



(86) Date de dépôt PCT/PCT Filing Date: 2002/10/03

(87) Date publication PCT/PCT Publication Date: 2003/04/10

(85) Entrée phase nationale/National Entry: 2004/03/31

(86) N° demande PCT/PCT Application No.: US 2002/031769

(87) N° publication PCT/PCT Publication No.: 2003/029216

(30) Priorités/Priorities: 2001/10/03 (60/326,721) US;
2001/10/24 (60/338,623) US; 2001/11/06 (60/332,857) US;
2001/11/07 (60/350,052) US; 2001/11/21 (60/331,891) US;
2001/11/21 (60/332,107) US

(51) Cl.Int.⁷/Int.Cl.⁷ C07D 211/98, A61K 31/535,
A61K 31/495, A61K 31/45, A61P 7/02, C07D 241/04,
C07D 239/10, C07D 253/06, C07D 239/22,
C07D 213/73, C07D 211/56, C07D 237/02

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(54) Titre : COMPOSES HETEROCYCLIQUES A 6 CHAINONS UTILES DANS L'INHIBITION SELECTIVE DE LA
CASCADE DE LA COAGULATION

(54) Title: 6-MEMBERED HETEROCYCLIC COMPOUNDS USEFUL FOR SELECTIVE INHIBITION OF THE
COAGULATION CASCADE

(57) **Abrégé/Abstract:**

The present invention relates to compounds, and prodrugs thereof, compositions and methods useful for preventing and treating thrombotic conditions in mammals. The compounds of the present invention, and prodrugs thereof, selectively inhibit certain proteases of the coagulation cascade.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number
WO 03/029216 A1

(51) International Patent Classification⁷: **C07D 211/98**,
A61K 31/45, C07D 239/22, 239/10, 253/06, 211/56,
241/04, 213/73, 237/02, A61K 31/535, 31/495, A61P 7/02

(21) International Application Number: PCT/US02/31769

(22) International Filing Date: 3 October 2002 (03.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/326,721	3 October 2001 (03.10.2001)	US
60/338,623	24 October 2001 (24.10.2001)	US
60/332,857	6 November 2001 (06.11.2001)	US
60/350,052	7 November 2001 (07.11.2001)	US
60/332,107	21 November 2001 (21.11.2001)	US
60/331,891	21 November 2001 (21.11.2001)	US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 6-MEMBERED HETEROCYCLIC COMPOUNDS USEFUL FOR SELECTIVE INHIBITION OF THE COAGULATION CASCADE

(57) Abstract: The present invention relates to compounds, and prodrugs thereof, compositions and methods useful for preventing and treating thrombotic conditions in mammals. The compounds of the present invention, and prodrugs thereof, selectively inhibit certain proteases of the coagulation cascade.



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6-MEMBERED HETEROCYCLIC COMPOUNDS USEFUL FOR SELECTIVE INHIBITION OF THE COAGULATION CASCADE

Field of the Invention

The present invention relates to compounds, compositions and methods for preventing and treating thrombotic conditions such as coronary artery and cerebrovascular disease. More particularly, the invention relates to compounds, and prodrugs thereof, that selectively inhibit serine proteases of the coagulation cascade.

Background of the Invention

Hemorrhage, intravascular thrombosis, and embolism are common clinical manifestations of many diseases (see R. I. Handin *in* Harrison's Principles of Internal Medicine (J.D. Wilson, et al. eds., 12th ed. 1991) New York, McGraw-Hill Book Co., pp. 348-351). The normal hemostatic system limits blood loss by precisely regulated interactions between components of the vessel wall, circulating blood platelets, and plasma proteins. Unregulated activation of the hemostatic system, however, may cause thrombosis, which can reduce blood flow to critical organs like the brain and myocardium.

Physiological systems control the fluidity of blood in mammals (see P.W. Majerus, et al. *in* Goodman & Gilman's The Pharmacological Basis of Therapeutics (J.G. Hardman & L.E. Limbird, eds., 9th ed. 1996) New York, McGraw-Hill Book

Co., pp. 1341-1343). Blood must remain fluid within the vascular systems and yet quickly be able to undergo hemostasis. Hemostasis, or clotting, begins when platelets first adhere to macromolecules in subendothelial regions of injured and/or damaged blood vessels. These platelets aggregate to form the primary hemostatic plug and stimulate local activation of plasma coagulation factors leading to generation of a fibrin clot that reinforces the aggregated platelets. Plasma coagulation factors, also referred to as protease zymogens, include factors II, V, VII, VIII, IX, X, XI, and XII. These coagulation factors or protease zymogens are activated by serine proteases leading to coagulation in a so called "coagulation cascade" or chain reaction.

Coagulation or clotting occurs in two ways through different pathways. An intrinsic or contact pathway leads from XII to XIIa to XIa to IXa and to the conversion of X to Xa. Factor Xa in combination with factor Va converts prothrombin (II) to thrombin (IIa) leading to conversion of fibrinogen to fibrin. Polymerization of fibrin leads to a fibrin clot. An extrinsic pathway is initiated by the conversion of coagulation factor VII to VIIa by factor Xa. Factor VIIa, a plasma protease, is exposed to, and combines with its essential cofactor tissue factor (TF) which resides constitutively beneath the endothelium. The resulting factor VIIa/TF complex proteolytically activates its substrates, factors IX and X, triggering a cascade of reactions that leads to the generation of thrombin and a fibrin clot as described above.

While clotting as a result of an injury to a blood vessel is a critical physiological process for mammals, clotting can also lead to disease states. A pathological process called thrombosis results when platelet aggregation and/or a fibrin clot blocks (i.e., occludes) a blood vessel. Arterial thrombosis may result in ischemic necrosis of the tissue supplied by the artery. When the

thrombosis occurs in a coronary artery, a myocardial infarction or heart attack can result. A thrombosis occurring in a vein may cause tissues drained by the vein to become edematous and inflamed. Thrombosis of a deep vein may be complicated by a pulmonary embolism. Preventing or treating clots in a blood vessel may be therapeutically useful by inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, inhibiting embolus formation, and for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

In order to treat such conditions, researchers have sought to discover chemical compounds that efficaciously and selectively control the clotting process. In addition, such compounds may provide a better understanding of the pathways involved in the coagulation process.

Thus far, many of the compounds that have been discovered possess a polar or basic functional group which is integrally responsible for the desired biological activity. Frequently, this polar functional group is a nitrogen atom of, for example, a guanidine, alkyl-amidine or aryl-amidine group. Because these functionalities are highly basic, they remain protonated at physiologically relevant pH's. The ionic nature of such protonated species hinders their permeability across lipophilic membranes, which can reduce bioavailability when the pharmaceutical agent is administered orally.

In order to circumvent such a problem, it is often advantageous to perform a derivatization or chemical modification of the polar functionality such that the pharmaceutical agent becomes neutrally charged and more lipophilic, thereby facilitating absorption of the drug.

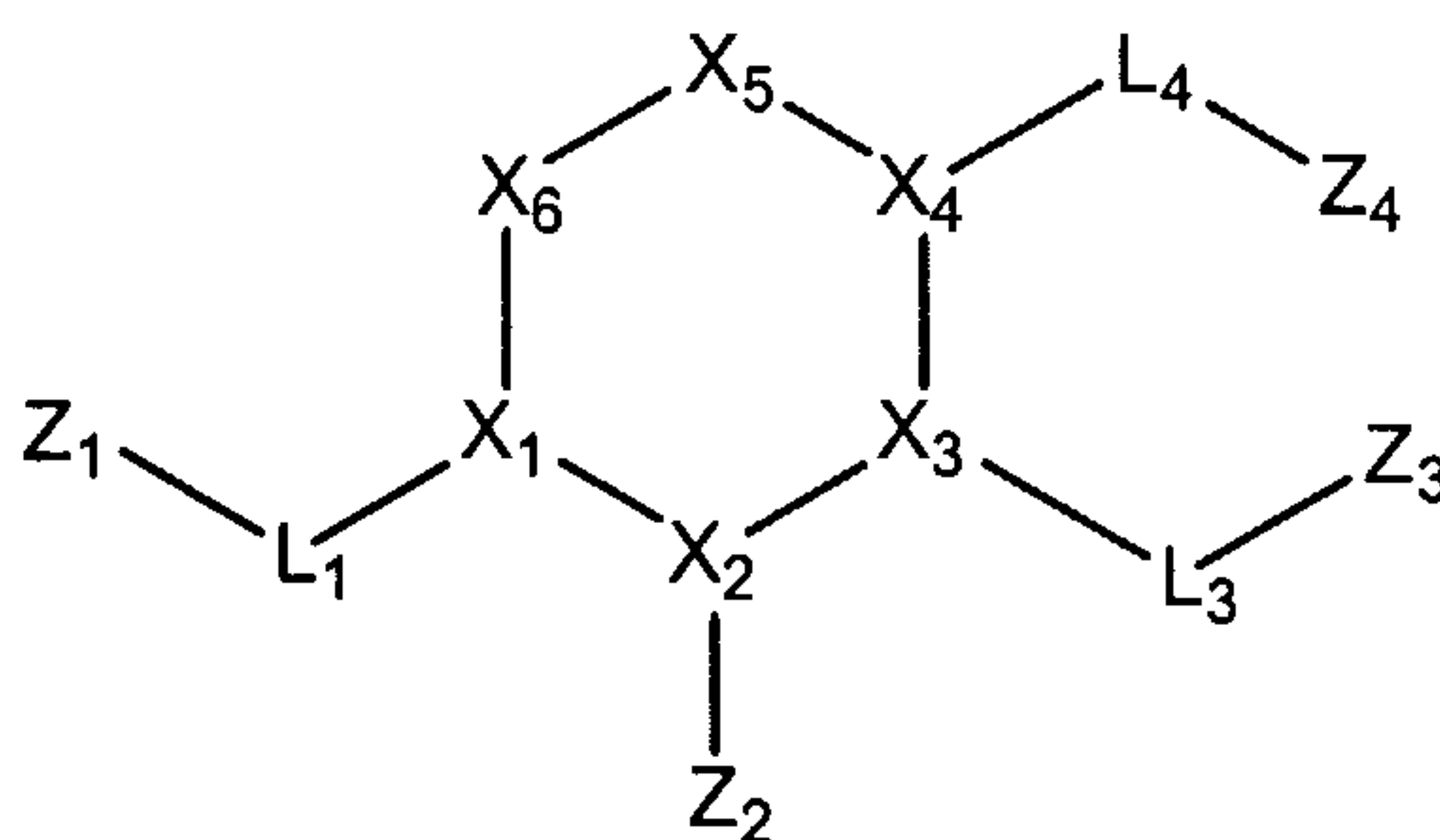
However, for the derivatization to be useful, the derivatization must be bioconvertable at the target site or sites of desired pharmacological activity and cleaved under normal physiological conditions to yield the biologically active drug. The term "prodrug" has been used to denote such a chemically modified intermediate.

Summary of the Invention

Among the various aspects of the present invention, therefore, is the provision of compounds useful for selective inhibition of certain enzymes that act upon the coagulation cascade thereby preventing and treating thrombotic conditions in mammals.

Another aspect of the present invention is the provision of prodrug compounds useful for selective inhibition of certain enzymes that act upon the coagulation cascade thereby preventing and treating thrombotic conditions in mammals. In general, these prodrug compounds undergo hydrolysis, oxidation, reduction or elimination at a derivatized amidine group to yield the active compound.

Briefly, therefore, the present invention is directed to a compound, *per se*, to the prodrug of the compound, to pharmaceutical compositions comprising the compound or prodrug and a pharmaceutically acceptable carrier, and to methods of use. The compound corresponds to formula (1):



(1)

wherein:

X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are each ring atoms defining a 6-membered heterocyclic ring;

X_1 , X_3 , and X_4 are independently carbon or nitrogen;

X_2 , X_5 , and X_6 are independently carbon, nitrogen, oxygen or sulfur, where X_5 and X_6 are optionally substituted with a halogen, provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

L_1 , L_3 and L_4 are linkages through which Z_1 , Z_3 , and Z_4 , respectively, are covalently bonded to different ring atoms of the 6-membered heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 , wherein Z_1 is covalently bonded to X_1 , Z_3 is covalently bonded to X_3 , and Z_4 is covalently bonded to X_4 , each of L_1 , L_3 and L_4 independently being a covalent bond or comprising one or more atoms through which Z_1 , Z_3 , and Z_4 are covalently bonded to X_1 , X_3 and X_4 , respectively;

Z_1 is hydrocarbyl or substituted hydrocarbyl;

Z_2 is hydrogen, an electron pair, or a hydrogen bond acceptor covalently or datively bonded to X_2 ;

Z_3 comprises a 5- or 6-membered heterocyclic or aromatic ring substituted with an amidine or a derivatized amidine group, the ring atoms of the 5- or 6-membered heterocyclic or aromatic ring of Z_3 being carbon, sulfur, nitrogen, or oxygen wherein the 5- or 6-membered ring is optionally substituted at any position with halogen, hydroxy, haloalkyl, alkyl, carboxy, alkoxycarbonyl, or hydrocarbyloxy; and

Z_4 comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of the 5- or 6-membered heterocyclic or carbocyclic ring of Z_4 being carbon, nitrogen, oxygen, or sulfur.

Other aspects and features of this invention will be in part apparent and in part pointed out hereafter.

Abbreviations and Definitions

The term "elimination" as used herein is generally meant to encompass any one or more of the following reactions: (1) a reaction that results in a compound fragmenting into two or more compounds; and (2) a reaction that results in one or more groups being removed from a compound without being replaced by other groups.

The term "oxidation" as used herein is generally meant to encompass any one or more of the following reactions: (1) a reaction that results in an increase in the oxidation number of an atom in a compound, whether the atom is uncharged or charged and whether free or covalently bound; (2) a reaction that results in the loss of hydrogen from a compound; (3) a reaction that results in the loss or removal of one or more electrons from a compound, with or without concomitant loss or removal of a proton or protons; (4) the action or process of reacting a compound with oxygen; and (5) a reaction that results in the addition of one or more oxygen atoms to a compound.

The term "reduction" as used herein is generally meant to encompass any one or more of the following reactions: (1) any reaction which results in a decrease in the oxidation number of an atom in a compound; and (2) any reaction that results in oxygen being withdrawn from, hydrogen being added to, or an electron being added to (with or without the addition of a proton) a compound.

The term "hydrolysis" as used herein is generally meant to encompass any one or more of the following reactions: (1) any reaction which results in the addition of a nucleophile to a compound to form a new bond with concurrent loss of a group from the compound; (2) any reaction which results in the addition of water to a compound; and (3) any reaction that results in the rupture of one or more chemical bonds by reaction with, and involving the addition of, the elements of water.

The term "physiological conditions" are those conditions characteristic to an organism's (to a human beings) healthy or normal functioning.

The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorus, boron, sulfur, or a halogen atom. Exemplary substituted hydrocarbyl moieties include, heterocyclo, alkoxyalkyl, alkenyloxyalkyl, alkynyloxyalkyl, aryloxyalkyl, hydroxyalkyl, protected hydroxyalkyl, keto, acyl, nitroalkyl, aminoalkyl, cyano, alkylalkylthio, arylalkylthio, ketals, acetals, amides, acids, esters and the like.

The term "heteroatom" shall mean atoms other than carbon and hydrogen.

Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, hexyl and the like.

Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched

chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

Unless otherwise indicated, the alkynyl groups described herein are preferably lower alkynyl containing
; from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

The terms "aryl" or "ar" as used herein alone or as
) part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl.
; Phenyl and substituted phenyl are the more preferred aryl.

The terms "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

The terms "heterocyclo" or "heterocyclic" as used
) herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1
; or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclos include heteroaromatics such as furanyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary
) substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano,
; thiol, ketals, acetals, esters and ethers.

The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "acetamidyl" as used herein describes a chemical moiety represented by the formula $\text{NR}_1\text{C}(\text{O})\text{R}_2$.

The term "carboxamido" as used herein, describes a chemical moiety represented by the formula $\text{C}(\text{O})\text{NR}_1\text{R}_2$.

The term "alkoxycarbonyl" as used herein describes a chemical moiety represented by the formula $\text{C}(\text{O})\text{OR}$.

The term "sulfonamido" as used herein describes a chemical moiety represented by the formula $\text{SO}_2\text{NR}_1\text{R}_2$.

