituted
68 or unsubstituted alkyl, substituted or unsubstituted
69 heteroalkyl, substituted or unsubstituted cycloalkyl,
70 substituted or unsubstituted heterocycloalkyl, substituted or
71 unsubstituted aryl, substituted or unsubstituted heteroaryl;

72 R_c is a member selected from H, substituted or unsubstituted alkyl and halogen;



73 R_d is a member selected from

74 wherein

75 $h1$ is a member selected from 0 to 4;

76 T is a member selected from NR^{x23} and O;

77 R^{x19} is a member selected from OR^{y5} , SR^{y5} , $NR^{y5}R^{y6}$, $NR^{x23}SO_2R^{x22}$,
78 substituted or unsubstituted alkyl, substituted or unsubstituted
79 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
80 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
81 and substituted or unsubstituted heteroaryl

82 wherein

83 R^{x22} is a member selected from substituted or unsubstituted alkyl,
84 substituted or unsubstituted heteroalkyl, substituted or
85 unsubstituted cycloalkyl, substituted or unsubstituted
86 heterocycloalkyl, substituted or unsubstituted aryl, and
87 substituted or unsubstituted heteroaryl

88 R^{x23} is a member selected from H, substituted or unsubstituted
89 alkyl, substituted or unsubstituted heteroalkyl, substituted
90 or unsubstituted cycloalkyl, substituted or unsubstituted
91 heterocycloalkyl, substituted or unsubstituted aryl, and
92 substituted or unsubstituted heteroaryl

93 R^{x20} is a member selected from H, $C(O)R^{x24}$, SO_2R^{x24} , substituted or
94 unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
95 substituted or unsubstituted cycloalkyl, substituted or
96 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
97 and substituted or unsubstituted heteroaryl

98 wherein

99 R^{x24} is a member selected from OR^{x22} , $NR^{x22}R^{x23}$, substituted or
100 unsubstituted alkyl, substituted or unsubstituted
101 heteroalkyl, substituted or unsubstituted cycloalkyl,
102 substituted or unsubstituted heterocycloalkyl, substituted
103 or unsubstituted aryl, and substituted or unsubstituted
104 heteroaryl

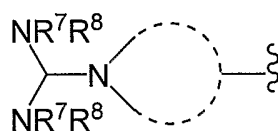
105 R^{x17} and R^{x18} are members independently selected from H, OR^{y5} ,
106 $S(O)_nR^{y5}$, $NR^{y5}R^{y6}$, halogen, substituted or unsubstituted alkyl,
107 substituted or unsubstituted heteroalkyl, substituted or
108 unsubstituted cycloalkyl, substituted or unsubstituted
109 heterocycloalkyl, substituted or unsubstituted aryl, and substituted
110 or unsubstituted heteroaryl

111 wherein
112 R^{y5} and R^{y6} are members independently selected from a charge
113 (positive or negative), a salt counterion, H, substituted or
114 unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
115 substituted or unsubstituted cycloalkyl, substituted or
116 unsubstituted heterocycloalkyl, substituted or unsubstituted
117 aryl, substituted or unsubstituted heteroaryl
118 R_d' is a member selected from H, substituted or unsubstituted alkyl and halogen;
119 wherein
120 R_c and R_d can be optionally joined, together with the atoms to which they
121 are attached, to form a 5-8 membered ring;
122 R_c and R_d' can be optionally joined, together with the atoms to which they
123 are attached, to form a 5-8 membered ring;
124 R^{x1} and R^{x2} can be optionally joined, together with the atoms to which they
125 are attached, to form a 5-8 membered ring;
126 R^{x2} and R^{x3} can be optionally joined, together with the atoms to which they
127 are attached, to form a 5-8 membered ring;
128 R^{x3} and R^{x4} can be optionally joined, together with the atoms to which they
129 are attached, to form a 5-8 membered ring;
130 R^{x4} and R^{x5} can be optionally joined, together with the atoms to which they
131 are attached, to form a 5-8 membered ring;
132 R^{x4} and R^{x6} can be optionally joined, together with the atoms to which they
133 are attached, to form a 5-8 membered ring;
134 R^{x5} and R^{x6} can be optionally joined, together with the atoms to which they
135 are attached, to form a 5-8 membered ring;
136 R^{x6} and R^{x7} can be optionally joined, together with the atoms to which they
137 are attached, to form a 5-8 membered ring;
138 R^{x4} and R^{x8} can be optionally joined, together with the atoms to which they
139 are attached, to form a 5-8 membered ring;
140 R^{x2} and R^{x9} can be optionally joined, together with the atoms to which they
141 are attached, to form a 5-8 membered ring;
142 two R^{x10} can be optionally joined, together with the atoms to which they
143 are attached, to form a 5-8 membered ring;

144 R^{x9} and R^{x10} can be optionally joined, together with the atoms to which
 145 they are attached, to form a 5-8 membered ring;
 146 R^{x12} and R^{x11} can be optionally joined, together with the atoms to which
 147 they are attached, to form a 5-8 membered ring;
 148 R^{x11} and R^{x10} can be optionally joined, together with the atoms to which
 149 they are attached, to form a 5-8 membered ring
 150 R^{y1} and R^{y2} can be optionally joined, together with the atoms to which they
 151 are attached, to form a 5-8 membered ring
 152 R^{y3} and R^{y4} can be optionally joined, together with the atoms to which they
 153 are attached, to form a 5-8 membered ring
 154 R^{x15} and R^{x16} can be optionally joined, together with the atoms to which
 155 they are attached, to form a 5-8 membered ring
 156 R^{x22} and R^{x23} can be optionally joined, together with the atoms to which
 157 they are attached, to form a 5-8 membered ring

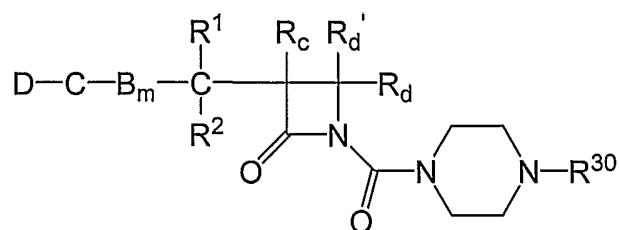
158 with the proviso that if

- 159 a) Y is C=O;
 160 ABC, in combination, form unsubstituted alkyl; and
 161 D is substituted or unsubstituted guanidine; or
 162 b) Y is C=O;
 163 AB, in combination, form unsubstituted alkyl; and
 164 CD, in combination, form



165
 166 wherein
 167 the dotted line represents carbon atoms necessary for the
 168 formation of one ring having 4 to 8 atoms;
 169 then R_c cannot be a member selected from CH_3 and CH_2CH_3 ; and R_d and
 170 R_d' cannot be members selected from CH_3 and CH_3 ; CH_2CH_3 and
 171 CH_2CH_3 ; CH_2CH_3 and CH_3 ; CH_3 and CH_2CH_3 ; H and COOH; H
 172 and $COOR^{y5}$; H and $CONR^{10}R^{10a}$; unsubstituted alkyl and COOH;
 173 unsubstituted alkyl and $COOR^{y5}$; H and unsubstituted phenylalkyl;
 174 unsubstituted alkyl and unsubstituted phenylalkyl

175 and with the further proviso that if the compound has the following structure:



176

177 wherein

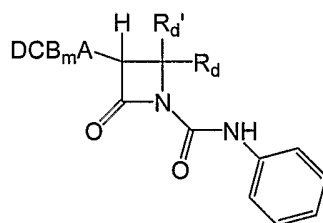
178 R^{30} is a member selected from H, SO_2-R^{31} , substituted or
 179 unsubstituted alkyl, substituted or unsubstituted
 180 heteroalkyl, substituted or unsubstituted cycloalkyl,
 181 substituted or unsubstituted heterocycloalkyl,
 182 substituted or unsubstituted aryl, and substituted or
 183 unsubstituted heteroaryl

184 wherein

185 R^{31} is unsubstituted alkyl

186 then at least one of R_d and R_d' does not comprise a carbonyl group which
 187 is directly attached, or alpha, to the azetidinone ring

188 and with the proviso that the compound cannot have the following structure:



189

190 wherein DCB_mA comprises a piperidine ring or a salt thereof

191 and with the proviso that when T is NR^{x23} , then R^{x20} must be $C(O)R^{x24}$ or SO_2R^{x24} .

1 **17.** A pharmaceutical composition comprising an effective amount of a
 2 compound of claims **1** or **3** or **16** including an inner salt or a pharmaceutically acceptable
 3 salt thereof, a hydrolysable ester thereof, or a solvate thereof and one or more
 4 pharmaceutically acceptable excipients.

1 **18.** The pharmaceutical composition according to claim **17**, wherein
 2 said composition is useful for enhancing thrombolysis or treating thrombosis, asthma,
 3 chronic asthma, or allergic rhinitis.

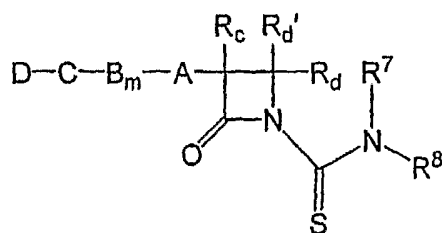
1 **19.** A method for treating asthma, chronic asthma or allergic rhinitis in
2 a mammalian species comprising administering an effective amount of the composition of
3 claim 1 or 3 or 16.

1 **20.** A method of inhibiting tryptase in a mammal by administration of
2 a compound according to claims 1 or 3 or 16.

1 **21.** A method of enhancing thrombolysis or treating thrombosis in a
2 mammalian species comprising administering an effective amount of the composition of
3 claim 1 or 3 or 16.

1 **22.** A method of inhibiting Factor XIa in a mammal by administration
2 of a compound according to claims 1 or 3 or 16.

FIGURE 1A



	DCB _m A	R _c	R _d	R _d '	R ⁷	R ⁸
A1		H		H		H
A2		CH ₃		H		H
A3		H		CH ₃		H
A4		H		H		H
A5		CH ₃		H		H
A6		H		CH ₃		H
A7		H		H		H
A8		CH ₃		H		H

FIGURE 1B

A9		H		CH ₃		H
A10		H		H		
A11		CH ₃		H		
A12		H		CH ₃		
A13		H		H		
A14		CH ₃		H		
A15		H		CH ₃		
A16		H		H		
A17		CH ₃		H		
A18		H		CH ₃		
A19		H		H		
A20		CH ₃		H		
A21		H		CH ₃		
A22		H		H		

FIGURE 1C

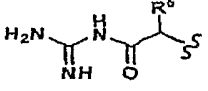
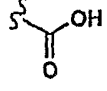
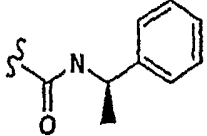
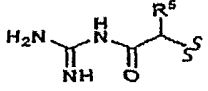
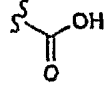
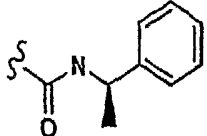
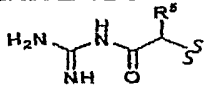
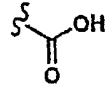
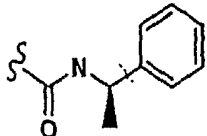
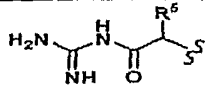
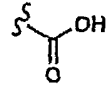
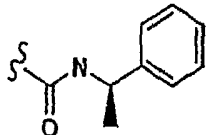
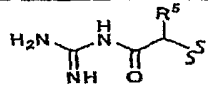
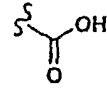
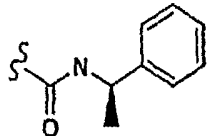
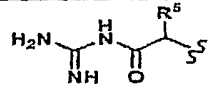
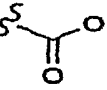
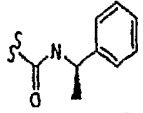
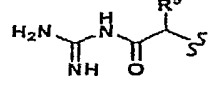
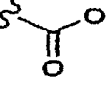
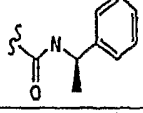
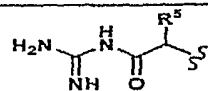
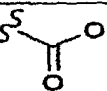
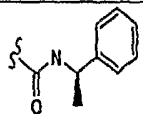
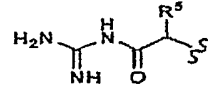
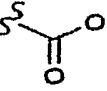
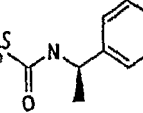
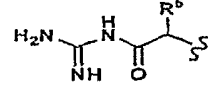
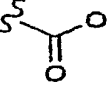
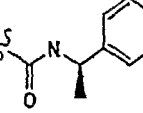
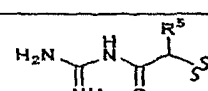
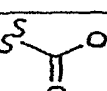
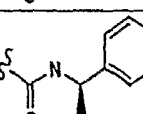
A23		CH ₃		H		
A24		H		CH ₃		
A25		H		H		
A26		CH ₃		H		
A27		H		CH ₃		
A28		H		H		H
A29		CH ₃		H		H
A30		H		CH ₃		H
A31		H		H		H
A32		CH ₃		H		H
A33		H		CH ₃		H

FIGURE 1D

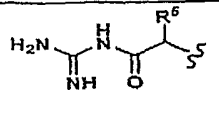
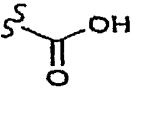
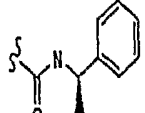
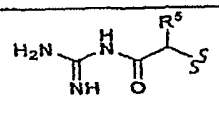
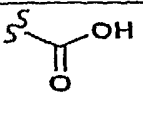
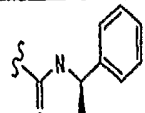
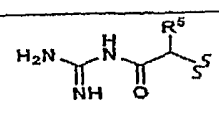
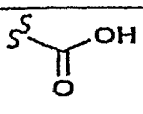
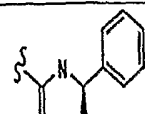
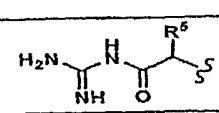
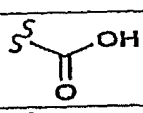
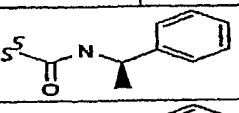
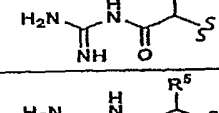
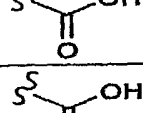
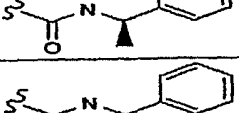
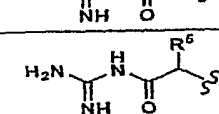
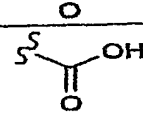
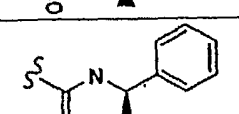
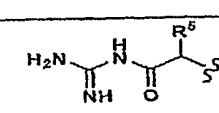
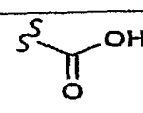
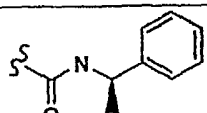
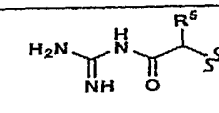
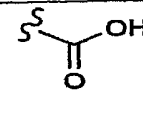
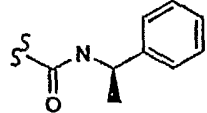
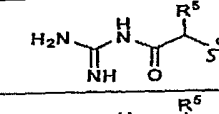
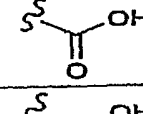
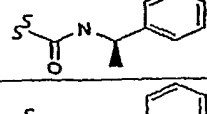
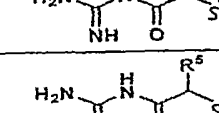
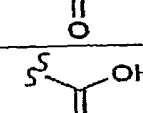
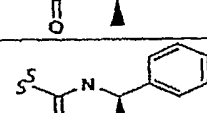
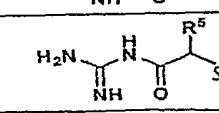
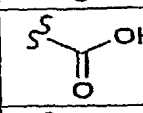
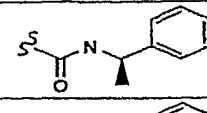
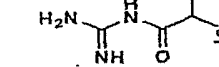
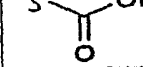







A34		H		H		H
A35		CH ₃		H		H
A36		H		CH ₃		H
A37		H		H		
A38		CH ₃		H		
A39		H		CH ₃		
A40		H		H		
A41		CH ₃		H		
A42		H		CH ₃		
A43		H		H		
A44		CH ₃		H		
A45		H		CH ₃		
A46		H		H		
A47		CH ₃		H		

FIGURE 1E

A48		H		CH ₃		
A49		H		H		
A50		CH ₃		H		
A51		H		CH ₃		
A52		H		H		
A53		CH ₃		H		
A54		H		CH ₃		
A55		H		H		H
A56		CH ₃		H		H
A57		H		CH ₃		H
A58		H		H		H

FIGURE 1F

A59		CH ₃		H		H
A60		H		CH ₃		H
A61		H		H		H
A62		CH ₃		H		H
A63		H		CH ₃		H
A64		H		H		
A65		CH ₃		H		
A66		H		CH ₃		
A67		H		H		
A68		CH ₃		H		
A69		H		CH ₃		
A70		H		H		

FIGURE 1G

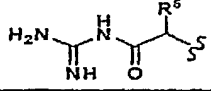
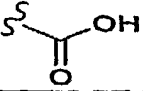
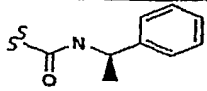
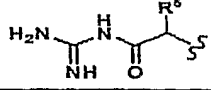
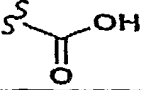
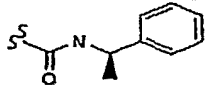
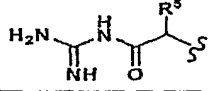
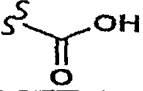
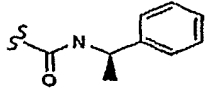
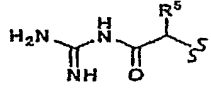
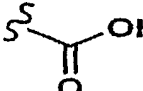
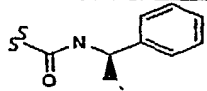
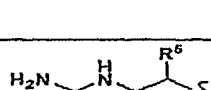
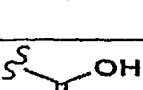
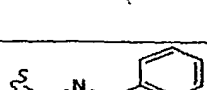
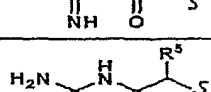
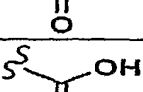

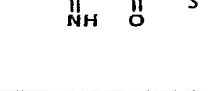
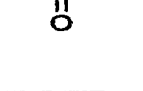
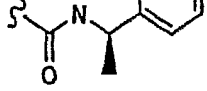
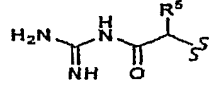
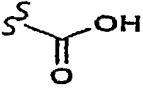
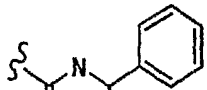



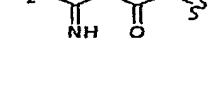
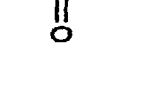
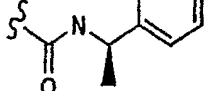
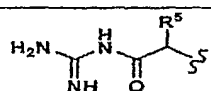
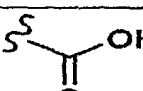
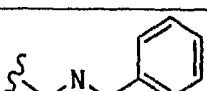
A71		CH ₃		H	
A72		H		CH ₃	
A73		H		H	
A74		CH ₃		H	
A75		H		CH ₃	
A76		H		H	
A77		CH ₃		H	
A78		H		CH ₃	
A79		H		H	
A80		CH ₃		H	
A81		H		CH ₃	

FIGURE 1H

A82		H		H		H
A83		CH ₃		H		H
A84		H		CH ₃		H
A85		H		H		H
A86		CH ₃		H		H
A87		H		CH ₃		H
A88		H		H		H
A89		CH ₃		H		H
A90		H		CH ₃		H
A91		H		H		H
A92		CH ₃		H		H
A93		H		CH ₃		H

FIGURE 11

A94		H		H	
A95		CH ₃		H	
A96		H		CH ₃	
A97		H		H	
A98		CH ₃		H	
A99		H		CH ₃	
A100		H		H	
A101		CH ₃		H	
A102		H		CH ₃	
A103		H		H	
A104		CH ₃		H	
A105		H		CH ₃	

FIGURE 1J

A106		H		H		
A107		CH ₃		H		
A108		H		CH ₃		
A109		H		H		H
A110		CH ₃		H		H
A111		H		CH ₃		H
A112		H		H		H
A113		CH ₃		H		H
A114		H		CH ₃		H
A115		H		H		H
A116		CH ₃		H		H

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FIGURE 1K

A117		H		CH ₃		H
A118		H		H		
A119		CH ₃		H		
A120		H		CH ₃		
A121		H		H		
A122		CH ₃		H		
A123		H		CH ₃		
A124		H		H		
A125		CH ₃		H		
A126		H		CH ₃		
A127		H		H		
A128		CH ₃		H		
A129		H		CH ₃		
A130		H		H		

FIGURE 1L

A131		CH ₃		H		
A132		H		CH ₃		
A133		H		H		
A134		CH ₃		H		
A135		H		CH ₃		
A136		H		H		H
A137		CH ₃		H		H
A138		H		CH ₃		H
A139		H		H		H
A140		CH ₃		H		H
A141		H		CH ₃		H

FIGURE 1M

A142		H		H		H
A143		CH ₃		H		H
A144		H		CH ₃		H
A145		H		H		H
A146		CH ₃		H		H
A147		H		CH ₃		H
A148		H		H		H
A149		CH ₃		H		H
A150		H		CH ₃		H
A151		H		H		H
A152		CH ₃		H		H
A153		H		CH ₃		H
A154		H		H		H
A155		CH ₃		H		H

FIGURE 1N

A156		H		CH ₃		
A157		H		H		
A158		CH ₃		H		
A159		H		CH ₃		
A160		H		H		
A161		CH ₃		H		
A162		H		CH ₃		
A163		H		H		H
A164		CH ₃		H		H
A165		H		CH ₃		H
A166		H		H		H

FIGURE 10

A167		CH ₃		H		H
A168		H		CH ₃		H
A169		H		H		H
A170		CH ₃		H		H
A171		H		CH ₃		H
A172		H		H		
A173		CH ₃		H		
A174		H		CH ₃		
A175		H		H		
A176		CH ₃		H		
A177		H		CH ₃		
A178		H		H		
A179		CH ₃		H		

FIGURE 1P

A180		H		CH ₃	
A181		H		H	
A182		CH ₃		H	
A183		H		CH ₃	
A184		H		H	
A185		CH ₃		H	
A186		H		CH ₃	
A187		H		H	
A188		CH ₃		H	
A189		H		CH ₃	
A190		H		H	
A191		CH ₃		H	

FIGURE 1Q

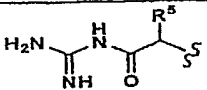
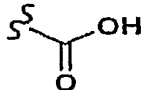
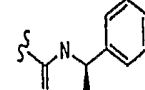
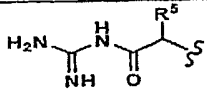
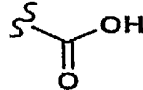
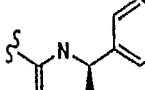
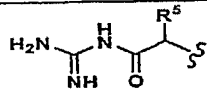
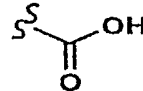
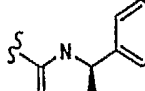
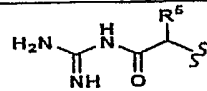
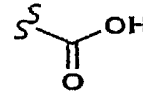
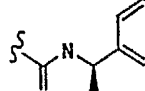
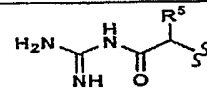
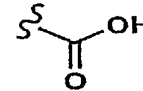
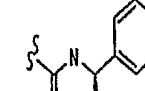
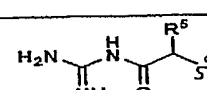
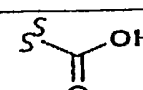
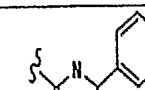
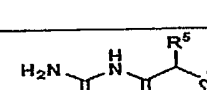
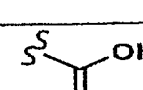
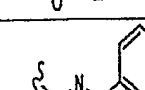
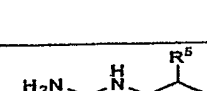
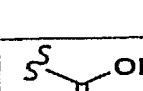
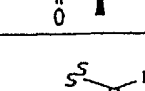
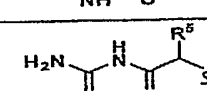
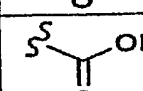
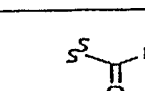
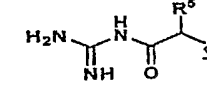
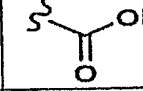
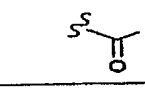
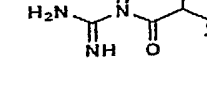
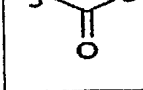

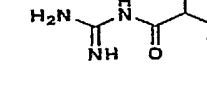
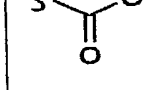
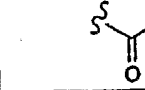
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A193		H		H		H
A194		CH ₃		H		H
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A196		H		H		H
A197		CH ₃		H		H
A198		H		CH ₃		H
A199		H		H		H
A200		CH ₃		H		H
A201		H		CH ₃		H
A202		H		H		H
A203		CH ₃		H		H

FIGURE 1R

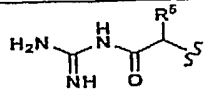
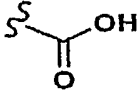
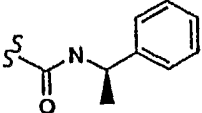
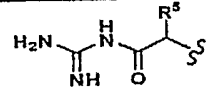
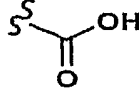
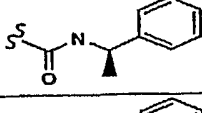
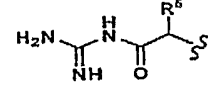
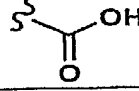
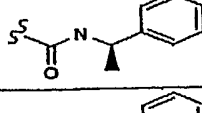
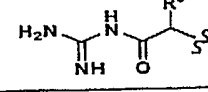
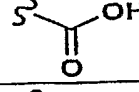
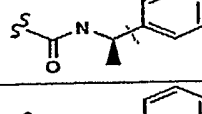
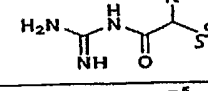
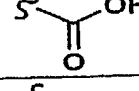
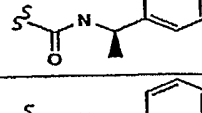
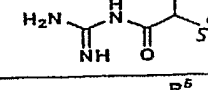
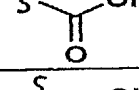
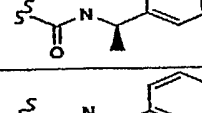
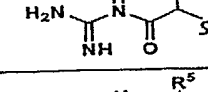
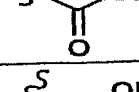
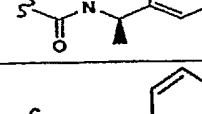
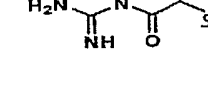
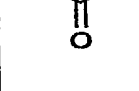
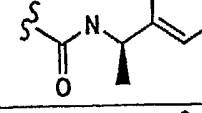
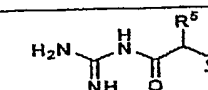
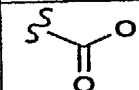
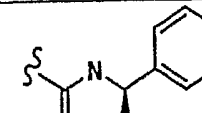
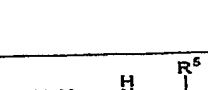
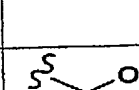
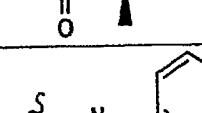
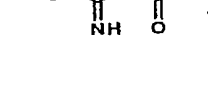
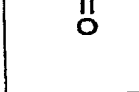
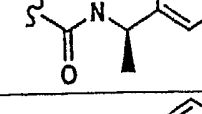
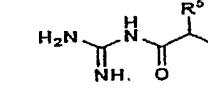
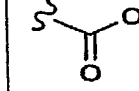
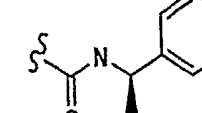
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A205		H		H	
A206		CH ₃		H	
A207		H		CH ₃	
A208		H		H	
A209		CH ₃		H	
A210		H		CH ₃	
A211		H		H	
A212		CH ₃		H	
A213		H		CH ₃	
A214		H		H	
A215		CH ₃		H	

FIGURE 1S

A216		H		CH ₃		
A217		H		H		H
A218		CH ₃		H		H
A219		H		CH ₃		H
A220		H		H		H
A221		CH ₃		H		H
A222		H		CH ₃		H
A223		H		H		H
A224		CH ₃		H		H
A225		H		CH ₃		H
A226		H		H		
A227		CH ₃		H		

FIGURE 1T

A228		H		CH ₃	
A229		H		H	
A230		CH ₃		H	
A231		H		CH ₃	
A232		H		H	
A233		CH ₃		H	
A234		H		CH ₃	
A235		H		H	
A236		CH ₃		H	
A237		H		CH ₃	
A238		H		H	
A239		CH ₃		H	

FIGURE 1U

A240		H		CH ₃		
A241		H		H		
A242		CH ₃		H		
A243		H		CH ₃		
A244		H		H		H
A245		CH ₃		H		H
A246		H		CH ₃		H
A247		H		H		H
A248		CH ₃		H		H
A249		H		CH ₃		H
A250		H		H		H

FIGURE 1V

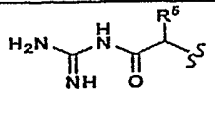
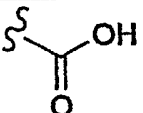
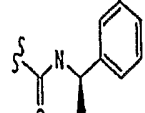
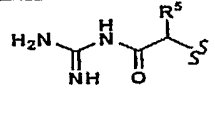
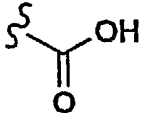
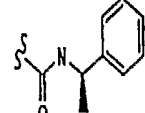
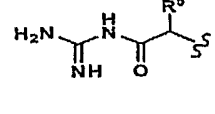
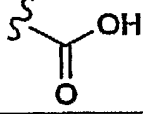
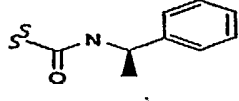
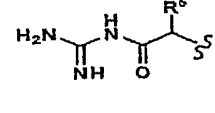
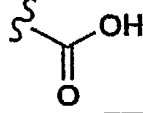
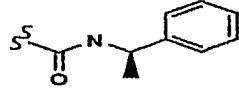
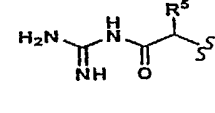
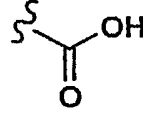
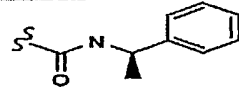
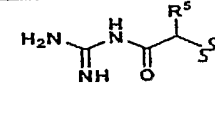
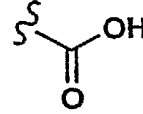
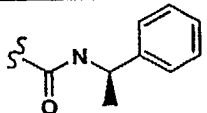
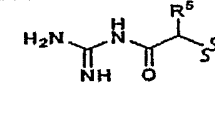
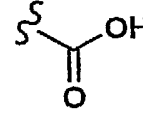
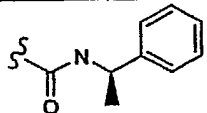
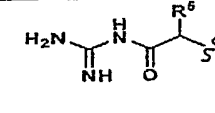
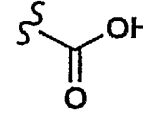
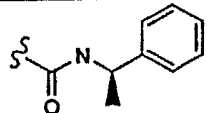
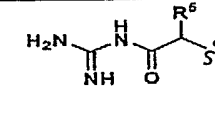
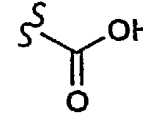
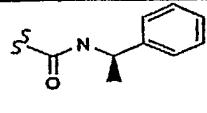
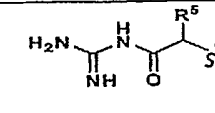
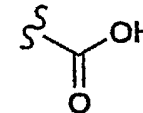
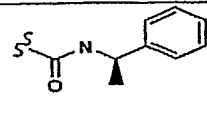
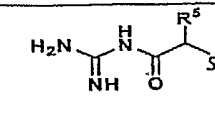
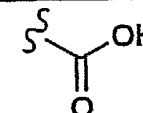
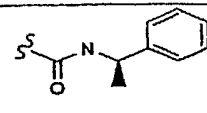
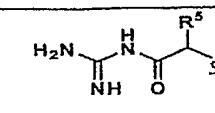
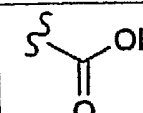
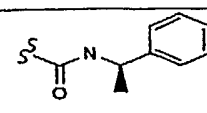
A251		CH ₃		H		H
A252		H		CH ₃		H
A253		H		H		
A254		CH ₃		H		
A255		H		CH ₃		
A256		H		H		
A257		CH ₃		H		
A258		H		CH ₃		
A259		H		H		
A260		CH ₃		H		
A261		H		CH ₃		
A262		H		H		

FIGURE 1W

A263		CH ₃		H	
A264		H		CH ₃	
A265		H		H	
A266		CH ₃		H	
A267		H		CH ₃	
A268		H		H	
A269		CH ₃		H	
A270		H		CH ₃	
A271		H		H	
A272		CH ₃		H	

FIGURE 1X

A273		H		CH ₃	
A274		H		H	
A275		CH ₃		H	
A276		H		CH ₃	
A277		H		H	
A278		CH ₃		H	
A279		H		CH ₃	
A280		H		H	
A281		CH ₃		H	
A282		H		CH ₃	
A283		H		H	