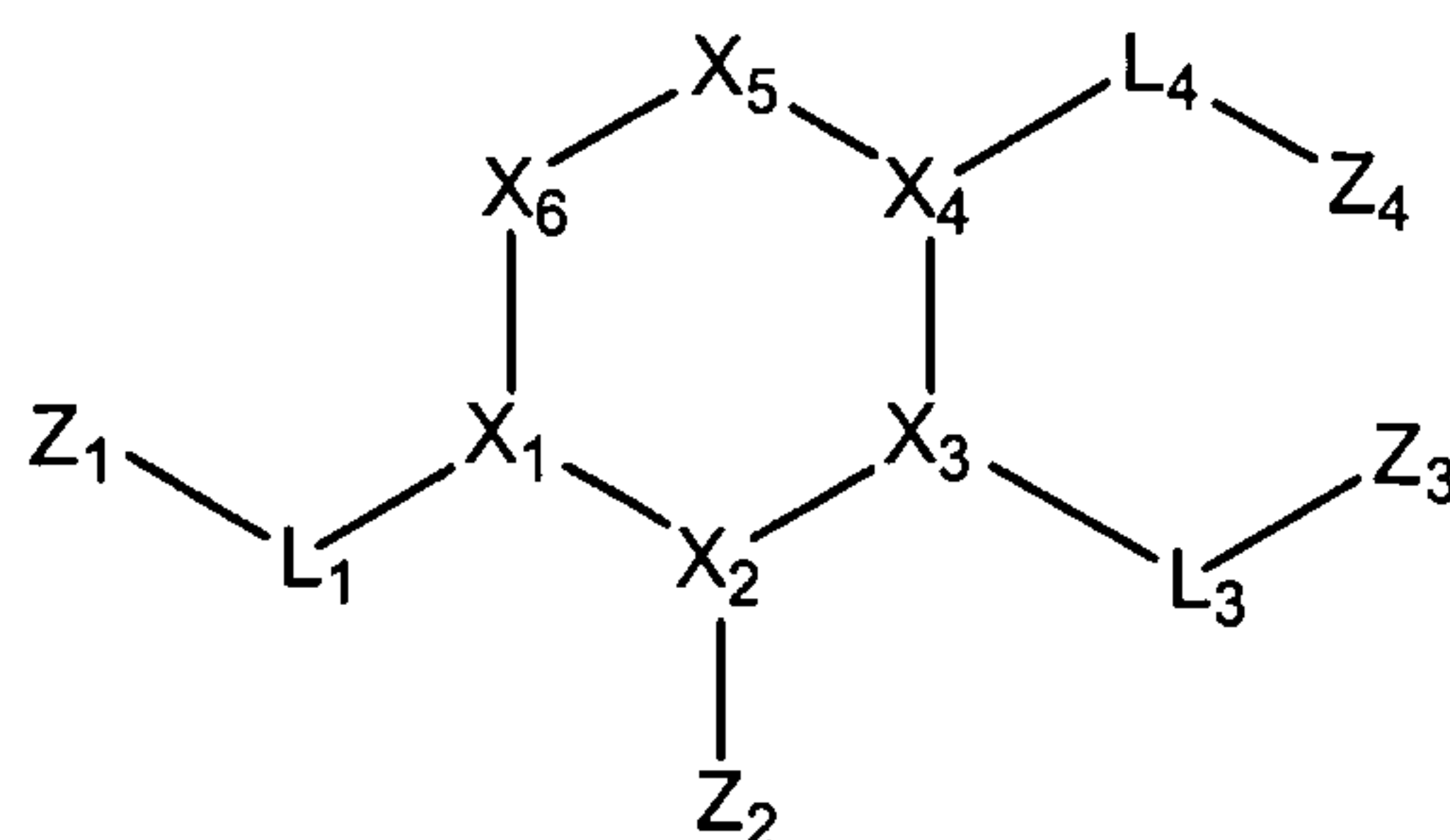
The term "alkylsulfonyl" as used herein describes a chemical moiety represented by the formula SO_2R .

The term "sulfonamidyl" as used herein describes a chemical moiety represented by the formula NRSO_2R .

As described herein for the terms "acetamidyl", "carboxamido", "alkoxycarbonyl", "sulfonamido", "alkylsulfonyl", and "sulfonamidyl", R, R_1 and R_2 are independently hydrogen, alkyl, aryl, and arylalkyl, optionally substituted with halogen, hydroxy or alkoxy.

Description of the Preferred Embodiment

In one embodiment of the present invention, the compounds correspond to formula (1):



(1)

wherein:

X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are each ring atoms defining a 6-membered heterocyclic ring;

X_1 , X_3 , and X_4 are independently carbon or nitrogen;

X_2 , X_5 , and X_6 are independently carbon, nitrogen, oxygen or sulfur where X_5 and X_6 are optionally substituted with a halogen, provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

L_1 , L_3 and L_4 are linkages through which Z_1 , Z_3 , and Z_4 , respectively, are covalently bonded to different ring atoms of the 6-membered heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 , wherein Z_1 is covalently bonded to X_1 , Z_3 is covalently bonded to X_3 , and Z_4 is covalently bonded to X_4 , each of L_1 , L_3 and L_4 independently being a covalent bond or comprising one or more atoms through which Z_1 , Z_3 , and Z_4 are covalently bonded to X_1 , X_3 and X_4 , respectively;

Z_1 is hydrocarbyl or substituted hydrocarbyl;

Z_2 is hydrogen, an electron pair, or a hydrogen bond acceptor covalently or datively bonded to X_2 ;

Z_3 comprises a 5- or 6-membered heterocyclic or aromatic ring substituted with an amidine or a derivatized amidine group, the ring atoms of the 5- or 6-membered heterocyclic or aromatic ring of Z_3 being carbon, sulfur, nitrogen, or oxygen wherein the 5- or 6-membered ring is optionally substituted at any position with halogen,

hydroxy, haloalkyl, alkyl, carboxy, alkoxycarbonyl, or hydrocarbyloxy; and

Z₄ comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of the 5- or 6-membered heterocyclic or carbocyclic ring of Z₄ being carbon, nitrogen, oxygen, or sulfur.

One aspect of the invention encompasses compounds corresponding to formula (1) wherein X₁, X₃, and X₄ are independently carbon or nitrogen and X₂, X₅, and X₆ are independently carbon, nitrogen, oxygen or sulfur. Typically, in this embodiment, no more than 4 of X₁, X₂, X₃, X₄, X₅, and X₆ are sp² hybridized. In one alternative of this embodiment, X₁, X₂, X₃, X₄, X₅, and X₆ are independently carbon or nitrogen, provided at least one of X₁, X₂, X₃, X₄, X₅, and X₆ is nitrogen. In another alternative of this embodiment, X₃ is nitrogen, X₂ is carbon, and Z₂ is hydrogen, fluorine, oxygen, or sulfur. In yet another alternative of this embodiment, X₂ is nitrogen, oxygen or sulfur and Z₂ is hydrogen, an electron pair, or a hydrogen bond acceptor. In yet another alternative of this embodiment, X₂ is nitrogen and Z₂ is hydrogen, oxygen, amino, or acyl. In still another alternative of this embodiment, X₂ is carbon and X₃ is nitrogen. Still another alternative of this embodiment embraces compounds where at least one of X₁, X₂, X₃, X₄, X₅, and X₆ is carbon and the carbon is sp³ hybridized. For each of the alternatives of this embodiment, X₅ may be optionally substituted with a halogen. A preferred halogen is chlorine. A more preferred halogen is fluorine.

In another aspect of compounds corresponding to formula (1), X₁, X₂, X₃, X₄, X₅, X₆, and Z₂ are as defined for compounds having formula (1) above and are selected to form the following 6-membered heterocyclic rings: piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, dehydropiperidinedione, dihydropyridazinone, dihydroisoxazinone, tetrahydrotriazinedione,

tetrahydrotriazinone, piperidine, and piperazine. In one alternative of this embodiment, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , and Z_2 are selected to form a heterocyclic ring selected from tetrahydrotriazinone, piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, piperidine, and piperazine. In another alternative of this embodiment, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , and Z_2 are selected to form a heterocyclic ring selected from tetrahydrotriazinone, piperidinone, dihydropyrimidinone, and tetrahydropyrimidinone. In a preferred alternative of this embodiment, the heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , and Z_2 is tetrahydrotriazinone.

In one embodiment of compounds having formula (1), L_1 is X_9NH wherein X_9 is covalently bonded to Z_1 and X_9 is a bond or $(CH_2)_m$ wherein m is 1 to 5. In one alternative of this embodiment (i.e., when L_1 is X_9NH), m is 1 to 2. In another alternative of this embodiment, L_1 is X_9NH wherein X_9 is covalently bonded to Z_1 and is a bond. In yet another alternative of this embodiment, L_1 is a methylene or ethylene group. In another alternative of this embodiment, L_1 optionally contains a bond to X_6 to form a fused ring with the heterocyclic ring.

In one embodiment of compounds corresponding to formula (1), L_3 is selected from the group consisting of a glycine derivative, an alanine derivative, an amino derivative, and a sulfonyl derivative. In one alternative of this embodiment, L_3 is a glycine derivative. In another alternative of this embodiment, L_3 is $CH_2CONHCH_2$ where Z_3 is bonded to the methylene bonded to the amine group.

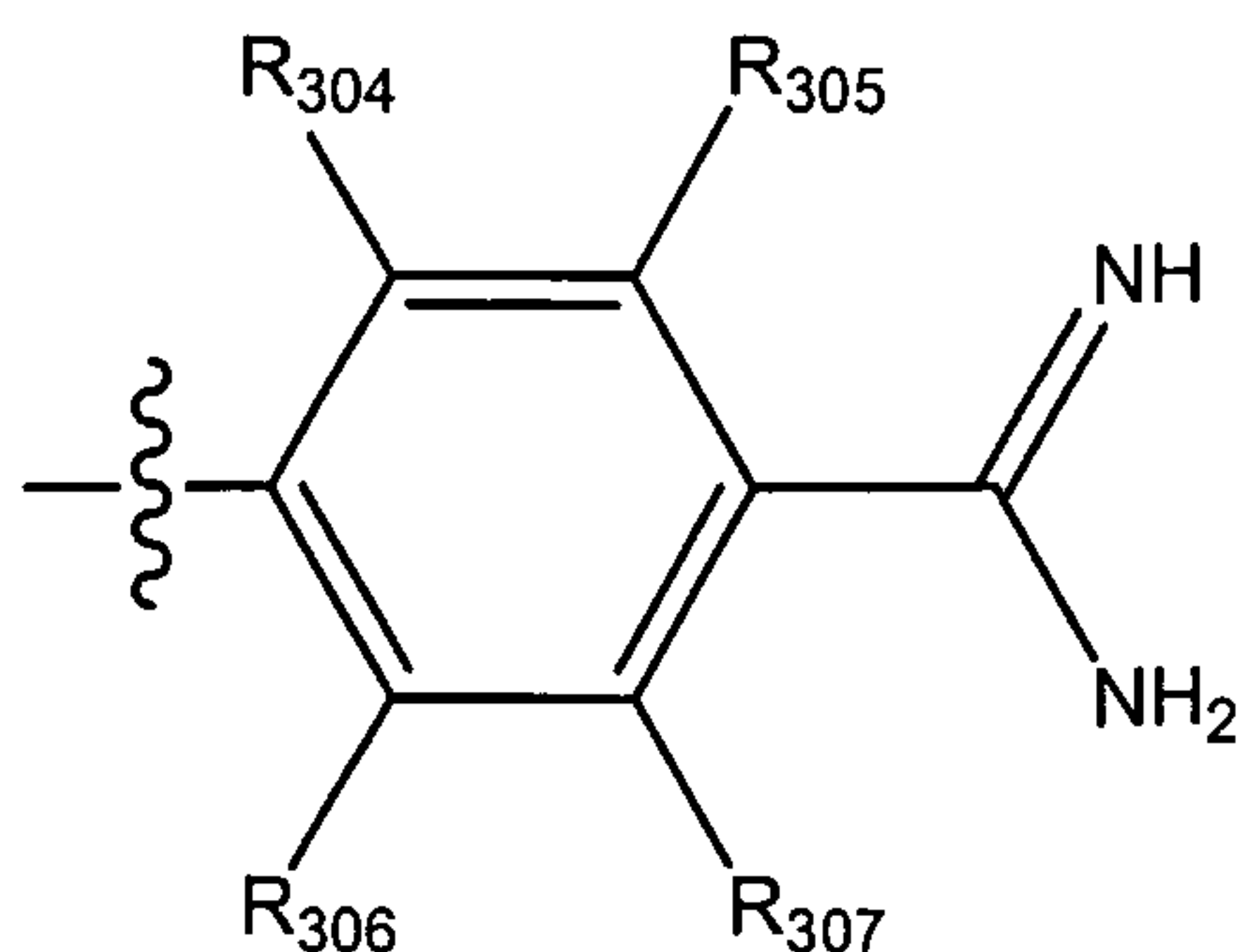
In one embodiment of compounds corresponding to formula (1), L_4 is selected from the group consisting of a bond, methylene, ethylene, or an optionally substituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus. In one alternative of this embodiment, L_4 is $(CH_2)_m$ wherein m is 0 to 2. In a preferred alternative of this embodiment, L_4 is a bond.

In one embodiment of compounds corresponding to formula (1), Z_1 is hydrocarbyl or substituted hydrocarbyl. In one alternative of this embodiment (i.e., when Z_1 is hydrocarbyl or substituted hydrocarbyl), Z_1 is optionally substituted C_2 to C_8 alkyl, optionally substituted C_3 to C_6 cycloalkyl and optionally substituted phenyl. In another alternative of this embodiment, Z_1 is selected from the group consisting of optionally substituted cyclopropyl, isopropyl, cyclobutyl, isobutyl, sec-butyl, methyl, ethyl, and phenyl. In another alternative of this embodiment, Z_1 is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, the alkyl, alkenyl, or alkynyl being optionally substituted with fluorine, hydroxy, carboxy, or alkoxycarbonyl. In yet another alternative of this embodiment, Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl. In yet another alternative of this embodiment, Z_1 is propyl, isopropyl, cyclopropyl, tert-butyl and cyclobutyl. In another alternative of this embodiment, Z_1 is cyclopropyl or isopropyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl. In still another alternative of this embodiment, Z_1 is phenyl optionally substituted with fluorine, hydroxy, carboxy, or alkoxycarbonyl. In yet another alternative of this embodiment, Z_1 is trifluoroethyl or carboxymethyl.

In one embodiment of compounds corresponding to formula (1), Z_2 is a hydrogen bond acceptor. Generally, hydrogen bond acceptors are heteroatoms that have a lone pair of electrons available for hydrogen bonding. When taken with the carbon to which Z_2 is attached, suitable hydrogen bond acceptors are selected from the group consisting of $C(O)$, $C(S)$, $C(Cl)$, $C(Br)$, $C(F)$, $C(OH)$, $COCH_3$, COR , $C(SH)$, CSR , and CNR_1R_2 wherein R , R_1 and R_2 are

independently hydrogen, alkyl, aryl, and arylalkyl, optionally substituted with halogen, hydroxy or alkoxy.

In one embodiment of compounds corresponding to formula (1), Z_3 is a 5- or 6-membered heterocyclic or aromatic ring substituted with an amidine or a derivatized amidine group and may be optionally substituted at any substitutable position with halogen, hydroxy, haloalkyl, alkyl, carboxy, alkoxycarbonyl, or hydrocarbyloxy, or any combination thereof. A preferred halogen is fluorine. In one alternative of this embodiment, directed toward the prodrugs of the compounds of formula (1), the 5- or 6-membered heterocyclic or aromatic ring comprising Z_3 is substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination, or any combination thereof, yields an amidine group. In another alternative of this embodiment, Z_3 is a 6-membered carbocyclic aromatic ring substituted with either an amidine group, or for embodiments directed toward the prodrug, with a derivatized amidine. In yet another embodiment, Z_3 comprises a substituted phenyl, thienyl, or furanyl ring, the phenyl, thienyl or furanyl ring being substituted with an amidine or a derivatized amidine group, and optionally further substituted at any substitutable position with fluorine, hydroxy, carboxy, alkoxycarbonyl, or hydrocarbyloxy. For embodiments directed toward the prodrug, the amidine group is derivatized according to any of the embodiments described more thoroughly below. In yet another alternative of this embodiment, Z_3 corresponds to formula (a):



(a)

wherein

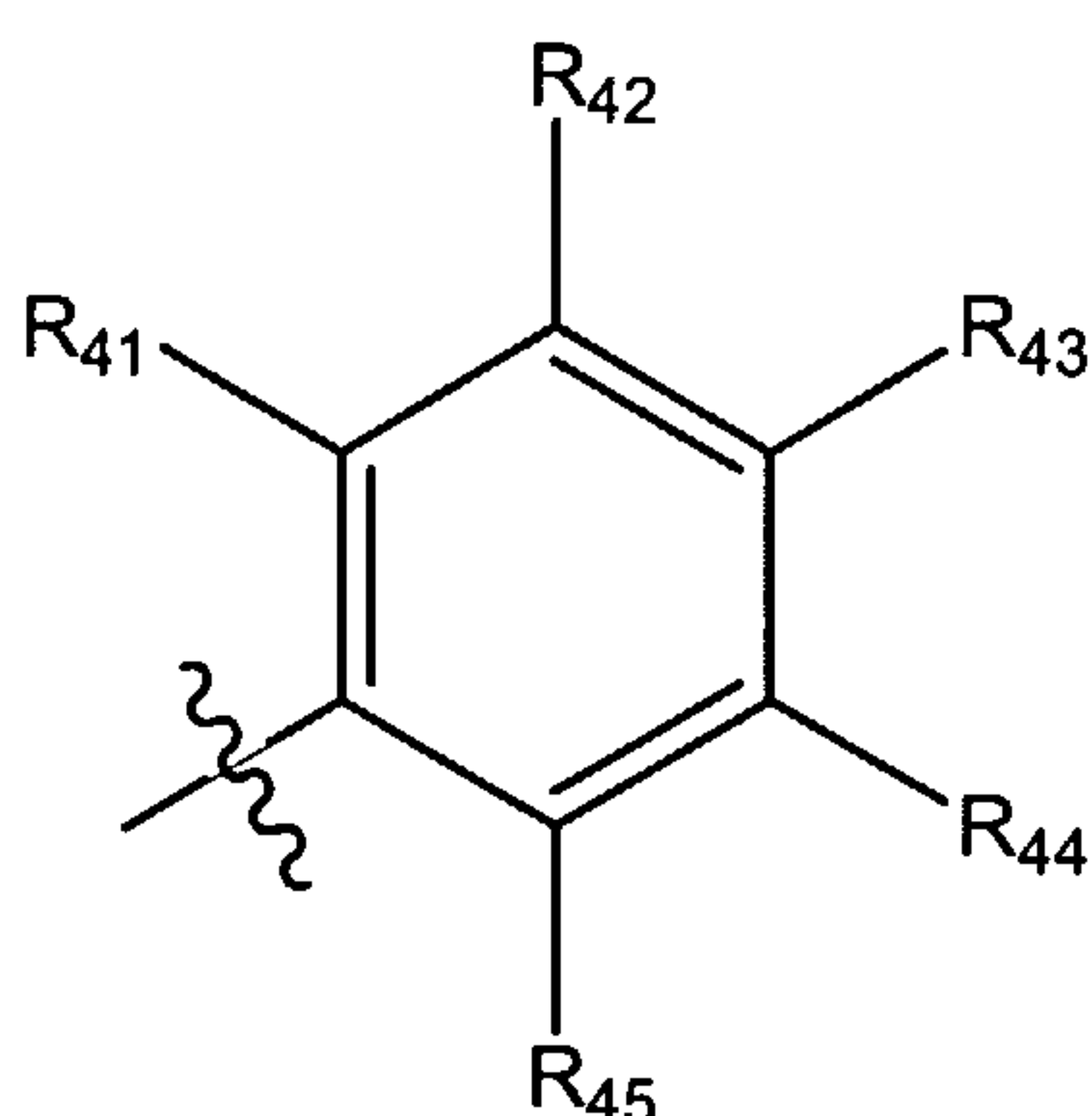
R₃₀₄ and R₃₀₆ are independently selected from the group consisting of hydrogen, fluorine, hydroxy, carboxy, hydrocarbyloxy and alkoxycarbonyl; and

R₃₀₅ and R₃₀₇ are independently selected from the group consisting of hydrogen, fluorine, methoxy, hydroxy and carboxy.

In one alternative of compounds wherein Z₃ corresponds to formula (a), Z₃ is selected from the group consisting of benzamidine-4-yl, 3-hydroxybenzamidine-4-yl, 3,5-dihydroxybenzamidine-4-yl, 2,5,6-trifluoro-3-hydroxybenzamidine-4-yl, 2-hydroxybenzamidine-4-yl and 3,5,6-trifluoro-2-hydroxybenzamidine-4-yl.

In one embodiment of compounds corresponding to formula (1), Z₄ comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of the 5- or 6-membered heterocyclic or carbocyclic ring of Z₄ being carbon, nitrogen, oxygen, or sulfur. In one alternative of this embodiment, Z₄ comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of Z₄ being Z₄₀, Z₄₁, Z₄₂, Z₄₄ and Z₄₅ when Z₄ is a 5-membered ring and Z₄₀, Z₄₁, Z₄₂, Z₄₃, Z₄₄ and Z₄₅ when Z₄ is a 6-membered ring, Z₄₀, Z₄₁, Z₄₂, Z₄₃, Z₄₄ and Z₄₅, being carbon, nitrogen, oxygen or sulfur, Z₄₀ being the ring atom through which Z₄ is attached to the heterocyclic core ring, Z₄₁ and Z₄₅ each being in an alpha

position relative to Z_{40} , Z_{42} and Z_{44} each being in a beta position relative to Z_{40} , Z_{43} being in the gamma position relative to Z_{40} when Z_4 is a 6-membered ring, Z_4 having a substituent R_{42} covalently attached to Z_{42} , and a second substituent bonded to one of Z_{41} , Z_{43} , Z_{44} , or Z_{45} , the substituent being R_{41} when bonded to Z_{41} , the substituent being R_{43} when bonded to Z_{43} , the substituent being R_{44} when bonded to Z_{44} , and the substituent being R_{45} when bonded to Z_{45} ; R_{42} is amino; and R_{41} , R_{43} , R_{44} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclo, halogen, or a substituted or unsubstituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus, provided at least one of R_{41} , R_{43} , R_{44} or R_{45} is other than hydrogen. In another alternative of this embodiment, Z_4 is a substituted, 6-membered, carbocyclic aromatic ring. In another alternative of this embodiment, Z_4 corresponds to formula (b):



(b)

wherein

R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, heterocyclo, halogen or a substituted or unsubstituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus; and R_{41} , R_{43} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

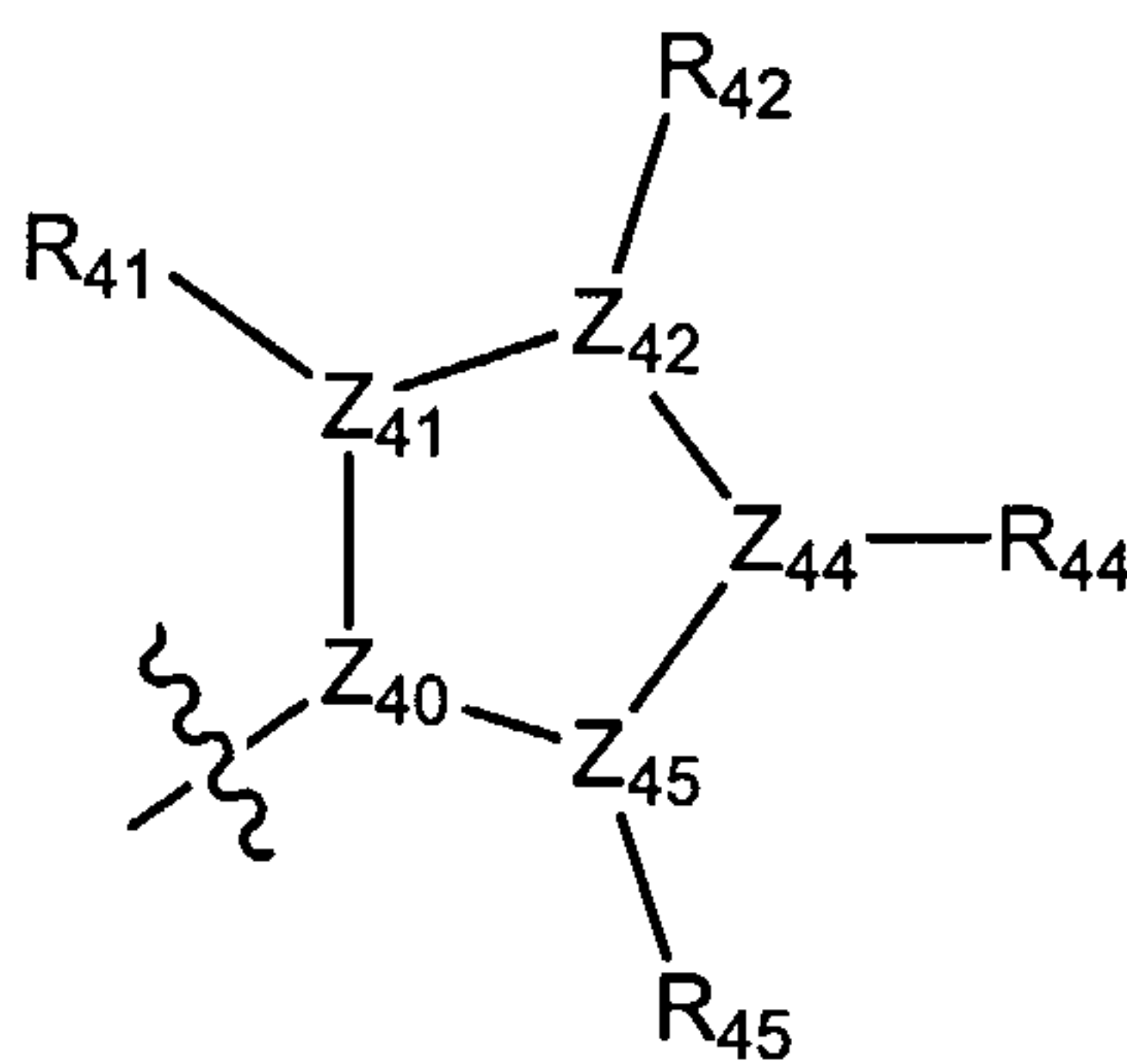
In one embodiment of compounds wherein Z_4 corresponds to formula (b), R_{44} is hydrocarbyl, substituted hydrocarbyl, heteroaryl, heterocyclo, halogen, acetamido, guanidino, hydroxy, nitro, amino, amidosulfonyl, acylamido, hydrocarbyloxy, substituted hydrocarbyloxy, hydrocarbylthio, substituted hydrocarbylthio, hydrocarbylsulfonyl, or substituted hydrocarbylsulfonyl. In one alternative of this embodiment, wherein Z_4 corresponds to formula (b), R_{44} is hydroxy, alkylsulfonyl, haloalkyl, carboxamidoalkyl, or carboxamidoalkylaryl. In another alternative of this embodiment, wherein Z_4 corresponds to formula (b), R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, acetamidyl, alkoxy, hydroxy, amino, alkylsulfonyl, haloalkoxy, haloalkylthio, alkoxycarbonyl, carboxy, sulfonamido, carboxamido and sulfonamidyl, optionally substituted with fluorine. In still another alternative of this embodiment, R_{44} is selected from the group consisting of hydroxy, carboxy, carboxamido, alkoxy, alkylsulfonyl, sulfonamido, and alkoxycarbonyl. In a preferred alternative of this embodiment, R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy. In yet another alternative of this embodiment, each of R_{41} , R_{43} and R_{45} is hydrogen. In still yet another alternative of this embodiment, Z_{41} , Z_{43} or Z_{45} is substituted with fluorine or chlorine. In another embodiment of this invention, R_{44} is hydroxy, alkylsulfonyl, haloalkyl, carboxamidoalkyl, or carboxamidoalkylaryl.

In one alternative of compounds wherein Z_4 corresponds to formula (b), R_{42} is amino; R_{43} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and R_{41} , R_{44} and R_{45} are independently hydrogen, halogen or alkoxy.

In another alternative of compounds wherein Z_4 corresponds to formula (b), R_{42} is amino; R_{45} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and R_{41} , R_{43} and R_{44} are independently hydrogen, halogen or alkoxy.

In yet another alternative of compounds wherein Z_4 corresponds to formula (b), R_{42} is amino; R_{41} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and R_{43} , R_{44} and R_{45} are independently hydrogen, halogen or alkoxy.

In an alternative embodiment of compounds of formula (1), Z_4 corresponds to formula (c):

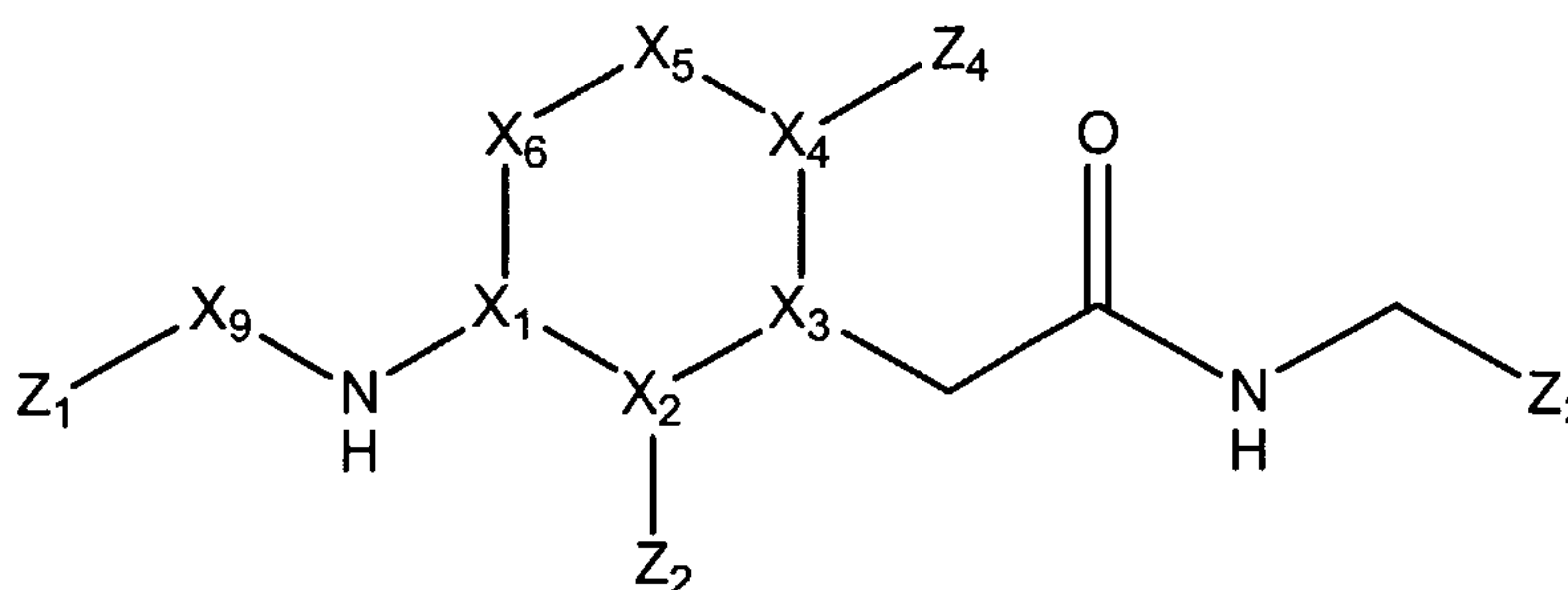


(c)

wherein

Z_{40} , Z_{41} , Z_{42} , Z_{44} , and Z_{45} are independently carbon, nitrogen, oxygen or sulfur, and R_{41} , R_{42} , R_{44} , and R_{45} are as defined in connection with the 6-membered carbocyclic aromatic ring.