FIGURE 1Y

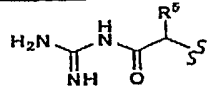
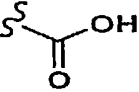
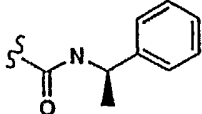
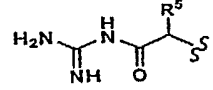
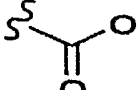
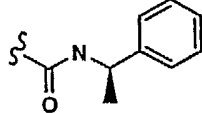
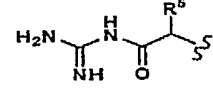
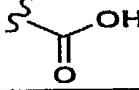
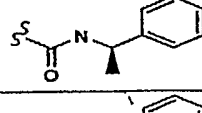
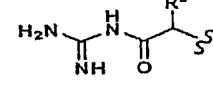
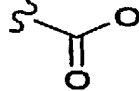
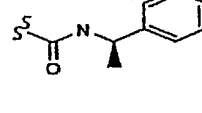
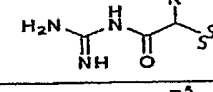
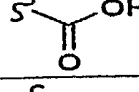
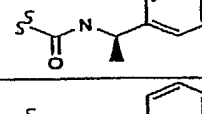
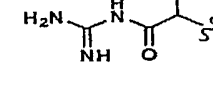
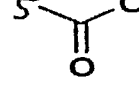
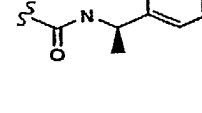
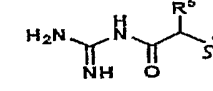
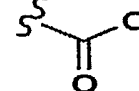
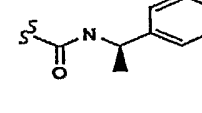
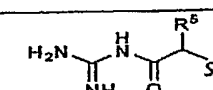
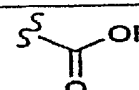
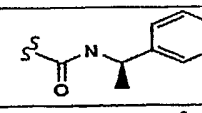
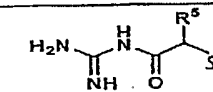
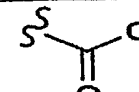
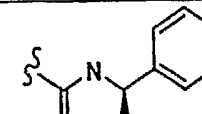
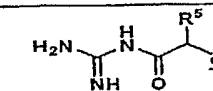
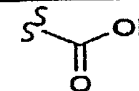
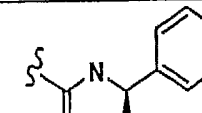
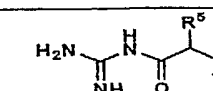
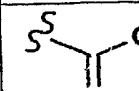
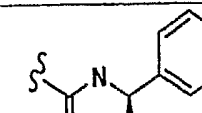
A284		CH ₃		H	
A285		H		CH ₃	
A286		H		H	
A287		CH ₃		H	
A288		H		CH ₃	
A289		H		H	
A290		CH ₃		H	
A291		H		CH ₃	
A292		H		H	
A293		CH ₃		H	
A294		H		CH ₃	

FIGURE 1Z

A295		H		H	
A296		CH ₃		H	
A297		H		CH ₃	
A298		H		H	
A299		CH ₃		H	
A300		H		CH ₃	
A301		H		H	
A302		CH ₃		H	
A303		H		CH ₃	
A304		H		H	
A305		CH ₃		H	

FIGURE 1AA

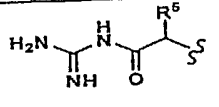
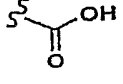
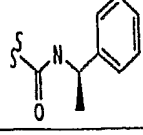
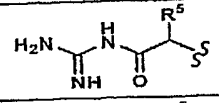
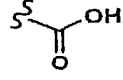
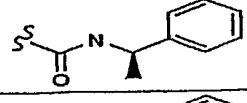
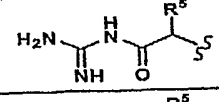
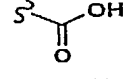
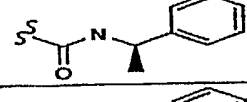
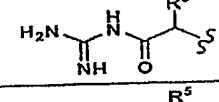
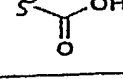

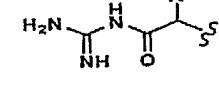
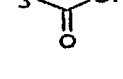
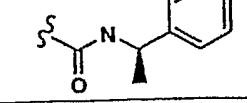
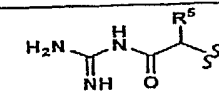
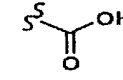
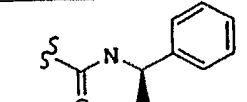
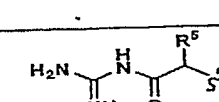
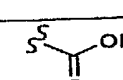
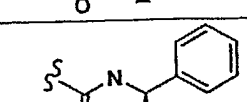
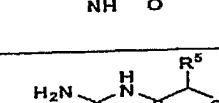

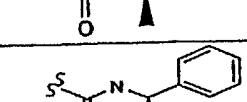
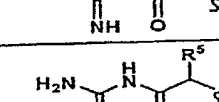
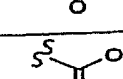
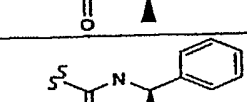
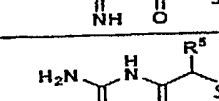
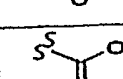
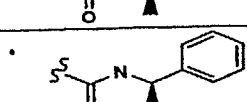
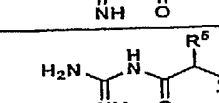
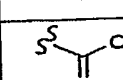
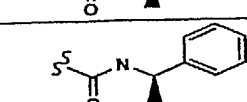
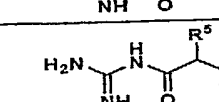
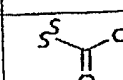
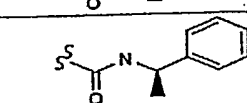
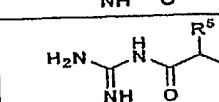
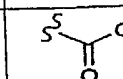
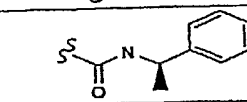
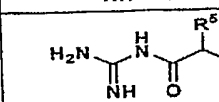
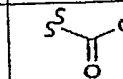
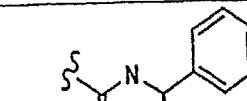
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A311		CH ₃		H	
A312		H		CH ₃	
A313		H		H	
A314		CH ₃		H	
A315		H		CH ₃	
A316		H		H	
A317		CH ₃		H	
A318		H		CH ₃	
A319		H		H	

FIGURE 1AB

A320		CH ₃		H	
A321		H		CH ₃	
A322		H		H	
A323		CH ₃		H	
A324		H		CH ₃	
A325		H		H	
A326		CH ₃		H	
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FIGURE 1AC

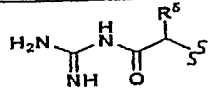
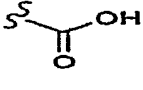
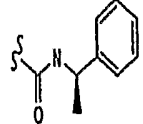
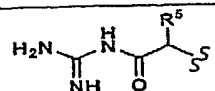
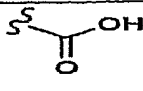
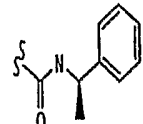
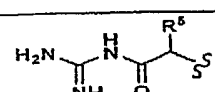
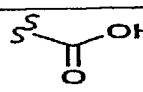
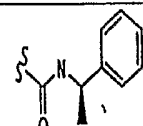
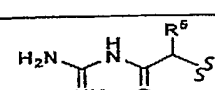

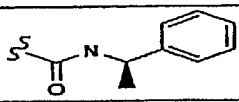
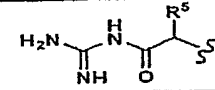
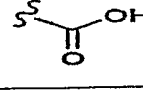
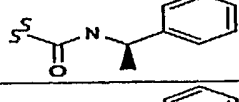
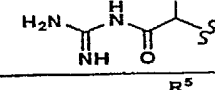
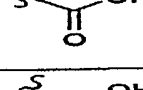
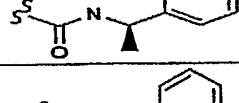
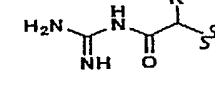
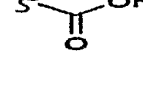
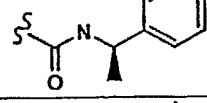
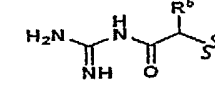
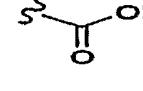
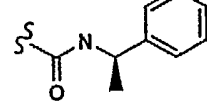
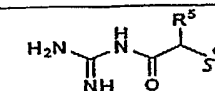
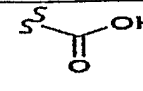
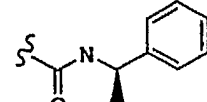
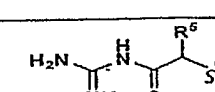
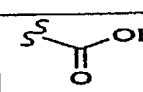
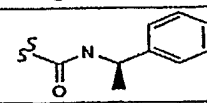
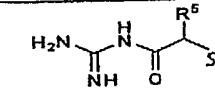
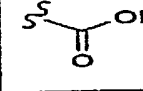
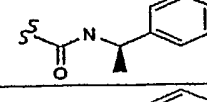
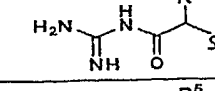
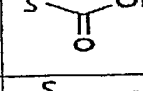
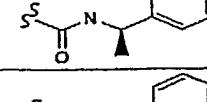
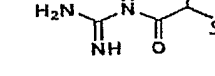


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FIGURE 1AD

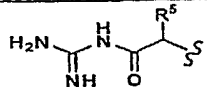
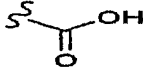
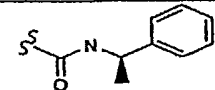
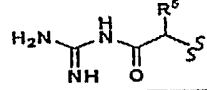
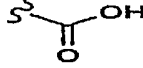
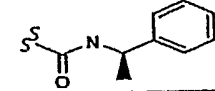
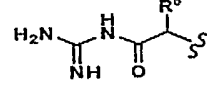
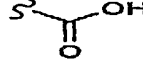
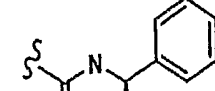
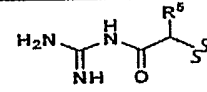
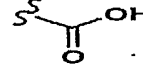
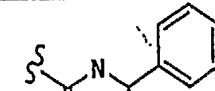
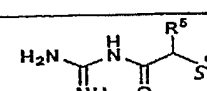

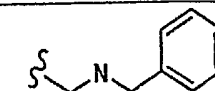
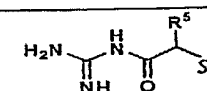
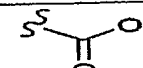
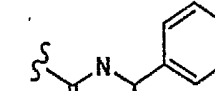
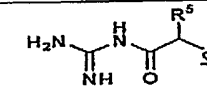
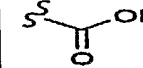
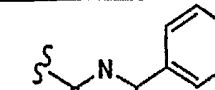
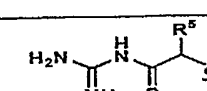

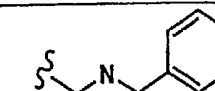
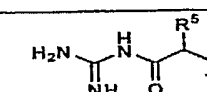
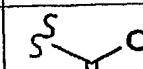
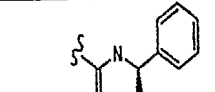
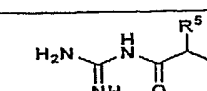
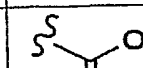
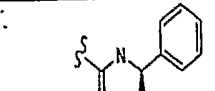
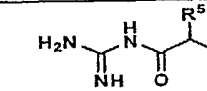

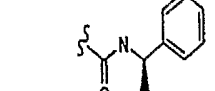
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A349		H		H	
A350		CH ₃		H	
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FIGURE 1AE

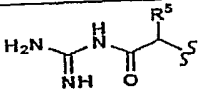
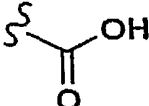
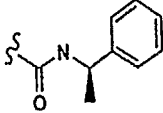
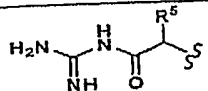
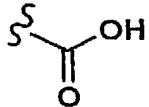
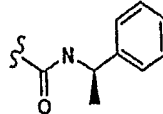
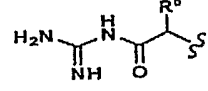
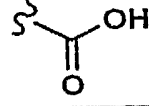
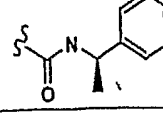
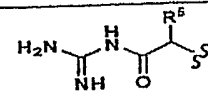
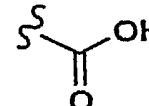
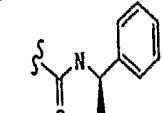
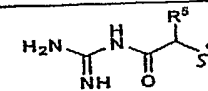
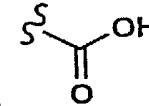
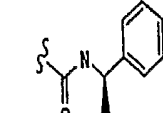
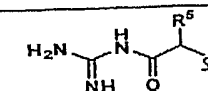
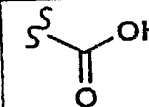
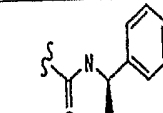
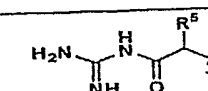
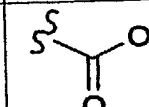
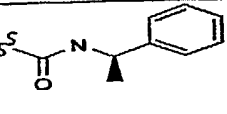
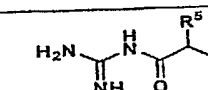
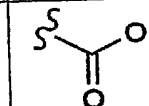
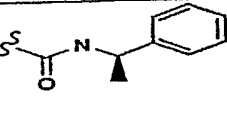
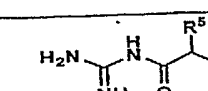
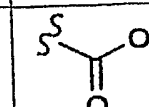
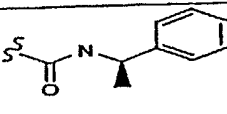
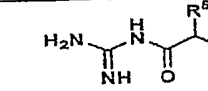
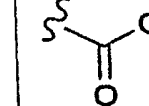
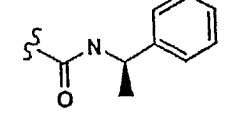
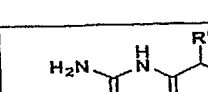
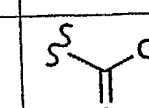
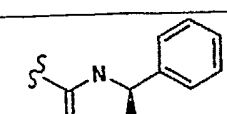
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A357		H		CH ₃	
A358		H		H	
A359		CH ₃		H	
A360		H		CH ₃	
A361		H		H	
A362		CH ₃		H	
A363		H		CH ₃	
A364		H		H	
A365		CH ₃		H	

FIGURE 1AF

A366		H		CH ₃	
A367		H		H	
A368		CH ₃		H	
A369		H		CH ₃	
A370		H		H	
A371		CH ₃		H	
A372		H		CH ₃	
A373		H		H	
A374		CH ₃		H	
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A376		H		H	

FIGURE 1AG

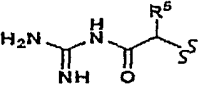
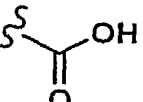
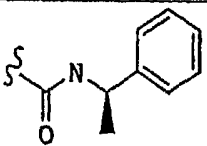
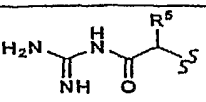
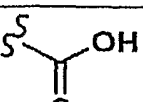
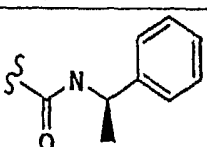
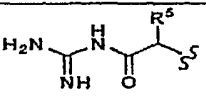
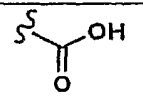
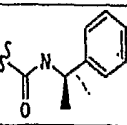
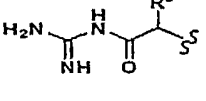
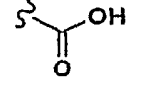
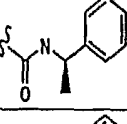
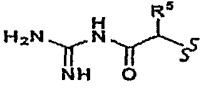
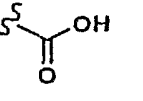
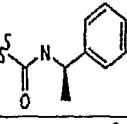
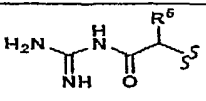
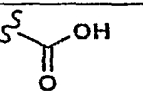
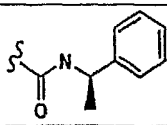
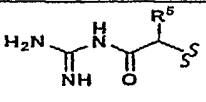
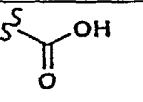
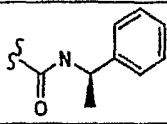
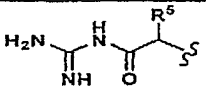
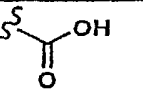
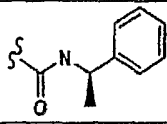
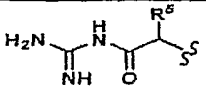
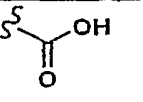
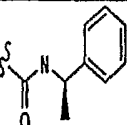
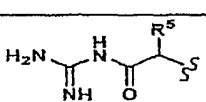
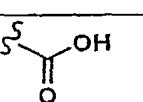
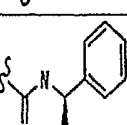
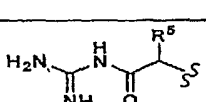
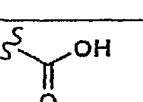
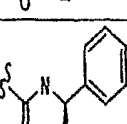
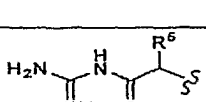
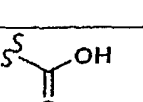
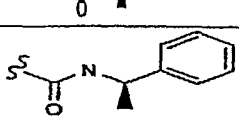
A377		CH ₃		H	
A378		H		CH ₃	
A379		H		H	
A380		CH ₃		H	
A381		H		CH ₃	
A382		H		H	
A383		CH ₃		H	
A384		H		CH ₃	
A385		H		H	
A386		CH ₃		H	
A387		H		CH ₃	
A388		H		H	

FIGURE 1AH

A389		CH ₃		H	
A390		H		CH ₃	
A391		H		H	
A392		CH ₃		H	
A393		H		CH ₃	
A394		H		H	
A395		CH ₃		H	
A396		H		CH ₃	
A397		H		H	
A398		CH ₃		H	
A399		H		CH ₃	
A400		H		H	
A401		CH ₃		H	

FIGURE 1A1

A402		H		CH ₃	
A403		H		H	
A404		CH ₃		H	
A405		H		CH ₃	
A406		H		H	
A407		CH ₃		H	
A408		H		CH ₃	
A409		H		H	
A410		CH ₃		H	
A411		H		CH ₃	
A412		H		H	

FIGURE 1AJ

A413		CH ₃		H	
A414		H		CH ₃	
A415		H		H	
A416		CH ₃		H	
A417		H		CH ₃	
A418		H		H	
A419		CH ₃		H	
A420		H		CH ₃	
A421		H		H	
A422		CH ₃		H	
A423		H		CH ₃	
A424		H		H	
A425		CH ₃		H	
A426		H		CH ₃	

FIGURE 1AK

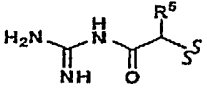
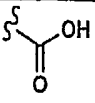
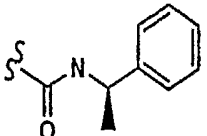
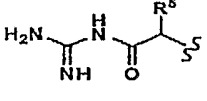
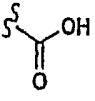
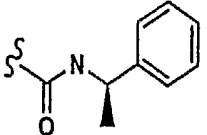
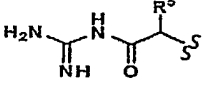
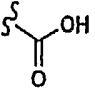
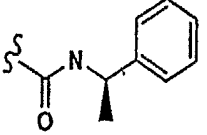
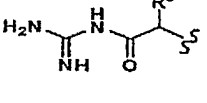
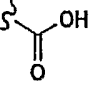
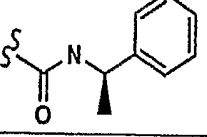
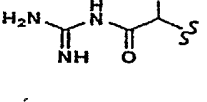
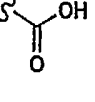
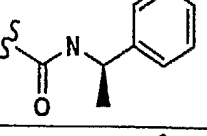
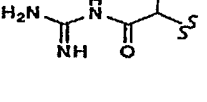
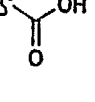
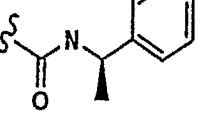
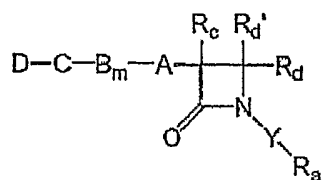
A427		H		H	
A428		CH ₃		H	
A429		H		CH ₃	
A430		H		H	
A431		CH ₃		H	
A432		H		CH ₃	

FIGURE 1AL



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A433		H		H	
A434		H		H	
A435		H		H	
A436		H		H	
A437		H		H	
A438		H		H	
A439		H		H	
A440		H		H	
A441		H		H	
A442		H		H	

FIGURE 1AM

A443		H		H	
A444		H		H	
A445		H		H	
A446		H		H	
A447		H		H	
A448		H		H	
A449		H		H	
A450		H		H	
A451		H		H	
A452		H		H	
A453		H		H	
A454		H		H	
A455		H		H	

FIGURE 1AN

A456		H		H	
A457		H		H	
A458		H		H	
A459		H		H	
A460		H		H	
A461		H		H	
A462		H		H	
A463		H		H	
A464		H		H	
A465		H		H	
A466		H		H	
A467		H		H	
A468		H		H	

FIGURE 1A0

A469		H		H	
A470		H		H	
A471		H		H	
A472		H		H	
A473		H		H	
A474		H		H	
A475		H		H	
A476		H		H	
A477		H		H	
A478		H		H	
A479		H		H	
A480		H		H	
A481		H		H	

FIGURE 1AP

A482		H		H	
A483		H		H	
A484		H		H	
A485		H		H	
A486		H		H	
A487		H		H	
A488		H		H	
A489		H		H	
A490		H		H	
A491		H		H	
A492		H		H	
A493		H		H	
A494		H		H	

FIGURE 1AQ

A495		H		H	
A496		H		H	
A497		H		H	
A498		H		H	
A499		H		H	
A500		H		H	
A501		H		H	
A502		H		H	
A503		H		H	
A504		H		H	
A505		H		H	
A506		H		H	
A507		H		H	

FIGURE 1AR

A508		H		H	
A509		H		H	
A510		H		H	
A511		H		H	
A512		H		H	
A513		H		H	
A514		H		H	
A515		H		H	
A516		H		H	
A517		H	H	H	
A518		H	H	H	
A519		H	H	H	
A520		H	H	H	

FIGURE 1AS

A521		H	H	H	
A522		H	H	H	
A523		H	H	H	
A524		H	H	H	
A525		H	H	H	
A526		H	H	H	
A527		H	H	H	
A528		H	H	H	
A529		H	H	H	
A530		H	H	H	
A531		H	H	H	
A532		H	H	H	
A533		H	H	H	

FIGURE 1AT

A534		CH ₃	H	H	
A535		CH ₃	H	H	
A536		CH ₃	H	H	
A537		CH ₃	H	H	
A538		CH ₃	H	H	
A539		CH ₃	H	H	
A540		CH ₃	H	H	
A541		CH ₃	H	H	
A542		CH ₃	H	H	
A543		CH ₃	H	H	
A544		CH ₃	H	H	
A545		CH ₃	H	H	
A546		CH ₃	H	H	

FIGURE 1AU

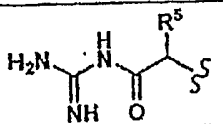
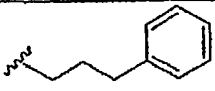
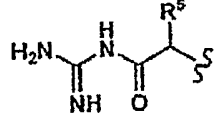
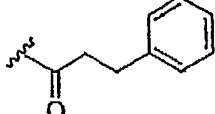
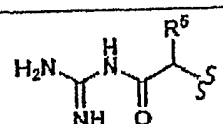
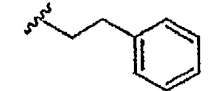
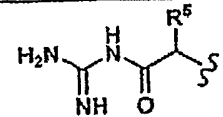
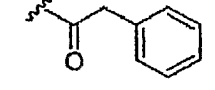
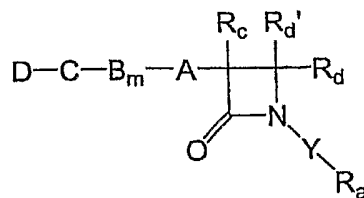
A547		CH ₃	H	H	
A548		CH ₃	H	H	
A549		CH ₃	H	H	
A550		CH ₃	H	H	

FIGURE 1AV



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A551		H		H	
A552		H		H	
A553		H		H	
A554		H		H	
A555		H		H	
A556		H		H	
A557		H		H	
A558		H		H	
A559		H		H	

FIGURE 1AW

A560		H		CH ₃	
A561		H		CH ₃	
A562		H		CH ₃	
A563		H		CH ₃	
A564		H		CH ₃	
A565		H		CH ₃	
A566		H		CH ₃	
A567		H		CH ₃	
A568		H		H	
A569		H		H	
A570		H		H	
A571		H		H	

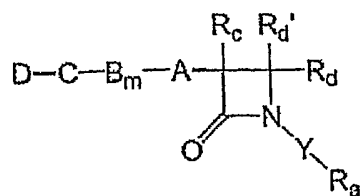
FIGURE 1AX

A572		CH ₃		H	
A573		CH ₃		H	
A574		CH ₃		H	
A575		CH ₃		H	
A576		H		H	
A577		H		H	
A578		H		H	
A579		H		H	
A580		CH ₃		H	
A581		CH ₃		H	
A582		CH ₃		H	
A583		CH ₃		H	
A584		H		H	

FIGURE 1AY

A585		H		H	
A586		H		H	
A587		H		H	

FIGURE 1AZ



	DCB _m -A	R _c	R _d	R ^{d'}	Y-R _a
A588		H		H	
A589		CH ₃		H	
A590		H		H	
A591		H		H	
A592		H		H	
A593		CH ₃		CH ₃	
A594		H		H	

FIGURE 1BA

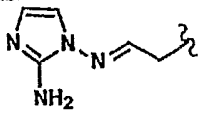
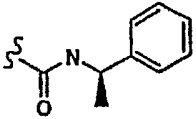
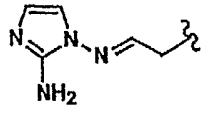
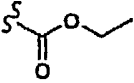
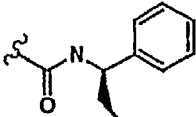
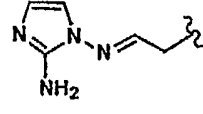
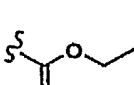
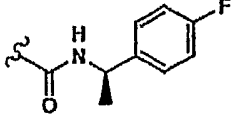
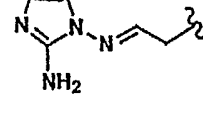
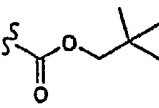
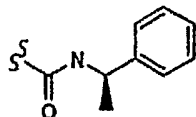
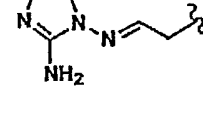
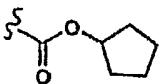
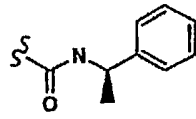
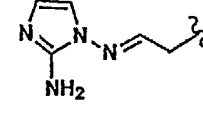
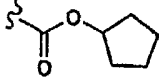
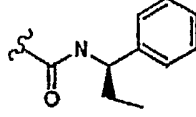
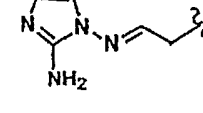
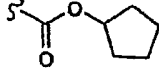
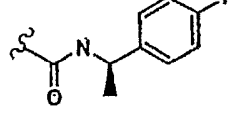
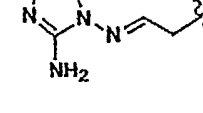
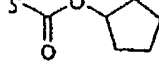
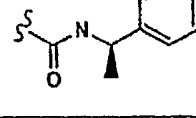
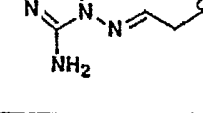
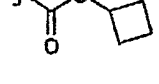
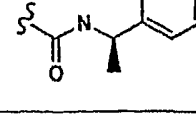
					
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A598		H		H	
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FIGURE 1BB

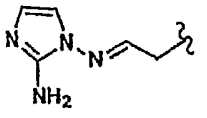
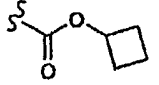
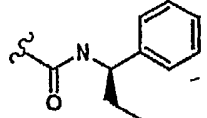
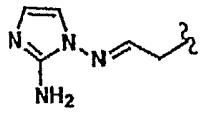
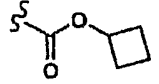
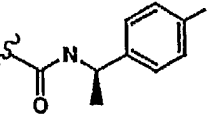
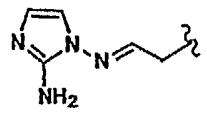
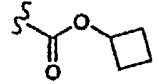
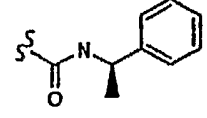
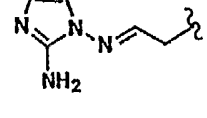
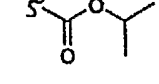
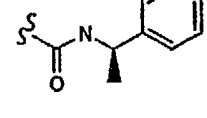
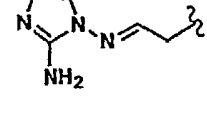
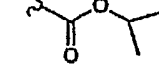
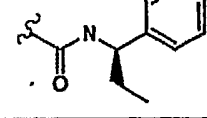
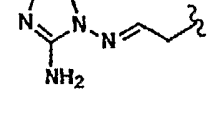
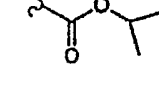
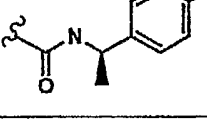
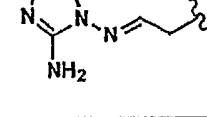
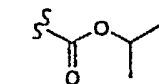
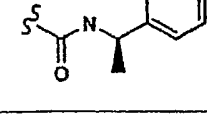
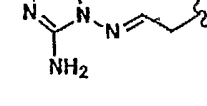
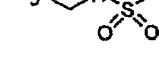
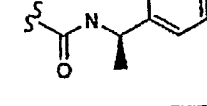
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FIGURE 1BC

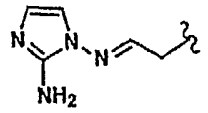
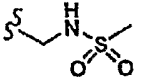
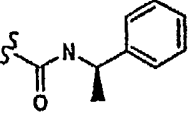
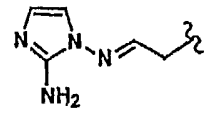
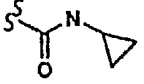
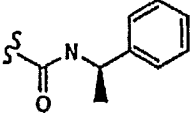
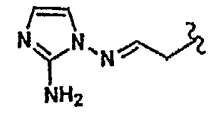
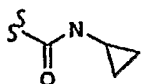
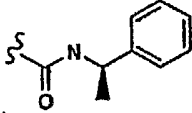
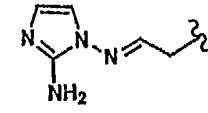
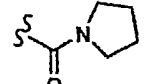
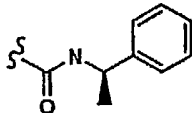
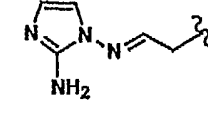
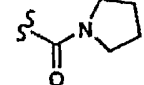
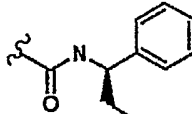
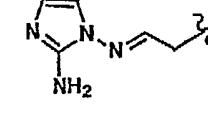
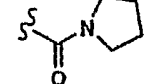
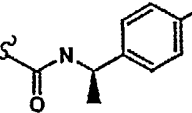
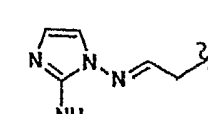
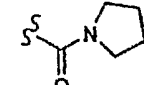
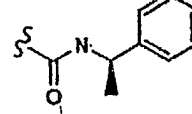
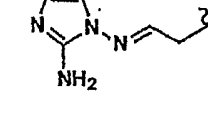
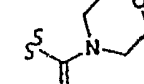
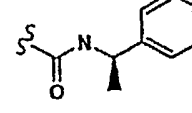
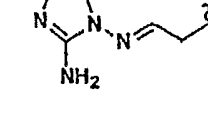
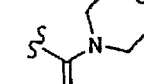
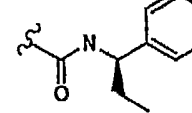
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FIGURE 1BD

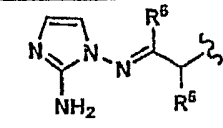
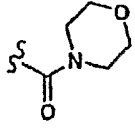
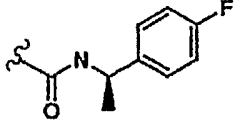
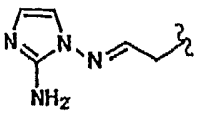
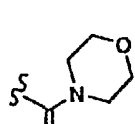
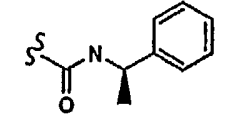
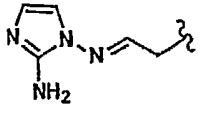
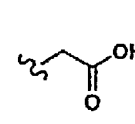
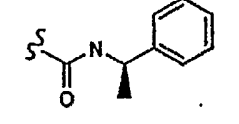
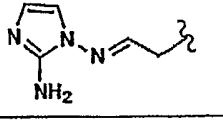
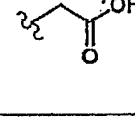
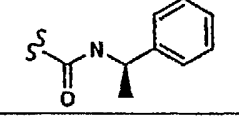
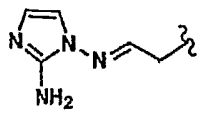
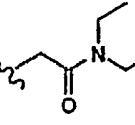
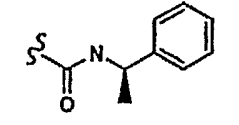
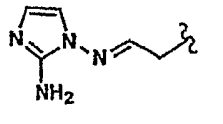
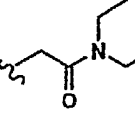
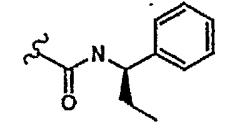
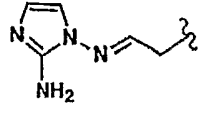
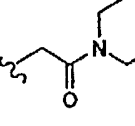
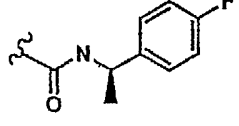
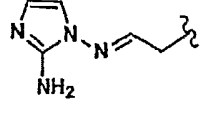
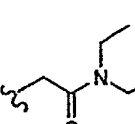
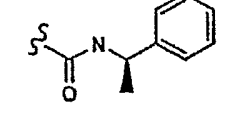
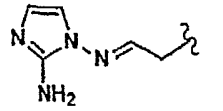
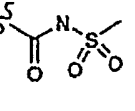
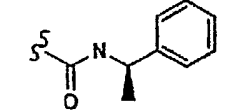
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A623		CH ₃		H	
A624		H		H	
A625		H		H	
A626		H		H	
A627		CH ₃		H	
A628		H		H	

FIGURE 1BE

A629		CH ₃		H	
A630		H		H	
A631		H		H	
A632		H		H	
A633		CH ₃		H	
A634		H		H	
A635		CH ₃		H	
A636		H		H	
A637		H		H	

FIGURE 1BF

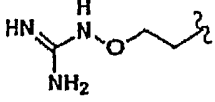

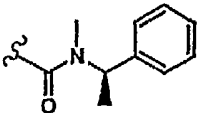
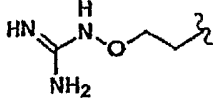

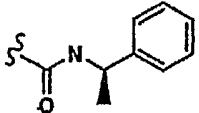
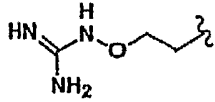
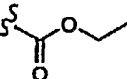
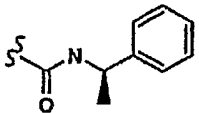
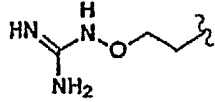
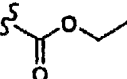
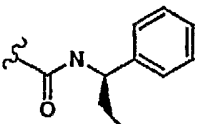
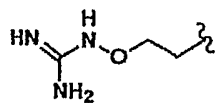
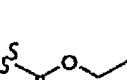
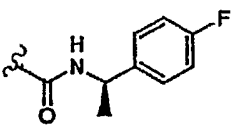
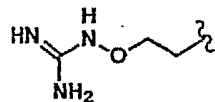
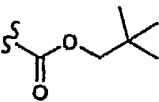
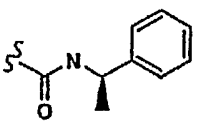
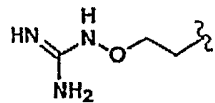
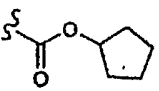
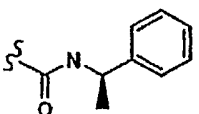
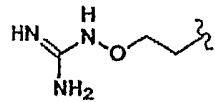
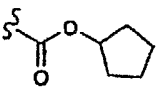
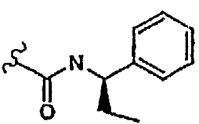
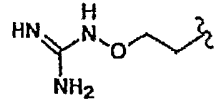
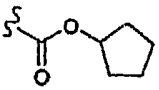
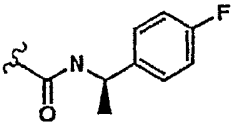
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A639		CH ₃		CH ₃	
A640		H		H	
A641		H		H	
A642		H		H	
A643		H		H	
A644		H		H	
A645		H		H	
A646		H		H	