In another aspect of the invention, the compounds of formula (1) may be represented by formula (2):



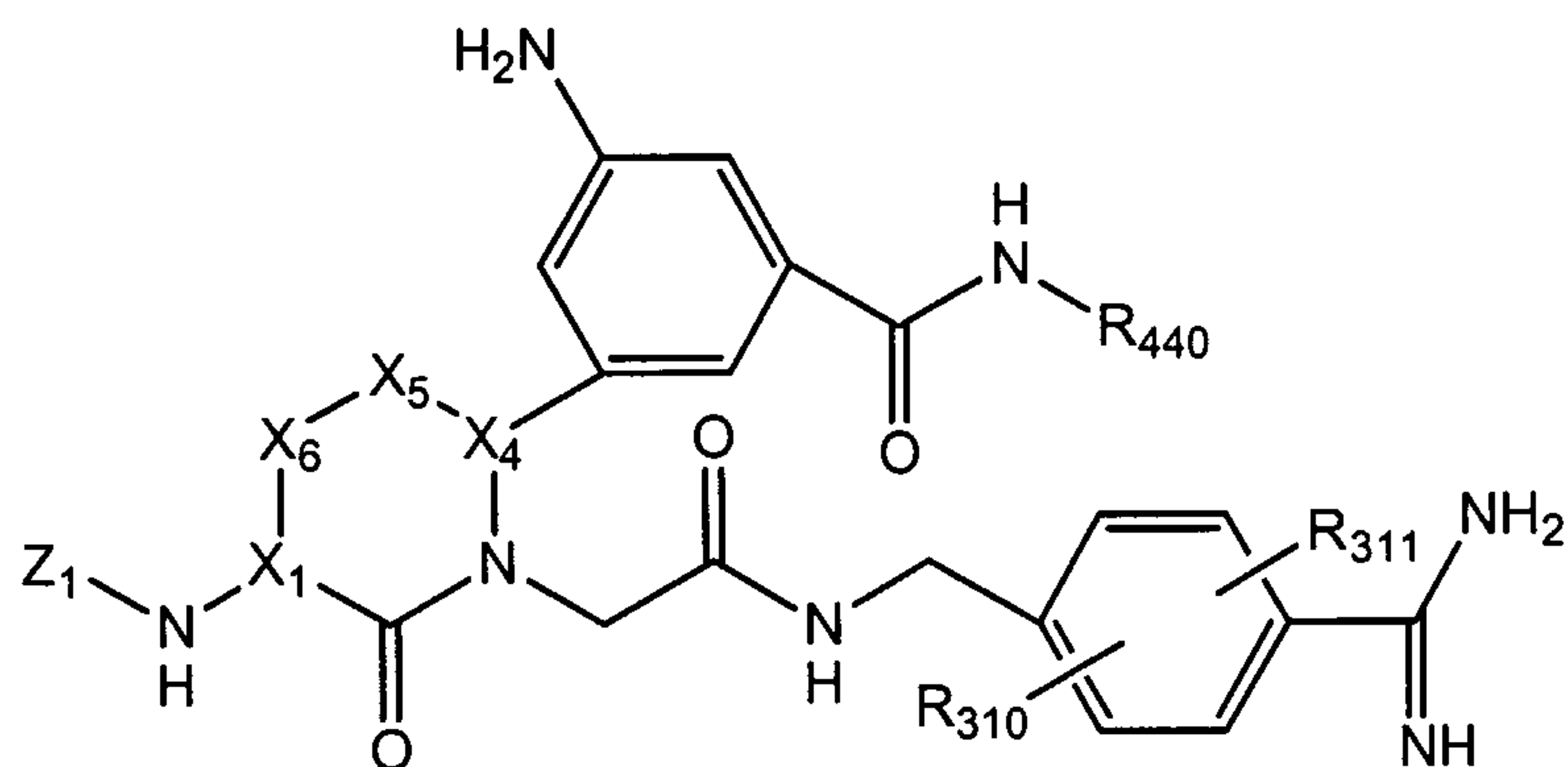
(2)

wherein X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , Z_1 , Z_2 , Z_3 , and Z_4 are as described for compounds having structural formula (1) and X_9 is a direct bond or $(CH_2)_m$ wherein m is 1 or 2. In one alternative of this embodiment, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , and Z_2 are selected to provide a piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, dehydropiperidinedione, dihydropyridazinone, dihydroisoxazinone, tetrahydrotriazinedione, tetrahydrotriazinone, piperidine, and piperazine heterocyclic ring and Z_1 , Z_3 , and Z_4 are as described for formula (1) and X_9 is a bond. In another alternative of this embodiment, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 and Z_2 are selected to provide a heterocyclic ring selected from tetrahydrotriazinone, piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, piperidine, and piperazine. In yet another alternative of this embodiment, X_1 , X_2 , X_3 , X_4 , X_5 , X_6 and Z_2 are selected to provide a heterocyclic ring selected from tetrahydrotriazinone, piperidinone, dihydropyrimidinone, and tetrahydropyrimidinone. In a preferred alternative of this embodiment, the heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , X_6 and Z_2 is tetrahydrotriazinone.

In a preferred embodiment of compounds corresponding to formula (2), X_9 is a bond; Z_1 is selected from the group consisting of cyclopropyl, methyl, ethyl, isobutyl, tert-butyl, and sec-butyl optionally substituted at any

substitutable position with fluorine, hydroxy, carboxy, or alkoxy carbonyl; Z_3 corresponds to formula (a) and is optionally substituted at any substitutable position with fluorine, hydroxy, carboxy, or hydrocarbyloxy; Z_4 corresponds to formula (b) wherein R_{42} is amino and R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, acetamidyl, alkoxy, hydroxy, amino, alkylsulfonyl, haloalkoxy, haloalkylthio, alkoxy carbonyl, carboxy, sulfonamido, carboxamido and sulfonamidyl, optionally substituted with fluorine; and X_1 , X_2 , X_3 , X_4 , X_5 , X_6 and Z_2 are as defined above for compounds having formula (1).

In a preferred embodiment, compounds corresponding to formula (2) may be represented by formula (2-a):



(2-a)

wherein

X_1 , X_4 , X_5 and X_6 are independently carbon or nitrogen;

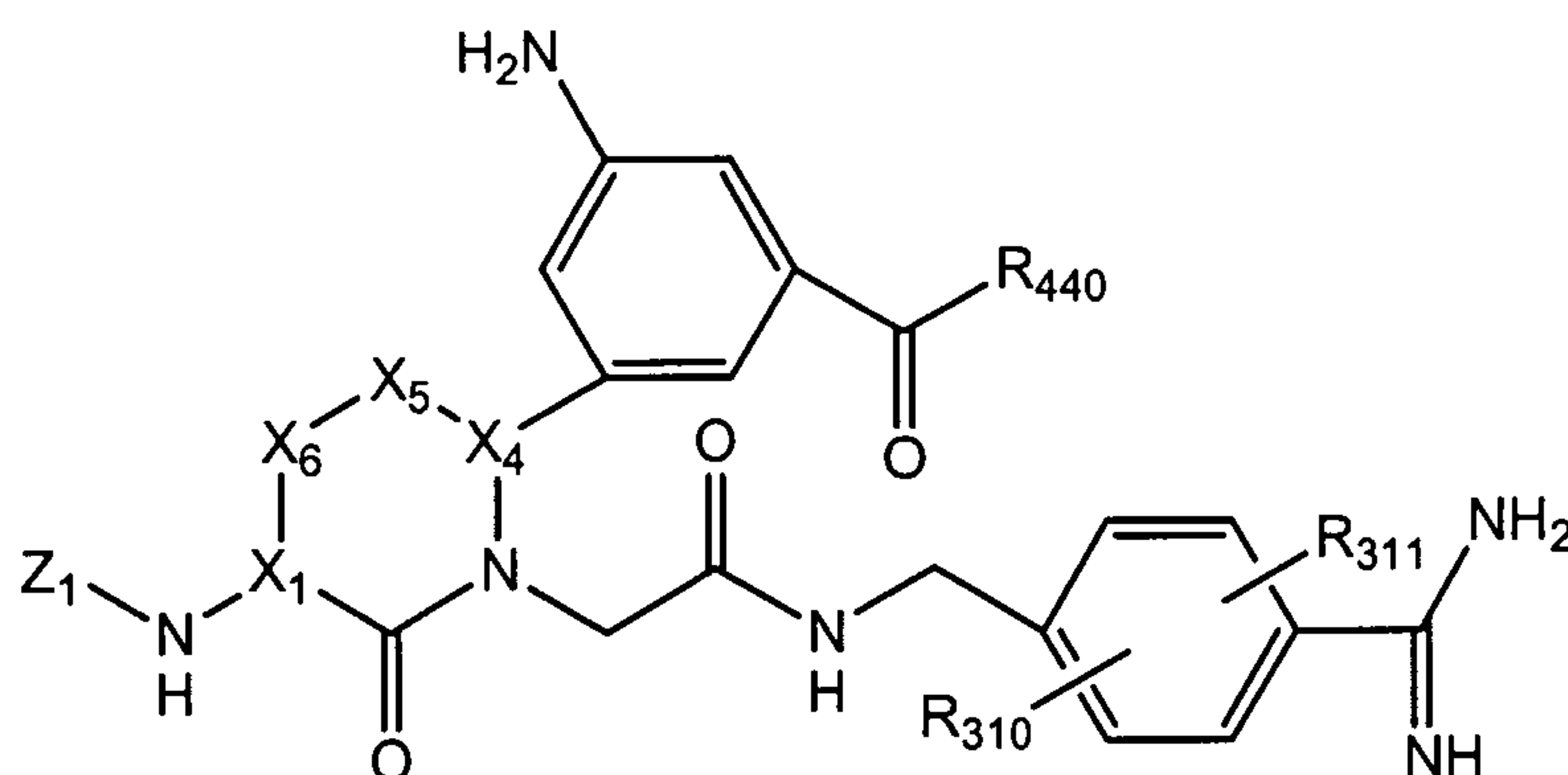
Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted with fluorine, hydroxy, carboxy, or alkoxy carbonyl;

R_{440} is C_1 - C_6 alkyl, aryl, aralkyl, carboxy, or carboxyalkyl, wherein said alkyl, aryl, aralkyl, carboxy,

or carboxyalkyl is optionally further substituted by fluorine; and

R_{310} and R_{311} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, alkoxy, and carboxy.

In another preferred embodiment, compounds corresponding to formula (2) may be represented by formula (2-b):



(2-b)

wherein

X_1 , X_4 , X_5 and X_6 are independently carbon or nitrogen;

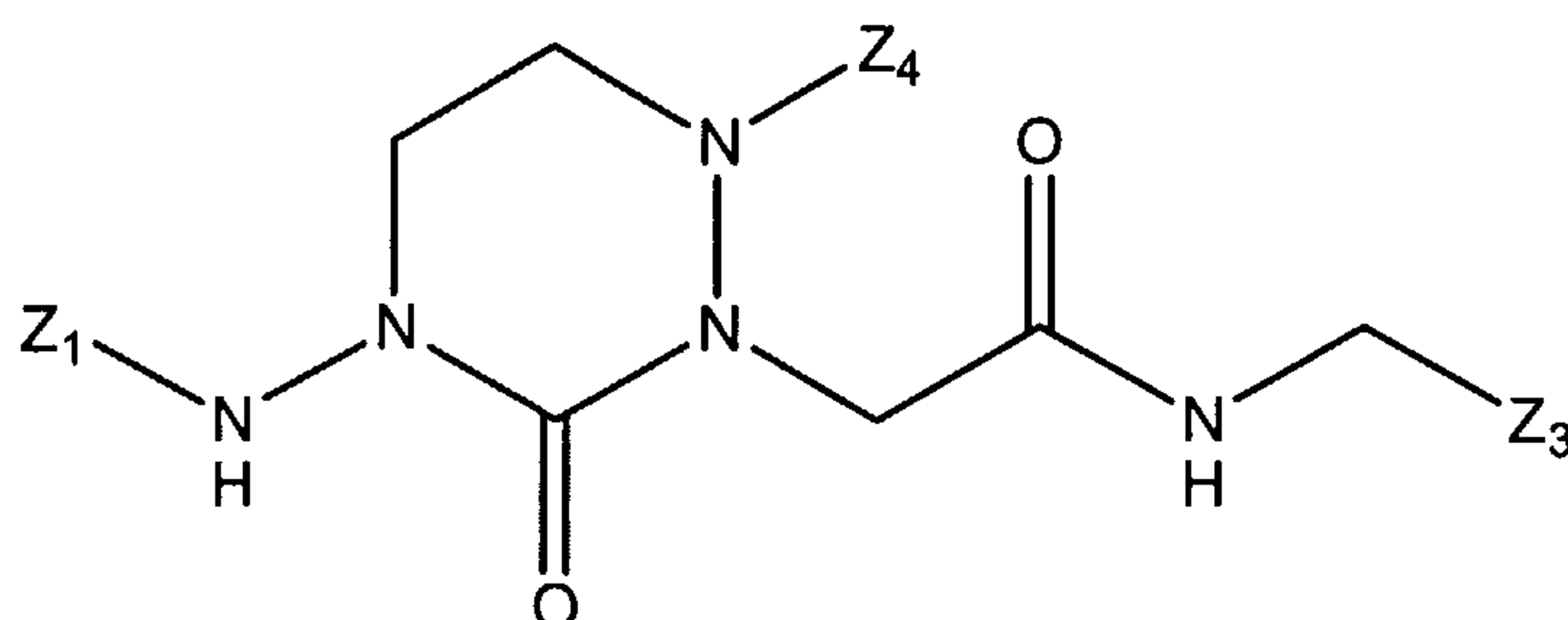
Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted with fluorine, hydroxy, carboxy, or alkoxy carbonyl;

R_{440} is C_1 - C_6 alkyl, aryl, aralkyl, carboxy, or carboxyalkyl, wherein said alkyl, aryl, aralkyl, carboxy, or carboxyalkyl is optionally further substituted by fluorine; and

R_{310} and R_{311} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, alkoxy, and carboxy.

In a preferred alternative of compounds corresponding to formula (2), the compounds possess a

tetrahydrotriazinone heterocyclic ring having formula (2-c):



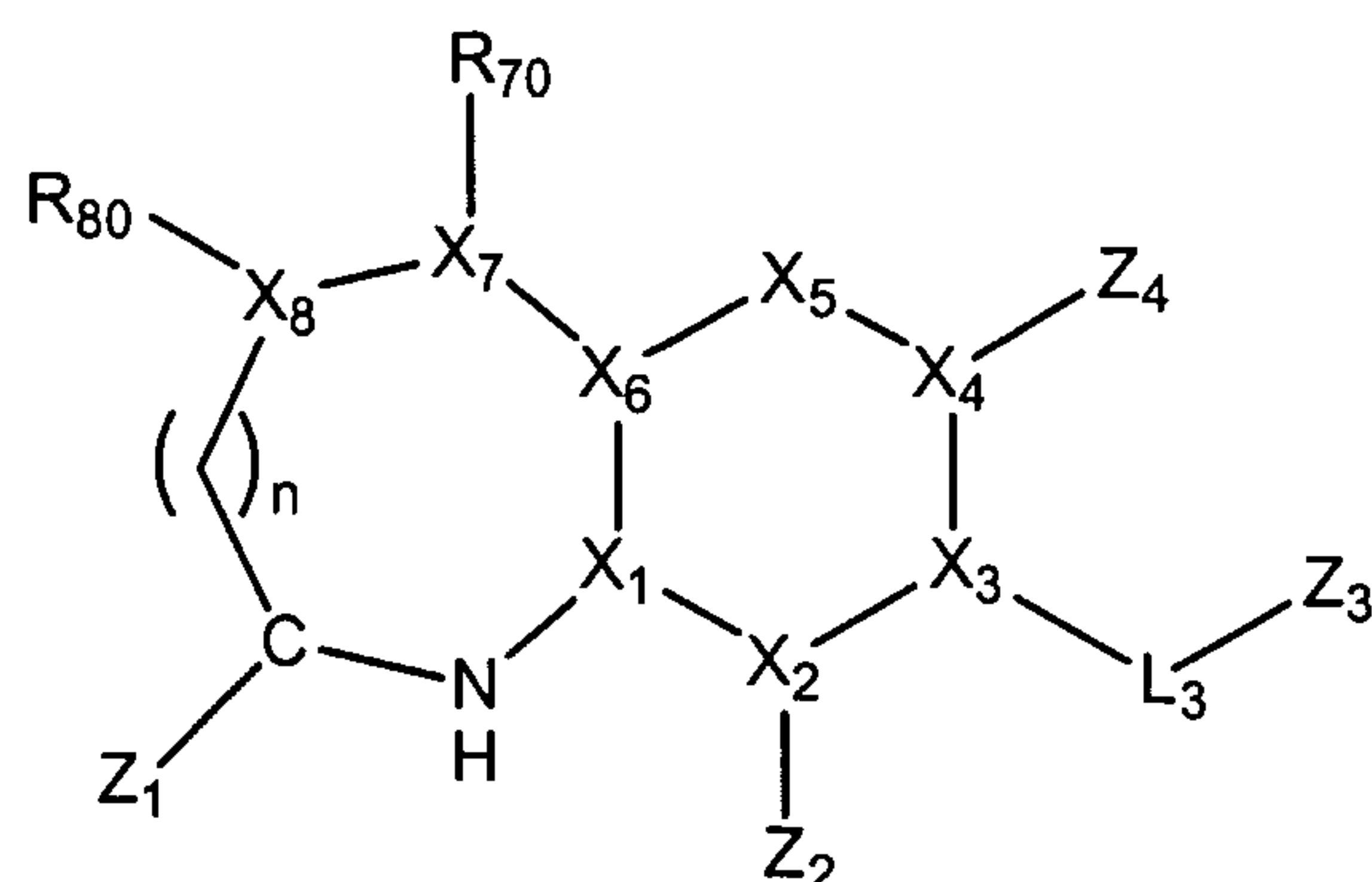
(2-c)

wherein:

Z₁, Z₂, and Z₃ are as defined for compounds having either of formula (1) and formula (2) above.

In one alternative of this embodiment (i.e., compounds having a tetrahydrotriazinone heterocyclic ring core), Z₁ is optionally substituted C₂ to C₈ alkyl, optionally substituted C₃ to C₆ cycloalkyl and optionally substituted phenyl. Preferred Z₁ substituents are optionally substituted cyclopropyl, isopropyl, cyclobutyl, methyl, ethyl and phenyl. In another alternative of this embodiment, Z₄ is a substituted, 6-membered, heterocyclic or carbocyclic aromatic ring.

Another aspect of the invention embraces compounds which correspond to formula (1) having the following fused ring formula (3):



(3)

wherein

Z_1 , Z_2 , Z_3 , Z_4 , L_3 , X_1 , X_2 , X_3 , X_4 , and X_5 are as defined for compounds having formula (1) or (2) above;

X_6 is carbon or nitrogen;

X_7 and X_8 are independently carbon, nitrogen, oxygen or sulfur;

R_{70} and R_{80} are independently selected from the group consisting of hydrogen, halogen, amino, hydrocarbyl, substituted hydrocarbyl, aryl, wherein aryl is phenyl optionally substituted by hydroxy, amino, C_1 - C_8 alkyl, or halogen provided that R_{70} is not present when X_7 is a bond and R_{80} is not present when X_8 is a bond; or R_{70} and R_{80} , along with the ring atoms to which each is attached, form a 5- or 6-membered saturated ring; and

n is 0 to 2.

In a preferred embodiment of compounds of formula (3), L_3 is $CH_2CONHCH_2$. In one alternative of this embodiment, (i.e., when L_3 is $CH_2CONHCH_2$), X_7 and X_8 are carbon. In another alternative of this embodiment, Z_3 corresponds to formula (a) and Z_4 corresponds to formula (b).

In another aspect of this invention, compounds corresponding to any of formulas (1), (2), or (3) possess a hydroxy or carboxy substituent at any one of Z_1 , Z_2 or Z_3 .

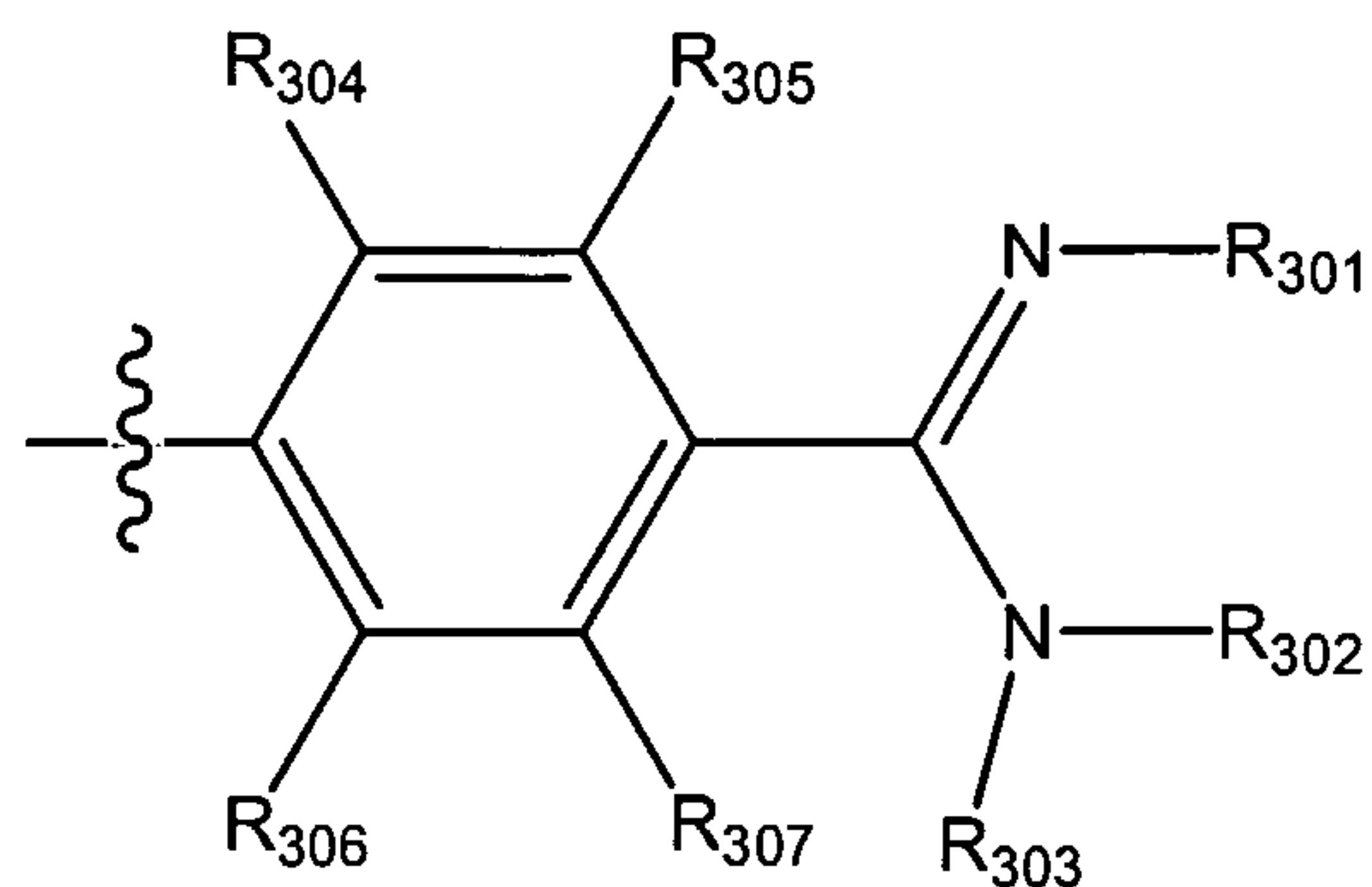
In another aspect of this invention for compounds corresponding to any of formulas (1), (2), or (3), Z_3 is

$-R_{300}C(=NR_{301})NR_{302}R_{303}$, wherein R_{300} is a 6-membered carbocyclic aromatic ring, R_{301} , R_{302} , R_{303} are independently selected from the group consisting of hydrogen, halogen, optionally substituted hydrocarbyl, and an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, phosphorus and sulfur, provided at least one of R_{301} , R_{302} , R_{303} is other than hydrogen. In yet another alternative of this embodiment, Z_3 is $-R_{300}C(=NR_{301})NR_{302}R_{303}$, wherein R_{300} is a 6-membered carbocyclic aromatic ring, and at least two of R_{301} , R_{302} , R_{303} are ring atoms of a heterocyclic ring. In an alternative of this embodiment, Z_3 is $-R_{300}C(=NR_{301})NR_{302}R_{303}$, wherein R_{300} is a 6-membered carbocyclic aromatic ring, and at least one of R_{301} , R_{302} , R_{303} are ring atoms of a heterocyclic ring fused to R_{300} .

In yet another aspect of this invention for compounds corresponding to any of formulas (1), (2), or (3), Z_3 is a benzamidine derivatized with one or more groups selected from carbonyl, thiocarbonyl, imino, enamino, phosphorus, and sulfur, where the benzamidine derivative hydrolyzes under physiological conditions to form benzamidine. In a further embodiment, Z_3 is a benzamidine derivatized with one or more groups selected from optionally substituted hydrocarbyl, provided that the carbon atom directly bonded to the amidine is sp^3 hybridized and aryl, where the benzamidine derivative is oxidized under physiological conditions to form benzamidine. In yet another embodiment, Z_3 is a benzamidine derivatized with one or more heteroatoms selected from oxygen, nitrogen in its most reduced state, and sulfur in its most reduced state, where the benzamidine derivative is reduced under physiological conditions to form benzamidine. In still another embodiment, Z_3 is a benzamidine derivatized with one or more substituents selected from a hydrocarbyl substituted at the beta carbon with carbonyl, sulfonyl, sulfinyl, cyano, nitro and an alkyl, aryl, or heterocyclic group substituted with oxygen, nitrogen, or sulfur at the carbon

directly bonded to the amidine group, where the benzamidine derivative undergoes elimination at physiological conditions to form benzamidine.

In a further embodiment for compounds corresponding to any of formulas (1), (2), or (3), Z_3 corresponds to formula (d):



(d)

wherein:

R_{301} , R_{302} , and R_{303} are independently selected from the group consisting of:

(i) hydrogen, $-C(=O)R_a$, $-C(=O)OR_a$, $-S(=O)OR_a$, $-S(=O)SR_a$, $-S(=O)_2OR_a$, $-S(=O)_2SR_a$ and alkenyl, wherein R_a is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, and heterocylo, provided, however, that the carbon atom of R_{301} , R_{302} , and R_{303} directly bonded to the amidine is sp^2 hybridized when R_{301} , R_{302} , and R_{303} is alkenyl,

(ii) hydrogen, optionally substituted hydrocarbyl and aryl, provided, however, the carbon atom of R_{301} , R_{302} , and R_{303} directly bonded to the amidine is sp^3 hybridized when R_{301} , R_{302} , and R_{303} is optionally substituted hydrocarbyl,

(iii) hydrogen, $-OR_b$, $-SR_b$, $-NR_b$, or $-N(R_b)_2$, wherein each R_b is independently optionally substituted hydrocarbyl, and heterocylo, and

(iv) hydrogen, substituted hydrocarbyl wherein the carbon bonded to the amidine group is substituted with $-OR_c$, $-SR_c$, $-NR_c$, or $-N(R_c)_2$, wherein each R_c is

independently $-C(O)R_d$, $-C(O)NR_d$, $-C(O)OR_d$, $-C(O)N(R_d)_2$ and each R_d is independently hydrocarbyl, substituted hydrocarbyl or heterocyclo, and substituted alkyl with the carbon atom beta to the point of attachment to the amidine group being an unsaturated electron withdrawing group, provided, however, at least one of R_{301} , R_{302} , and R_{303} is other than hydrogen;

R_{304} is selected from the group consisting of halogen, hydrogen, hydroxyl, alkyl, sulfhydryl, alkoxy, and alkylthio;

R_{305} is selected from the group consisting of oxygen, sulfur, halogen, hydrogen, hydroxyl, alkyl, sulfhydryl, alkoxy, and alkylthio;

R_{306} is selected from the group consisting of halogen, hydrogen, hydroxyl, alkyl, sulfhydryl, alkoxy, and alkylthio; and

R_{307} is selected from the group consisting of oxygen, sulfur, halogen, hydrogen, hydroxyl, alkyl, sulfhydryl, alkoxy, and alkylthio.

In one embodiment, the benzamidine derivative is hydrolyzed under physiological conditions to form benzamidine when Z_3 is a benzamidine derivative having formula (d) and R_{301} , R_{302} , and R_{303} are independently selected from hydrogen, $-C(=O)R_a$, $-C(=O)OR_a$, $-S(=O)OR_a$, $-S(=O)SR_a$, $-S(=O)_2OR_a$, $-S(=O)_2SR_a$ and alkenyl, wherein R_a is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, and heterocyclo, provided, however, that the carbon atom of R_{301} , R_{302} , and R_{303} directly bonded to the amidine is sp^2 hybridized when R_{301} , R_{302} , and R_{303} is alkenyl.

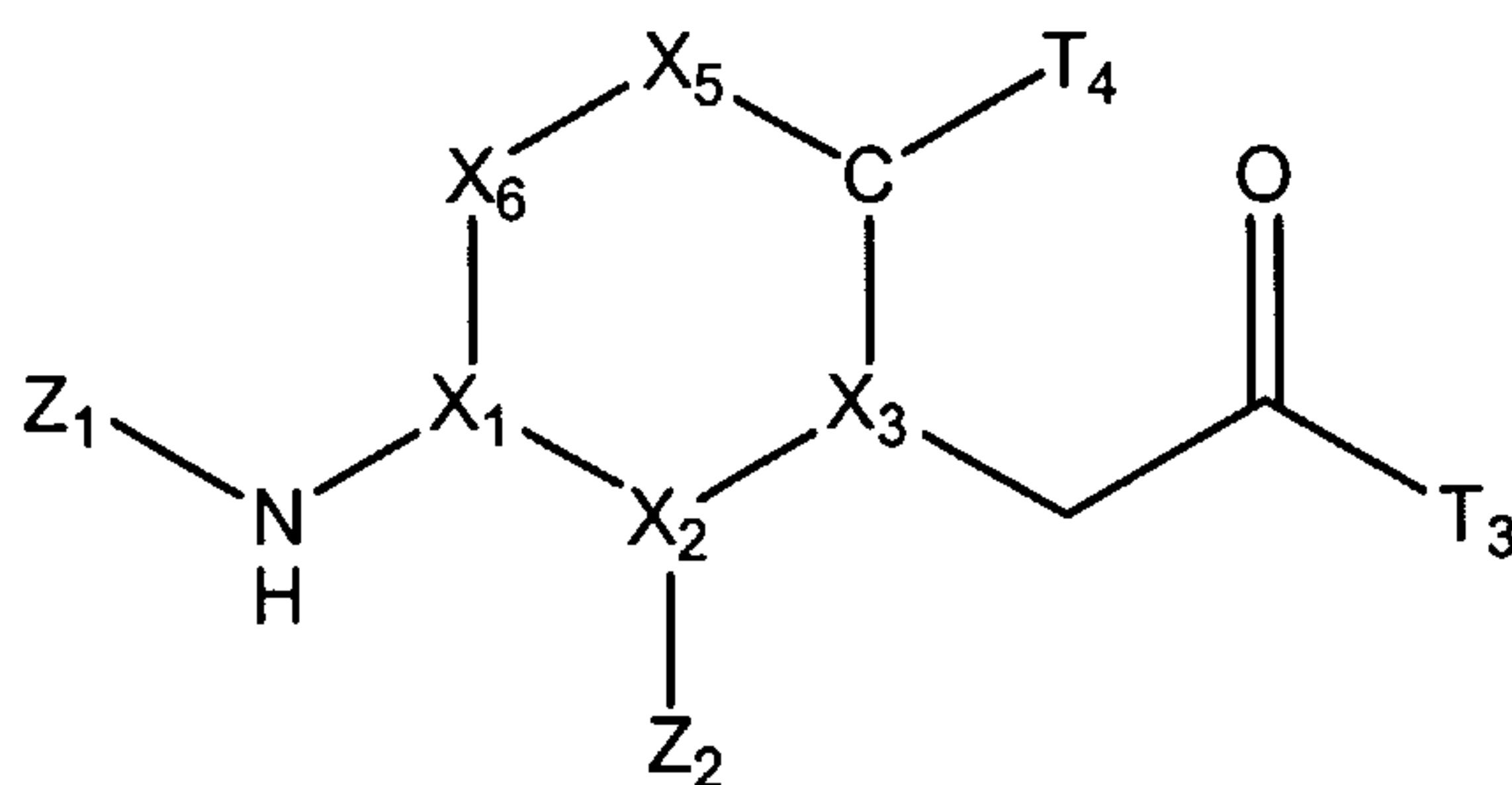
In a further embodiment, the benzamidine derivative is oxidized under physiological conditions to form benzamidine when Z_3 is a benzamidine derivative having formula (d) and R_{301} , R_{302} , and R_{303} are independently selected from hydrogen, optionally substituted hydrocarbyl and aryl, provided, however, the carbon atom of R_{301} , R_{302} , and R_{303} directly

bonded to the amidine is sp^3 hybridized when R_{301} , R_{302} , and R_{303} is optionally substituted hydrocarbyl.

In still another embodiment, the benzamidine derivative is reduced under physiological conditions to form benzamidine when Z_3 is a benzamidine derivative having formula (d) and R_{301} , R_{302} , and R_{303} are independently selected from hydrogen, $-OR_b$, $-SR_b$, $-NR_b$, or $-N(R_b)_2$, wherein each R_b is independently optionally substituted hydrocarbyl, and heterocyclo.

In an alternative embodiment, the benzamidine derivative undergoes elimination at physiological conditions to form benzamidine when Z_3 is a benzamidine derivative having formula (d) and R_{301} , R_{302} , and R_{303} are independently selected from hydrogen, substituted hydrocarbyl wherein the carbon bonded to the amidine group is substituted with $-OR_c$, $-SR_c$, $-NR_c$, or $-N(R_c)_2$, wherein each R_c is independently $-C(O)R_d$, $-C(O)NR_d$, $-C(O)OR_d$, $-C(O)N(R_d)_2$ and each R_d is independently hydrocarbyl, substituted hydrocarbyl or heterocyclo, and substituted alkyl with the carbon atom beta to the point of attachment to the amidine group being an unsaturated electron withdrawing group.