FIGURE 1BG

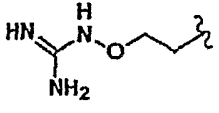
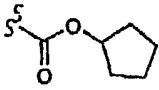
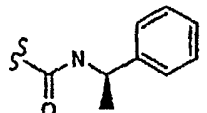
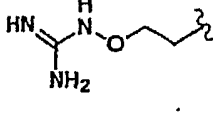
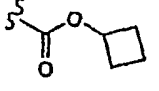
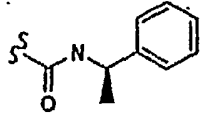
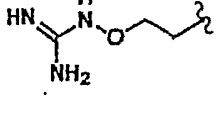
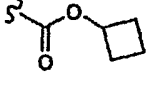
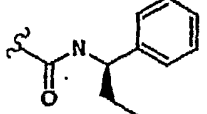
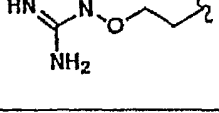
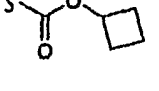
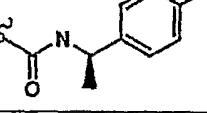
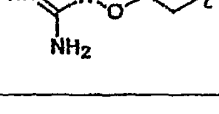
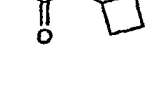
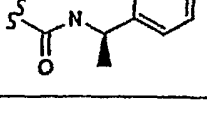
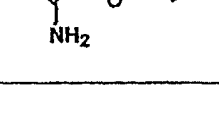
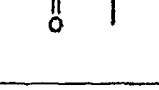
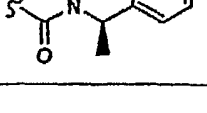
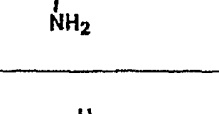
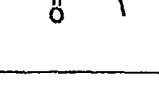
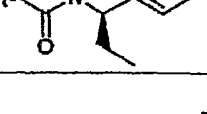
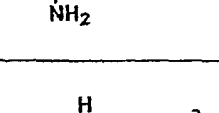
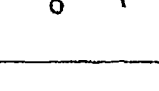
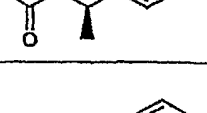
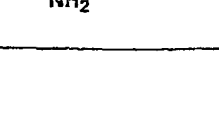
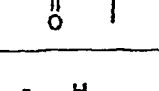
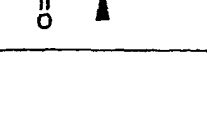
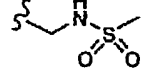
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A650		H		H	
A651		CH ₃		H	
A652		H		H	
A653		H		H	
A654		H		H	
A655		CH ₃		H	
A656		H		H	

FIGURE 1BH

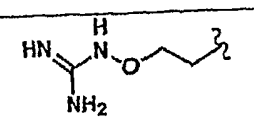
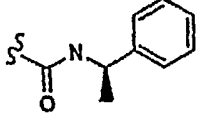
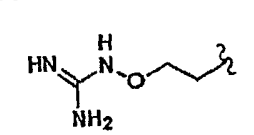
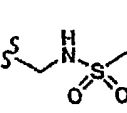
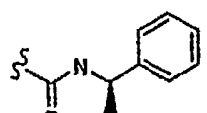
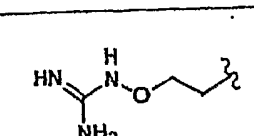
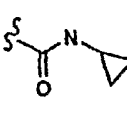
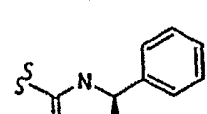
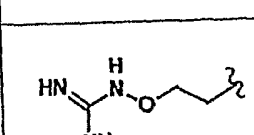
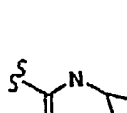
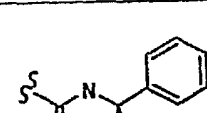
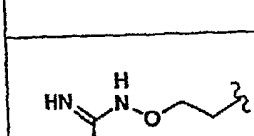
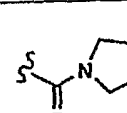
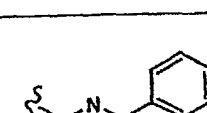
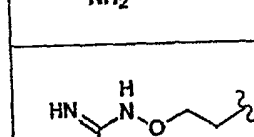
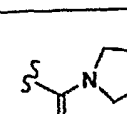
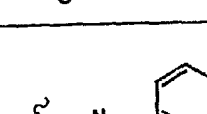
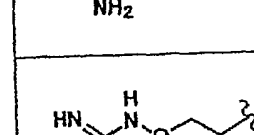
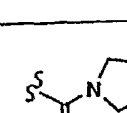
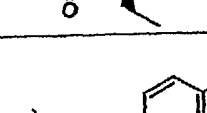
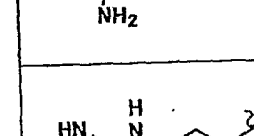
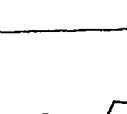
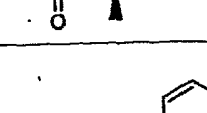
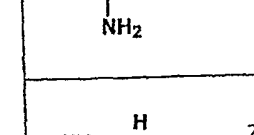
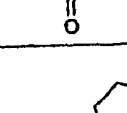
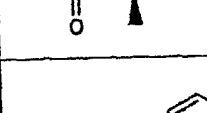
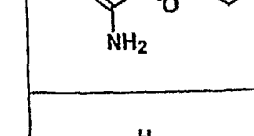
					
A657		CH ₃		H	
A658		H		H	
A659		CH ₃		H	
A660		H		H	
A661		H		H	
A662		H		H	
A663		CH ₃		H	
A664		H		H	
A665		H		H	

FIGURE 1BI

A666		H		H	
A667		CH ₃		H	
A668		H		H	
A669		CH ₃		H	
A670		H		H	
A671		H		H	
A672		H		H	
A673		CH ₃		H	

FIGURE 1BJ

A674		H		H	
A675		CH ₃		H	
A676		H		H	
A677		H		H	
A678		H		H	
A679		CH ₃		H	
A680		CH ₃		H	
A681		H		H	
A682		H		H	
A683		H		H	

FIGURE 1BK

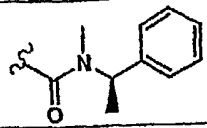
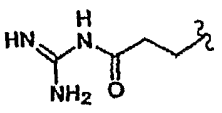

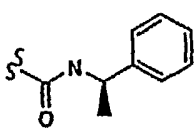
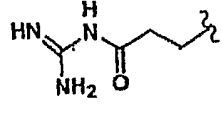
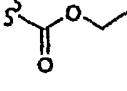
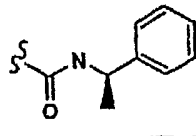
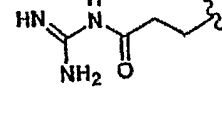
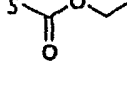
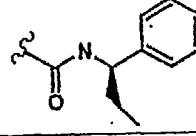
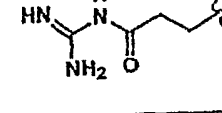
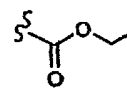
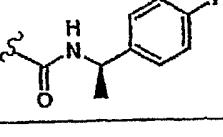
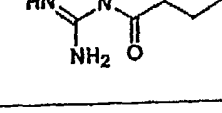
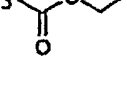
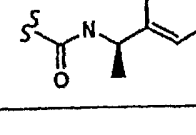
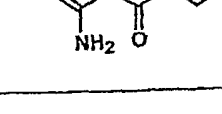
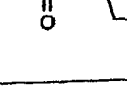
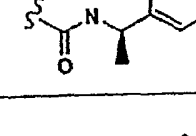
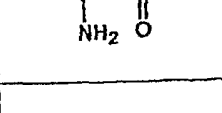
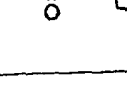
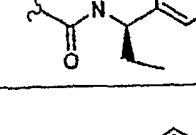
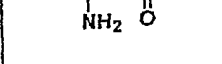
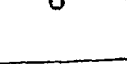

					
A684		CH ₃		CH ₃	
A685		H		H	
A686		H		H	
A687		H		H	
A688		H		H	
A689		H		H	
A690		H		H	
A691		H		H	

FIGURE 1BL

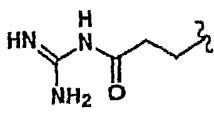
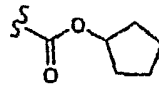
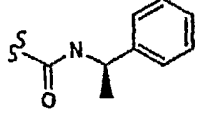
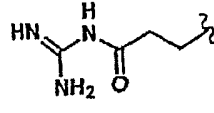
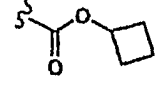
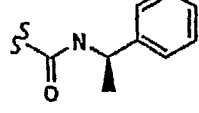
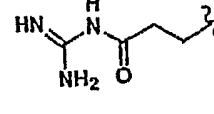
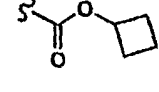
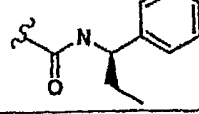
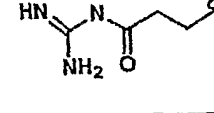
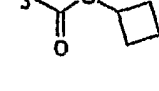
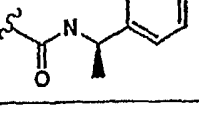
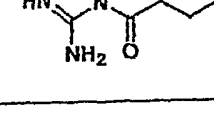
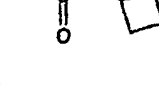
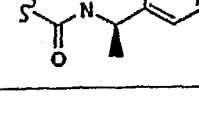
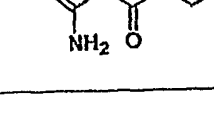
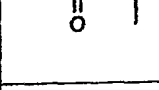
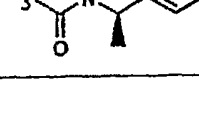
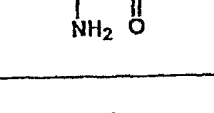
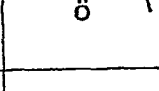

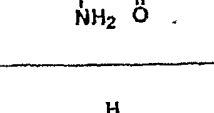
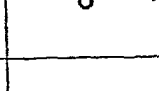
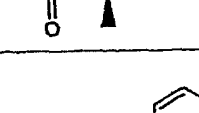
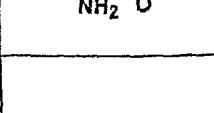
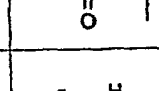
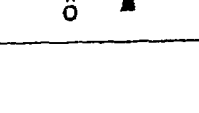
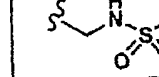
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A693		H		H	
A694		H		H	
A695		H		H	
A696		CH ₃		H	
A697		H		H	
A698		H		H	
A699		H		H	
A700		CH ₃		H	
A701		H		H	

FIGURE 1BM

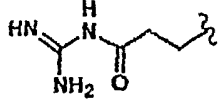
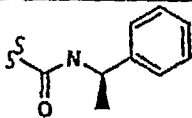
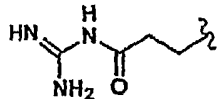
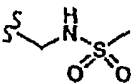
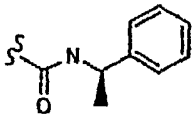
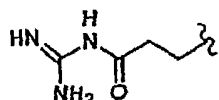
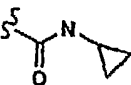
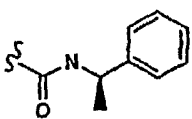
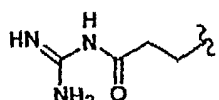
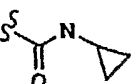
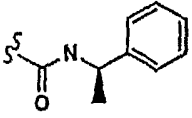
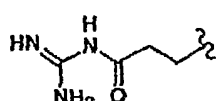
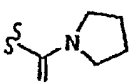
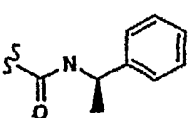
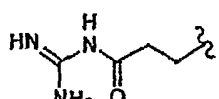
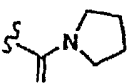
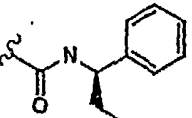
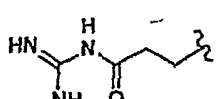
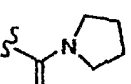
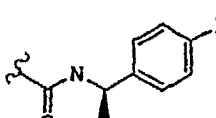
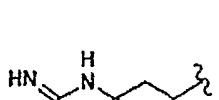
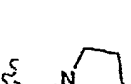
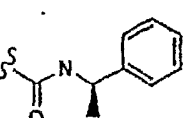
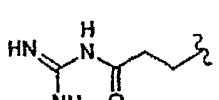
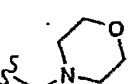
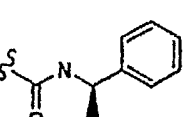
					
A702		CH ₃		H	
A703		H		H	
A704		CH ₃		H	
A705		H		H	
A706		H		H	
A707		H		H	
A708		CH ₃		H	
A709		H		H	
A710		H		H	

FIGURE 1BN

A711		H		H	
A712		CH ₃		H	
A713		H		H	
A714		CH ₃		H	
A715		H		H	
A716		H		H	
A717		H		H	
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A719		H		H	

FIGURE 1B0

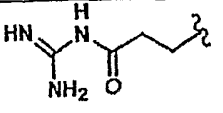
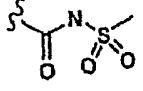
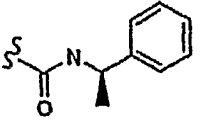
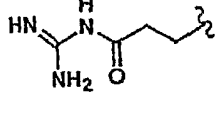
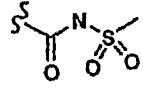
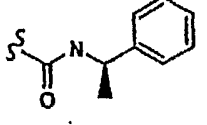
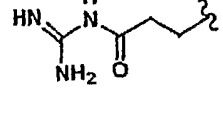
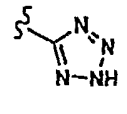
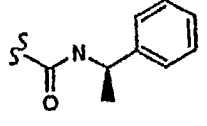
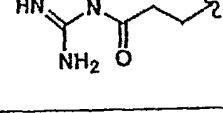
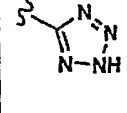
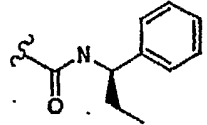
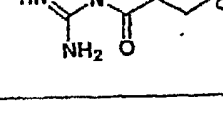
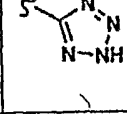
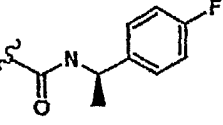
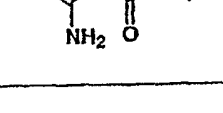
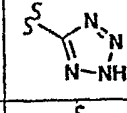
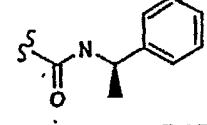
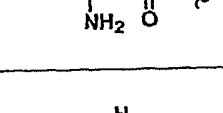
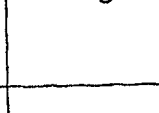
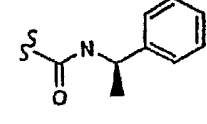
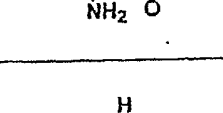
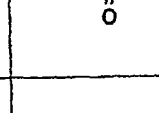
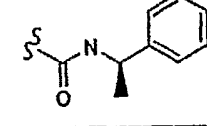
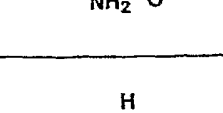
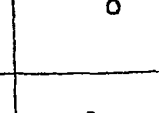
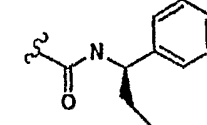
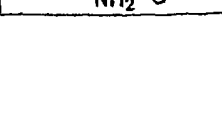
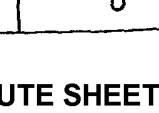
					
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A723		H		H	
A724		CH ₃		H	
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A727		H		H	
A728		H		H	

FIGURE 1BP

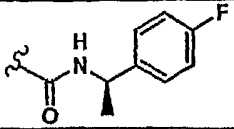
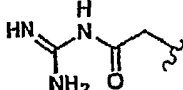
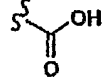
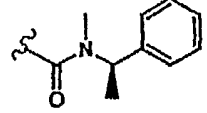
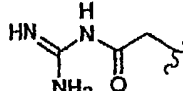
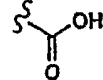
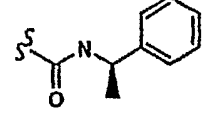
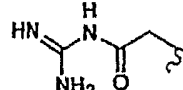
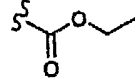
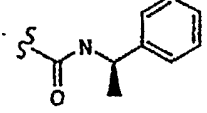
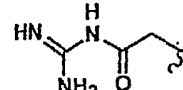
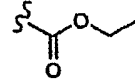
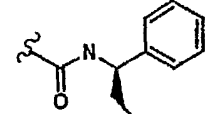
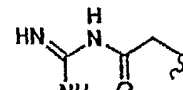
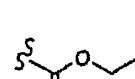
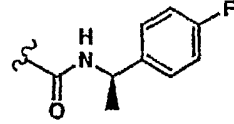
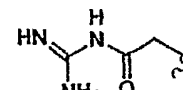
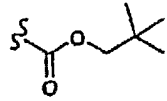
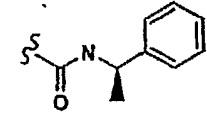
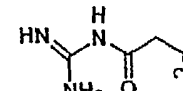
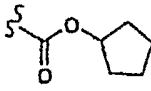
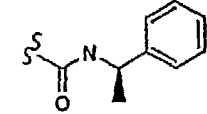
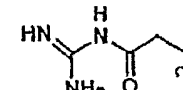
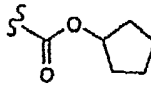
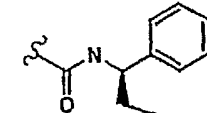
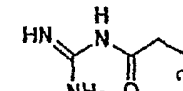
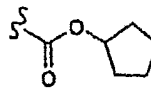
					
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FIGURE 1BQ

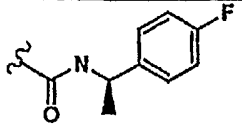
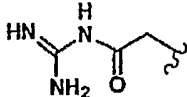
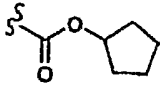
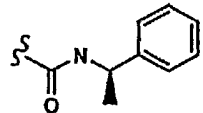
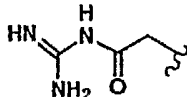
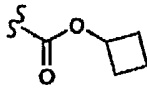
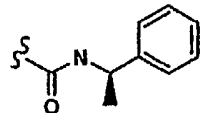
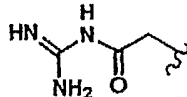
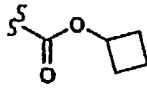
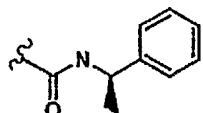
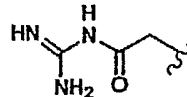
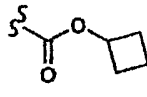
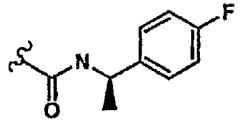
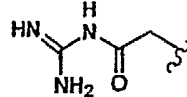
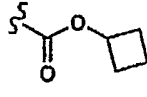
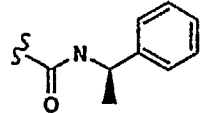
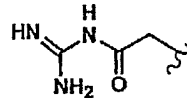
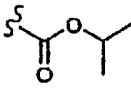
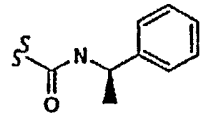
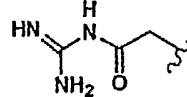
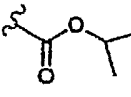
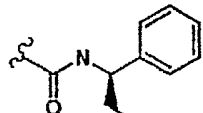
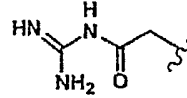
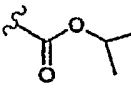
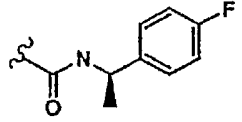
					
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FIGURE 1BR

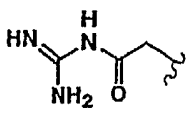
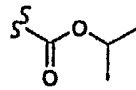
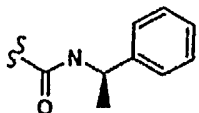
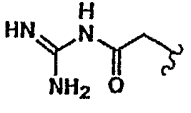
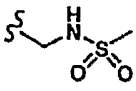
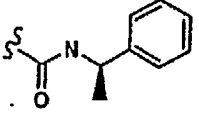
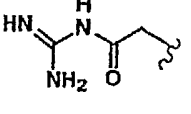
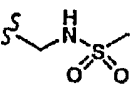
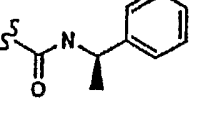
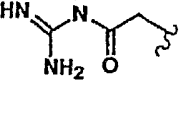
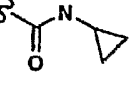
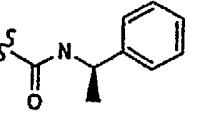
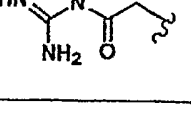
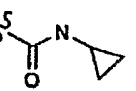
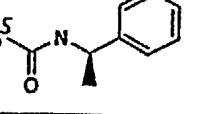
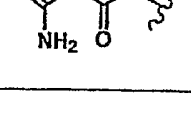
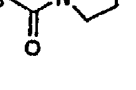
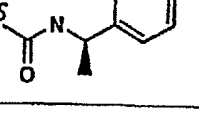
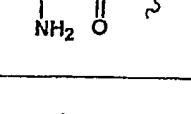
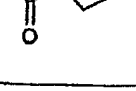
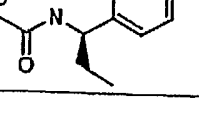
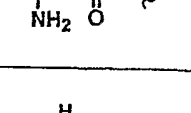
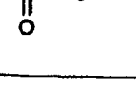
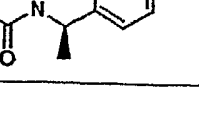
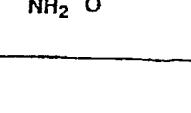
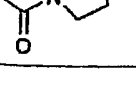

A746		CH ₃		H	
A747		H		H	
A748		CH ₃		H	
A749		H		H	
A750		CH ₃		H	
A751		H		H	
A752		H		H	
A753		H		H	
A754		CH ₃		H	
A755		H		H	

FIGURE 1BS

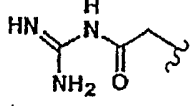
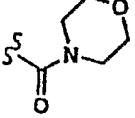
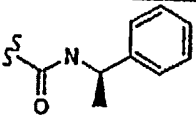
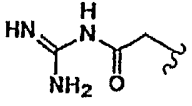
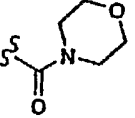
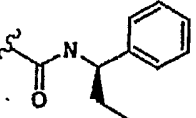
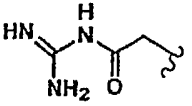
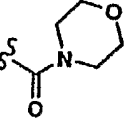
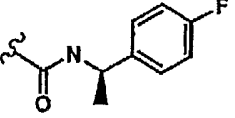
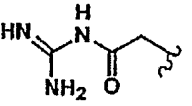
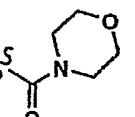
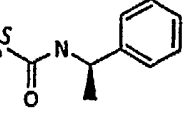
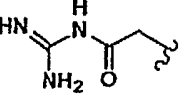
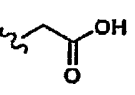
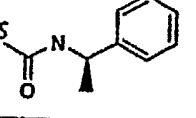
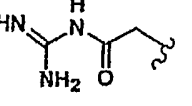
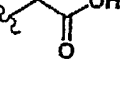
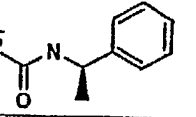
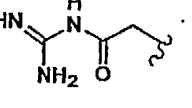
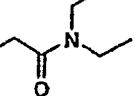
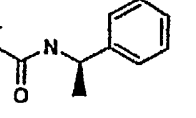
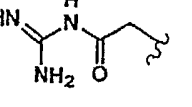
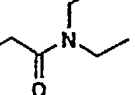
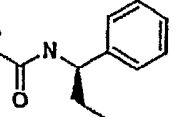
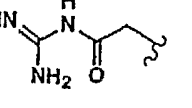
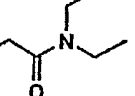
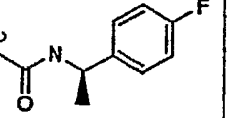
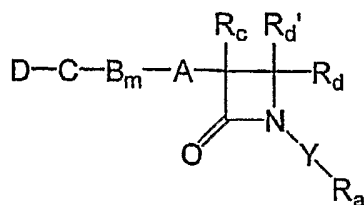
A756					
A757		H		H	
A758		H		H	
A759		CH ₃		H	
A760		H		H	
A761		CH ₃		H	
A762		H		H	
A763		H		H	
A764		H		H	

FIGURE 1BT

A765		CH ₃		H	
A766		H		H	
A767		CH ₃		H	
A768		H		H	
A769		H		H	
A770		H		H	
A771		CH ₃		H	

FIGURE 1BU



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A772		H		H	
A773		CH ₃		H	
A774		H		CH ₃	
A775		CH ₃		CH ₃	
A776		H		H	
A777		CH ₃		H	
A778		H		CH ₃	

FIGURE 1BV

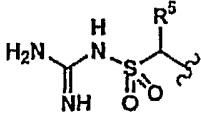
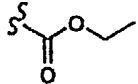
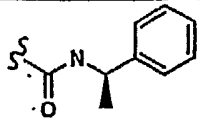
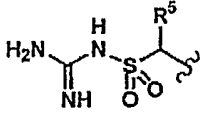
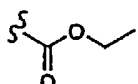
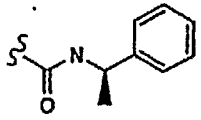
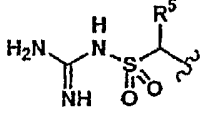
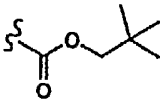
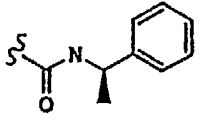
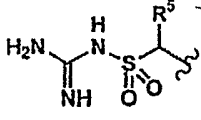
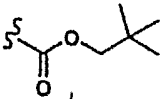
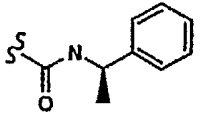
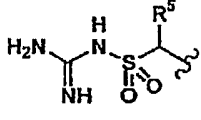
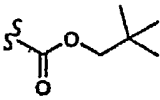
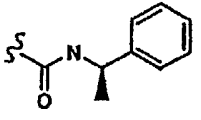
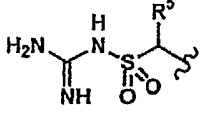
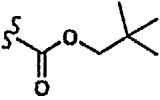
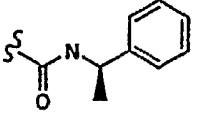
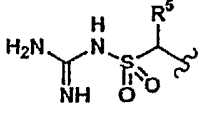
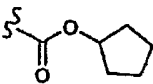
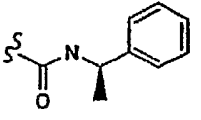
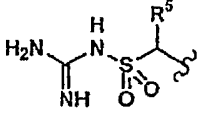
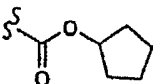
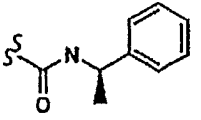
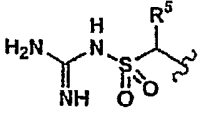
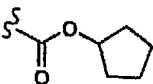
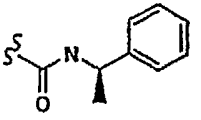
A779					
A780		CH ₃		CH ₃	
A781		H		H	
A782		CH ₃		H	
A783		H		CH ₃	
A784		CH ₃		CH ₃	
A785		H		H	
A786		CH ₃		H	
A787		H		CH ₃	

FIGURE 1BW

A788		CH ₃		CH ₃	
A789		H		H	
A790		CH ₃		H	
A791		H		CH ₃	
A792		CH ₃		CH ₃	
A793		H		H	
A794		CH ₃		H	
A795		H		CH ₃	
A796		CH ₃		CH ₃	

FIGURE 1BX

			:		
A797		H		H	
A798		CH ₃		H	
A799		H		CH ₃	
A800		CH ₃		CH ₃	
A801		H		H	
A802		CH ₃		H	
A803		H		CH ₃	

FIGURE 1BY

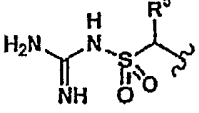
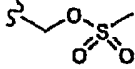
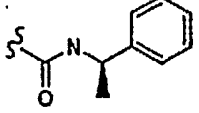
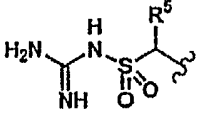
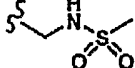
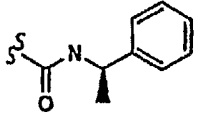
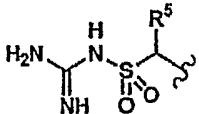
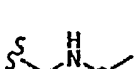
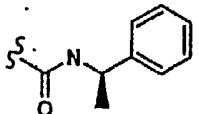
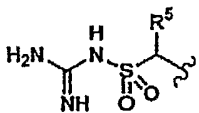
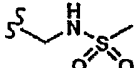
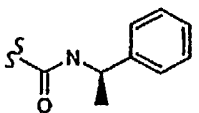
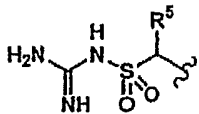
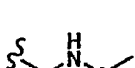
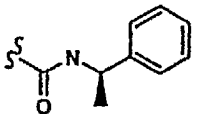
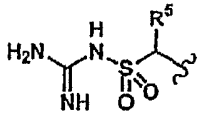
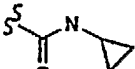
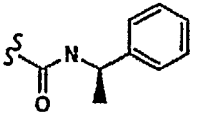
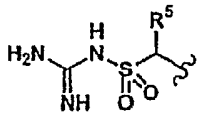
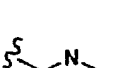
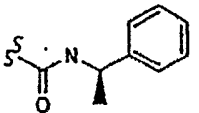
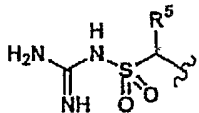
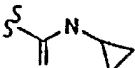
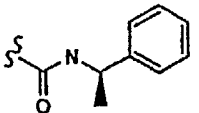
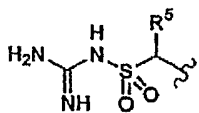
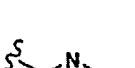
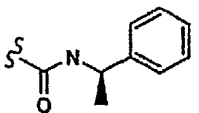
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A809		H		H	
A810		CH ₃		H	
A811		H		CH ₃	
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FIGURE 1BZ

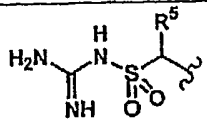
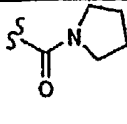
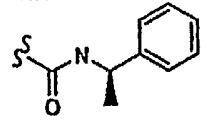
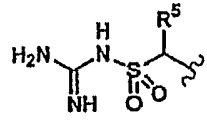
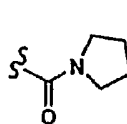
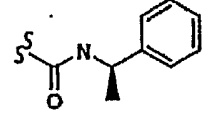
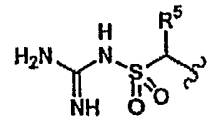
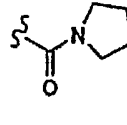
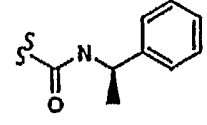
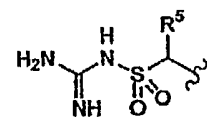
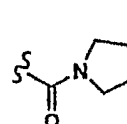
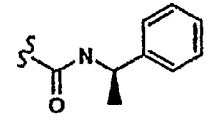
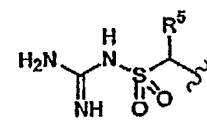
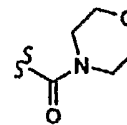
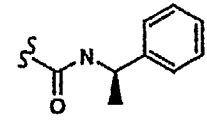
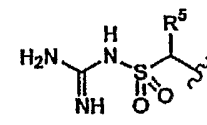
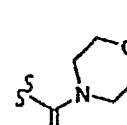
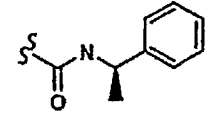
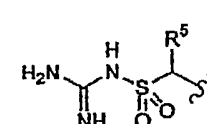
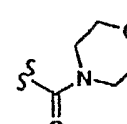
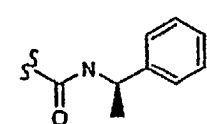
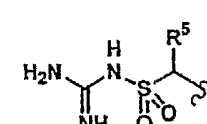
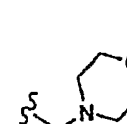
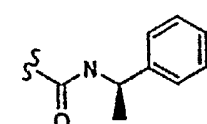
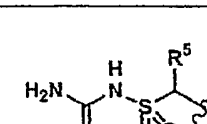
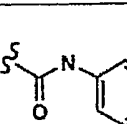
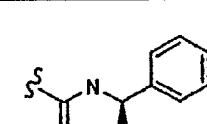
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A818		CH ₃		H	
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FIGURE 1CM

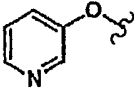
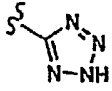
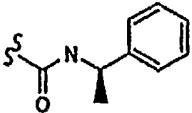
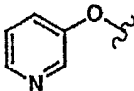
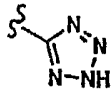
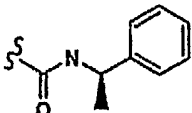
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A923		CH ₃		CH ₃	

FIGURE 1CA

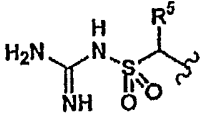
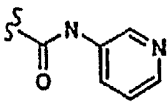
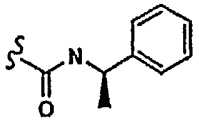
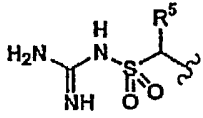
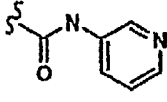
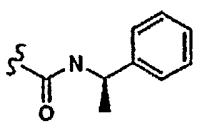
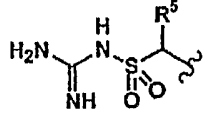
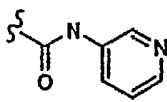
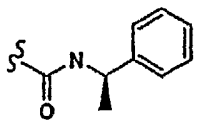
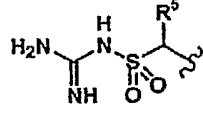
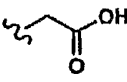
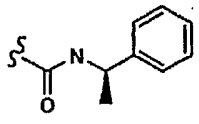
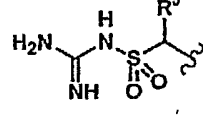
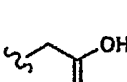
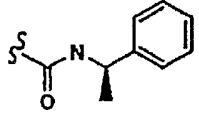
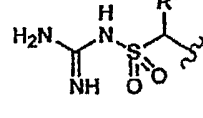
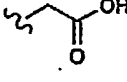
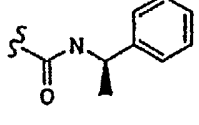
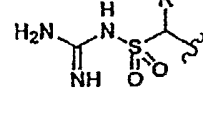
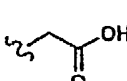
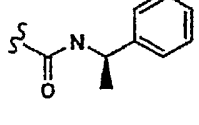
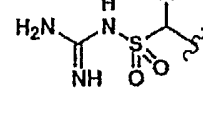
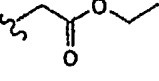
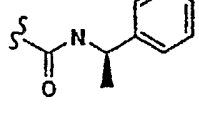
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A823		H		CH ₃	
A824		CH ₃		CH ₃	
A825		H		H	
A826		CH ₃		H	
A827		H		CH ₃	
A828		CH ₃		CH ₃	
A829		H		H	