Another aspect of the invention embraces intermediate compounds having either of two formulae. Compounds corresponding to one of the formulae may be represented by formula (4):



(4)

wherein

X_1 , X_2 , X_5 , and X_6 are members of a heterocyclic ring;

X_1 , X_2 and X_3 are independently carbon or nitrogen;

X_5 and X_6 are independently selected from the group consisting of nitrogen, oxygen, sulfur, carbon, C(F) and C(Br);

provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

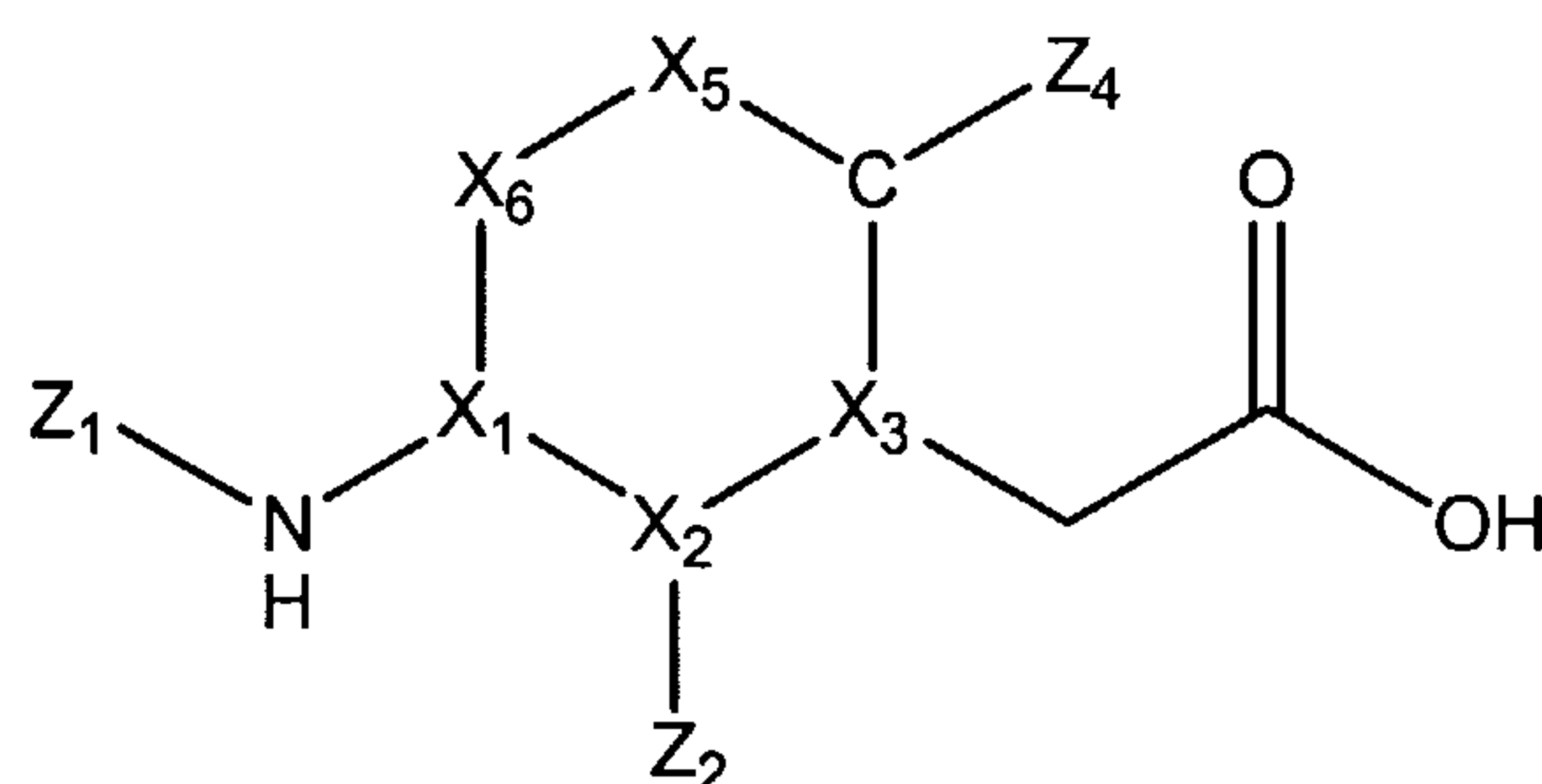
Z_1 is hydrocarbyl, or substituted hydrocarbyl;

Z_2 is a hydrogen bond acceptor covalently or datively bonded to X_2 ;

T_3 is selected from the group consisting of hydroxy, alkoxy, substituted alkoxy, and substituted amino; and

T_4 is selected from the group consisting of -Cl, -Br, -I, -S(CH₃), and -OSO₂(CF₃).

Intermediate compounds represented by the other formula correspond to formula (5):



(5)

wherein

X_1 , X_2 , X_5 , and X_6 are members of a heterocyclic ring;

X_1 , X_2 and X_3 are independently carbon or nitrogen;

X_5 and X_6 are independently selected from the group consisting of nitrogen, oxygen, sulfur, carbon, C(F) and C(Br);

provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

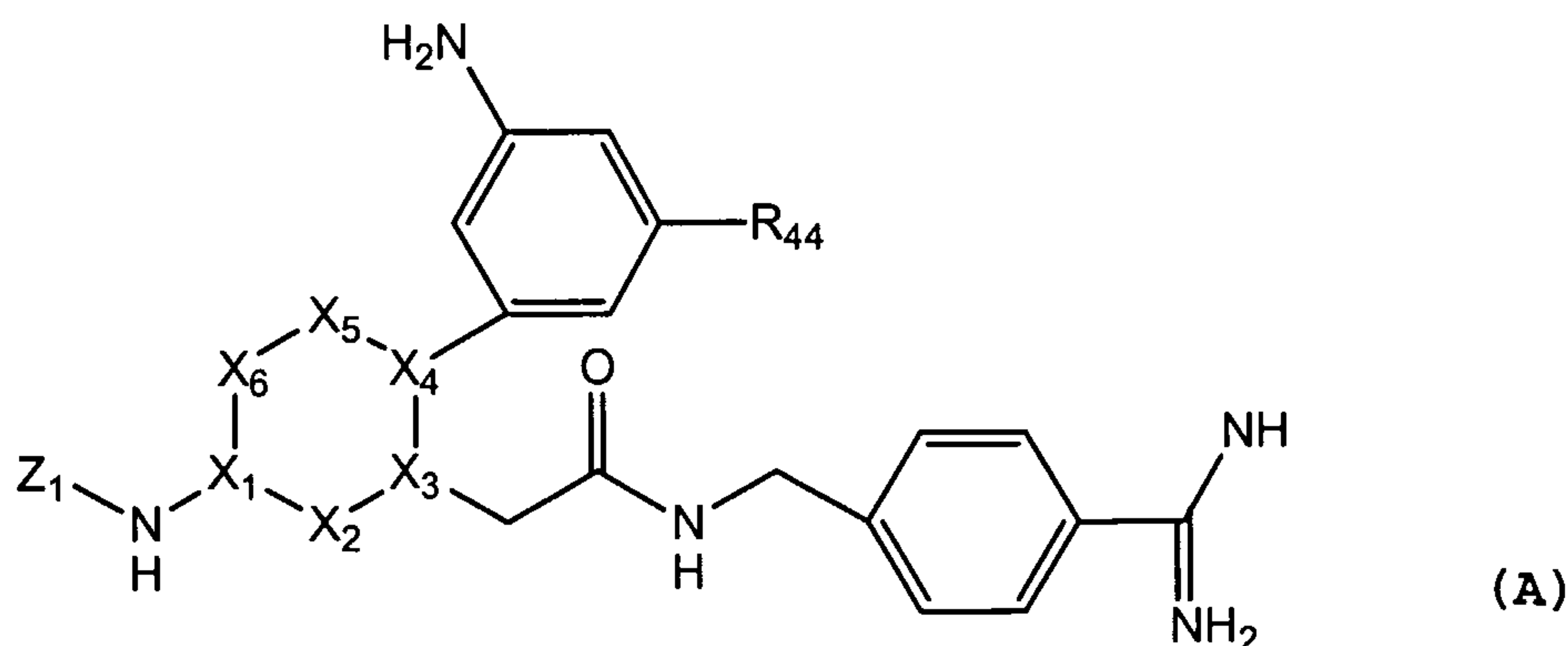
Z_1 is hydrocarbyl, or substituted hydrocarbyl;

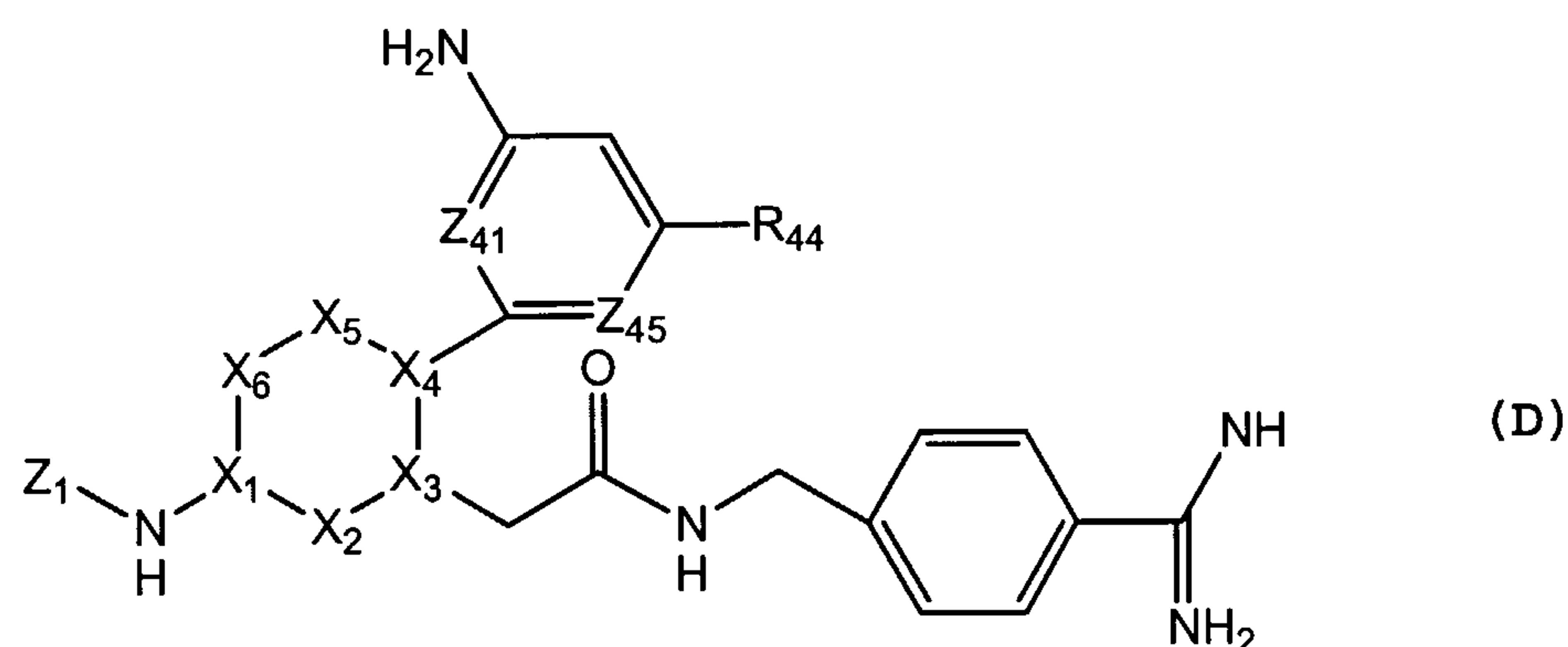
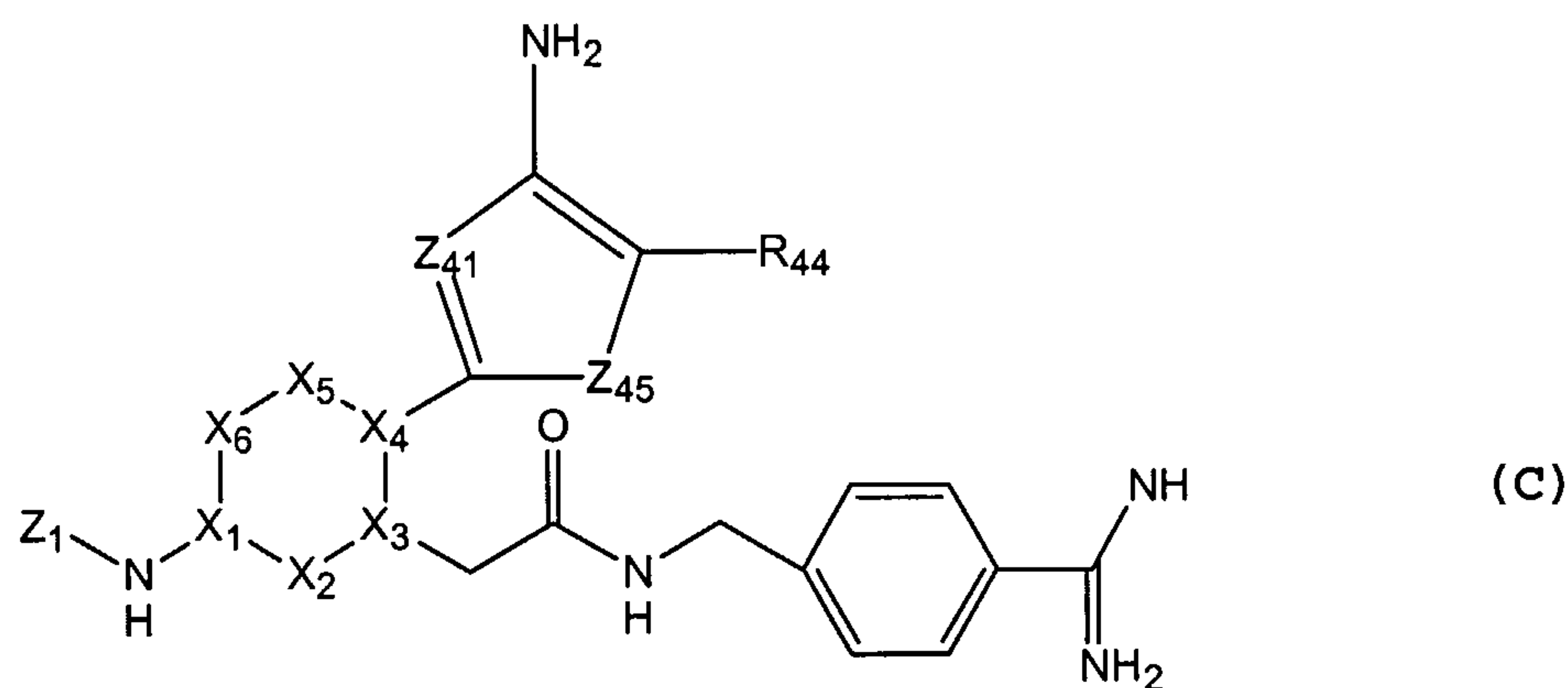
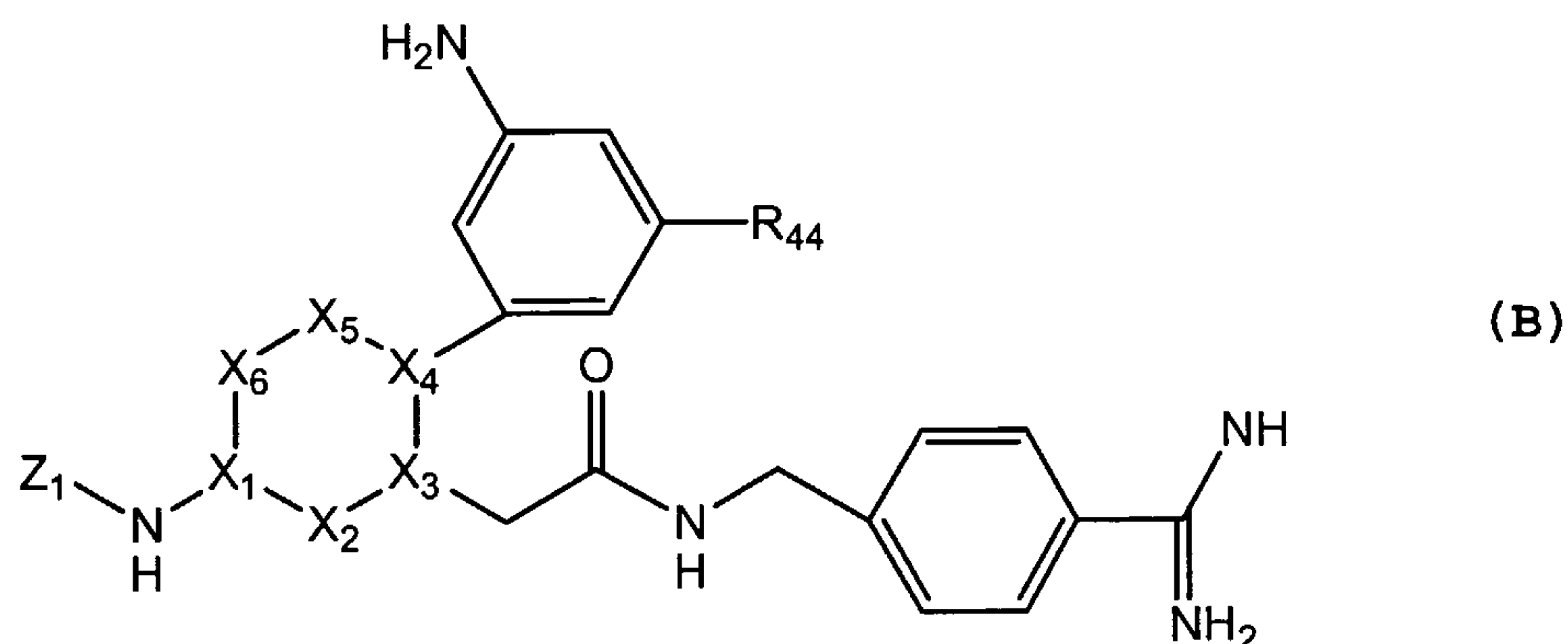
Z_2 is a hydrogen bond acceptor covalently or datively bonded to X_2 ; and

Z_4 comprises hydrocarbyl, substituted hydrocarbyl or a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of the 5 or 6 membered heterocyclic or carboxylic ring of Z_4 being carbon, nitrogen, oxygen, or sulfur.