FIGURE 1CB

A830		CH ₃		H	
A831		H		CH ₃	
A832		CH ₃		CH ₃	
A833		H		H	
A834		CH ₃		H	
A835		H		CH ₃	
A836		CH ₃		CH ₃	
A837		H		H	

FIGURE 1CC

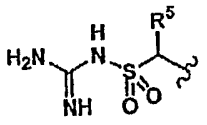
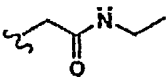
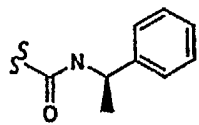
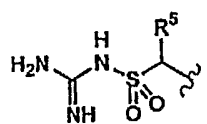
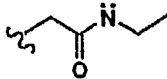
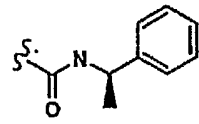
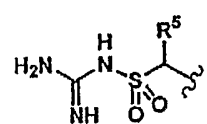
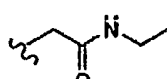
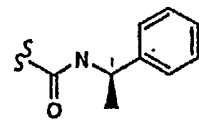
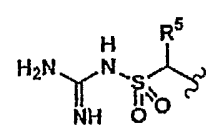
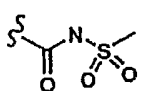
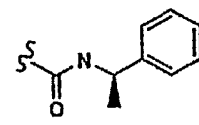
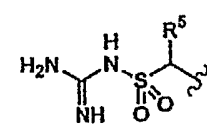
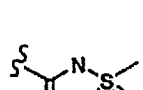
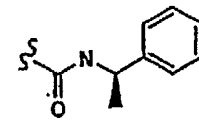
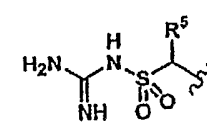
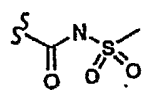
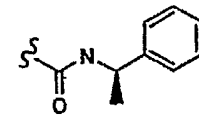
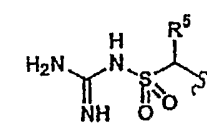
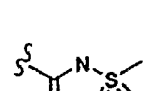
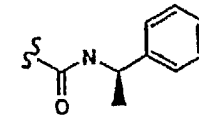
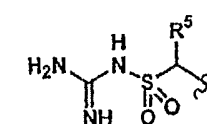
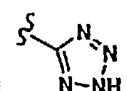
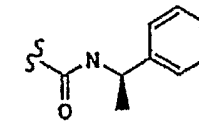
A838		CH ₃		H	
A839		H		CH ₃	
A840		CH ₃		CH ₃	
A841		H		H	
A842		CH ₃		H	
A843		H		CH ₃	
A844		CH ₃		CH ₃	
A845		H		H	

FIGURE 1CD

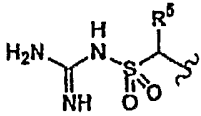
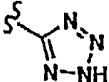
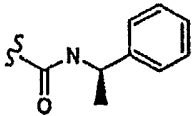
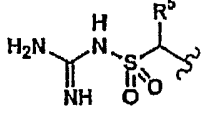
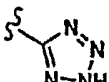
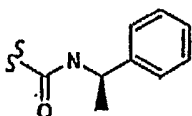
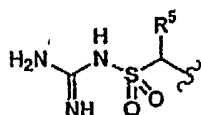
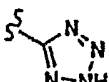
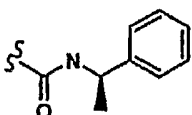
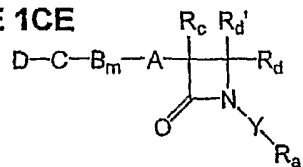
A846		CH ₃		H	
A847		H		CH ₃	
A848		CH ₃		CH ₃	

FIGURE 1CE



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A849		H		H	
A850		CH ₃		H	
A851		H		CH ₃	
A852		CH ₃		CH ₃	
A853		H		H	
A854		CH ₃		H	
A855		H		CH ₃	
A856		CH ₃		CH ₃	
A857		H		H	

FIGURE 1CF

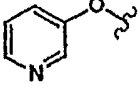
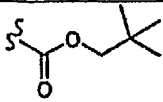
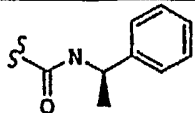
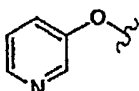
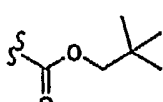
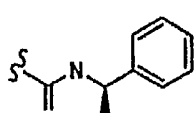
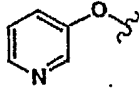
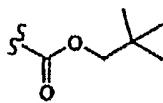
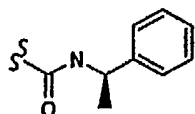
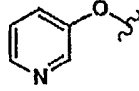
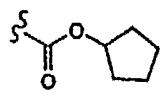
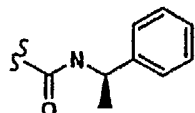
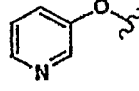
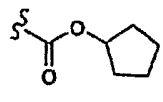
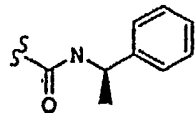
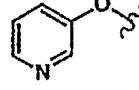
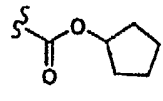
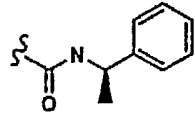
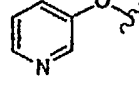
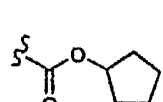
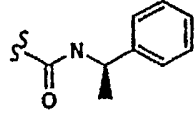
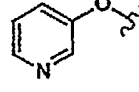
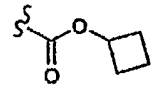
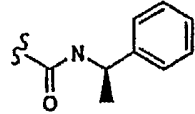
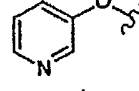
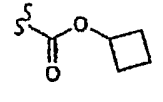
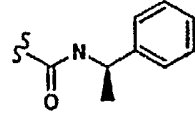
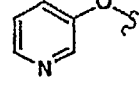
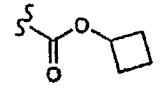
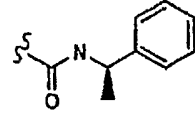
A858		CH ₃		H	
A859		H		CH ₃	
A860		CH ₃		CH ₃	
A861		H		H	
A862		CH ₃		H	
A863		H		CH ₃	
A864		CH ₃		CH ₃	
A865		H		H	
A866		CH ₃		H	
A867		H		CH ₃	

FIGURE 1CG

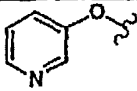
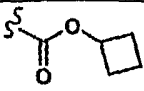
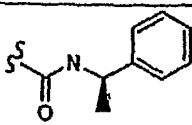
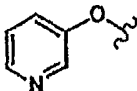
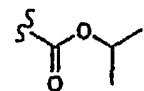
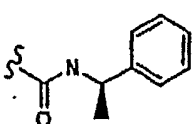
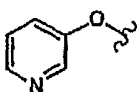
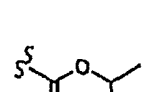
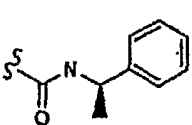
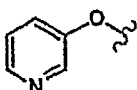
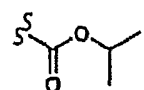
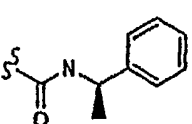
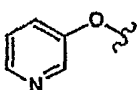
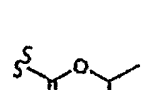
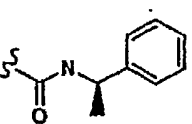
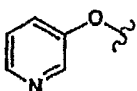
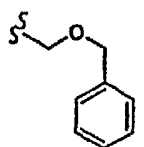
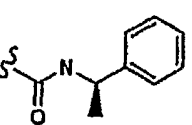
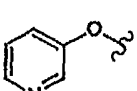
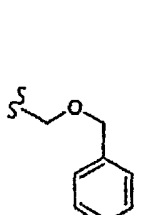
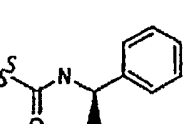
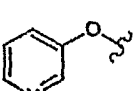
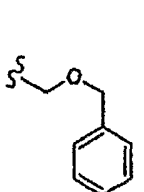
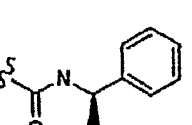
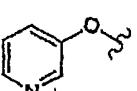
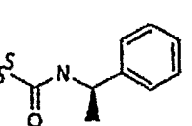
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A869		H		H	
A870		CH ₃		H	
A871		H		CH ₃	
A872		CH ₃		CH ₃	
A873		H		H	
A874		CH ₃		H	
A875		H		CH ₃	
A876		CH ₃		CH ₃	

FIGURE 1CH

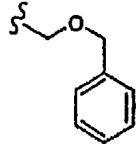
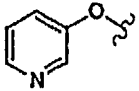
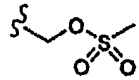
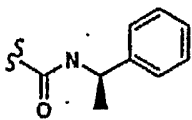
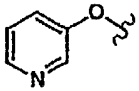
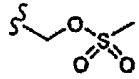
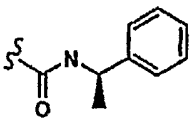
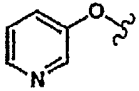
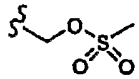
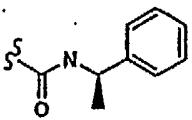
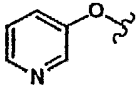
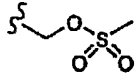
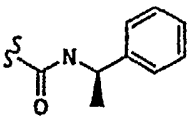
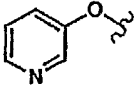
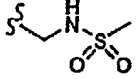
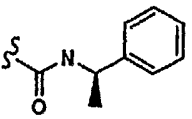
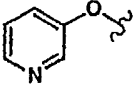
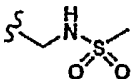
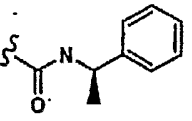
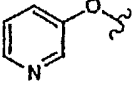
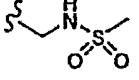
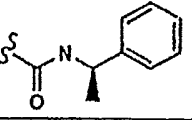
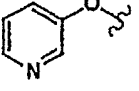
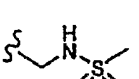
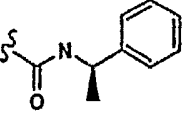
					
A877		H		H	
A878		CH ₃		H	
A879		H		CH ₃	
A880		CH ₃		CH ₃	
A881		H		H	
A882		CH ₃		H	
A883		H		CH ₃	
A884		CH ₃		CH ₃	

FIGURE 1C1

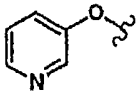
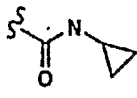
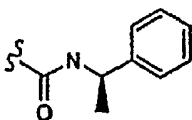
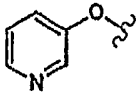
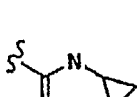
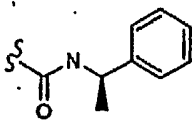
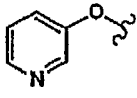
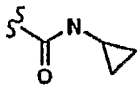
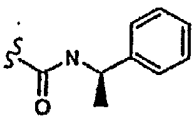
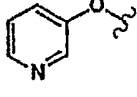
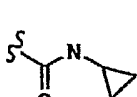
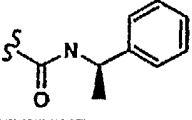
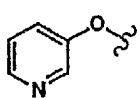
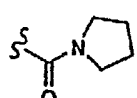
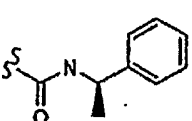
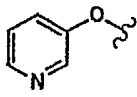
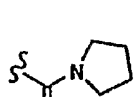
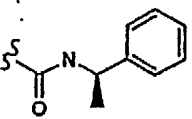
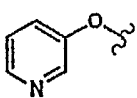
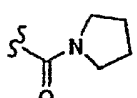
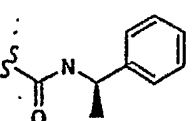
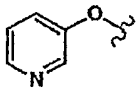
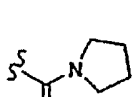
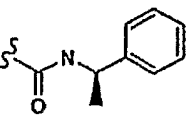
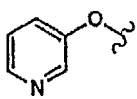
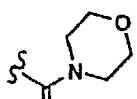
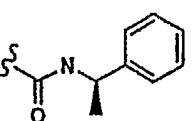
A885		H		H	
A886		CH ₃		H	
A887		H		CH ₃	
A888		CH ₃		CH ₃	
A889		H		H	
A890		CH ₃		H	
A891		H		CH ₃	
A892		CH ₃		CH ₃	
A893		H		H	

FIGURE 1CJ

A894		CH ₃		H	
A895		H		CH ₃	
A896		CH ₃		CH ₃	
A897		H		H	
A898		CH ₃		H	
A899		H		CH ₃	
A900		CH ₃		CH ₃	
A901		H		H	
A902		CH ₃		H	
		H		CH ₃	

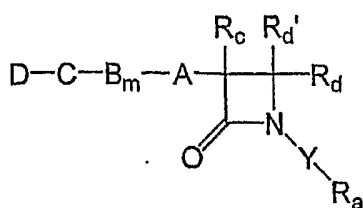
FIGURE 1CK

A903		CH ₃		CH ₃	
A904		H		H	
A905		CH ₃		H	
A906		H		CH ₃	
A907		CH ₃		CH ₃	
A908		H		H	
A909		CH ₃		H	
A910		H		CH ₃	
A911		CH ₃		CH ₃	

FIGURE 1CL

A912		H		H	
A913		CH ₃		H	
A914		H		CH ₃	
A915		CH ₃		CH ₃	
A916		H		H	
A917		CH ₃		H	
A918		H		CH ₃	
A919		CH ₃		CH ₃	
A920		H		H	
A921		CH ₃		H	

FIGURE 1CN



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A924		H		H	
A925		CH ₃		H	
A926		H		CH ₃	
A927		CH ₃		CH ₃	
A928		H		H	
A929		CH ₃		H	
A930		H		CH ₃	
A931		CH ₃		CH ₃	
A932		H		H	

FIGURE 1CO

A933		CH ₃		H	
A934		H		CH ₃	
A935		CH ₃		CH ₃	
A936		H		H	
A937		CH ₃		H	
A938		H		CH ₃	
A939		CH ₃		CH ₃	
A940		H		H	
A941		CH ₃		H	
A942		H		CH ₃	

FIGURE 1CP

A943		CH ₃		CH ₃	
A944		H		H	
A945		CH ₃		H	
A946		H		CH ₃	
A947		CH ₃		CH ₃	
A948		H		H	
A949		CH ₃		H	
A950		H		CH ₃	

FIGURE 1CQ

A951		CH ₃		CH ₃	
A952		H		H	
A953		CH ₃		H	
A954		H		CH ₃	
A955		CH ₃		CH ₃	
A956		H		H	
A957		CH ₃		H	
A958		H		CH ₃	
A959		CH ₃		CH ₃	

FIGURE 1CR

A849		H		H	
A850		CH ₃		H	
A851		H		CH ₃	
A852		CH ₃		CH ₃	
A853		H		H	
A854		CH ₃		H	
A855		H		CH ₃	
A856		CH ₃		CH ₃	
A857		H		H	

FIGURE 1CS

A960		CH ₃		H	
A961		H		CH ₃	
A962		CH ₃		CH ₃	
A963		H		H	
A964		CH ₃		H	
A965		H		CH ₃	
A966		CH ₃		CH ₃	
A967		H		H	
A968		CH ₃		H	

FIGURE 1CT

A969		H		CH ₃	
A970		CH ₃		CH ₃	
A971		H		H	
A972		CH ₃		H	
A973		H		CH ₃	
A974		CH ₃		CH ₃	
A975		H		H	
A976		CH ₃		H	
A977		H		CH ₃	
A978		CH ₃		CH ₃	

FIGURE 1CU

A979		H		H	
A980		CH ₃		H	
A981		H		CH ₃	
A982		CH ₃		CH ₃	
A983		H		H	
A984		CH ₃		H	
A985		H		CH ₃	
A986		CH ₃		CH ₃	
A987		H		H	

FIGURE 1CV

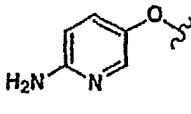
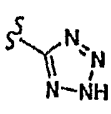
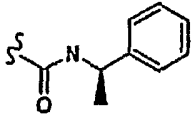
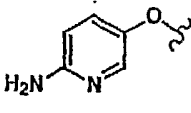
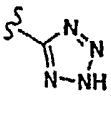
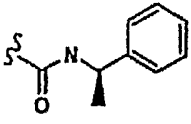
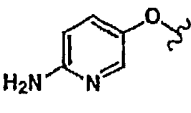
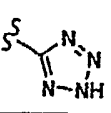
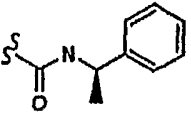
A988		CH ₃		H	
A989		H		CH ₃	
A990		CH ₃		CH ₃	

FIGURE 1CW

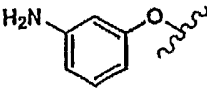

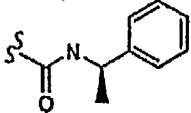
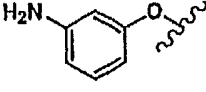

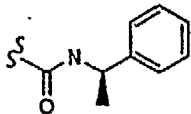
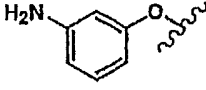

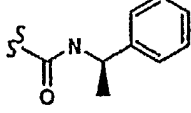
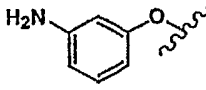

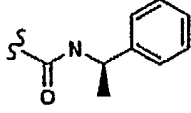
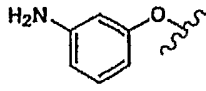
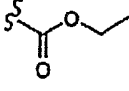
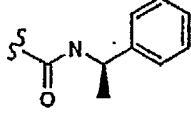
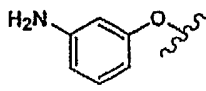
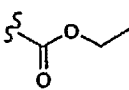
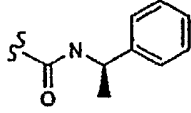
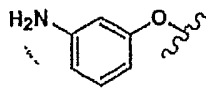
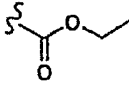
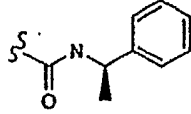
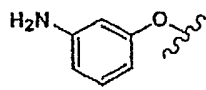
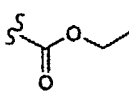
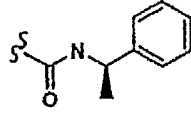
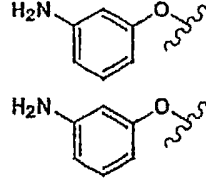
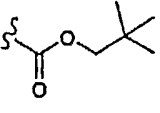
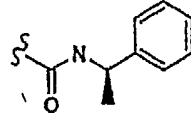
	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A991		H		H	
A992		CH ₃		H	
A993		H		CH ₃	
A994		CH ₃		CH ₃	
A995		H		H	
A996		CH ₃		H	
A997		H		CH ₃	
A998		CH ₃		CH ₃	
A999		H		H	

FIGURE 1CX

A1000		CH ₃		H	
A1001		H		CH ₃	
A1002		CH ₃		CH ₃	
A1003		H		H	
A1004		CH ₃		H	
A1005		H		CH ₃	
A1006		CH ₃		CH ₃	
A1007		H		H	
A1008		CH ₃		H	
A1009		H		CH ₃	

FIGURE 1CY

A1010		CH ₃		CH ₃	
A1011		H		H	
A1012		CH ₃		H	
A1013		H		CH ₃	
A1014		CH ₃		CH ₃	
A1015		H		H	
A1016		CH ₃		H	
A1017		H		CH ₃	
A1018		CH ₃		CH ₃	

FIGURE 1CZ

A1019		H		H	
A1020		CH ₃		H	
A1021		H		CH ₃	
A1022		CH ₃		CH ₃	
A1023		H		H	
A1024		CH ₃		H	
A1025		H		CH ₃	
A1026		CH ₃		CH ₃	

FIGURE 1DA

A1027		H		H	
A1028		CH ₃		H	
A1029		H		CH ₃	
A1030		CH ₃		CH ₃	
A1031		H		H	
A1032		CH ₃		H	
A1033		H		CH ₃	
A1034		CH ₃		CH ₃	
A1035		H		H	

FIGURE 1DB

A1036		CH ₃		H	
A1037		H		CH ₃	
A1038		CH ₃		CH ₃	
A1039		H		H	
A1040		CH ₃		H	
A1041		H		CH ₃	
A1042		CH ₃		CH ₃	
A1043		H		H	
A1044		CH ₃		H	
A1045		H		CH ₃	

FIGURE 1DC

A1046		CH ₃		CH ₃	
A1047		H		H	
A1048		CH ₃		H	
A1049		H		CH ₃	
A1050		CH ₃		CH ₃	
A1051		H		H	
A1052		CH ₃		H	
A1053		H		CH ₃	
A1054		CH ₃		CH ₃	

FIGURE 1DD

A1055		H		H	
A1056		CH ₃		H	
A1057		H		CH ₃	
A1058		CH ₃		CH ₃	
A1059		H		H	
A1060		CH ₃		H	
A1061		H		CH ₃	
A1062		CH ₃		CH ₃	
A1063		H		H	
A1064		CH ₃		H	

FIGURE 1DE

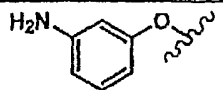
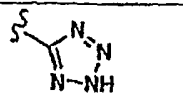
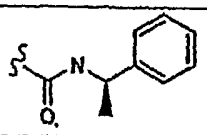
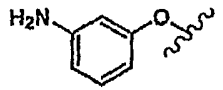
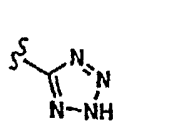
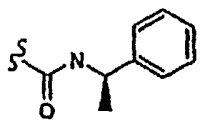
A1065		H		CH ₃	
A1066		CH ₃		CH ₃	

FIGURE 1DF

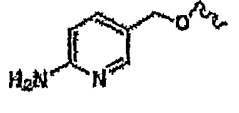

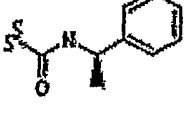
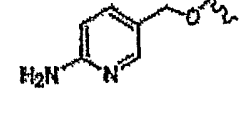

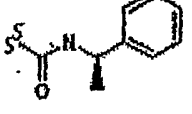
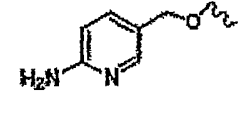

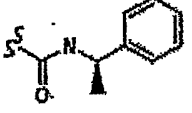
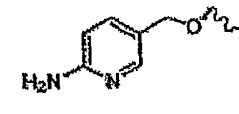

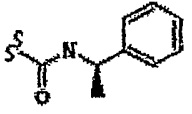
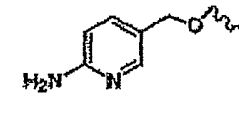
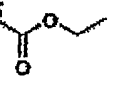
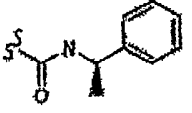
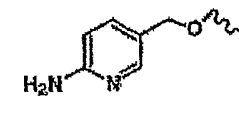
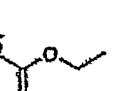
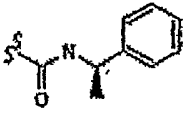
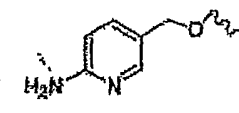
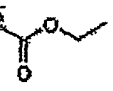
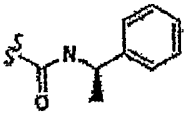
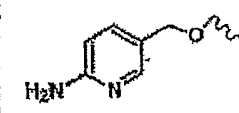
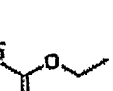
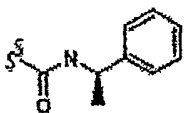
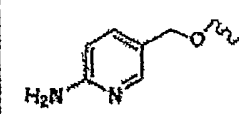
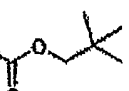
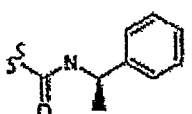
	DCB _m A	R _c	R _d	R ^{d'}	Y-R ₃
A1067		H		H	
A1068		CH ₃		H	
A1069		H		CH ₃	
A1070		CH ₃		CH ₃	
A1071		H		H	
A1072		CH ₃		H	
A1073		H		CH ₃	
A1074		CH ₃		CH ₃	
A1075		H		H	

FIGURE 1DG

A1076		CH ₃		H	
A1077		H		CH ₃	
A1078		CH ₃		CH ₃	
A1079		H		H	
A1080		CH ₃		H	
A1081		H		CH ₃	
A1082		CH ₃		CH ₃	
A1083		H		H	
A1084		CH ₃		H	
A1085		H		CH ₃	

FIGURE 1DH

A1086		CH ₃		CH ₃	
A1087		H		H	
A1088		CH ₃		H	
A1089		H		CH ₃	
A1090		CH ₃		CH ₃	
A1091		H		H	
A1092		CH ₃		H	
A1093		H		CH ₃	

FIGURE 1DI

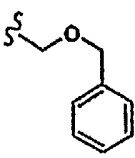
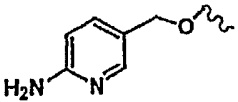
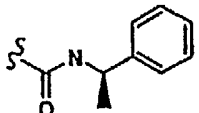
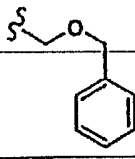
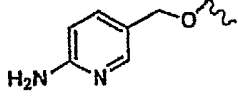
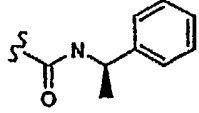
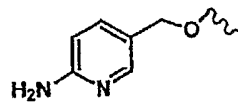
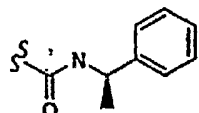
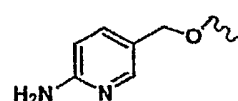
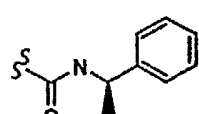
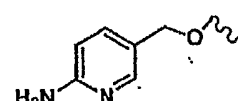
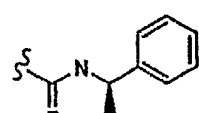
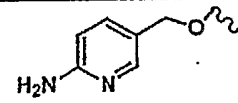
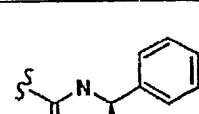
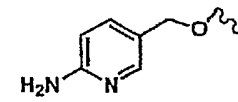
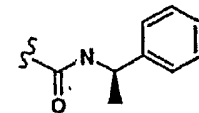
				
A1094	 H ₂ N	CH ₃	CH ₃	
				
A1095	 H ₂ N	H	H	
A1096	 H ₂ N	CH ₃	H	
A1097	 H ₂ N	H	CH ₃	
A1098	 H ₂ N	CH ₃	CH ₃	
A1099	 H ₂ N	H	H	
A1100	 H ₂ N	CH ₃	H	
A1101		H	CH ₃	

FIGURE 1DJ

A1102		CH ₃		CH ₃	
A1103		H		H	
A1104		CH ₃		H	
A1105		H		CH ₃	
A1106		CH ₃		CH ₃	
A1107		H		H	
A1108		CH ₃		H	
A1109		H		CH ₃	
A1110		CH ₃		CH ₃	

FIGURE 1DK

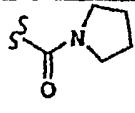
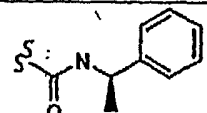
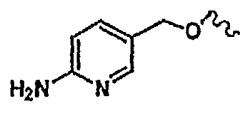
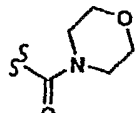
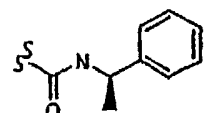
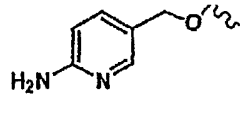
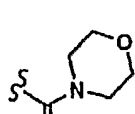
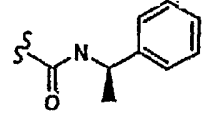
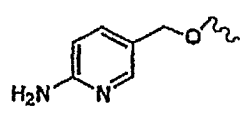
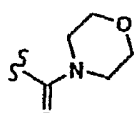
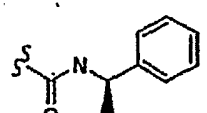
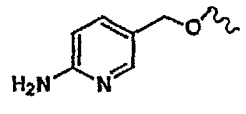
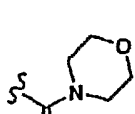
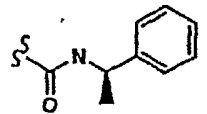
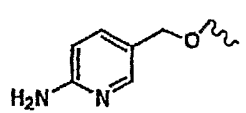
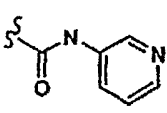
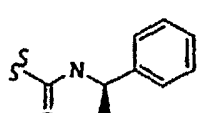
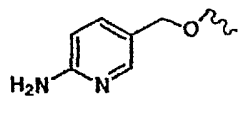
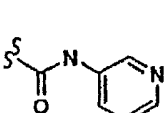
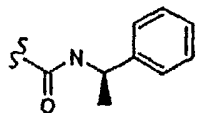
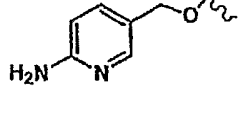
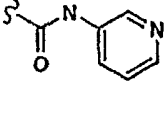
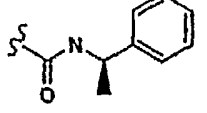
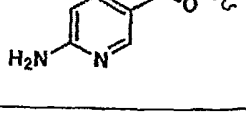
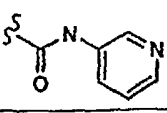
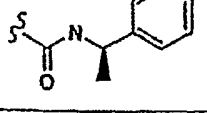
					
A1111		H		H	
A1112		CH ₃		H	
A1113		H		CH ₃	
A1114		CH ₃		CH ₃	
A1115		H		H	
A1116		CH ₃		H	
A1117		H		CH ₃	
A1118		CH ₃		CH ₃	
A1119		H		H	

FIGURE 1DL

A1120		CH ₃		H	
A1121		H		CH ₃	
A1122		CH ₃		CH ₃	
A1123		H		H	
A1124		CH ₃		H	
A1125		H		CH ₃	
A1126		CH ₃		CH ₃	
A1127		H		H	

FIGURE 1DM

A1128		CH ₃		H	
A1129		H		CH ₃	
A1130		CH ₃		CH ₃	
A1131		H		H	
A1132		CH ₃		H	
A1133		H		CH ₃	
A1134		CH ₃		CH ₃	
A1135		H		H	
A1136		CH ₃		H	
A1137		H		CH ₃	

FIGURE 1DN

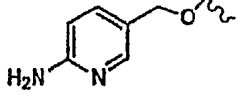
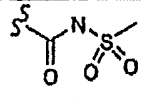
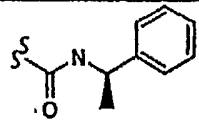
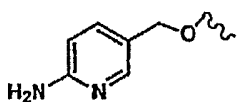
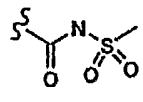
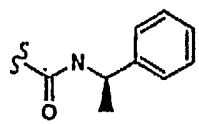
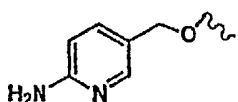
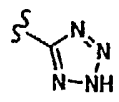
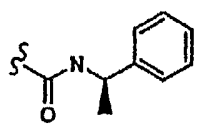
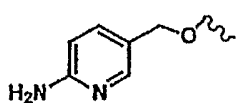
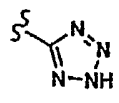
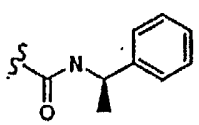
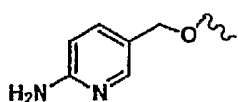
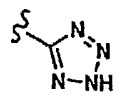
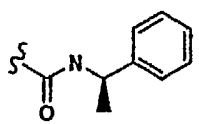
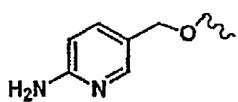
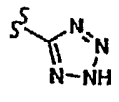
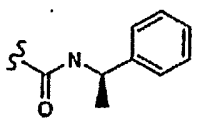
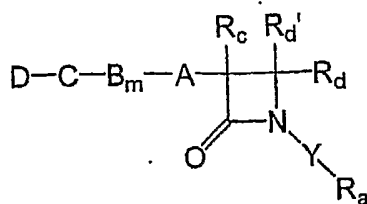
A1138					
A1139		CH ₃		CH ₃	
A1140		H		H	
A1141		CH ₃		H	
A1142		H		CH ₃	
A1143		CH ₃		CH ₃	

FIGURE 1DO



	DCB _m A	R _c	R _d	R _d '	Y-R _a
A1144		H		H	
A1145		CH ₃		H	
A1146		H		CH ₃	
A1147		CH ₃		CH ₃	
A1148		H		H	
A1149		CH ₃		H	
A1150		H		CH ₃	
A1151		CH ₃		CH ₃	

FIGURE 1DP

A1152					
A1153		H		H	
A1154		CH ₃		H	
A1155		H		CH ₃	
A1156		CH ₃		CH ₃	
A1157		H		H	
A1158		CH ₃		H	
A1159		H		CH ₃	
A1160		CH ₃		CH ₃	
A1161		H		H	

FIGURE 1DQ

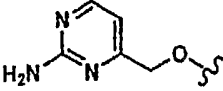

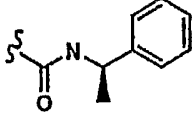
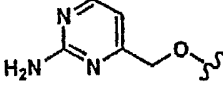

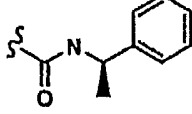
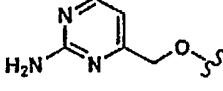

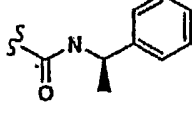
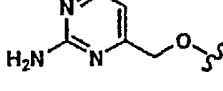
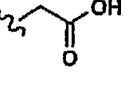
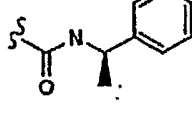
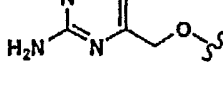
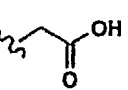
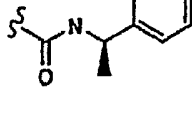
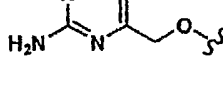
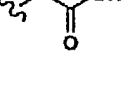
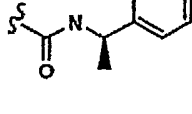
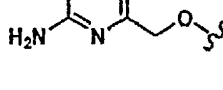
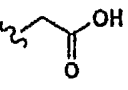
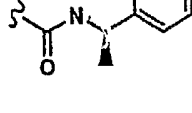
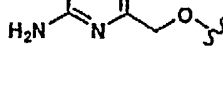
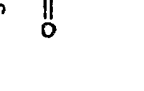
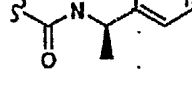
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A1163		H		CH ₃	
A1164		CH ₃		CH ₃	
A1165		H		H	
A1166		CH ₃		H	
A1167		H		CH ₃	
A1168		CH ₃		CH ₃	
A1169		H		H	

FIGURE 1DR

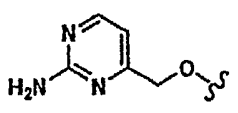
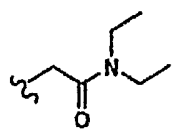
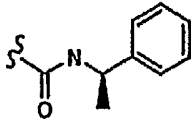
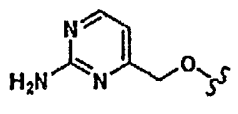
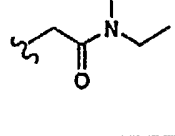
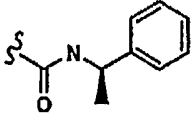
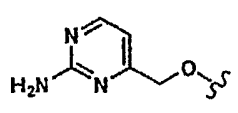
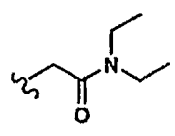
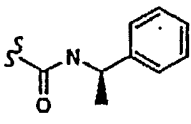
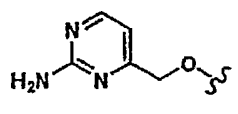
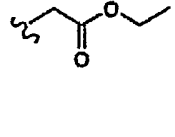
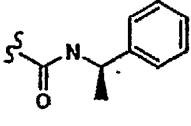
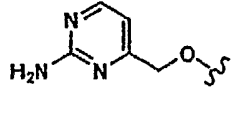
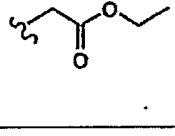
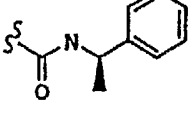
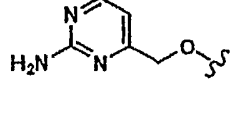
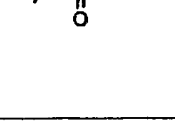
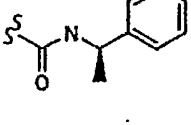
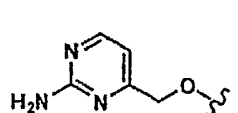
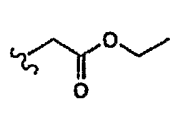
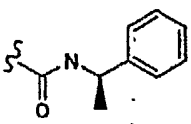
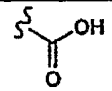
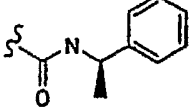
A1170		CH ₃		H	
A1171		H		CH ₃	
A1172		CH ₃		CH ₃	
A1173		H		H	
A1174		CH ₃		H	
A1175		H		CH ₃	
A1176		CH ₃		CH ₃	
A1177		H		H	

FIGURE 1DS

A1178		CH ₃		H	
A1179		H		CH ₃	
A1180		CH ₃		CH ₃	
A1181		H		H	
A1182		CH ₃		H	
A1183		H		CH ₃	
A1184		CH ₃		CH ₃	
A1185		H		H	

FIGURE 1DT

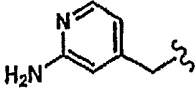
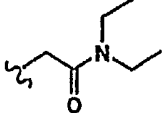
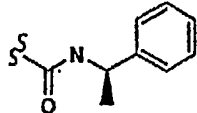
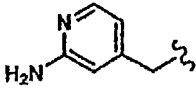
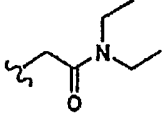
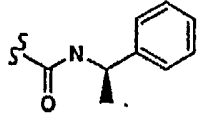
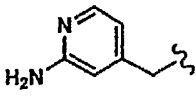
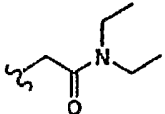
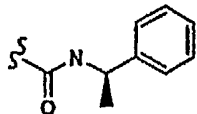
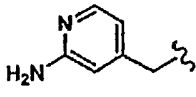
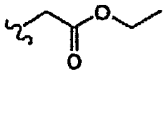
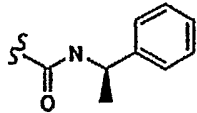
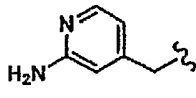
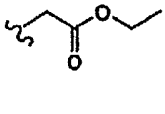
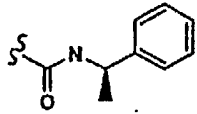
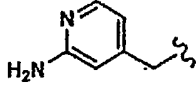
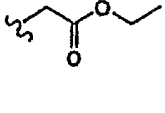
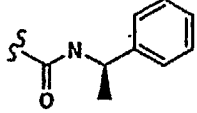
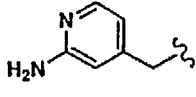
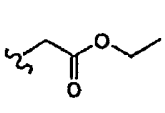
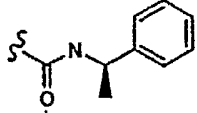
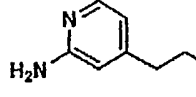
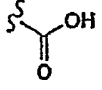
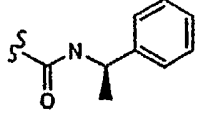
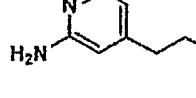
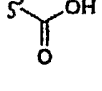
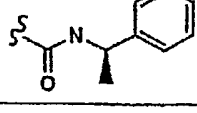
A1186		CH ₃		H	
A1187		H		CH ₃	
A1188		CH ₃		CH ₃	
A1189		H		H	
A1190		CH ₃		H	
A1191		H		CH ₃	
A1192		CH ₃		CH ₃	
A1193		H		H	
A1194		CH ₃		H	
A1195		H		CH ₃	

FIGURE 1DU

A1196		CH ₃		CH ₃	
A1197		H		H	
A1198		CH ₃		H	
A1199		H		CH ₃	
A1200		CH ₃		CH ₃	
A1201		H		H	
A1202		CH ₃		H	
A1203		H		CH ₃	
A1204		CH ₃		CH ₃	

FIGURE 1DV

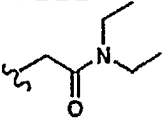
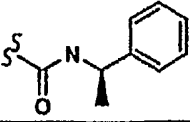
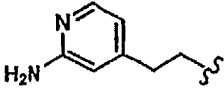
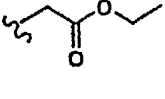
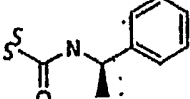
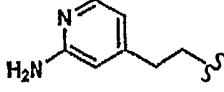
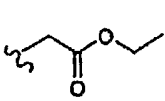
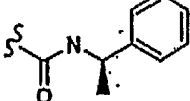
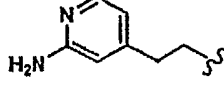
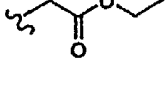
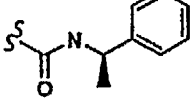
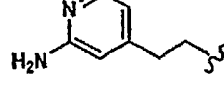
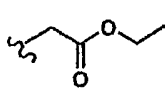
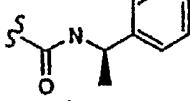
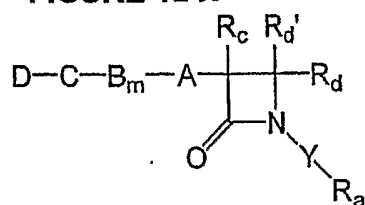
				
A1205	 H		H	
A1206	 CH ₃		H	
A1207	 H		CH ₃	
A1208	 CH ₃		CH ₃	

FIGURE 1DW



	DCB _m A	R _c	R _d	R ^{d'}	Y-R _a
A1209		H		H	
A1210		H		H	
A1211		H		H	
A1212		H		H	
A1213		H		H	
A1214		H		H	
A1215		H		H	

FIGURE 1DX

A1216		H		H	
A1217		H		H	
A1218		H		H	
A1219		H		H	
A1220		H		H	
A1221		H		H	
A1222		H		H	
A1223		H		H	
A1224		CH ₃		H	

FIGURE 1DY

A1225		CH ₃		H	
A1226		CH ₃		H	
A1227		CH ₃		H	
A1228		CH ₃		H	
A1229		CH ₃		H	
A1230		CH ₃		H	
A1231		CH ₃		H	
A1232		CH ₃		H	

FIGURE 1DZ

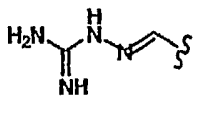
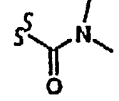
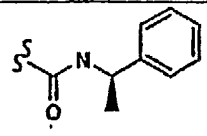
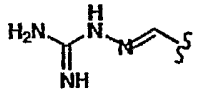
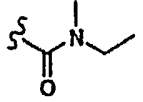
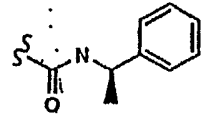
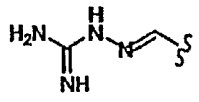
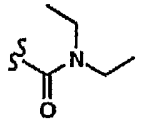
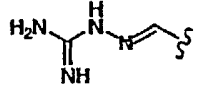
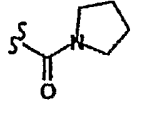
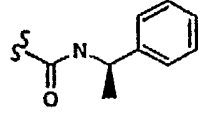
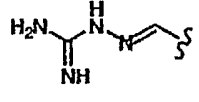
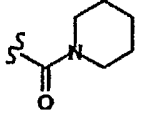
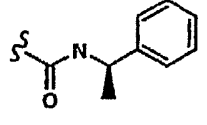
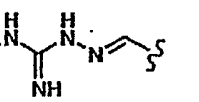
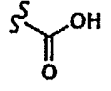
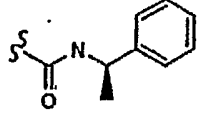
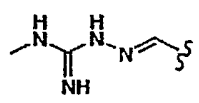
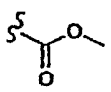
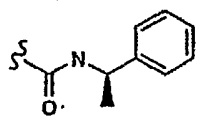
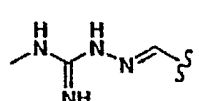
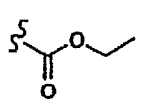
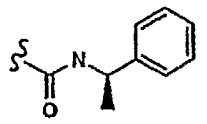
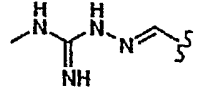
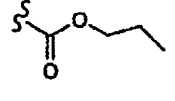
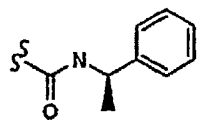
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A1234		CH ₃		H	
A1235		CH ₃		H	
A1236		CH ₃		H	
A1237		CH ₃		H	
A1238		H		H	
A1239		H		H	
A1240		H		H	
A1241		H		H	

FIGURE 1EA

A1242		H		H	
A1243		H		H	
A1244		H		H	
A1245		H		H	
A1246		H		H	
A1247		H		H	
A1248		H		H	
A1249		H		H	
A1250		H		H	

FIGURE 1EB

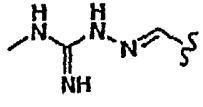
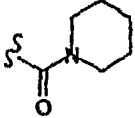
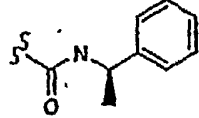
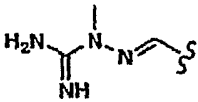
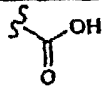
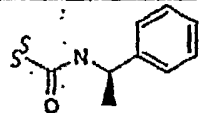
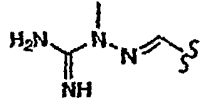
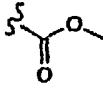
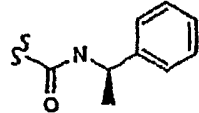
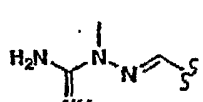
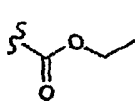
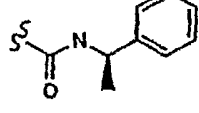
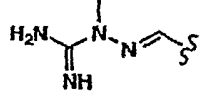
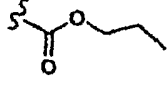
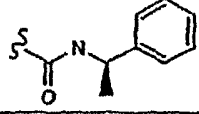
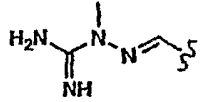
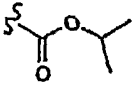
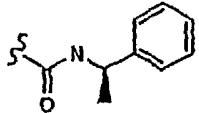
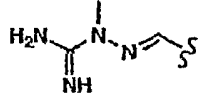
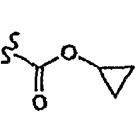
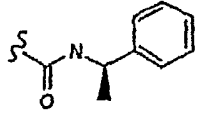
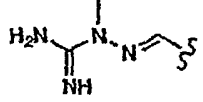
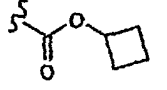
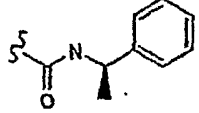
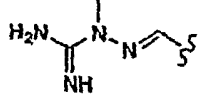
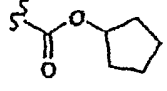
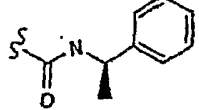
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A1253		H		H	
A1254		H		H	
A1255		H		H	
A1256		H		H	
A1257		H		H	
A1258		H		H	
A1259		H		H	

FIGURE 1EC

A1260		H		H	
A1261		H		H	
A1262		H		H	
A1263		H		H	
A1264		H		H	
A1265		H		H	
A1266		H		H	
A1267		H		H	
A1268		H		H	

FIGURE 1ED

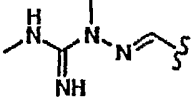
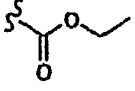
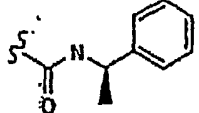
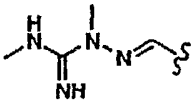
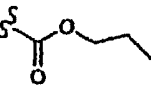
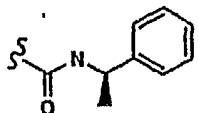
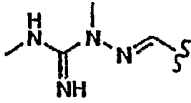
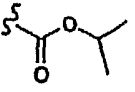
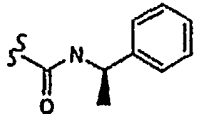
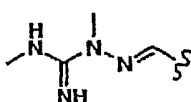
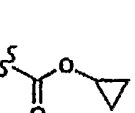
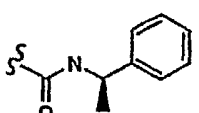
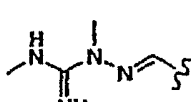
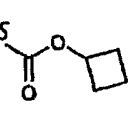
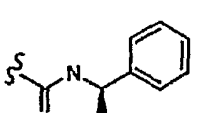
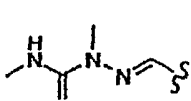
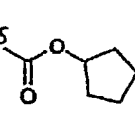
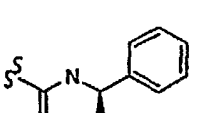
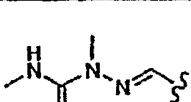
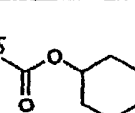
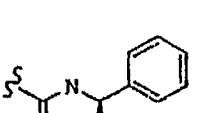
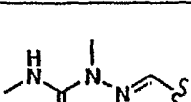
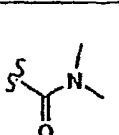
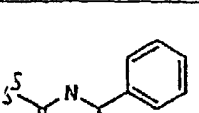
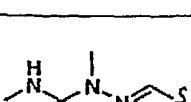
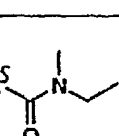
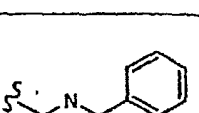
					
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A1272		H		H	
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A1275		H		H	
A1276		H		H	

FIGURE 1EE

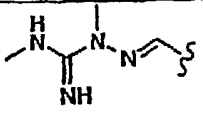
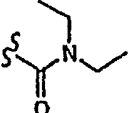
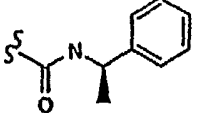
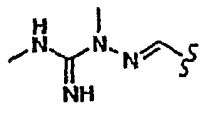
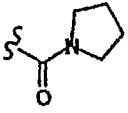
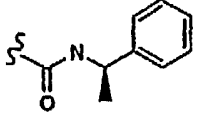
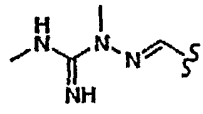
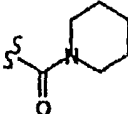
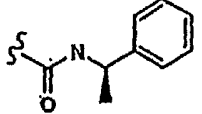
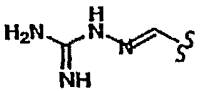
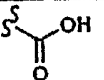
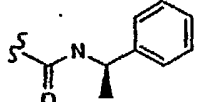
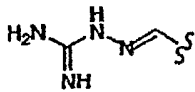
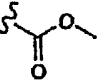
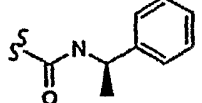
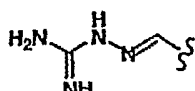
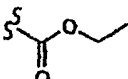
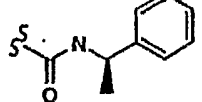
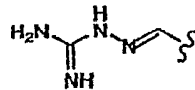
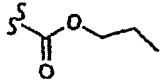
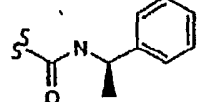
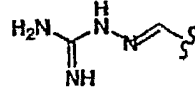
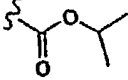
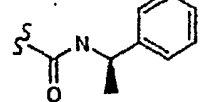
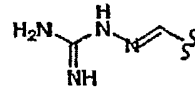
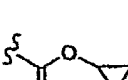
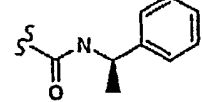
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A1278		H		H	
A1279		H		H	
A1280		H		CH ₃	
A1281		H		CH ₃	
A1282		H		CH ₃	
A1283		H		CH ₃	
A1284		H		CH ₃	
A1285		H		CH ₃	

FIGURE 1EF

A1286		H		CH ₃	
A1287		H		CH ₃	
A1288		H		CH ₃	
A1289		H		CH ₃	
A1290		H		CH ₃	
A1291		H		CH ₃	
A1292		H		CH ₃	
A1293		H		CH ₃	
A1294		H		CH ₃	

FIGURE 1EG

A1295		H		H	
A1296		H		H	
A1297		H		H	
A1298		H		H	
A1299		H		H	
A1300		H		H	
A1301		H		H	
A1302		H		H	
A1303		H		H	

FIGURE 1EH

A1304		H		H	
A1305		H		H	
A1306		H		H	
A1307		H		H	
A1308		H		H	
A1309		H		H	
A1310		H		H	
A1311		H		H	

FIGURE 1E1

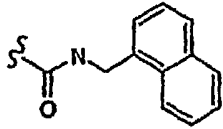
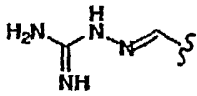
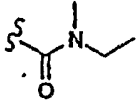
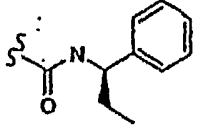
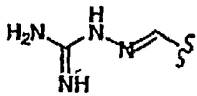
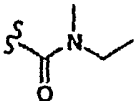
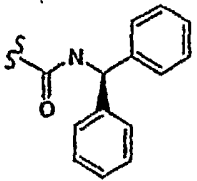
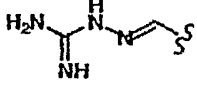
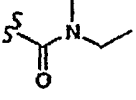
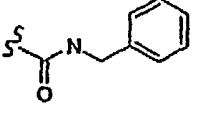
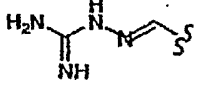
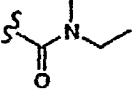
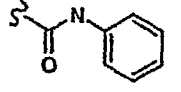
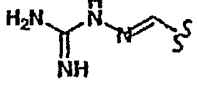
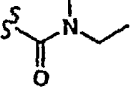
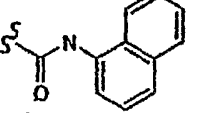
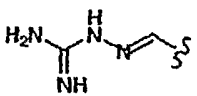
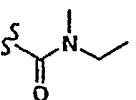
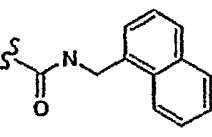
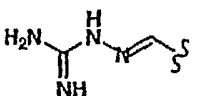
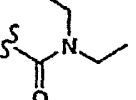
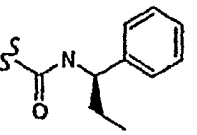
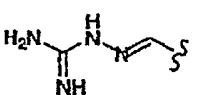
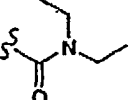
					
A1312		H		H	
A1313		H		H	
A1314		H		H	
A1315		H		H	
A1316		H		H	
A1317		H		H	
A1318		H		H	
A1319		H		H	

FIGURE 1EJ

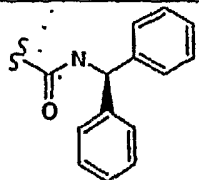
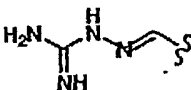
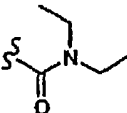
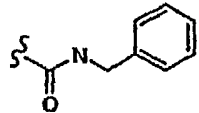
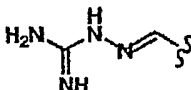
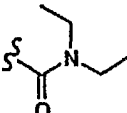
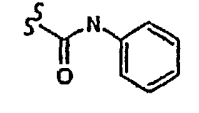
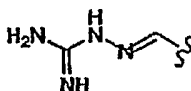
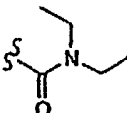
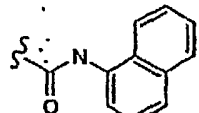
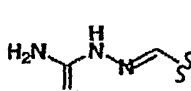
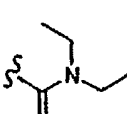
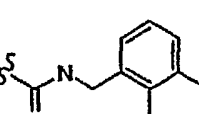
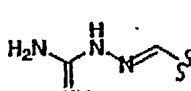
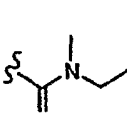
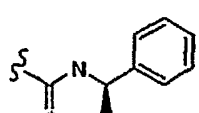
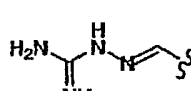
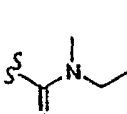
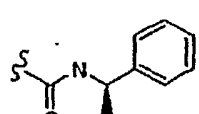
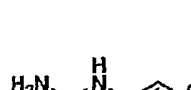
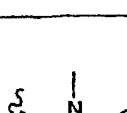
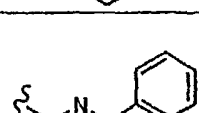
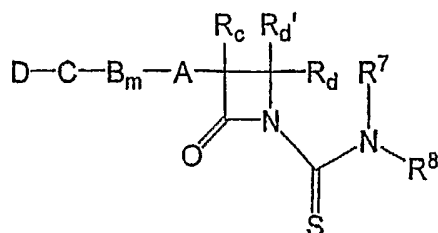
					
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A1321		CH ₃		H	
A1322		CH ₃		H	
A1323		CH ₃		H	
A1324		CH ₃		H	
A1325		CH ₃		H	
A1326		CH ₃		H	
A1327		CH ₃		H	

FIGURE 1EK

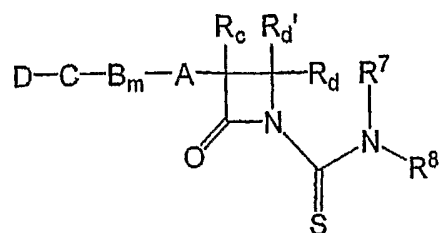
A1328					
A1329		CH ₃		H	
A1330		CH ₃		H	

FIGURE 1EL



	DCB _m A	R _c	R _d	R _{d'}	R ⁷	R ⁸
A1331		H		H		H
A1332		CH ₃		H		H
A1333		H		CH ₃		H
A1334		H		H		H
A1335		CH ₃		H		H
A1336		H		CH ₃		H
A1337		H		H		H
A1338		CH ₃		H		H
A1339		H		CH ₃		H

FIGURE 1EM



DCB _m A	R _c	R _d	R _{d'}	R ⁷	R ⁸
	H		H		H
	CH ₃		H		H
	H		CH ₃		H
	H		H		H
	CH ₃		H		H
	H		CH ₃		H
	H		H		H
	CH ₃		H		H
	H		CH ₃		H

FIGURE 1EN

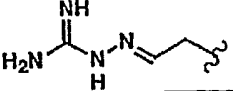

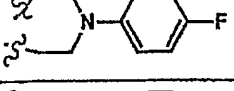
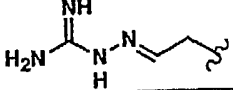

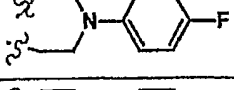
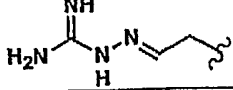

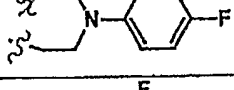
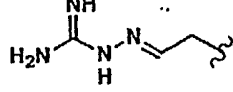

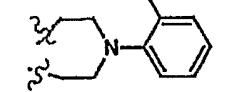
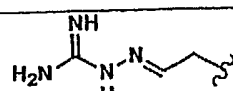

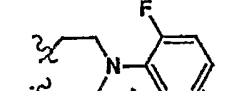
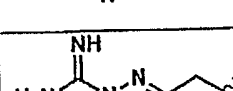

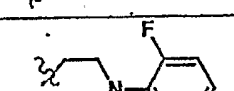
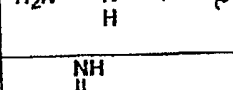


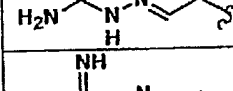

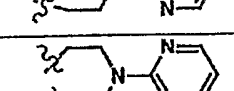
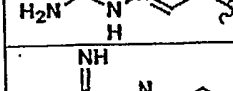

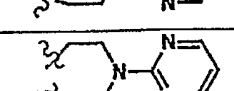
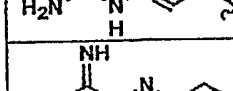

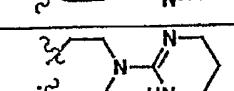
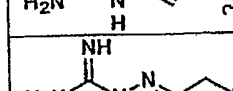

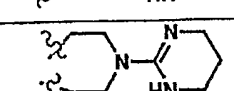
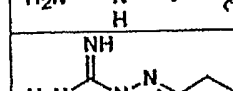

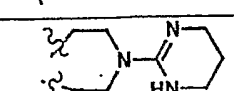
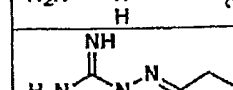

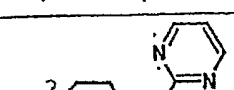
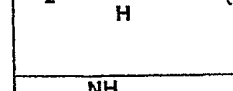

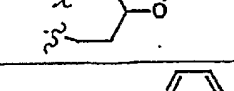
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FIGURE 1EO

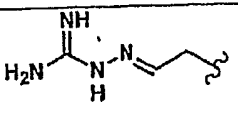
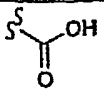
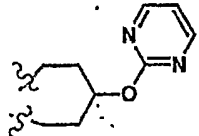
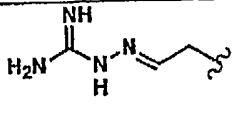
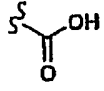
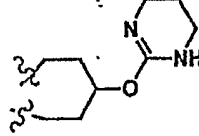
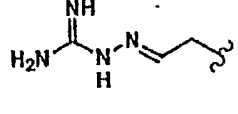
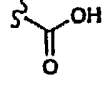
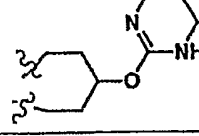
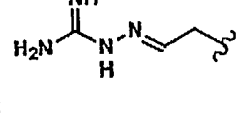
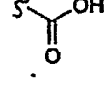
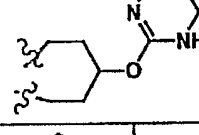
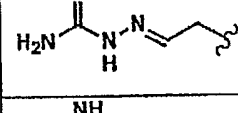
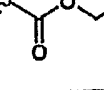
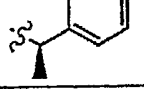
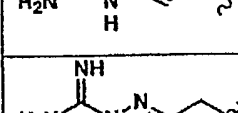
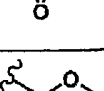
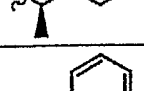
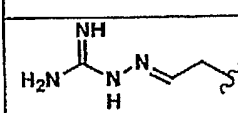
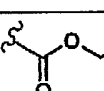
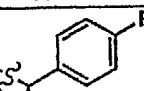
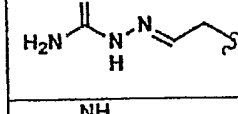
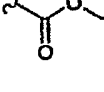
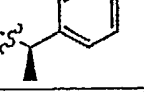
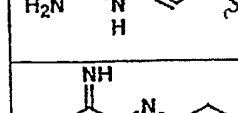
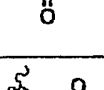
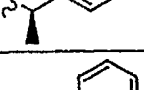
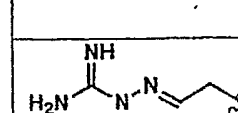
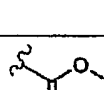

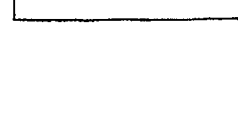

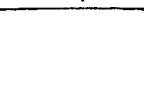



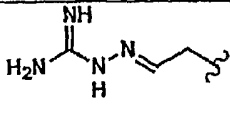
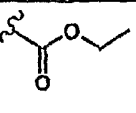
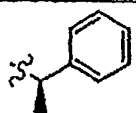
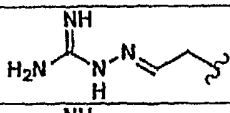
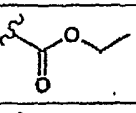
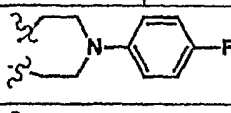
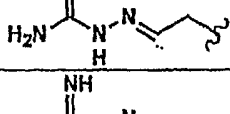
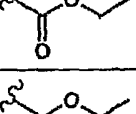
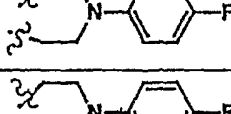
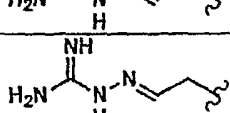
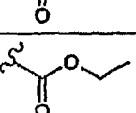
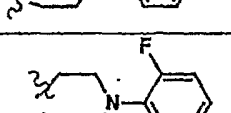
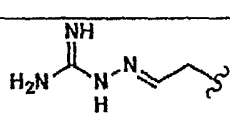
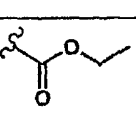
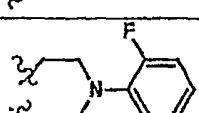
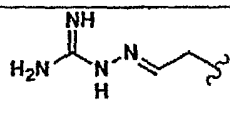
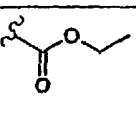
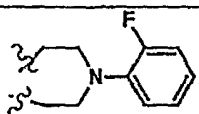
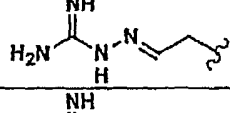
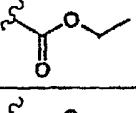
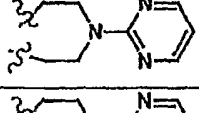
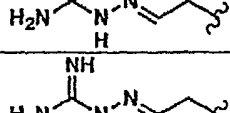
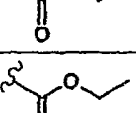
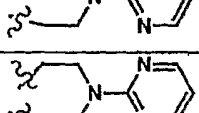
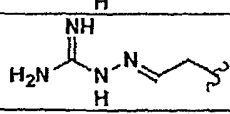
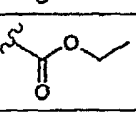
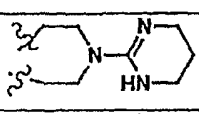
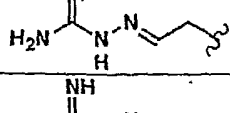
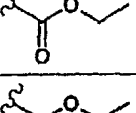
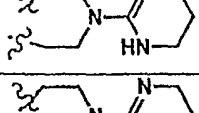
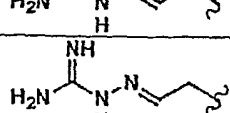
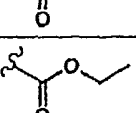
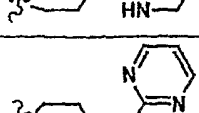

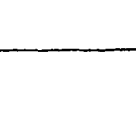
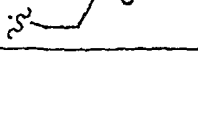






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A1359		CH ₃		H	
A1360		H		CH ₃	
A1361		H		H	
A1362		CH ₃		H	
A1363		H		CH ₃	
A1364		H		H	
A1365		CH ₃		H	

FIGURE 1EP

A1366		H		CH ₃		H
A1367		H		H		
A1368		CH ₃		H		
A1369		H		CH ₃		
A1370		H		H		
A1371		CH ₃		H		
A1372		H		CH ₃		
A1373		H		H		
A1374		CH ₃		H		
A1375		H		CH ₃		
A1376		H		H		
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SUBSTITUTE SHEET (RULE 26)

FIGURE 1EQ

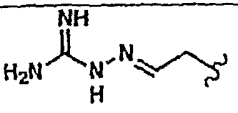
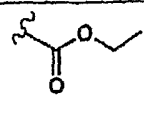
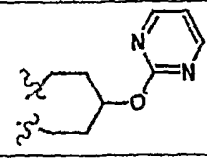
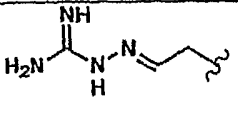
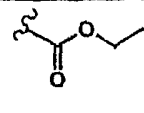
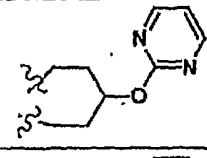
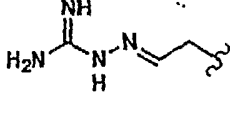
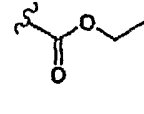
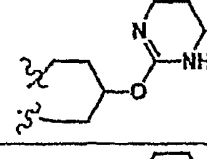
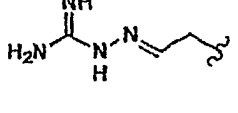
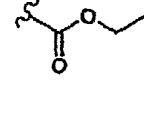
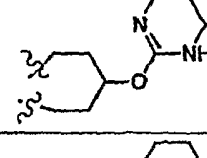
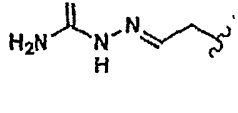
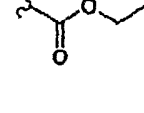
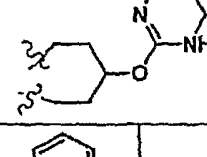
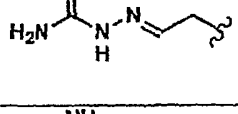
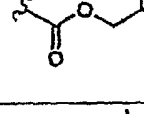
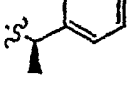
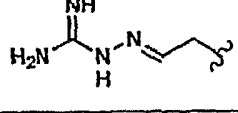
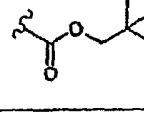
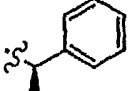
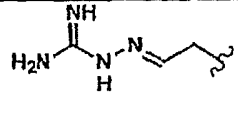
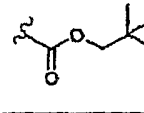
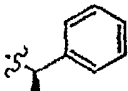
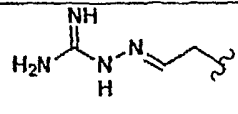
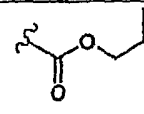
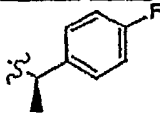
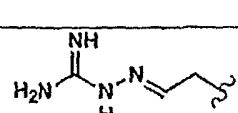
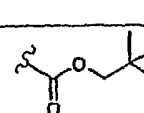
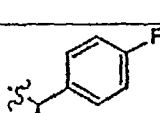
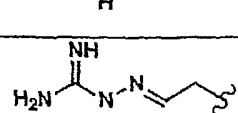
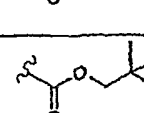
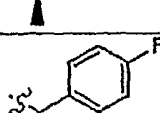
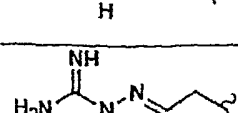
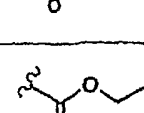
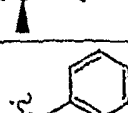
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FIGURE 1ER