Among the preferred embodiments, therefore, are compounds corresponding to any one of formulas (1), (2), or (3) wherein X_9 is a direct bond, Z_4 is a substituted, 6-membered, carbocyclic aromatic ring, Z_3 is benzene substituted with an amidine or a derivatized amidine group which, upon hydrolysis, oxidation, reduction or elimination under physiological conditions yields an amidine group, and Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, cyclobutyl, trifluoroethyl, carboxymethyl and phenyl. In an alternative of this embodiment, Z_4 is phenyl substituted with two substituents, R_{42} and R_{44} wherein R_{42} and R_{44} are as described for any of formulas (1), (2), or (3).

Following the processes described in the Schemes, Examples or elsewhere herein, compounds corresponding to each of formulae A, B, C, and D and having any of the combinations of substituents identified in Table 1 may be prepared.





wherein X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are selected to provide the following heterocyclic rings: piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, dehydropiperidinedione, dihydropyridazinone, dihydroisoxazinone, tetrahydrotriazinedione, tetrahydrotriazinone, piperidine, and piperazine and, for structure (C), one of Z_{41} and Z_{45} is sulfur while the other is carbon and, for structure (D), one of Z_{41} and Z_{45} is nitrogen while the other is carbon. As employed herein, unless otherwise indicated, "core" refers to the 6-membered

ring to which Z_1 , Z_3 and Z_4 , through their respective linkages, are attached.

TABLE 1		
Core	Z_1	R_{44}
Piperidinone	substituted alkyl	hydroxy
Piperidinone	substituted alkyl	isobutylsulfonyl
Piperidinone	substituted alkyl	trifluoromethyl
Piperidinone	substituted alkyl	carboxamidobenzyl
Piperidinone	substituted alkyl	carboxamidobutyl-2-yl
Piperidinone	substituted alkyl	isobutyramido
Piperidinone	substituted alkyl	isobutoxy
Piperidinone	substituted alkyl	carboethoxy
Piperidinone	substituted alkyl	carboxyl
Piperidinone	substituted alkyl	amino
Dihydropyrimidinone	substituted alkyl	hydroxy
Dihydropyrimidinone	substituted alkyl	isobutylsulfonyl
Dihydropyrimidinone	substituted alkyl	trifluoromethyl
Dihydropyrimidinone	substituted alkyl	carboxamidobenzyl
Dihydropyrimidinone	substituted alkyl	carboxamidobutyl-2-yl
Dihydropyrimidinone	substituted alkyl	isobutyramido
Dihydropyrimidinone	substituted alkyl	isobutoxy

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyrimidinone	substituted alkyl	carboethoxy
Dihydropyrimidinone	substituted alkyl	carboxyl
Dihydropyrimidinone	substituted alkyl	amino
Tetrahydropyrimidinone	substituted alkyl	hydroxy
Tetrahydropyrimidinone	substituted alkyl	isobutylsulfonyl
Tetrahydropyrimidinone	substituted alkyl	trifluoromethyl
Tetrahydropyrimidinone	substituted alkyl	carboxamidobenzyl
Tetrahydropyrimidinone	substituted alkyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	substituted alkyl	isobutyramido
Tetrahydropyrimidinone	substituted alkyl	isobutoxy
Tetrahydropyrimidinone	substituted alkyl	carboethoxy
Tetrahydropyrimidinone	substituted alkyl	carboxyl
Tetrahydropyrimidinone	substituted alkyl	amino
Dehydropiperidinedione	substituted alkyl	hydroxy
Dehydropiperidinedione	substituted alkyl	isobutylsulfonyl
Dehydropiperidinedione	substituted alkyl	trifluoromethyl
Dehydropiperidinedione	substituted alkyl	carboxamidobenzyl
Dehydropiperidinedione	substituted alkyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Dehydropiperidinedione	substituted alkyl	isobutyramido
Dehydropiperidinedione	substituted alkyl	isobutoxy
Dehydropiperidinedione	substituted alkyl	carboethoxy
Dehydropiperidinedione	substituted alkyl	carboxyl
Dehydropiperidinedione	substituted alkyl	amino
Dihydropyridazinone	substituted alkyl	hydroxy
Dihydropyridazinone	substituted alkyl	isobutylsulfonyl
Dihydropyridazinone	substituted alkyl	trifluoromethyl
Dihydropyridazinone	substituted alkyl	carboxamidobenzyl
Dihydropyridazinone	substituted alkyl	carboxamidobutyl-2-yl
Dihydropyridazinone	substituted alkyl	isobutyramido
Dihydropyridazinone	substituted alkyl	isobutoxy
Dihydropyridazinone	substituted alkyl	carboethoxy
Dihydropyridazinone	substituted alkyl	carboxyl
Dihydropyridazinone	substituted alkyl	amino
Dihydroisoxazinone	substituted alkyl	hydroxy
Dihydroisoxazinone	substituted alkyl	isobutylsulfonyl
Dihydroisoxazinone	substituted alkyl	trifluoromethyl

TABLE 1		
Core	Z ₁	R ₄₄
Dihydroisoxazinone	substituted alkyl	carboxamidobenzyl
Dihydroisoxazinone	substituted alkyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	substituted alkyl	isobutyramido
Dihydroisoxazinone	substituted alkyl	isobutoxy
Dihydroisoxazinone	substituted alkyl	carboethoxy
Dihydroisoxazinone	substituted alkyl	carboxyl
Dihydroisoxazinone	substituted alkyl	amino
Tetrahydrotriazinedione	substituted alkyl	hydroxy
Tetrahydrotriazinedione	substituted alkyl	isobutylsulfonyl
Tetrahydrotriazinedione	substituted alkyl	trifluoromethyl
Tetrahydrotriazinedione	substituted alkyl	carboxamidobenzyl
Tetrahydrotriazinedione	substituted alkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinedione	substituted alkyl	isobutyramido
Tetrahydrotriazinedione	substituted alkyl	isobutoxy
Tetrahydrotriazinedione	substituted alkyl	carboethoxy
Tetrahydrotriazinedione	substituted alkyl	carboxyl
Tetrahydrotriazinedione	substituted alkyl	amino
Tetrahydrotriazinone	substituted alkyl	hydroxy

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinone	substituted alkyl	isobutylsulfonyl
Tetrahydrotriazinone	substituted alkyl	trifluoromethyl
Tetrahydrotriazinone	substituted alkyl	carboxamidobenzyl
Tetrahydrotriazinone	substituted alkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	substituted alkyl	isobutyramido
Tetrahydrotriazinone	substituted alkyl	isobutoxy
Tetrahydrotriazinone	substituted alkyl	carboethoxy
Tetrahydrotriazinone	substituted alkyl	carboxyl
Tetrahydrotriazinone	substituted alkyl	amino
Piperidine	substituted alkyl	hydroxy
Piperidine	substituted alkyl	isobutylsulfonyl
Piperidine	substituted alkyl	trifluoromethyl
Piperidine	substituted alkyl	carboxamidobenzyl
Piperidine	substituted alkyl	carboxamidobutyl-2-yl
Piperidine	substituted alkyl	isobutyramido
Piperidine	substituted alkyl	isobutoxy
Piperidine	substituted alkyl	carboethoxy
Piperidine	substituted alkyl	carboxyl

TABLE 1		
Core	Z ₁	R ₄₄
Piperidine	substituted alkyl	amino
Piperazine	substituted alkyl	hydroxy
Piperazine	substituted alkyl	isobutylsulfonyl
Piperazine	substituted alkyl	trifluoromethyl
Piperazine	substituted alkyl	carboxamidobenzyl
Piperazine	substituted alkyl	carboxamidobutyl-2-yl
Piperazine	substituted alkyl	isobutyramido
Piperazine	substituted alkyl	isobutoxy
Piperazine	substituted alkyl	carboethoxy
Piperazine	substituted alkyl	carboxyl
Piperazine	substituted alkyl	amino
Piperidinone	alkyl	hydroxy
Piperidinone	alkyl	isobutylsulfonyl
Piperidinone	alkyl	trifluoromethyl
Piperidinone	alkyl	carboxamidobenzyl
Piperidinone	alkyl	carboxamidobutyl-2-yl
Piperidinone	alkyl	isobutyramido
Piperidinone	alkyl	isobutoxy
Piperidinone	alkyl	carboethoxy
Piperidinone	alkyl	carboxyl
Piperidinone	alkyl	amino
Dihydropyrimidinone	alkyl	hydroxy

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyrimidinone	alkyl	isobutylsulfonyl
Dihydropyrimidinone	alkyl	trifluoromethyl
Dihydropyrimidinone	alkyl	carboxamidobenzyl
Dihydropyrimidinone	alkyl	carboxamidobutyl-2-yl
Dihydropyrimidinone	alkyl	isobutyramido
Dihydropyrimidinone	alkyl	isobutoxy
Dihydropyrimidinone	alkyl	carboethoxy
Dihydropyrimidinone	alkyl	carboxyl
Dihydropyrimidinone	alkyl	amino
Tetrahydropyrimidinone	alkyl	hydroxy
Tetrahydropyrimidinone	alkyl	isobutylsulfonyl
Tetrahydropyrimidinone	alkyl	trifluoromethyl
Tetrahydropyrimidinone	alkyl	carboxamidobenzyl
Tetrahydropyrimidinone	alkyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	alkyl	isobutyramido
Tetrahydropyrimidinone	alkyl	isobutoxy
Tetrahydropyrimidinone	alkyl	carboethoxy
Tetrahydropyrimidinone	alkyl	carboxyl
Tetrahydropyrimidinone	alkyl	amino
Dehydropiperidinedione	alkyl	hydroxy
Dehydropiperidinedione	alkyl	isobutylsulfonyl
Dehydropiperidinedione	alkyl	trifluoromethyl
Dehydropiperidinedione	alkyl	carboxamidobenzyl
Dehydropiperidinedione	alkyl	carboxamidobutyl-2-yl
Dehydropiperidinedione	alkyl	isobutyramido
Dehydropiperidinedione	alkyl	isobutoxy
Dehydropiperidinedione	alkyl	carboethoxy

TABLE 1		
Core	Z ₁	R ₄₄
Dehydropiperidinedione	alkyl	carboxyl
Dehydropiperidinedione	alkyl	amino
Dihydropyridazinone	alkyl	hydroxy
Dihydropyridazinone	alkyl	isobutylsulfonyl
Dihydropyridazinone	alkyl	trifluoromethyl
Dihydropyridazinone	alkyl	carboxamidobenzyl
Dihydropyridazinone	alkyl	carboxamidobutyl-2-yl
Dihydropyridazinone	alkyl	isobutyramido
Dihydropyridazinone	alkyl	isobutoxy
Dihydropyridazinone	alkyl	carboethoxy
Dihydropyridazinone	alkyl	carboxyl
Dihydropyridazinone	alkyl	amino
Dihydroisoxazinone	alkyl	hydroxy
Dihydroisoxazinone	alkyl	isobutylsulfonyl
Dihydroisoxazinone	alkyl	trifluoromethyl
Dihydroisoxazinone	alkyl	carboxamidobenzyl
Dihydroisoxazinone	alkyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	alkyl	isobutyramido
Dihydroisoxazinone	alkyl	isobutoxy
Dihydroisoxazinone	alkyl	carboethoxy
Dihydroisoxazinone	alkyl	carboxyl
Dihydroisoxazinone	alkyl	amino
Tetrahydrotriazinedione	alkyl	hydroxy
Tetrahydrotriazinedione	alkyl	isobutylsulfonyl
Tetrahydrotriazinedione	alkyl	trifluoromethyl
Tetrahydrotriazinedione	alkyl	carboxamidobenzyl
Tetrahydrotriazinedione	alkyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinedione	alkyl	isobutyramido
Tetrahydrotriazinedione	alkyl	isobutoxy
Tetrahydrotriazinedione	alkyl	carboethoxy
Tetrahydrotriazinedione	alkyl	carboxyl
Tetrahydrotriazinedione	alkyl	amino
Tetrahydrotriazinone	alkyl	hydroxy
Tetrahydrotriazinone	alkyl	isobutylsulfonyl
Tetrahydrotriazinone	alkyl	trifluoromethyl
Tetrahydrotriazinone	alkyl	carboxamidobenzyl
Tetrahydrotriazinone	alkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	alkyl	isobutyramido
Tetrahydrotriazinone	alkyl	isobutoxy
Tetrahydrotriazinone	alkyl	carboethoxy
Tetrahydrotriazinone	alkyl	carboxyl
Tetrahydrotriazinone	alkyl	amino
Piperidine	alkyl	hydroxy
Piperidine	alkyl	isobutylsulfonyl
Piperidine	alkyl	trifluoromethyl
Piperidine	alkyl	carboxamidobenzyl
Piperidine	alkyl	carboxamidobutyl-2-yl
Piperidine	alkyl	isobutyramido
Piperidine	alkyl	isobutoxy
Piperidine	alkyl	carboethoxy
Piperidine	alkyl	carboxyl
Piperidine	alkyl	amino
Piperazine	alkyl	hydroxy
Piperazine	alkyl	isobutylsulfonyl
Piperazine	alkyl	trifluoromethyl

TABLE 1		
Core	Z ₁	R ₄₄
Piperazine	alkyl	carboxamidobenzyl
Piperazine	alkyl	carboxamidobutyl-2-yl
Piperazine	alkyl	isobutyramido
Piperazine	alkyl	isobutoxy
Piperazine	alkyl	carboethoxy
Piperazine	alkyl	carboxyl
Piperazine	alkyl	amino
Piperidinone	substituted phenyl	hydroxy
Piperidinone	substituted phenyl	isobutylsulfonyl
Piperidinone	substituted phenyl	trifluoromethyl
Piperidinone	substituted phenyl	carboxamidobenzyl
Piperidinone	substituted phenyl	carboxamidobutyl-2-yl
Piperidinone	substituted phenyl	isobutyramido
Piperidinone	substituted phenyl	isobutoxy
Piperidinone	substituted phenyl	carboethoxy
Piperidinone	substituted phenyl	carboxyl
Piperidinone	substituted phenyl	amino
Dihydropyrimidinone	substituted phenyl	hydroxy
Dihydropyrimidinone	substituted phenyl	isobutylsulfonyl
Dihydropyrimidinone	substituted phenyl	trifluoromethyl

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyrimidinone	substituted phenyl	carboxamidobenzyl
Dihydropyrimidinone	substituted phenyl	carboxamidobutyl-2-yl
Dihydropyrimidinone	substituted phenyl	isobutyramido
Dihydropyrimidinone	substituted phenyl	isobutoxy
Dihydropyrimidinone	substituted phenyl	carboethoxy
Dihydropyrimidinone	substituted phenyl	carboxyl
Dihydropyrimidinone	substituted phenyl	amino
Tetrahydropyrimidinone	substituted phenyl	hydroxy
Tetrahydropyrimidinone	substituted phenyl	isobutylsulfonyl
Tetrahydropyrimidinone	substituted phenyl	trifluoromethyl
Tetrahydropyrimidinone	substituted phenyl	carboxamidobenzyl
Tetrahydropyrimidinone	substituted phenyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	substituted phenyl	isobutyramido
Tetrahydropyrimidinone	substituted phenyl	isobutoxy
Tetrahydropyrimidinone	substituted phenyl	carboethoxy
Tetrahydropyrimidinone	substituted phenyl	carboxyl
Tetrahydropyrimidinone	substituted phenyl	amino
Dehydropiperidinedione	substituted phenyl	hydroxy

TABLE 1		
Core	Z ₁	R ₄₄
Dehydropiperidinedione	substituted phenyl	isobutylsulfonyl
Dehydropiperidinedione	substituted phenyl	trifluoromethyl
Dehydropiperidinedione	substituted phenyl	carboxamidobenzyl
Dehydropiperidinedione	substituted phenyl	carboxamidobutyl-2-yl
Dehydropiperidinedione	substituted phenyl	isobutyramido
Dehydropiperidinedione	substituted phenyl	isobutoxy
Dehydropiperidinedione	substituted phenyl	carboethoxy
Dehydropiperidinedione	substituted phenyl	carboxyl
Dehydropiperidinedione	substituted phenyl	amino
Dihydropyridazinone	substituted phenyl	hydroxy
Dihydropyridazinone	substituted phenyl	isobutylsulfonyl
Dihydropyridazinone	substituted phenyl	trifluoromethyl
Dihydropyridazinone	substituted phenyl	carboxamidobenzyl
Dihydropyridazinone	substituted phenyl	carboxamidobutyl-2-yl
Dihydropyridazinone	substituted phenyl	isobutyramido
Dihydropyridazinone	substituted phenyl	isobutoxy
Dihydropyridazinone	substituted phenyl	carboethoxy
Dihydropyridazinone	substituted phenyl	carboxyl