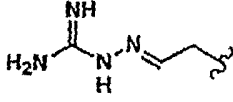
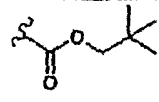
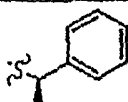
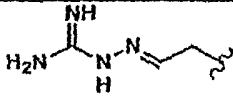
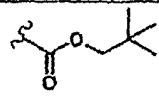
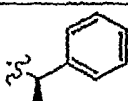
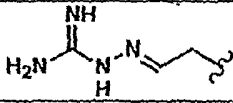
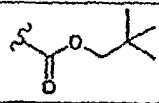
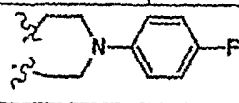
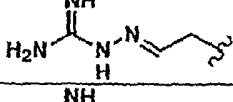
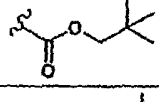
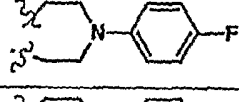
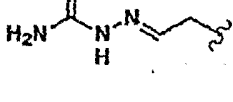
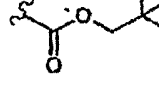
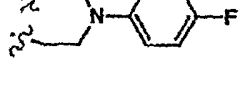
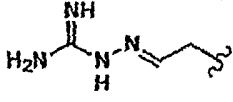
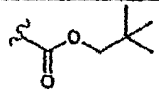
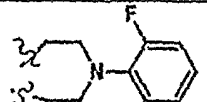
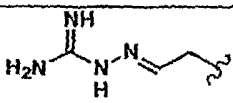
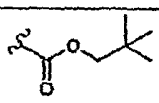
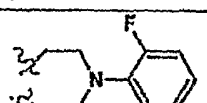
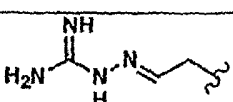
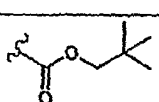
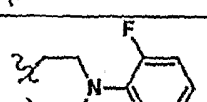
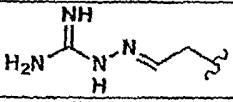
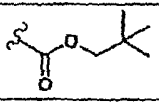
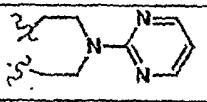
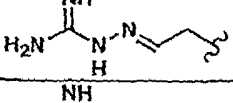
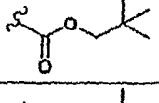
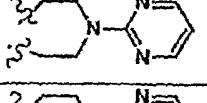
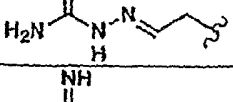
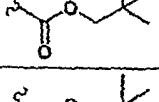
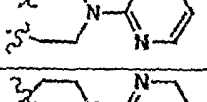
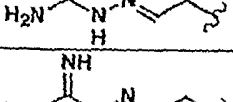
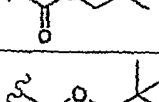
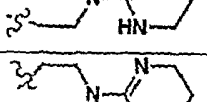
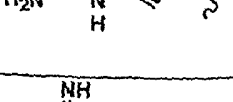
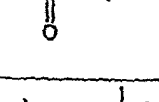
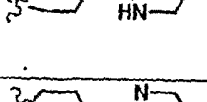
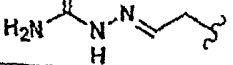
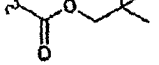
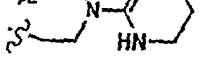
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A1400		H		H		
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FIGURE 1ES

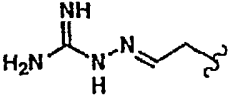
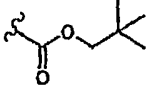
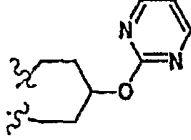
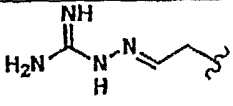
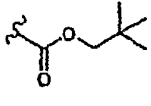
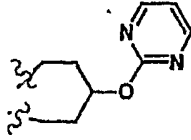
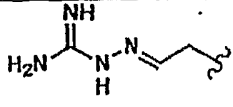
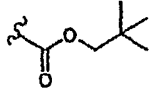
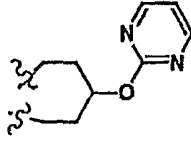
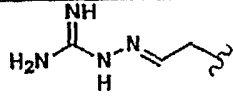
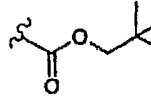
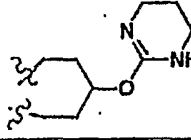
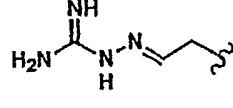
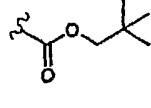
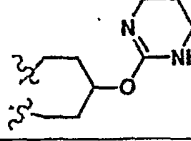
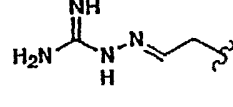
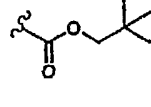
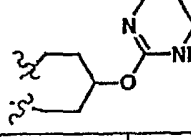
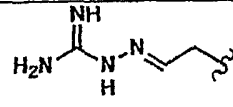
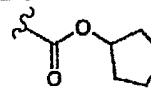
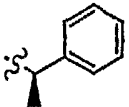
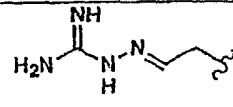
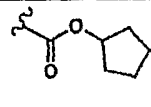
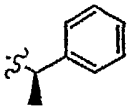
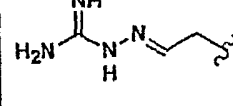
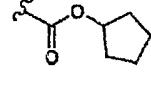
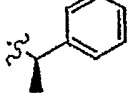
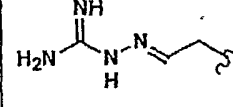
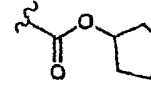
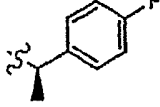
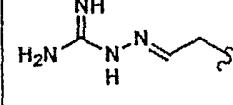
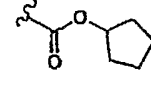
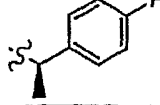
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FIGURE 1ET

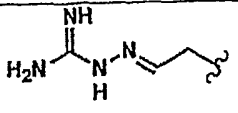
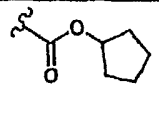
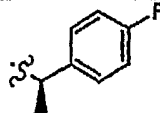
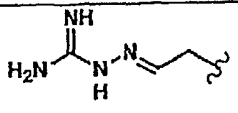
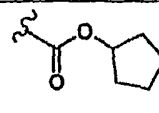
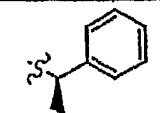
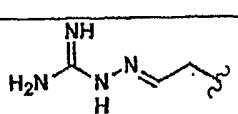
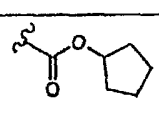
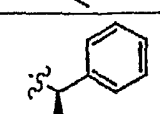
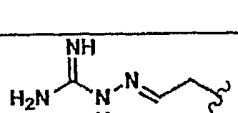
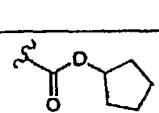
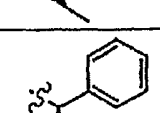
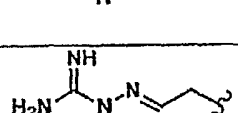
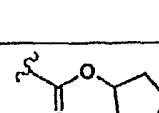

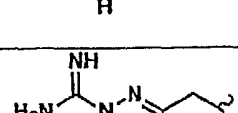
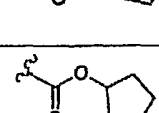
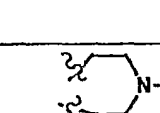
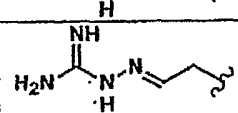
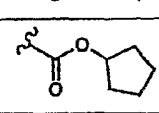
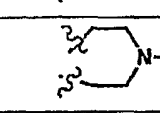
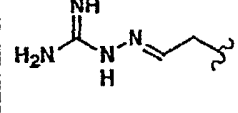
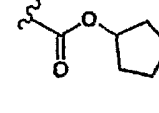
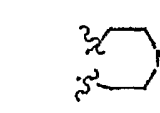
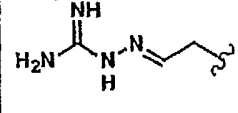
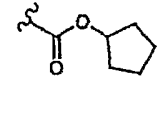
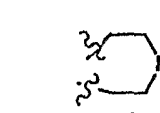
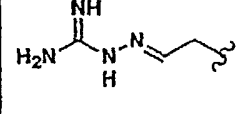
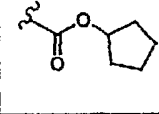
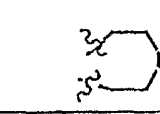
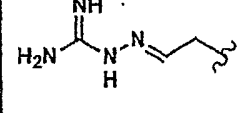
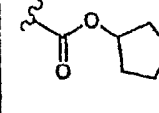
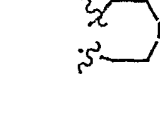
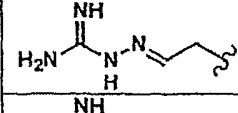
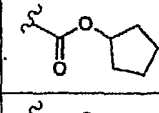
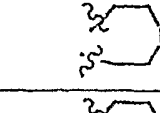
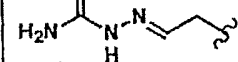
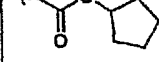
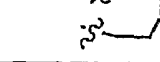
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A1421		H		H		
A1422		CH ₃		H		
A1423		H		CH ₃		
A1424		H		H		
A1425		CH ₃		H		
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FIGURE 1EU

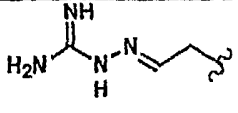
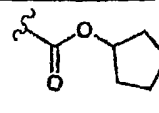
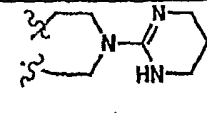
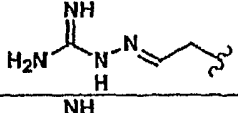
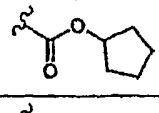
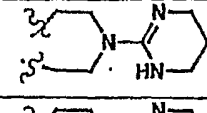
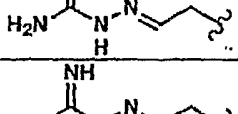
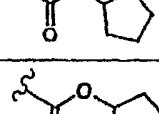
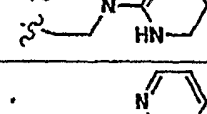
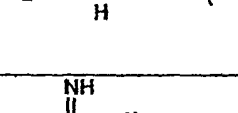
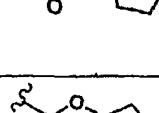
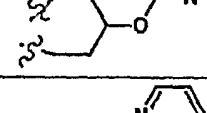
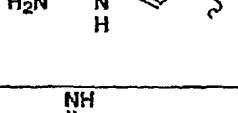
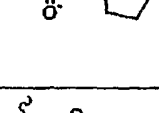
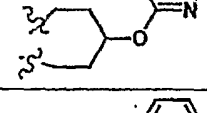
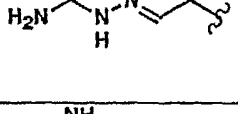
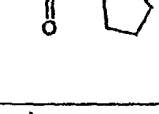
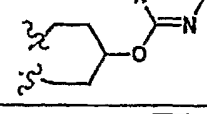
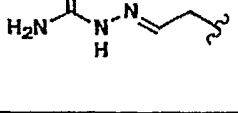
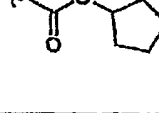
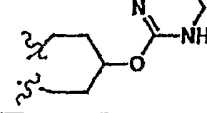
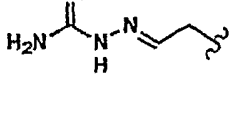
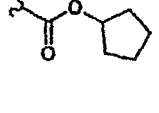
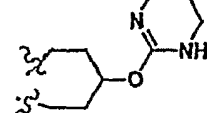
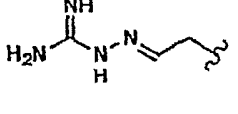
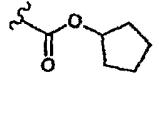
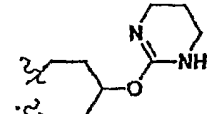
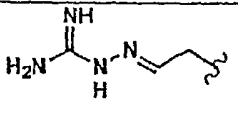
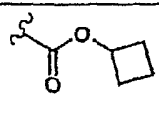
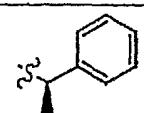
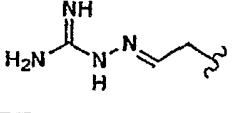
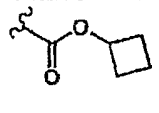
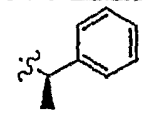
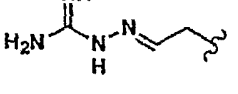
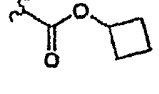
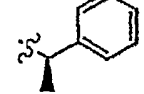
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FIGURE 1EV

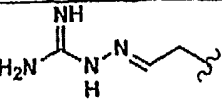
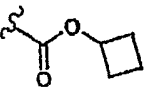
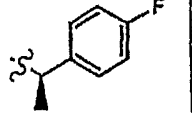
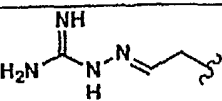
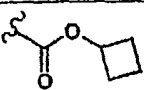
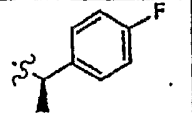
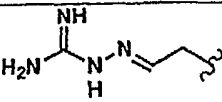
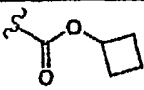
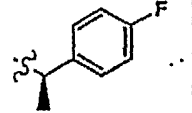
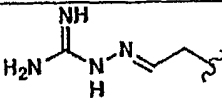
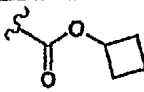
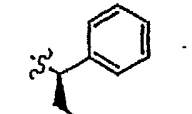
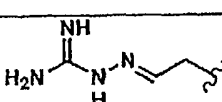
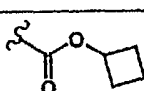
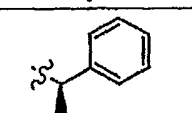
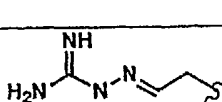
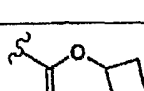
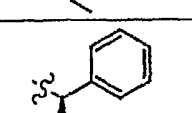
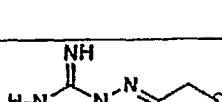
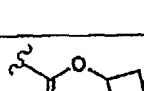
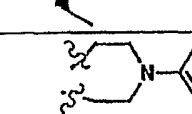
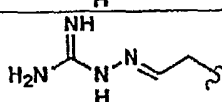
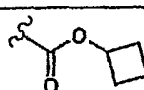
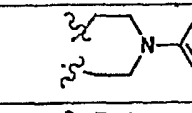
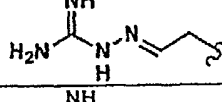
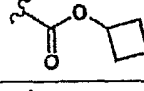
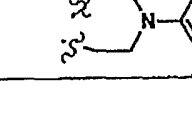
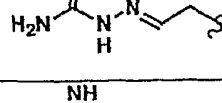
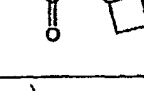
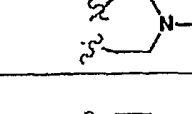
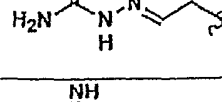
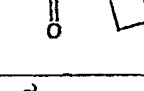
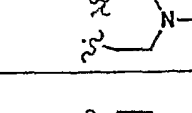
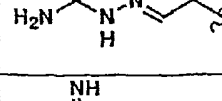
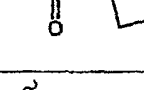
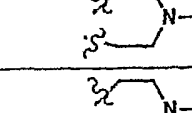
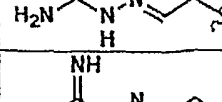
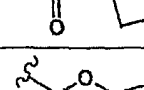
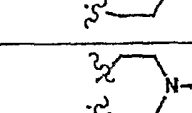
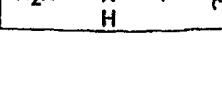
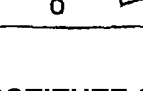
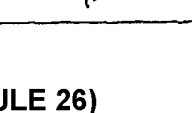
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A1448		H		H		
A1449		CH ₃		H		
A1450		H		CH ₃		
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FIGURE 1EW

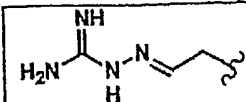
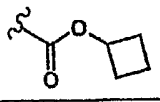
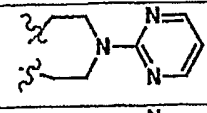
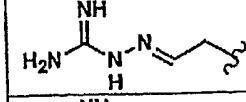
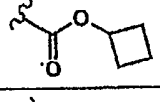
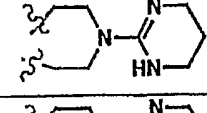
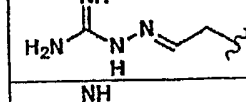
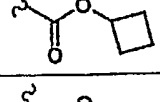
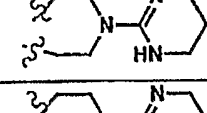
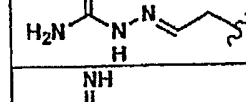
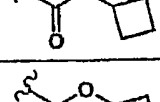
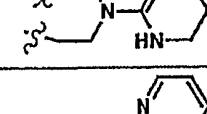
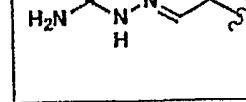
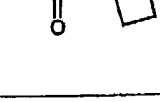
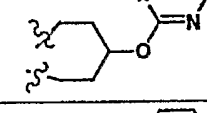
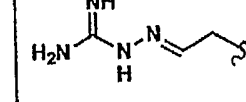
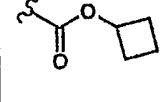
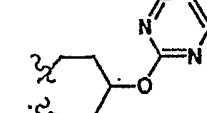
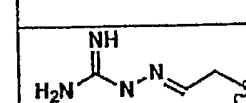
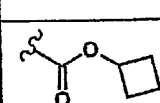

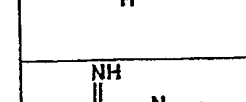
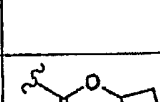
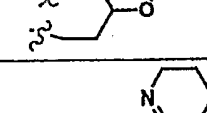
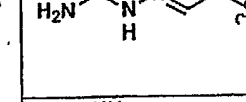
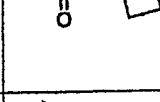
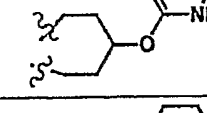
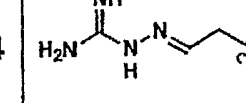
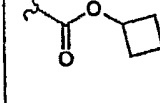
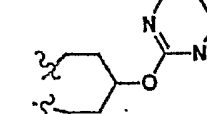
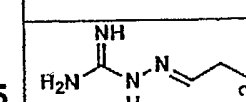
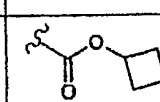
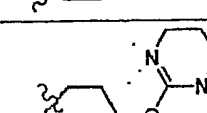
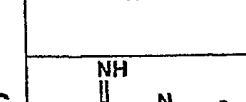
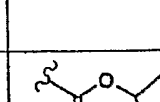
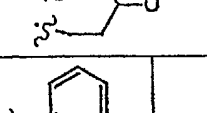
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FIGURE 1EX

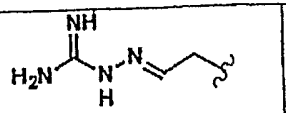
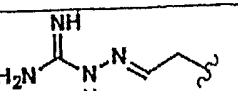
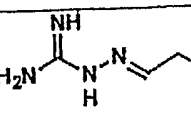
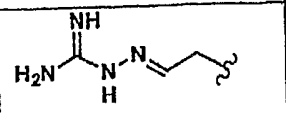
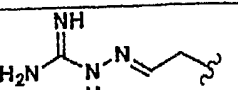
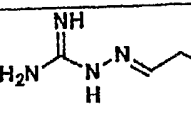
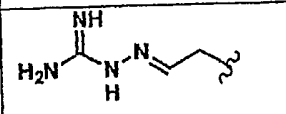
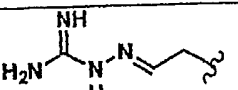
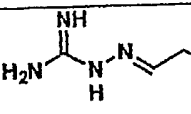
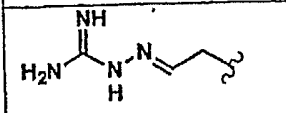
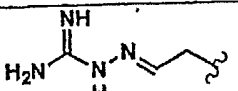
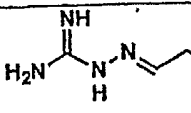
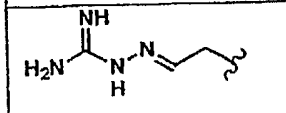
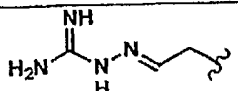
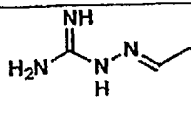
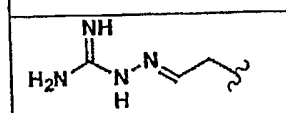
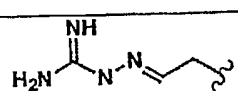
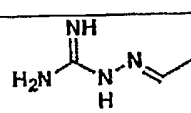
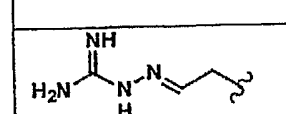
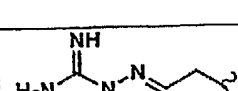
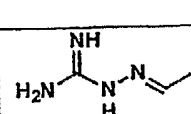
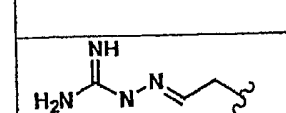
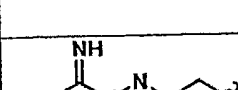
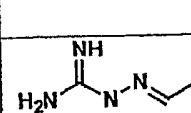
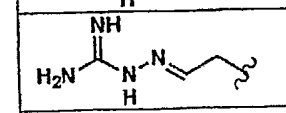
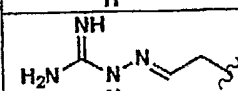
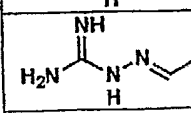
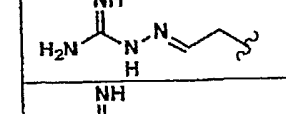
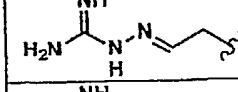
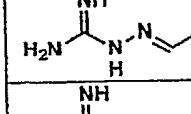
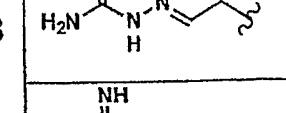
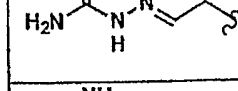
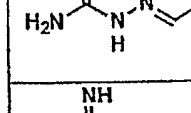
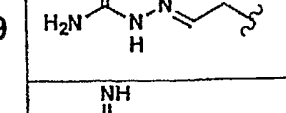
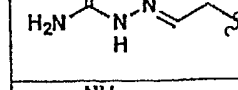
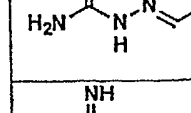
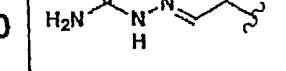
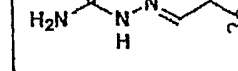
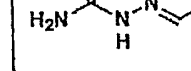
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A1475		H		H		H
A1476		CH ₃		H		H
A1477		H		CH ₃		H
A1478		H		H		H
A1479		CH ₃		H		H
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FIGURE 1EY

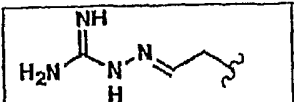
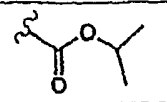
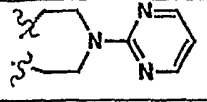
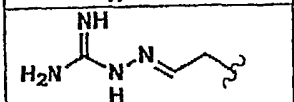
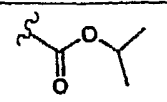
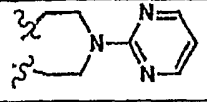
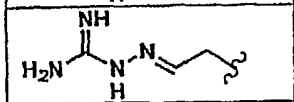
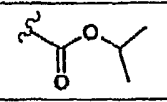
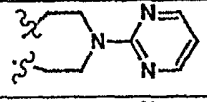
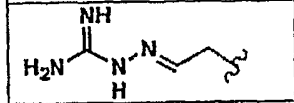
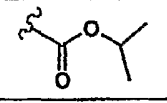
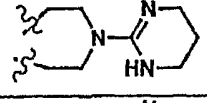
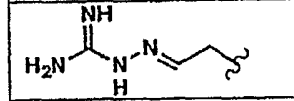
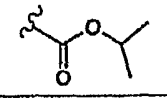
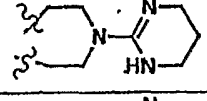
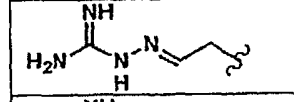
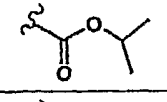
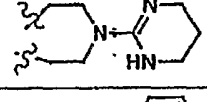
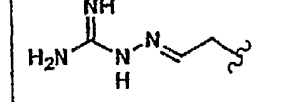
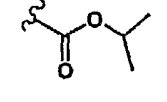
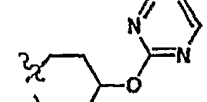
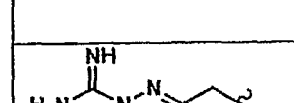
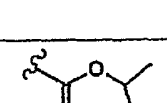
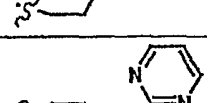
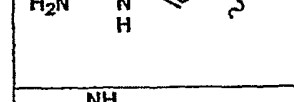
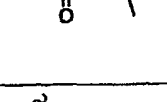
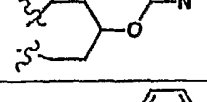
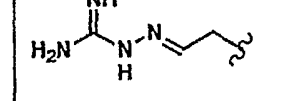
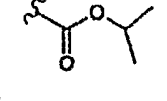
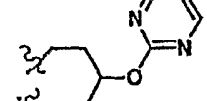
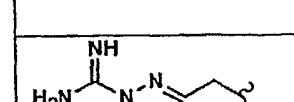
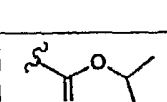
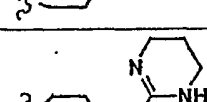
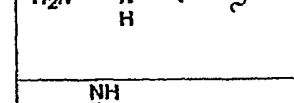
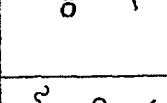
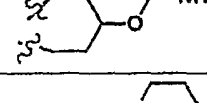
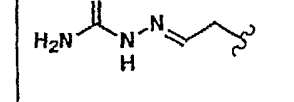
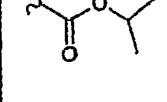
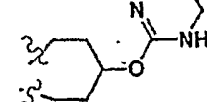
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A1489		H		CH ₃	
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FIGURE 1EZ

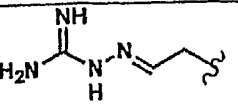
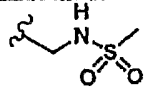
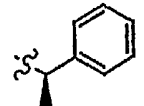
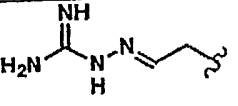
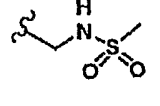
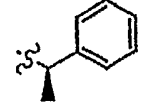
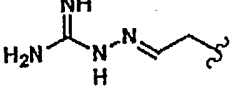
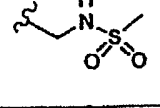
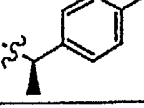
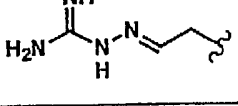
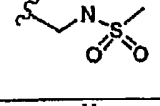
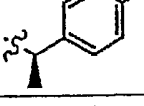
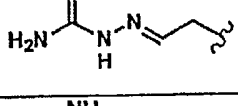
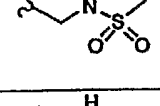
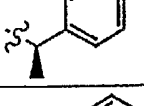
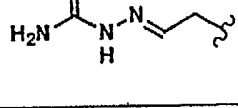
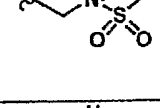
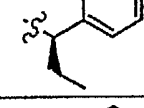
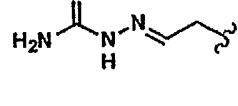
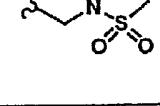
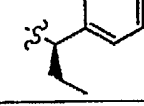
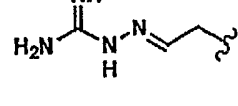
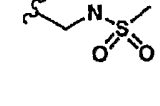
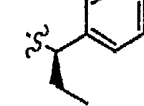
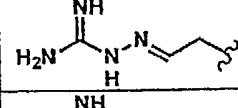
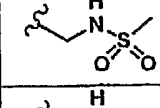
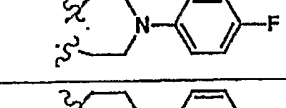
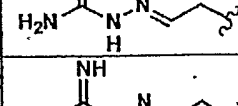
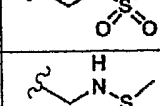
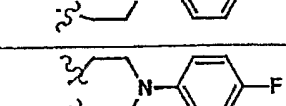
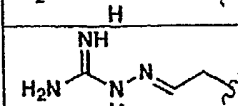
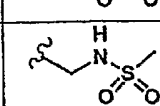
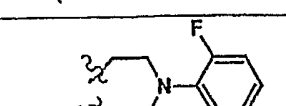
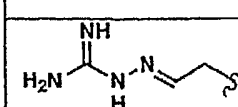
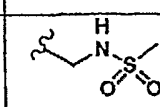
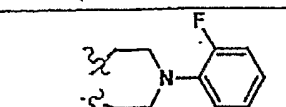
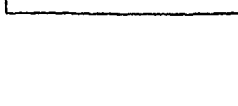


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A1501		H		CH ₃		H
A1502		H		H		H
A1503		CH ₃		H		H
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FIGURE 1FA

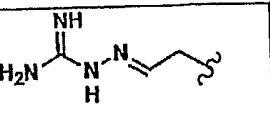
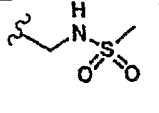
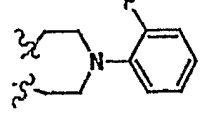
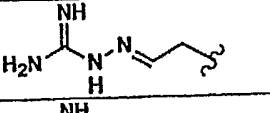
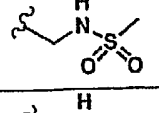
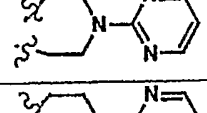
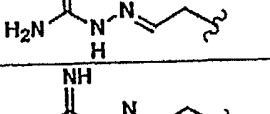
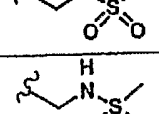
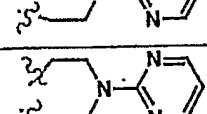
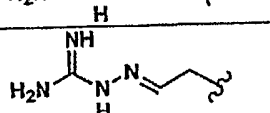
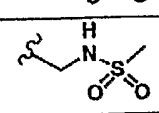
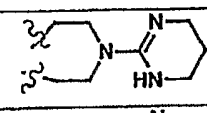
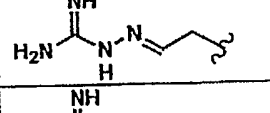
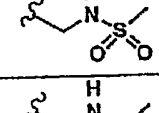
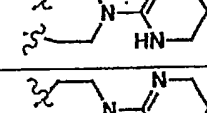
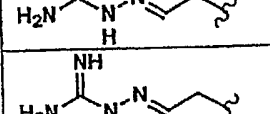
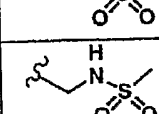
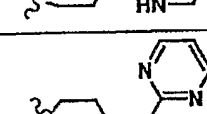
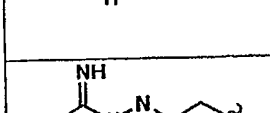
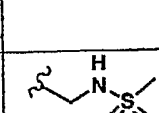
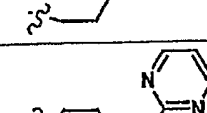
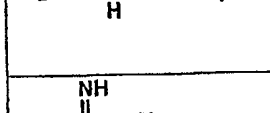
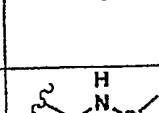
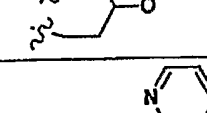
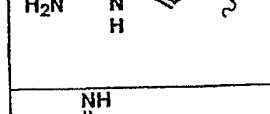
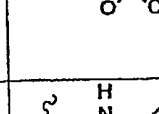
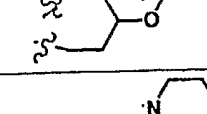
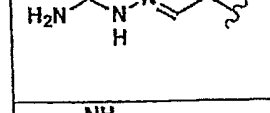
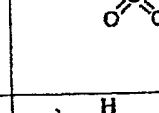
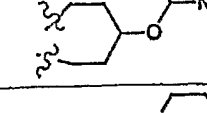
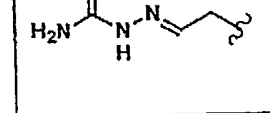
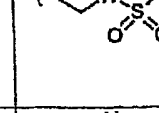
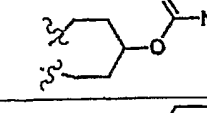
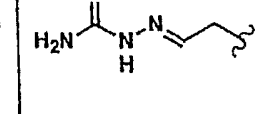
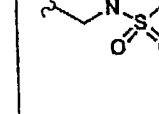
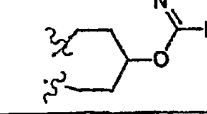



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A1512		CH ₃		H	
A1513		H		CH ₃	
A1514		H		H	
A1515		CH ₃		H	
A1516		H		CH ₃	
A1517		H		H	
A1518		CH ₃		H	
A1519		H		CH ₃	

FIGURE 1FB

A1520		H		H		H
A1521		CH ₃		H		H
A1522		H		CH ₃		H
A1523		H		H		H
A1524		CH ₃		H		H
A1525		H		CH ₃		H
A1526		H		H		H
A1527		CH ₃		H		H
A1528		H		CH ₃		H
A1529		H		H		H
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FIGURE 1FC

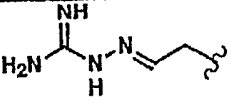
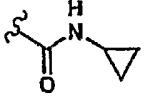
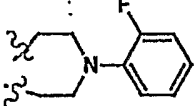
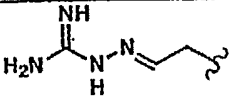
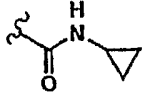
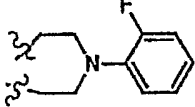
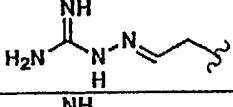
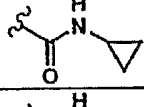
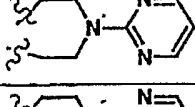
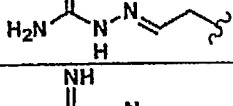
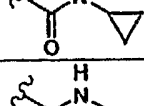
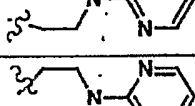
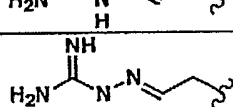
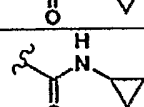
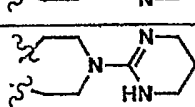
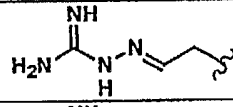
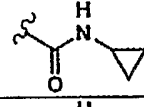
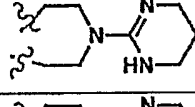
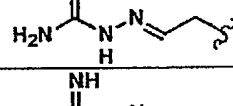
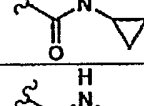
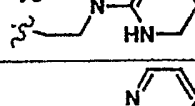
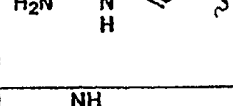
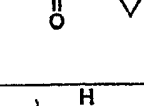
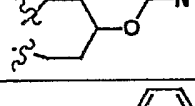
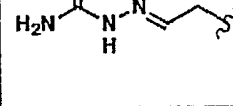
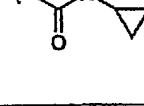
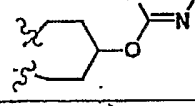
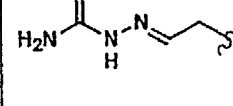
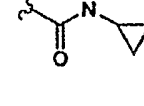
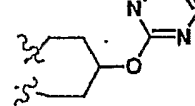
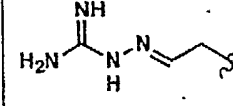
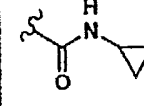
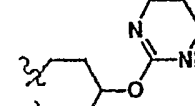
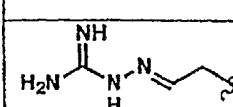
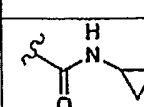


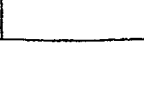
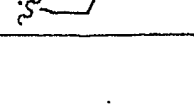
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FIGURE 1FD

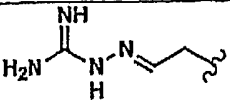
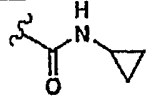
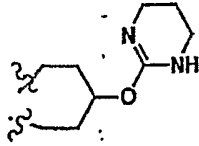
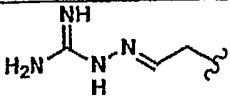
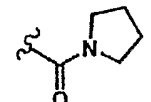
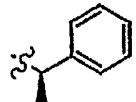
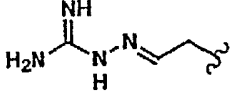
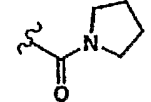
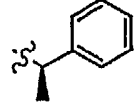
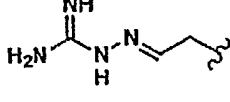
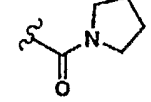
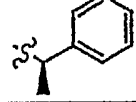
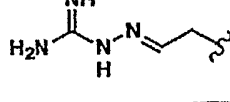
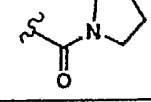
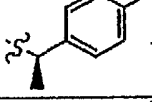
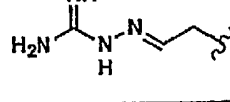
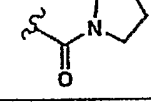
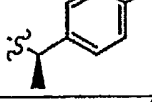
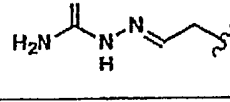
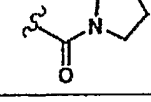
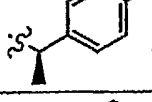
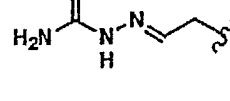
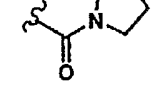
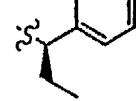
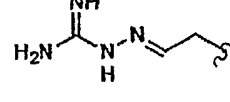
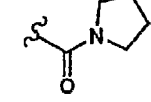
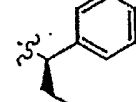
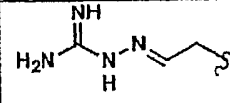
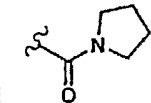
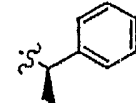
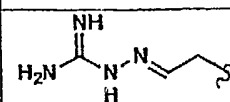
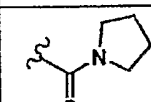
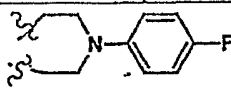
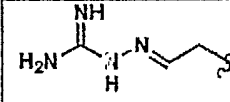
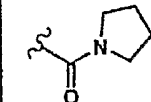
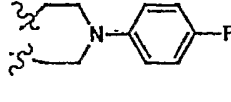
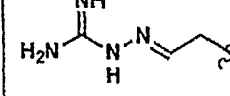
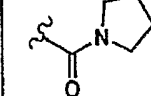
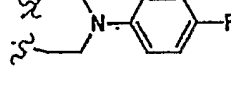
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A1555		H		CH ₃		H
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FIGURE 1FD

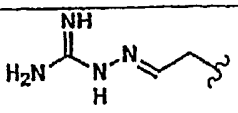
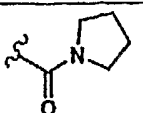
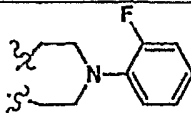
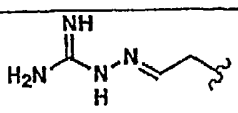
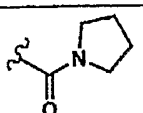
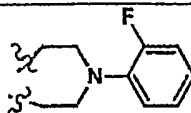
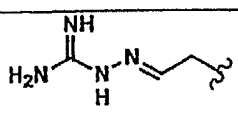
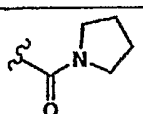
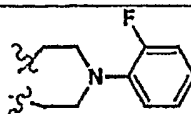
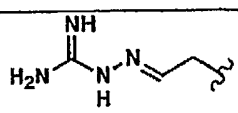
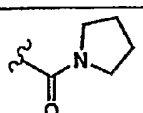
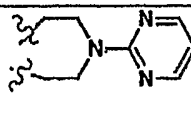
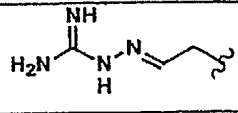
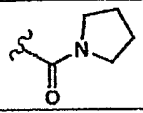
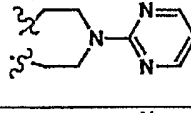
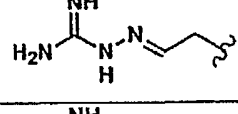
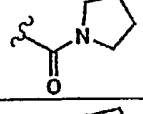
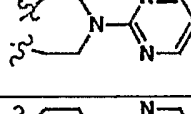
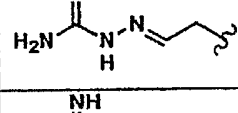
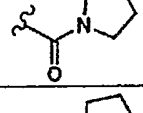
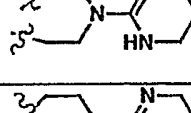
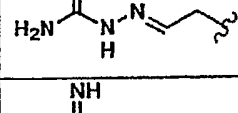
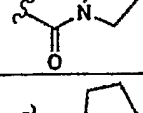
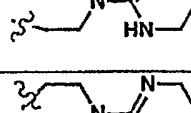
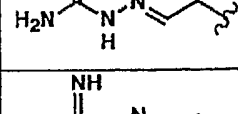
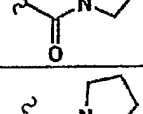
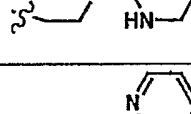
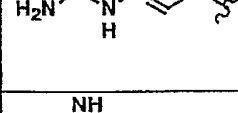
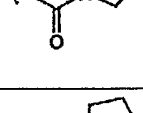
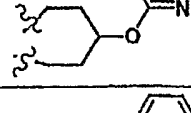
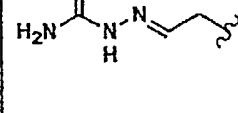
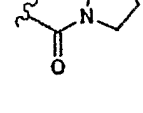
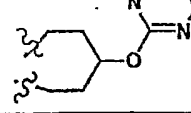
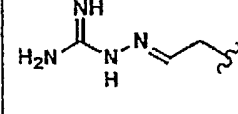
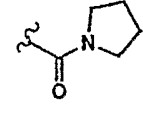
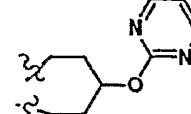
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FIGURE 1FE

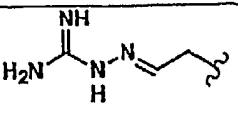
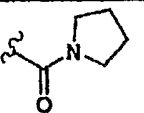
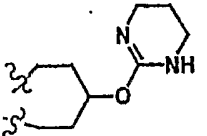
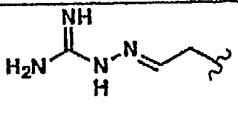
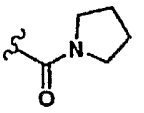
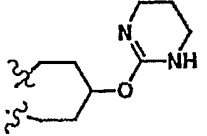
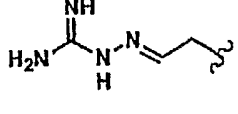
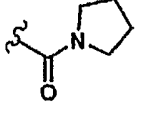
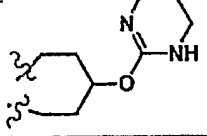
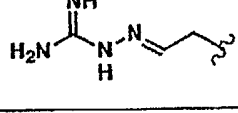
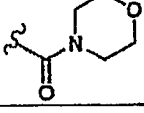
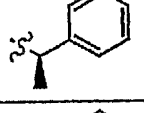
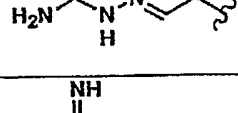
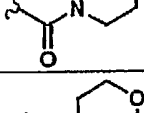
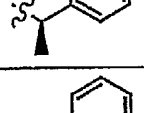
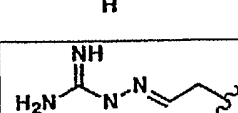
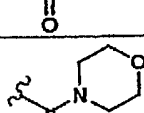
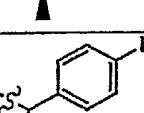
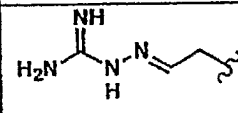
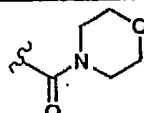
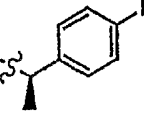
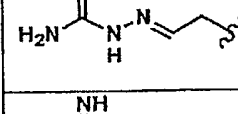
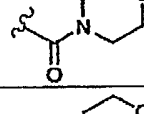
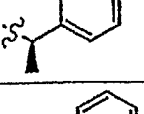
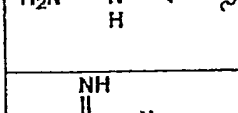
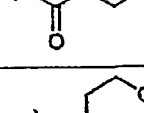

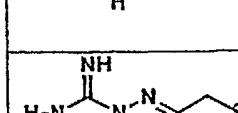
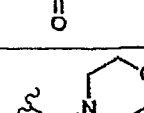
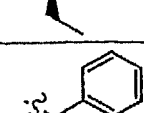

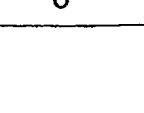
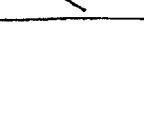



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A1576		H		CH ₃	
A1577		H		H	
A1578		CH ₃		H	
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FIGURE 1FF

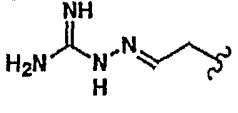
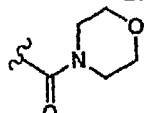
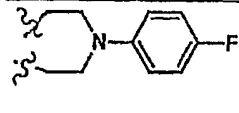
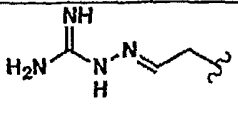
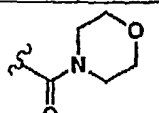
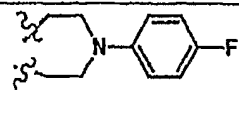
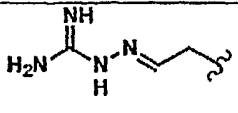
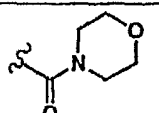
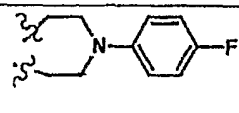
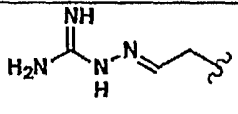
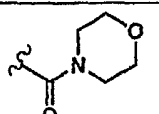
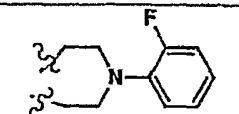
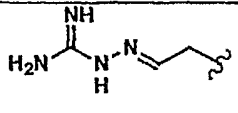
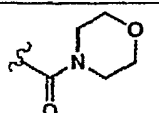
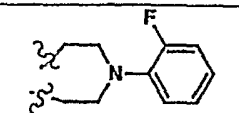
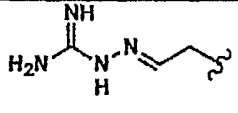
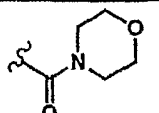
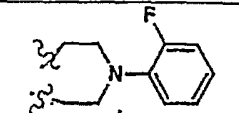
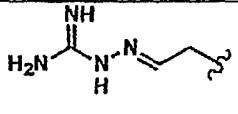
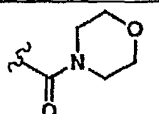
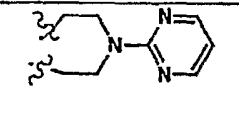
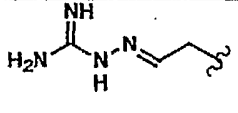
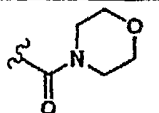
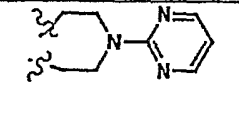
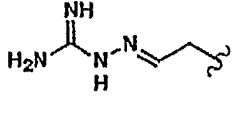
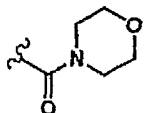
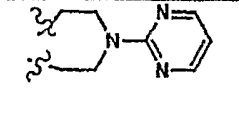
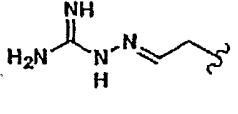
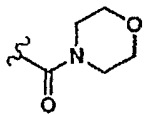
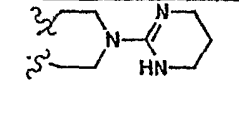
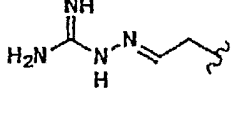
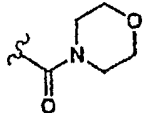
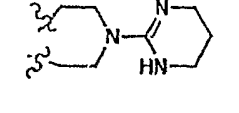
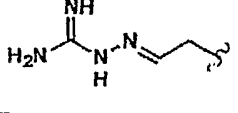
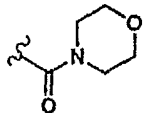
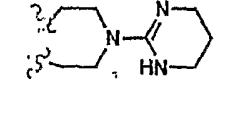
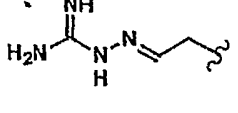
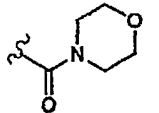
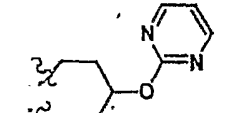
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A1588		H		CH ₃	
A1589		H		H	
A1590		CH ₃		H	
A1591		H		CH ₃	
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FIGURE 1FG

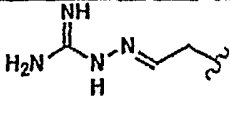
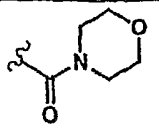
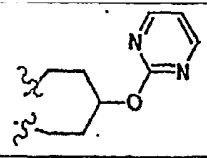
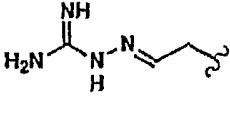
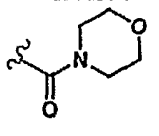
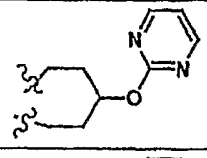
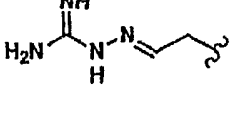
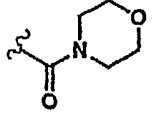
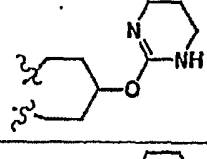
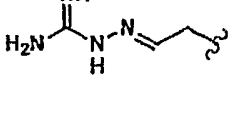
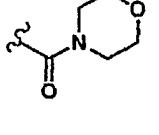
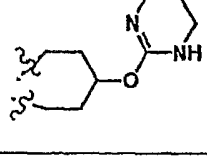
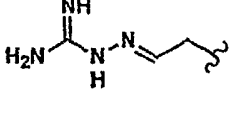
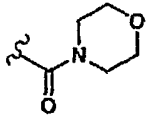
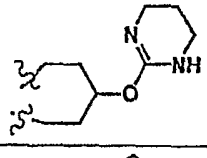
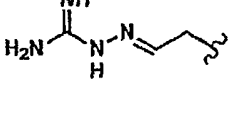
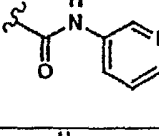
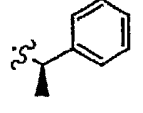
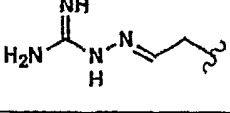
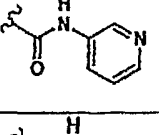
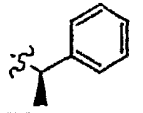
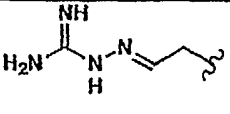
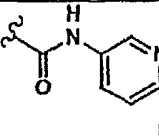
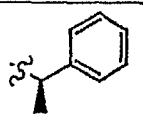
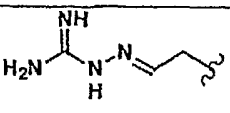
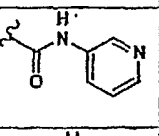
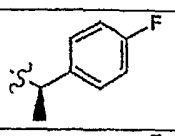
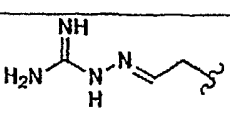
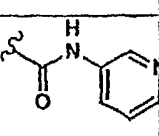
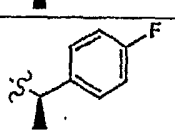
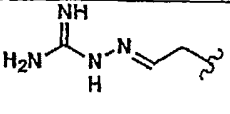
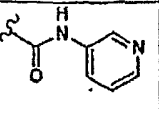
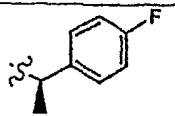
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A1601		H		H	
A1602		CH ₃		H	
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FIGURE 1FH

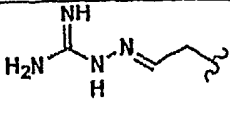
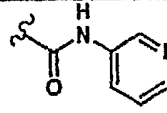
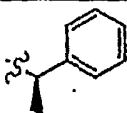
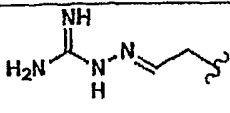
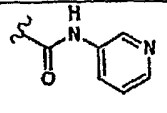
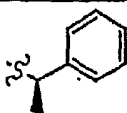
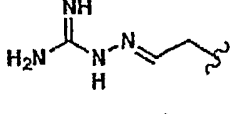
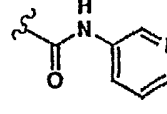
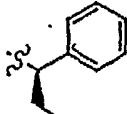
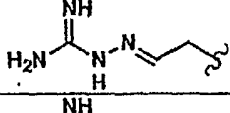
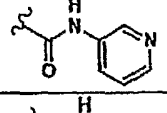
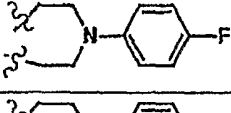
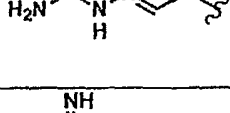
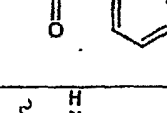

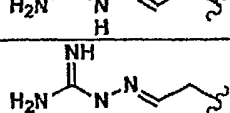
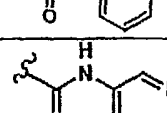
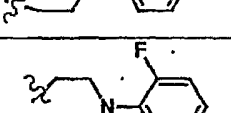
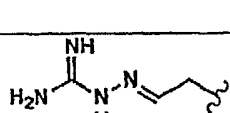
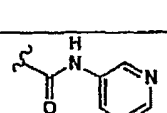
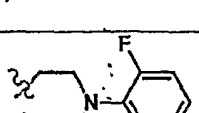
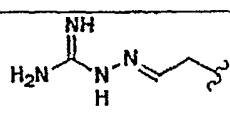
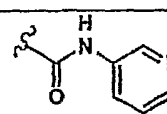
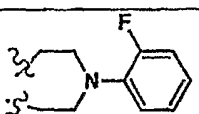
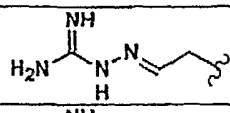
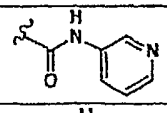
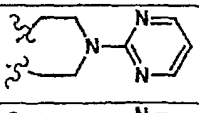
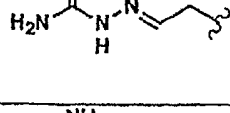
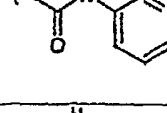
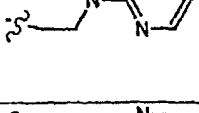
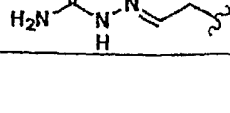
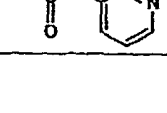
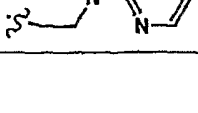



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A1612		H		CH ₃	
A1613		H		H	
A1614		CH ₃		H	
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FIGURE 1FI

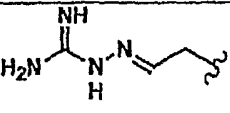
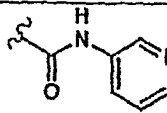
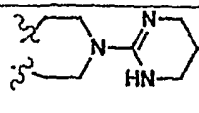
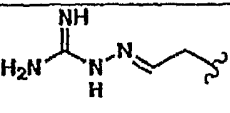
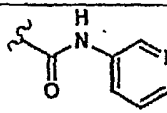
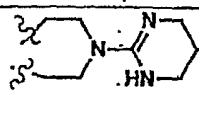
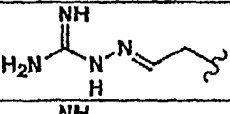
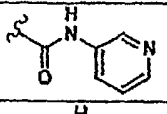
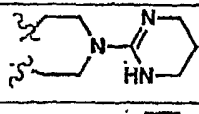
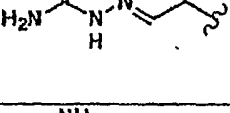
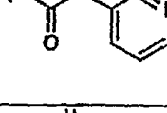
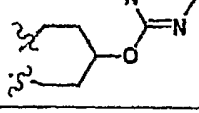
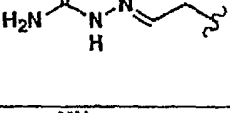
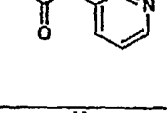
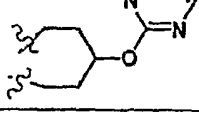
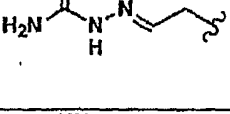
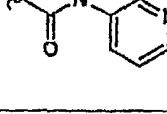
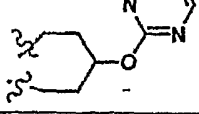
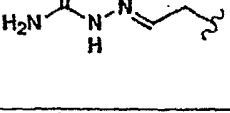
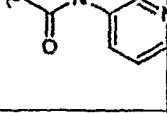
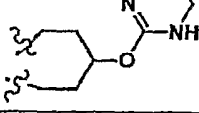
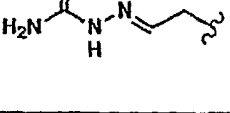
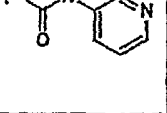
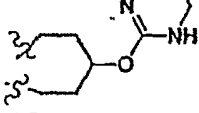
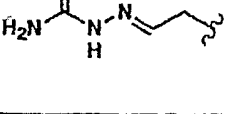
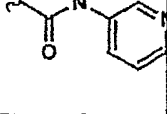
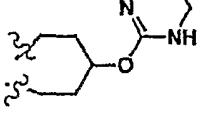
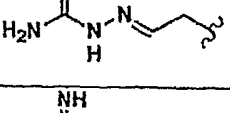
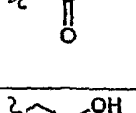
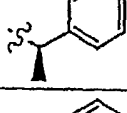
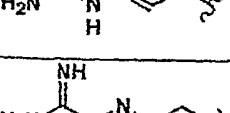
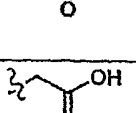
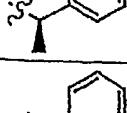
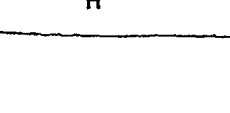


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FIGURE 1FJ

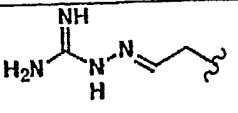
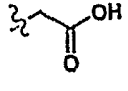
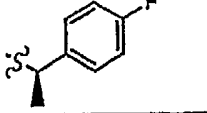
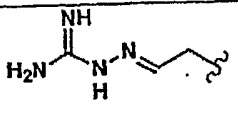
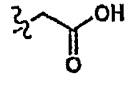
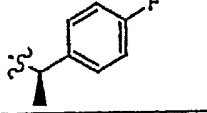
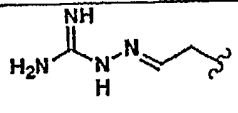
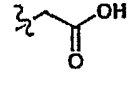
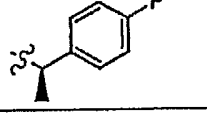
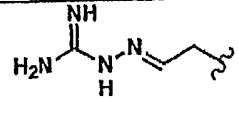
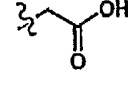
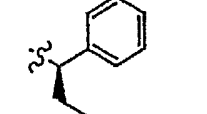
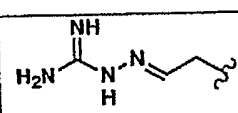
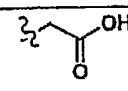
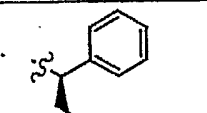
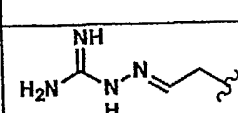
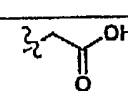
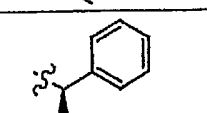
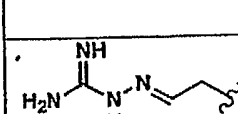
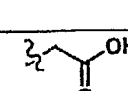
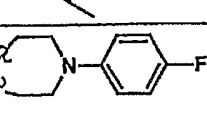
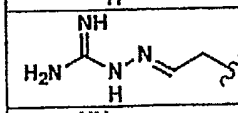
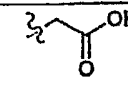
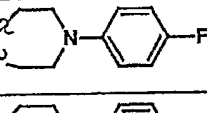
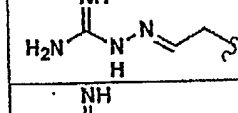
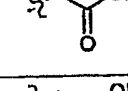
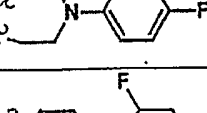
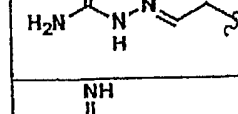
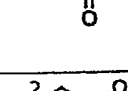
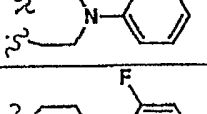
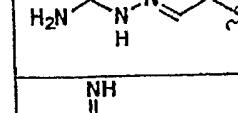
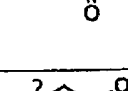
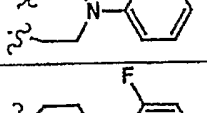
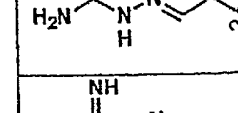
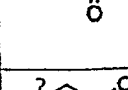
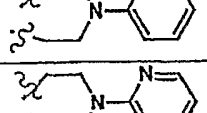
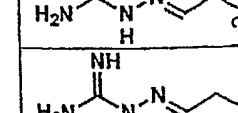
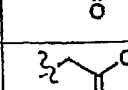
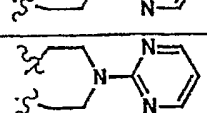
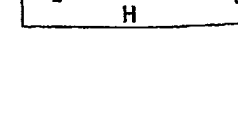

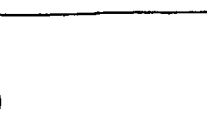
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A1636		H		CH ₃	
A1637		H		H	
A1638		CH ₃		H	
A1639		H		CH ₃	
A1640		H		H	
A1641		CH ₃		H	
A1642		H		CH ₃	
A1643		H		H	
A1644		CH ₃		H	

FIGURE 1FK

A1645		H		CH ₃	
A1646		H		H	
A1647		CH ₃		H	
A1648		H		CH ₃	
A1649		H		H	
A1650		CH ₃		H	
A1651		H		CH ₃	
A1652		H		H	
A1653		CH ₃		H	
A1654		H		CH ₃	
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A1656		CH ₃		H	

FIGURE 1FL

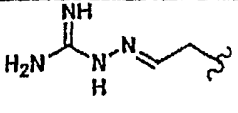
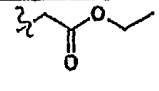
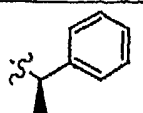
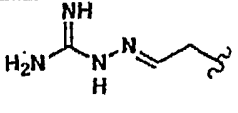
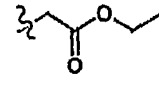
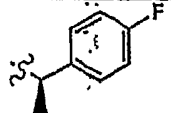
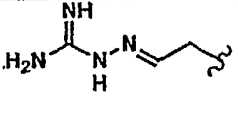
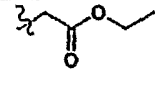
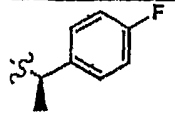
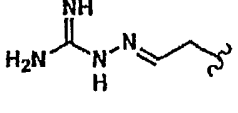
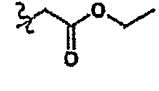
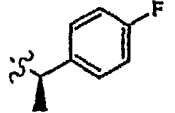
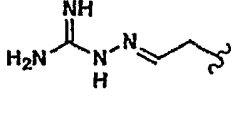
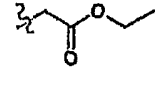
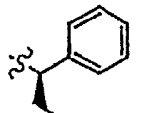
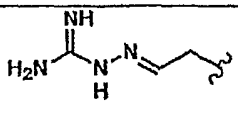
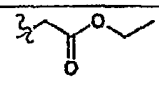
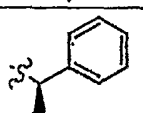
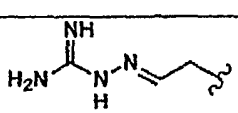
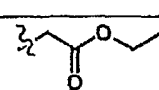
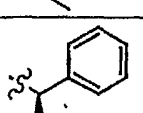
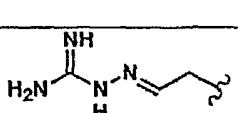
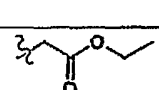
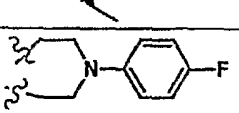
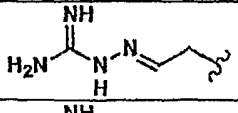
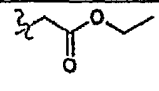
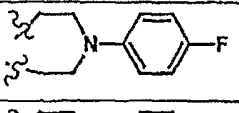
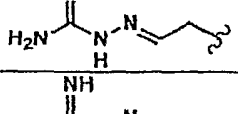
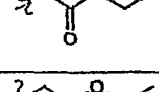
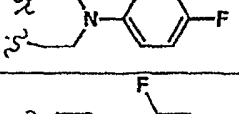
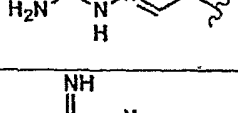
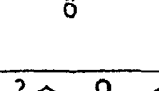
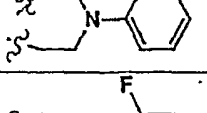
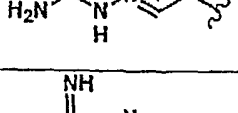
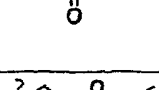
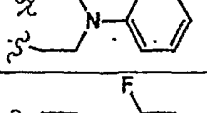
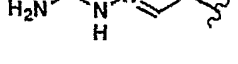
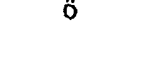
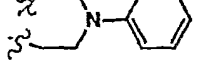
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A1663		H		CH ₃	
A1664		H		H	
A1665		CH ₃		H	
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FIGURE 1FM

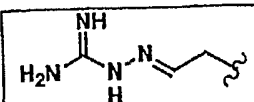
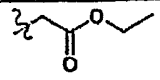
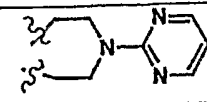
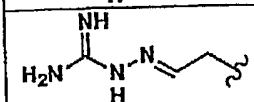
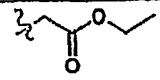
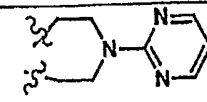
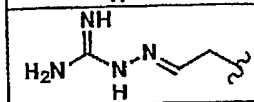
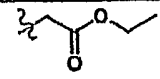
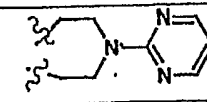
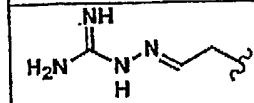
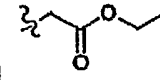
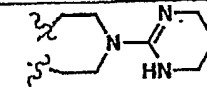
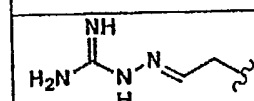
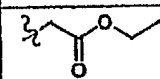
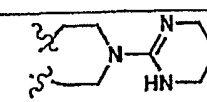
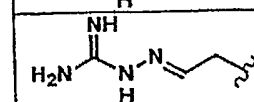
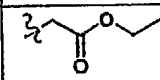
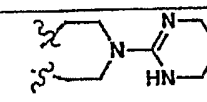
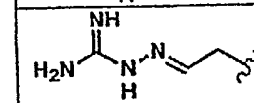
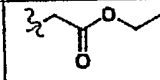
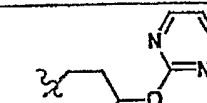
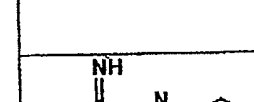
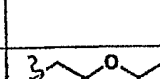
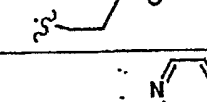
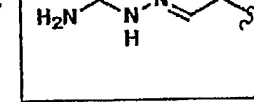

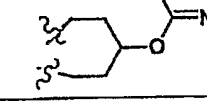
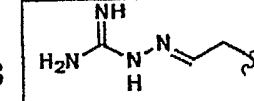
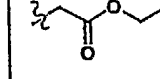
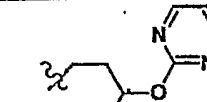
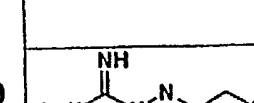
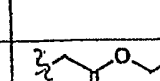
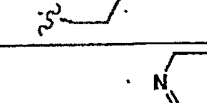
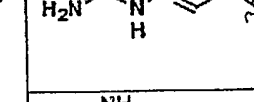
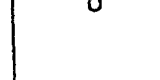
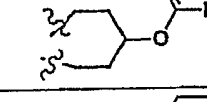
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FIGURE 1FN

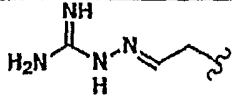
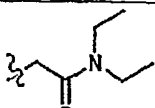
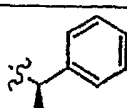
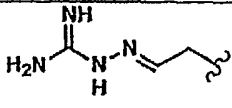
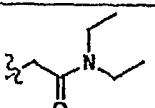
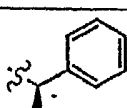
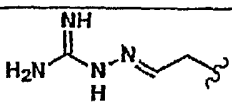
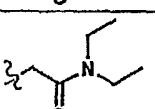
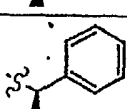
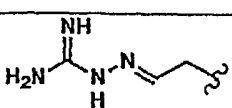
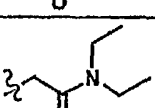
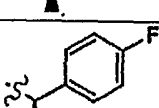
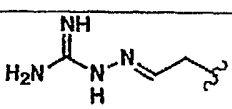
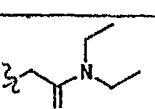
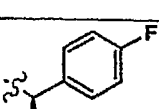
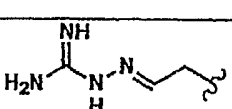
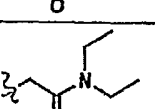
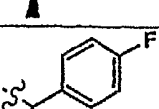
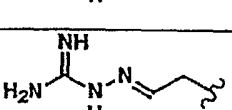
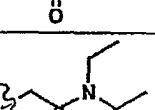
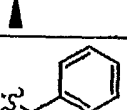
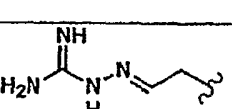
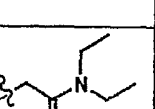
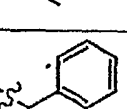
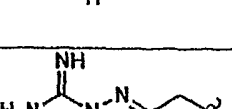
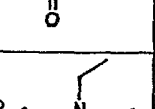

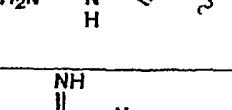
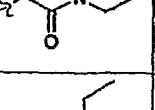
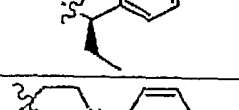
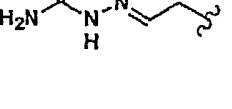
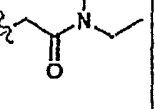
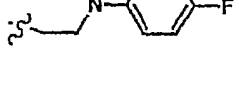
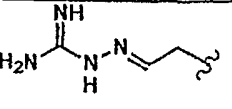
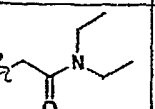
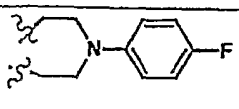
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FIGURE 1FO

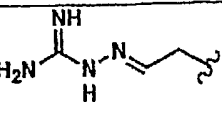
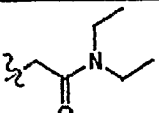
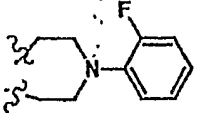
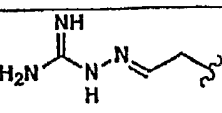
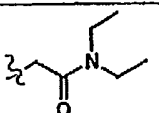
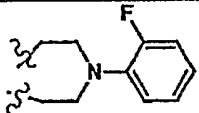
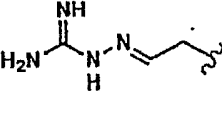
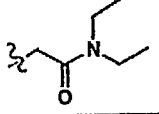
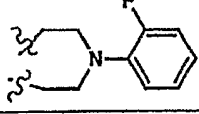
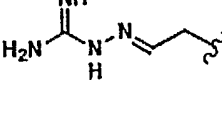
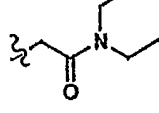
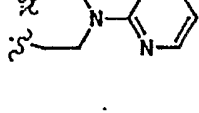
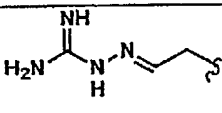
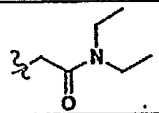
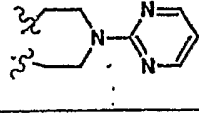
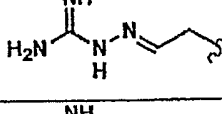
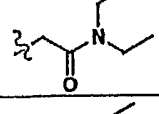
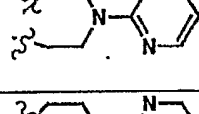
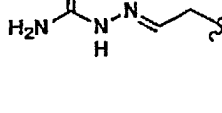
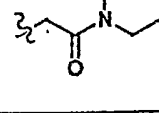
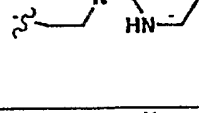
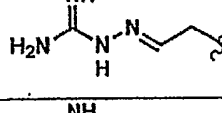
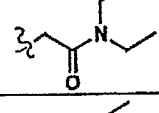
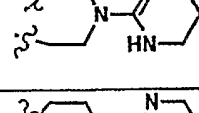
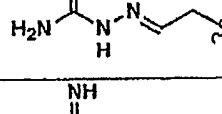
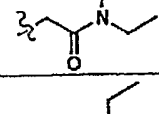
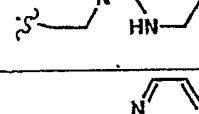
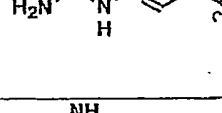
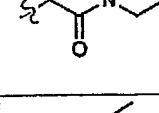
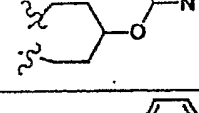
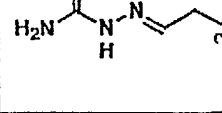
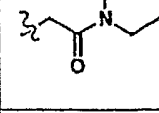
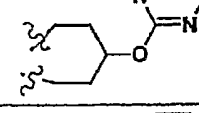
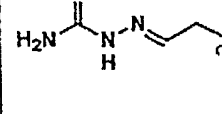
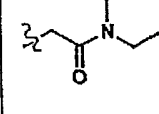
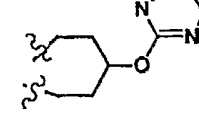
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A1699		H		CH ₃	
A1700		H		H	
A1701		CH ₃		H	
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FIGURE 1FP

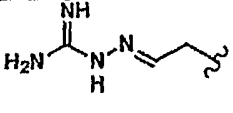
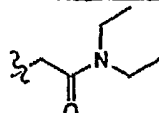
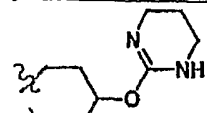
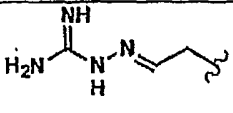
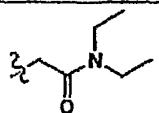
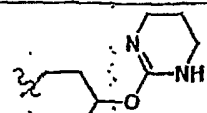
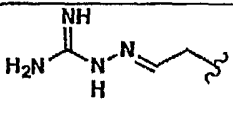
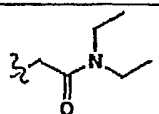
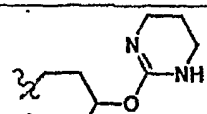
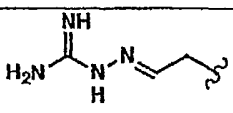
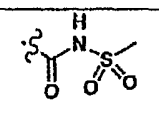
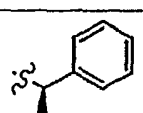
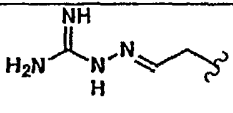
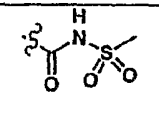
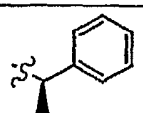
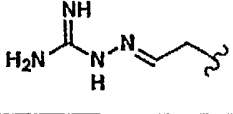
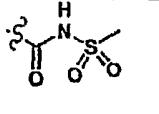
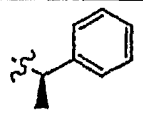
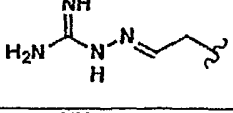
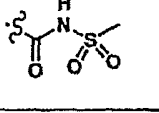
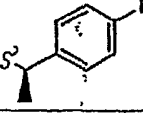
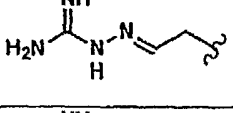
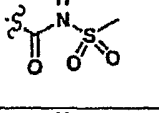
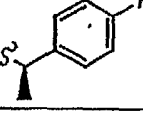
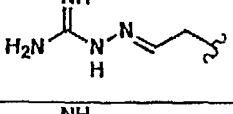
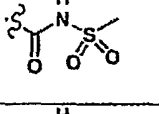
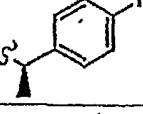
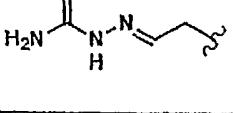
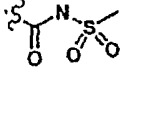
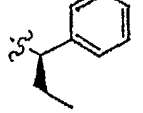
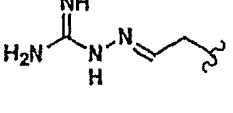
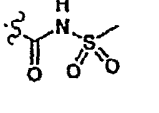
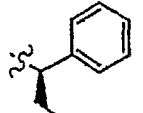
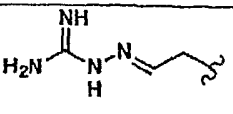
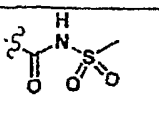
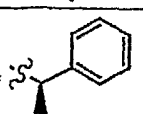
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FIGURE 1FQ

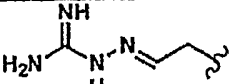
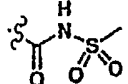
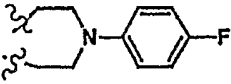
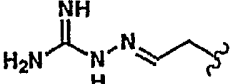
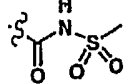
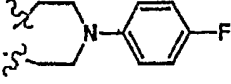
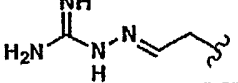
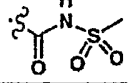
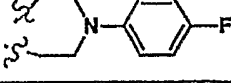
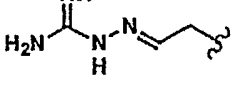
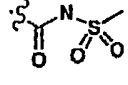
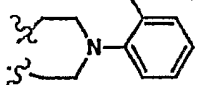
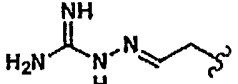
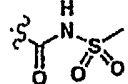
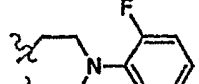
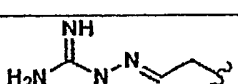
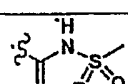

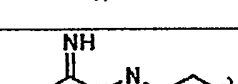
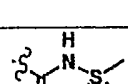
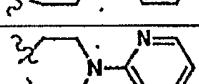
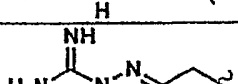
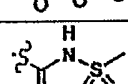
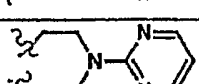
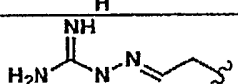
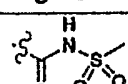
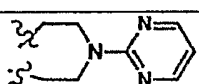
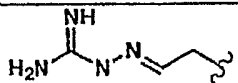
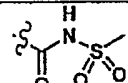
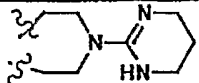
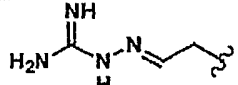
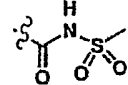
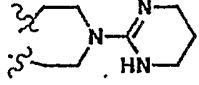
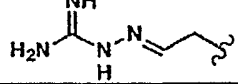
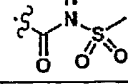
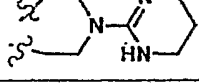
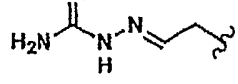
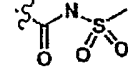
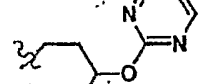
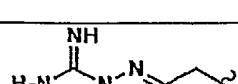
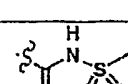
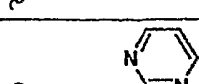
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A1720		CH ₃		H	
A1721		H		CH ₃	
A1722		H		H	
A1723		CH ₃		H	
A1724		H		CH ₃	
A1725		H		H	
A1726		CH ₃		H	
A1727		H		CH ₃	
A1728		H		H	
A1729		CH ₃		H	
A1730		H		CH ₃	
A1731		H		H	
A1732		CH ₃		H	

FIGURE 1FR

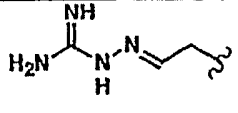
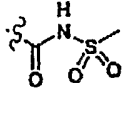
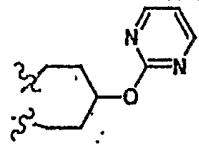
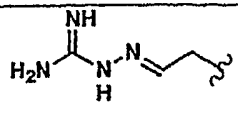
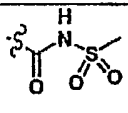
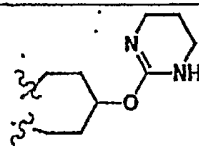
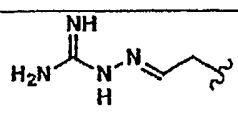
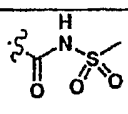
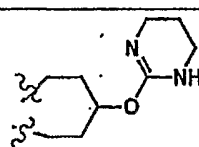
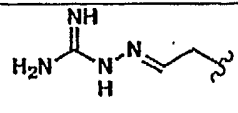
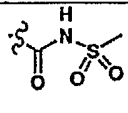
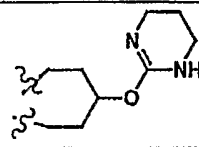
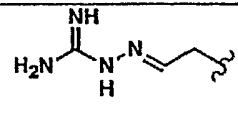
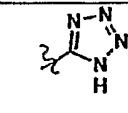
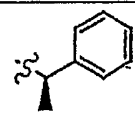
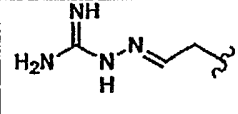
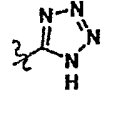
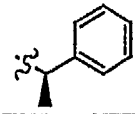
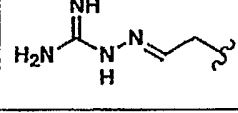
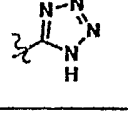
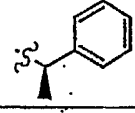
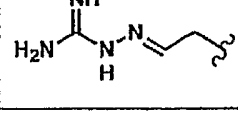
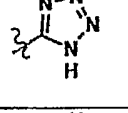
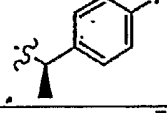
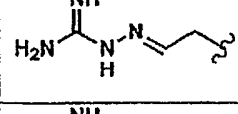
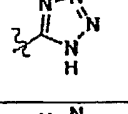
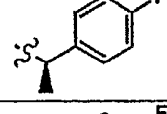
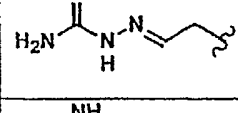
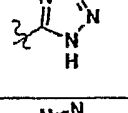
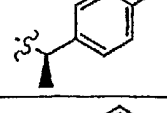
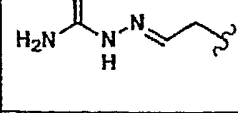
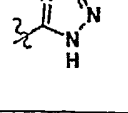
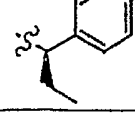
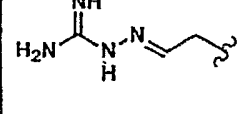
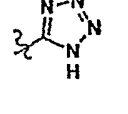
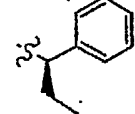
A1733		H		CH ₃	
A1734		H		H	
A1735		CH ₃		H	
A1736		H		CH ₃	
A1737		H		H	
A1738		CH ₃		H	
A1739		H		CH ₃	
A1740		H		H	
A1741		CH ₃		H	
A1742		H		CH ₃	
A1743		H		H	
A1744		CH ₃		H	

FIGURE 1FS

A1745		H		CH ₃	
A1746		H		H	
A1747		CH ₃		H	
A1748		H		CH ₃	
A1749		H		H	
A1750		CH ₃		H	
A1751		H		CH ₃	
A1752		H		H	
A1753		CH ₃		H	
A1754		H		CH ₃	
A1755		H		H	
A1756		CH ₃		H	
A1757		H		CH ₃	
A1758		H		H	

FIGURE 1FT

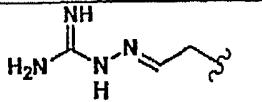
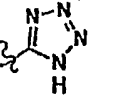
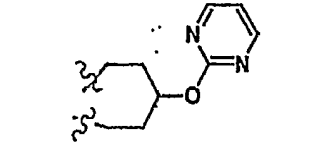
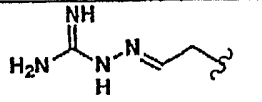
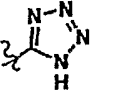
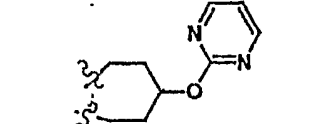
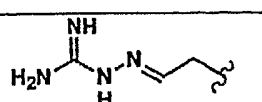
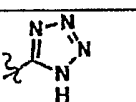
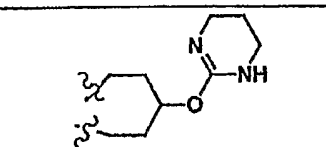
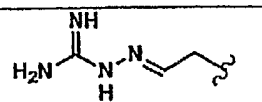
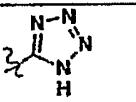
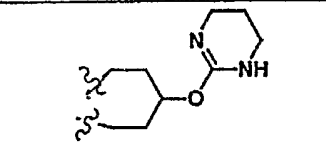
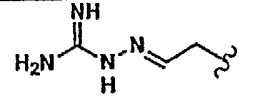
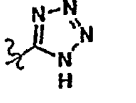
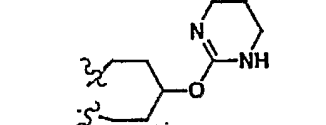
A1759		CH ₃		H	
A1760		H		CH ₃	
A1761		H		H	
A1762		CH ₃		H	
A1763		H		CH ₃	

FIGURE 1FU

A1759		CH ₃		H	
A1760		H		CH ₃	
A1761		H		H	
A1762		CH ₃		H	
A1763		H		CH ₃	

FIGURE 2A

Compound No.	Compound Name	IC ₅₀	TP ₅₀
155	(2S,3R)-3-(3-guanidinopropyl)-1-((R)-1-(naphthalen-1-yl)ethylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
160	(2S,3R)-3-(3-guanidinopropyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+++)	
64	(2S,3R)-cyclobutyl 3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
65	(2S,3R)-methyl 3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	
63	(2S,3R)-3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-((R)-1-phenylpropylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
93	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
90	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamothioyl)azetidine-2-carboxylate	(+++)	(+++)
9	(2S,3R)-3-(3-aminobenzyl)-1-((2S)-2-(benzyloxy)cyclopentylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	(+++)
66	(2S,3R)-3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-N ₂ ,N ₂ -diethyl-4-oxo-N ₁ -((R)-1-phenylethyl)azetidine-1,2-dicarboxamide	(+++)	
29	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N ₂ ,N ₂ -diethyl-4-oxo-N ₁ -((R)-1-phenylethyl)azetidine-1,2-dicarboxamide	(+++)	(+++)

FIGURE 2B

25	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-1-((R)-1-(naphthalen-1-yl)ethylcarbamoyl)-4-oxoazetidine-2-carboxylate	(+++)	(+++)
152	(2S,3R)-ethyl 3-(3-guanidinopropyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(+++)	
96	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-(methylsulfonyl)-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide	(+++)	(+++)
101	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-(4-fluorophenylsulfonyl)-N2-methyl-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide	(+++)	(+++)
24	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-((R)-1-(naphthalen-1-yl)ethylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
30	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N2-ethyl-N2-methyl-4-oxo-N1-((R)-1-phenylethyl)azetidine-1,2-dicarboxamide	(+++)	(+++)
28	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
8	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(benzhydrylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	(+++)
159	(2S,3R)-1-(4-ethylphenylcarbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
10	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N1,N2-bis((1S,2S)-2-(benzyloxy)cyclopentyl)-4-oxoazetidine-1,2-dicarboxamide	(+++)	(+++)
23	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)

FIGURE 2C

22	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
67	(2S,3R,E)-1-(biphenyl-4-ylcarbamoyl)-3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxoazetidine-2-carboxylic acid	(+++)	(+++)
15	(2S,3R)-methyl 3-((2-aminopyridin-4-yl)methyl)-1-(2-benzylphenylcarbamoyl)-4-oxoazetidine-2-carboxylate	(+++)	(+++)
68	(2S,3R,E)-methyl 3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
69	(2S,3R)-3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
151	(2S,3R)-3-(3-guanidinopropyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+++)	
31	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(morpholine-4-carbonyl)-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide	(+++)	(+++)
154	(2S,3R)-3-(3-guanidinopropyl)-1-(4-methoxyphenethylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
157	(2S,3R)-3-(3-guanidinopropyl)-4-oxo-1-((S)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+++)	
153	(2S,3R)-3-(3-guanidinopropyl)-1-(4-methoxybenzylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
158	(2S,3R)-3-(3-guanidinopropyl)-1-((S)-1-(naphthalen-1-yl)ethylcarbamoyl)-4-oxoazetidine-2-carboxylic acid	(+++)	

FIGURE 2D

156	(2S,3R)-1-(3-ethylphenylcarbamoyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid	(+++)	
86	(2R,3R)-ethyl 3-(3-aminophenylthio)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	(++)
106	((2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidin-2-yl)methyl methanesulfonate	(+++)	(+++)
72	(2S,3R,E)-3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-(4-phenoxyphenylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
87	(2R,3S)-ethyl 3-(3-aminophenylthio)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
70	(2S,3R)-4-oxo-1-((R)-1-phenylethylcarbamoyl)-3-((E)-2-(2-(N-((R)-1-phenylethylcarbamoyl)carbamimidoyl)hydrazono)ethyl)azetidine-2-carboxylic acid	(+++)	
73	(2S,3R,E)-3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+++)	(+++)
74	(2S,3R)-cyclobutyl 3-((E)-2-(2-(N-methylcarbamimidoyl)hydrazono)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
16	(2S,3R)-methyl 3-(3-aminobenzyl)-4-oxo-1-((1R,2S)-2-phenylcyclopropylcarbamoyl)azetidine-2-carboxylate	(+++)	(+++)
75	(2S;3R,E)-benzyl 1-(biphenyl-4-ylcarbamoyl)-3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxoazetidine-2-carboxylate	(+++)	(+++)
39	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(hydroxymethyl)-N-((R)-1-(naphthalen-1-yl)ethyl)-4-oxoazetidine-1-carboxamide	(+++)	(++)

FIGURE 2E

17	(2S,3R)-methyl 3-((2-aminopyridin-4-yl)methyl)-1-((1R,2R)-2-(benzyloxy)cyclopentylcarbamoyl)-4-oxoazetidine-2-carboxylate	(+++)	(+++)
119	ethyl 2-((2R,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetid-2-yl)acetate	(+++)	
76	(2S,3R)-ethyl 3-((E)-2-(2-(N-methylcarbamimidoyl)hydrazono)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+++)	
32	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-N1-((R)-1-phenylethyl)-N2-(pyridin-3-yl)azetidine-1,2-dicarboxamide	(+++)	(+++)
77	(2S,3R)-3-((E)-2-(2-(N-methylcarbamimidoyl)hydrazono)ethyl)-4-oxo-1-((R)-1-phenylpropylcarbamoyl)azetidine-2-carboxylic acid	(++)	
11	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-N1,N2-bis(3-benzylphenyl)-4-oxoazetidine-1,2-dicarboxamide	(++)	
26	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(++)	
27	(2S,3R)-benzyl 3-((2-aminopyridin-4-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(++)	
71	(2S,3R)-4-oxo-3-((E)-2-(2-(N-((R)-1-phenylethylcarbamoyl)carbamimidoyl)hydrazono)ethyl)azetidine-2-carboxylic acid	(++)	
45d	(2S,3R)-4-methoxybenzyl 3-((2-aminopyridin-4-yl)methyl)-1-(benzofuran-2-yl)-4-oxoazetidine-2-carboxylate	(++)	
78	(2S,3R,E)-4-methoxybenzyl 3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(++)	

FIGURE 2F

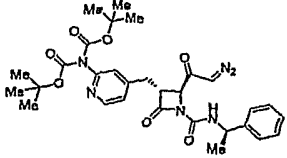
51	(2S,3R)-methyl 3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-3-methyl-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(++)	(++)
B1		(++)	
12	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-4-oxo-N1,N2-bis(3-phenoxyphenyl)azetidine-1,2-dicarboxamide	(++)	
B2	2-((2S,3R)-2-(methoxycarbonyl)-4-oxo-1-(phenylcarbamoyl)azetidin-3-yl)acetic acid	(++)	
112	(2R,3R)-ethyl 3-((2-aminopyridin-4-yl)methylthio)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(++)	
79	(2S,3R)-3-((E)-2-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazono)ethyl)-4-oxo-1-((R)-1-phenylpropylcarbamoyl)azetidine-2-carboxylic acid	(++)	
B3	(2S,3R)-methyl 3-allyl-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(++)	
B4	(2S,3R)-isopropyl 3-(3-methoxybenzyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	(++)	
B5	(2S,3R)-ethyl 4-oxo-1-((R)-1-phenylethylcarbamoyl)-3-(pyridin-3-yloxy)azetidine-2-carboxylate	(++)	
41	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-2-(hydroxymethyl)-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide	(++)	(++)
40	((2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-((R)-1-(naphthalen-1-yl)ethylcarbamoyl)-4-oxoazetidin-2-yl)methyl 1-(naphthalen-2-yl)ethylcarbamate	(++)	

FIGURE 2G

B6	(R)-3-((2-aminopyridin-4-yl)methyl)-2,2-dimethyl-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide	(++)	(++)
B7	(2S,3R)-3-(benzo[d][1,3]dioxol-4-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(++)	
B8	(2S,3R)-1-(2,4-dimethoxybenzyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxylic acid	(++)	
B9	(2S,3R)-3-(2-hydrazinylethyl)-4-oxo-1-((R)-1-phenylpropylcarbamoyl)azetidine-2-carboxylic acid	(++)	
45a	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(4-(4-fluorophenylcarbamoyl)phenyl)-4-oxoazetidine-2-carboxylic acid	(++)	
B10	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(4-(benzyloxy)-2-fluorophenyl)-4-oxoazetidine-2-carboxylic acid	(++)	
114	(2R,3S)-ethyl 3-((2-aminopyridin-4-yl)methylthio)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	(++)	
46	(2S,3R)-benzyl 3-((2-aminopyridin-4-yl)methyl)-1-(4-(benzyloxy)-2-fluorophenyl)-4-oxoazetidine-2-carboxylate	(++)	
B11	(2S,3R)-3-(3-methoxybenzyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(++)	
129	(2S,3R)-3-((3-aminobenzo[d]isoxazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(++)	
B12	(2R,3S)-2-(2-(2-carbamimidoylhydrazinyl)ethyl)-4-ethoxy-4-oxo-3-(3-((S)-1-phenylethyl)ureido)butanoic acid	(++)	

FIGURE 2H

B13	(2S,3R)-3-((E)-2-hydrazonoethyl)-4-oxo-1-((R)-1-phenylpropylcarbamoyl)azetidine-2-carboxylic acid	(++)	
53	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methyl)-3-methyl-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(++)	(++)
B14	(2S,3R)-methyl 3-((E)-2-(3-methoxyphenylimino)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(++)	
B15	(2S,3R)-N-(3,4-dihydroxybenzyl)-1-(2,4-dimethoxybenzyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxamide	(++)	
130	(2S,3R)-3-((3-amino-1H-indazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(++)	
113	(2R,3R)-ethyl 3-((2-aminopyridin-4-yl)methylthio)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	(++)	
B16	(2S,3R)-methyl 3-((E)-2-(2-chlorophenylimino)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+)	
45b	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(3-(4-fluorophenylcarbamoyl)phenyl)-4-oxoazetidine-2-carboxylic acid	(+)	
B17	1-(3-((2S,3R)-1-(2,4-dimethoxybenzyl)-2-(hydroxymethyl)-4-oxoazetidin-3-yl)propyl)guanidine	(+)	
37	(2S,3R)-3-(3-chlorobenzyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+)	
33	(2S,3R)-benzyl 3-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-oxoazetidine-2-carboxylate	(+)	

FIGURE 21

35	(2S,3R)-3-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+)	
B18	(2S,3R)-N-(3,4-dihydroxybenzyl)-1-(2,4-dimethoxybenzyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxamide	(+)	
B19	(2S,3R)-ethyl 3-((R)-3-(2-aminopyridin-4-yl)-1-oxo-1-(thiophen-2-yl)propan-2-yl)-4-oxoazetidine-2-carboxylate	(+)	
137	(2S,3R)-ethyl 3-((R)-3-(2-aminopyridin-4-yl)-1-oxo-1-((R)-1-phenylethylamino)propan-2-yl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+)	
54	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-3-methyl-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+)	(+)
45c	(2S,3R)-3-((2-aminopyridin-4-yl)methyl)-1-(3-(benzyloxy)phenyl)-4-oxoazetidine-2-carboxylic acid	(+)	
52	(2S,3R)-3-((E)-2-(2-carbamimidoylhydrazono)ethyl)-3-methyl-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylic acid	(+)	
B20	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methylamino)-4-oxo-1-(thiophene-2-carbonyl)azetidine-2-carboxylate	(+)	
34	(2S,3R)-3-(benzofuran-5-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+)	
36	(2S,3R)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	(+)	
B21	(2S,3R)-methyl 3-((E)-2-(benzo[d][1,3]dioxol-5-ylimino)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	(+)	

FIGURE 2J

83	(2S,3R,E)-3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxo-1-(pyridin-2-yl)azetidine-2-carboxylic acid	(+)	
B22	(2S,3R)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-1-(2,4-dimethoxybenzyl)-3-(3-guanidinopropyl)-4-oxoazetidine-2-carboxamide	(+)	
B23	(2S,3R)-ethyl 3-((2-aminopyridin-4-yl)methylamino)-4-oxoazetidine-2-carboxylate	>(+)	
B24	(2S,3R)-methyl 3-(biphenyl-2-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B25	(2S,3R,E)-4-methoxybenzyl 3-(2-(2-carbamimidoylhydrazono)ethyl)-4-oxoazetidine-2-carboxylate	>(+)	
142	(2S,3R)-methyl 3-allyl-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B26	(S)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	>(+)	
B27	(S)-benzyl 4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B28	(2S,3R)-benzyl 3-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B29	(2S,3R)-4-methoxybenzyl 3-(3-chlorobenzyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B30	(2S,3R)-N2-isopropyl-3-(3-methoxybenzyl)-4-oxo-N1-phenylazetidine-1,2-dicarboxamide	>(+)	

FIGURE 2K

B31	(2S,3R)-3-(biphenyl-2-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	>(+)	
B32	(S)-3,3-dibenzyl-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	>(+)	
B33	1-(4-tert-butylphenylsulfonyl)-3-(3-chlorobenzyl)-4,4-dimethylazetidin-2-one	>(+)	
B34	1-(4-tert-butylbenzoyl)-3-(3-chlorobenzyl)-4,4-dimethylazetidin-2-one	>(+)	
B35	(R)-3-(3-chlorobenzyl)-2,2-dimethyl-4-oxo-N-phenylazetidine-1-carboxamide	>(+)	
B36	1,3-bis(3-chlorobenzyl)-4,4-dimethylazetidin-2-one	>(+)	
B37	3-(3-chlorobenzyl)-4,4-dimethylazetidin-2-one	>(+)	
B38	1-(3-(2,2-dimethyl-4-oxoazetidin-3-yl)propyl)guanidine	>(+)	
B39	(2S,3R)-benzyl 3-(benzofuran-5-ylmethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B40	(S)-3,3-bis((3-aminobenzo[d]isoxazol-5-yl)methyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylic acid	>(+)	
B41	(2S,3R)-methyl 3-((E)-2-(3-chlorophenylimino)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	>(+)	

FIGURE 2L

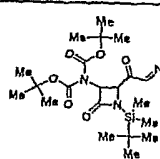
B42	(2S,3R)-methyl 3-((E)-2-(4-chlorophenylimino)ethyl)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidine-2-carboxylate	>(+)	
B43	(2S)-methyl 3-(bis(2-aminoethyl)amino)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B44	(2S,3R)-methyl 3-(2-tert-butoxy-2-oxoethyl)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B45	(2S)-methyl 3-(1-((2-aminopyridin-4-yl)methyl)-3-phenylureido)-4-oxo-1-(phenylcarbamoyl)azetidine-2-carboxylate	>(+)	
B46	(2S)-ethyl 3-(benzyloxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	>(+)	
B47	(2S)-ethyl 3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	>(+)	
B48	(2S)-ethyl 3-hydroxy-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	>(+)	
B49	(2S)-ethyl 3-(tert-butyldimethylsilyloxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	>(+)	
B50		>(+)	
B51	(R)-3-((2-aminopyridin-4-yl)methylamino)-1-(benzo[d][1,3]dioxol-5-yl)azetidin-2-one	>(+)	
B52	(R)-3-((2-aminopyridin-4-yl)methylamino)-2-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide	>(+)	

FIGURE 2M

B53	(2R,3S)-2-((2-aminopyridin-4-yl)methyl)-2-methyl-3-(3-((R)-1-phenylethyl)ureido)succinic acid	>(+)	
B54	(2R,3R)-ethyl 3-mercapto-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate	>(+)	
B55	(S)-2-(2-diazoacetyl)-4-oxo-N-((R)-1-phenylethyl)azetidine-1-carboxamide	>(+)	
B56	ethyl 2-((S)-4-oxo-1-((R)-1-phenylethylcarbamoyl)azetidin-2-yl)acetate	>(+)	
B57	(3R,4S)-1-(tert-butyltrimethylsilyl)-4-(2-(diethylamino)acetyl)-3-(2-hydroxyethyl)azetidin-2-one	>(+)	
B58	(2S,3R)-4-amino-3-((2-aminopyridin-4-yl)methyl)-2-(3-((S)-1-(naphthalen-1-yl)ethyl)ureido)-4-oxobutanoic acid	>(+)	