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyridazinone	substituted phenyl	amino
Dihydroisoxazinone	substituted phenyl	hydroxy
Dihydroisoxazinone	substituted phenyl	isobutylsulfonyl
Dihydroisoxazinone	substituted phenyl	trifluoromethyl
Dihydroisoxazinone	substituted phenyl	carboxamidobenzyl
Dihydroisoxazinone	substituted phenyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	substituted phenyl	isobutyramido
Dihydroisoxazinone	substituted phenyl	isobutoxy
Dihydroisoxazinone	substituted phenyl	carboethoxy
Dihydroisoxazinone	substituted phenyl	carboxyl
Dihydroisoxazinone	substituted phenyl	amino
Tetrahydrotriazinedione	substituted phenyl	hydroxy
Tetrahydrotriazinedione	substituted phenyl	isobutylsulfonyl
Tetrahydrotriazinedione	substituted phenyl	trifluoromethyl
Tetrahydrotriazinedione	substituted phenyl	carboxamidobenzyl
Tetrahydrotriazinedione	substituted phenyl	carboxamidobutyl-2-yl
Tetrahydrotriazinedione	substituted phenyl	isobutyramido
Tetrahydrotriazinedione	substituted phenyl	isobutoxy

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinedione	substituted phenyl	carboethoxy
Tetrahydrotriazinedione	substituted phenyl	carboxyl
Tetrahydrotriazinedione	substituted phenyl	amino
Tetrahydrotriazinone	substituted phenyl	hydroxy
Tetrahydrotriazinone	substituted phenyl	isobutylsulfonyl
Tetrahydrotriazinone	substituted phenyl	trifluoromethyl
Tetrahydrotriazinone	substituted phenyl	carboxamidobenzyl
Tetrahydrotriazinone	substituted phenyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	substituted phenyl	isobutyramido
Tetrahydrotriazinone	substituted phenyl	isobutoxy
Tetrahydrotriazinone	substituted phenyl	carboethoxy
Tetrahydrotriazinone	substituted phenyl	carboxyl
Tetrahydrotriazinone	substituted phenyl	amino
Piperidine	substituted phenyl	hydroxy
Piperidine	substituted phenyl	isobutylsulfonyl
Piperidine	substituted phenyl	trifluoromethyl
Piperidine	substituted phenyl	carboxamidobenzyl
Piperidine	substituted phenyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Piperidine	substituted phenyl	isobutyramido
Piperidine	substituted phenyl	isobutoxy
Piperidine	substituted phenyl	carboethoxy
Piperidine	substituted phenyl	carboxyl
Piperidine	substituted phenyl	amino
Piperazine	substituted phenyl	hydroxy
Piperazine	substituted phenyl	isobutylsulfonyl
Piperazine	substituted phenyl	trifluoromethyl
Piperazine	substituted phenyl	carboxamidobenzyl
Piperazine	substituted phenyl	carboxamidobutyl-2-yl
Piperazine	substituted phenyl	isobutyramido
Piperazine	substituted phenyl	isobutoxy
Piperazine	substituted phenyl	carboethoxy
Piperazine	substituted phenyl	carboxyl
Piperazine	substituted phenyl	amino
Piperidinone	phenyl	hydroxy
Piperidinone	phenyl	isobutylsulfonyl
Piperidinone	phenyl	trifluoromethyl
Piperidinone	phenyl	carboxamidobenzyl
Piperidinone	phenyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Piperidinone	phenyl	isobutyramido
Piperidinone	phenyl	isobutoxy
Piperidinone	phenyl	carboethoxy
Piperidinone	phenyl	carboxyl
Piperidinone	phenyl	amino
Dihydropyrimidinone	phenyl	hydroxy
Dihydropyrimidinone	phenyl	isobutylsulfonyl
Dihydropyrimidinone	phenyl	trifluoromethyl
Dihydropyrimidinone	phenyl	carboxamidobenzyl
Dihydropyrimidinone	phenyl	carboxamidobutyl-2-yl
Dihydropyrimidinone	phenyl	isobutyramido
Dihydropyrimidinone	phenyl	isobutoxy
Dihydropyrimidinone	phenyl	carboethoxy
Dihydropyrimidinone	phenyl	carboxyl
Dihydropyrimidinone	phenyl	amino
Tetrahydropyrimidinone	phenyl	hydroxy
Tetrahydropyrimidinone	phenyl	isobutylsulfonyl
Tetrahydropyrimidinone	phenyl	trifluoromethyl
Tetrahydropyrimidinone	phenyl	carboxamidobenzyl
Tetrahydropyrimidinone	phenyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	phenyl	isobutyramido
Tetrahydropyrimidinone	phenyl	isobutoxy
Tetrahydropyrimidinone	phenyl	carboethoxy
Tetrahydropyrimidinone	phenyl	carboxyl
Tetrahydropyrimidinone	phenyl	amino
Dehydropiperidinedione	phenyl	hydroxy
Dehydropiperidinedione	phenyl	isobutylsulfonyl
Dehydropiperidinedione	phenyl	trifluoromethyl

TABLE 1		
Core	Z ₁	R ₄₄
Dehydropiperidinedione	phenyl	carboxamidobenzyl
Dehydropiperidinedione	phenyl	carboxamidobutyl-2-yl
Dehydropiperidinedione	phenyl	isobutyramido
Dehydropiperidinedione	phenyl	isobutoxy
Dehydropiperidinedione	phenyl	carboethoxy
Dehydropiperidinedione	phenyl	carboxyl
Dehydropiperidinedione	phenyl	amino
Dihydropyridazinone	phenyl	hydroxy
Dihydropyridazinone	phenyl	isobutylsulfonyl
Dihydropyridazinone	phenyl	trifluoromethyl
Dihydropyridazinone	phenyl	carboxamidobenzyl
Dihydropyridazinone	phenyl	carboxamidobutyl-2-yl
Dihydropyridazinone	phenyl	isobutyramido
Dihydropyridazinone	phenyl	isobutoxy
Dihydropyridazinone	phenyl	carboethoxy
Dihydropyridazinone	phenyl	carboxyl
Dihydropyridazinone	phenyl	amino
Dihydroisoxazinone	phenyl	hydroxy
Dihydroisoxazinone	phenyl	isobutylsulfonyl
Dihydroisoxazinone	phenyl	trifluoromethyl
Dihydroisoxazinone	phenyl	carboxamidobenzyl
Dihydroisoxazinone	phenyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	phenyl	isobutyramido
Dihydroisoxazinone	phenyl	isobutoxy
Dihydroisoxazinone	phenyl	carboethoxy
Dihydroisoxazinone	phenyl	carboxyl
Dihydroisoxazinone	phenyl	amino

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinedione	phenyl	hydroxy
Tetrahydrotriazinedione	phenyl	isobutylsulfonyl
Tetrahydrotriazinedione	phenyl	trifluoromethyl
Tetrahydrotriazinedione	phenyl	carboxamidobenzyl
Tetrahydrotriazinedione	phenyl	carboxamidobutyl-2-yl
Tetrahydrotriazinedione	phenyl	isobutyramido
Tetrahydrotriazinedione	phenyl	isobutoxy
Tetrahydrotriazinedione	phenyl	carboethoxy
Tetrahydrotriazinedione	phenyl	carboxyl
Tetrahydrotriazinedione	phenyl	amino
Tetrahydrotriazinone	phenyl	hydroxy
Tetrahydrotriazinone	phenyl	isobutylsulfonyl
Tetrahydrotriazinone	phenyl	trifluoromethyl
Tetrahydrotriazinone	phenyl	carboxamidobenzyl
Tetrahydrotriazinone	phenyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	phenyl	isobutyramido
Tetrahydrotriazinone	phenyl	isobutoxy
Tetrahydrotriazinone	phenyl	carboethoxy
Tetrahydrotriazinone	phenyl	carboxyl
Tetrahydrotriazinone	phenyl	amino
Piperidine	phenyl	hydroxy
Piperidine	phenyl	isobutylsulfonyl
Piperidine	phenyl	trifluoromethyl
Piperidine	phenyl	carboxamidobenzyl
Piperidine	phenyl	carboxamidobutyl-2-yl
Piperidine	phenyl	isobutyramido
Piperidine	phenyl	isobutoxy

TABLE 1		
Core	Z ₁	R ₄₄
Piperidine	phenyl	carboethoxy
Piperidine	phenyl	carboxyl
Piperidine	phenyl	amino
Piperazine	phenyl	hydroxy
Piperazine	phenyl	isobutylsulfonyl
Piperazine	phenyl	trifluoromethyl
Piperazine	phenyl	carboxamidobenzyl
Piperazine	phenyl	carboxamidobutyl-2-yl
Piperazine	phenyl	isobutyramido
Piperazine	phenyl	isobutoxy
Piperazine	phenyl	carboethoxy
Piperazine	phenyl	carboxyl
Piperazine	phenyl	amino
Piperidinone	cycloalkyl	hydroxy
Piperidinone	cycloalkyl	isobutylsulfonyl
Piperidinone	cycloalkyl	trifluoromethyl
Piperidinone	cycloalkyl	carboxamidobenzyl
Piperidinone	cycloalkyl	carboxamidobutyl-2-yl
Piperidinone	cycloalkyl	isobutyramido
Piperidinone	cycloalkyl	isobutoxy
Piperidinone	cycloalkyl	carboethoxy
Piperidinone	cycloalkyl	carboxyl
Piperidinone	cycloalkyl	amino
Dihydropyrimidinone	cycloalkyl	hydroxy
Dihydropyrimidinone	cycloalkyl	isobutylsulfonyl
Dihydropyrimidinone	cycloalkyl	trifluoromethyl
Dihydropyrimidinone	cycloalkyl	carboxamidobenzyl

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyrimidinone	cycloalkyl	carboxamidobutyl-2-yl
Dihydropyrimidinone	cycloalkyl	isobutyramido
Dihydropyrimidinone	cycloalkyl	isobutoxy
Dihydropyrimidinone	cycloalkyl	carboethoxy
Dihydropyrimidinone	cycloalkyl	carboxyl
Dihydropyrimidinone	cycloalkyl	amino
Tetrahydropyrimidinone	cycloalkyl	hydroxy
Tetrahydropyrimidinone	cycloalkyl	isobutylsulfonyl
Tetrahydropyrimidinone	cycloalkyl	trifluoromethyl
Tetrahydropyrimidinone	cycloalkyl	carboxamidobenzyl
Tetrahydropyrimidinone	cycloalkyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	cycloalkyl	isobutyramido
Tetrahydropyrimidinone	cycloalkyl	isobutoxy
Tetrahydropyrimidinone	cycloalkyl	carboethoxy
Tetrahydropyrimidinone	cycloalkyl	carboxyl
Tetrahydropyrimidinone	cycloalkyl	amino
Dehydropiperidinedione	cycloalkyl	hydroxy
Dehydropiperidinedione	cycloalkyl	isobutylsulfonyl
Dehydropiperidinedione	cycloalkyl	trifluoromethyl
Dehydropiperidinedione	cycloalkyl	carboxamidobenzyl
Dehydropiperidinedione	cycloalkyl	carboxamidobutyl-2-yl
Dehydropiperidinedione	cycloalkyl	isobutyramido
Dehydropiperidinedione	cycloalkyl	isobutoxy
Dehydropiperidinedione	cycloalkyl	carboethoxy
Dehydropiperidinedione	cycloalkyl	carboxyl
Dehydropiperidinedione	cycloalkyl	amino
Dihydropyridazinone	cycloalkyl	hydroxy

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyridazinone	cycloalkyl	isobutylsulfonyl
Dihydropyridazinone	cycloalkyl	trifluoromethyl
Dihydropyridazinone	cycloalkyl	carboxamidobenzyl
Dihydropyridazinone	cycloalkyl	carboxamidobutyl-2-yl
Dihydropyridazinone	cycloalkyl	isobutyramido
Dihydropyridazinone	cycloalkyl	isobutoxy
Dihydropyridazinone	cycloalkyl	carboethoxy
Dihydropyridazinone	cycloalkyl	carboxyl
Dihydropyridazinone	cycloalkyl	amino
Dihydroisoxazinone	cycloalkyl	hydroxy
Dihydroisoxazinone	cycloalkyl	isobutylsulfonyl
Dihydroisoxazinone	cycloalkyl	trifluoromethyl
Dihydroisoxazinone	cycloalkyl	carboxamidobenzyl
Dihydroisoxazinone	cycloalkyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	cycloalkyl	isobutyramido
Dihydroisoxazinone	cycloalkyl	isobutoxy
Dihydroisoxazinone	cycloalkyl	carboethoxy
Dihydroisoxazinone	cycloalkyl	carboxyl
Dihydroisoxazinone	cycloalkyl	amino
Tetrahydrotriazinedione	cycloalkyl	hydroxy
Tetrahydrotriazinedione	cycloalkyl	isobutylsulfonyl
Tetrahydrotriazinedione	cycloalkyl	trifluoromethyl
Tetrahydrotriazinedione	cycloalkyl	carboxamidobenzyl
Tetrahydrotriazinedione	cycloalkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinedione	cycloalkyl	isobutyramido
Tetrahydrotriazinedione	cycloalkyl	isobutoxy
Tetrahydrotriazinedione	cycloalkyl	carboethoxy

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinedione	cycloalkyl	carboxyl
Tetrahydrotriazinedione	cycloalkyl	amino
Tetrahydrotriazinone	cycloalkyl	hydroxy
Tetrahydrotriazinone	cycloalkyl	isobutylsulfonyl
Tetrahydrotriazinone	cycloalkyl	trifluoromethyl
Tetrahydrotriazinone	cycloalkyl	carboxamidobenzyl
Tetrahydrotriazinone	cycloalkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	cycloalkyl	isobutyramido
Tetrahydrotriazinone	cycloalkyl	isobutoxy
Tetrahydrotriazinone	cycloalkyl	carboethoxy
Tetrahydrotriazinone	cycloalkyl	carboxyl
Tetrahydrotriazinone	cycloalkyl	amino
Piperidine	cycloalkyl	hydroxy
Piperidine	cycloalkyl	isobutylsulfonyl
Piperidine	cycloalkyl	trifluoromethyl
Piperidine	cycloalkyl	carboxamidobenzyl
Piperidine	cycloalkyl	carboxamidobutyl-2-yl
Piperidine	cycloalkyl	isobutyramido
Piperidine	cycloalkyl	isobutoxy
Piperidine	cycloalkyl	carboethoxy
Piperidine	cycloalkyl	carboxyl
Piperidine	cycloalkyl	amino
Piperazine	cycloalkyl	hydroxy
Piperazine	cycloalkyl	isobutylsulfonyl
Piperazine	cycloalkyl	trifluoromethyl
Piperazine	cycloalkyl	carboxamidobenzyl
Piperazine	cycloalkyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Piperazine	cycloalkyl	isobutyramido
Piperazine	cycloalkyl	isobutoxy
Piperazine	cycloalkyl	carboethoxy
Piperazine	cycloalkyl	carboxyl
Piperazine	cycloalkyl	amino
Piperidinone	substituted cycloalkyl	hydroxy
Piperidinone	substituted cycloalkyl	isobutylsulfonyl
Piperidinone	substituted cycloalkyl	trifluoromethyl
Piperidinone	substituted cycloalkyl	carboxamidobenzyl
Piperidinone	substituted cycloalkyl	carboxamidobutyl-2-yl
Piperidinone	substituted cycloalkyl	isobutyramido
Piperidinone	substituted cycloalkyl	isobutoxy
Piperidinone	substituted cycloalkyl	carboethoxy
Piperidinone	substituted cycloalkyl	carboxyl
Piperidinone	substituted cycloalkyl	amino
Dihydropyrimidinone	substituted cycloalkyl	hydroxy
Dihydropyrimidinone	substituted cycloalkyl	isobutylsulfonyl
Dihydropyrimidinone	substituted cycloalkyl	trifluoromethyl
Dihydropyrimidinone	substituted cycloalkyl	carboxamidobenzyl
Dihydropyrimidinone	substituted cycloalkyl	carboxamidobutyl-2-yl

TABLE 1		
Core	Z ₁	R ₄₄
Dihydropyrimidinone	substituted cycloalkyl	isobutyramido
Dihydropyrimidinone	substituted cycloalkyl	isobutoxy
Dihydropyrimidinone	substituted cycloalkyl	carboethoxy
Dihydropyrimidinone	substituted cycloalkyl	carboxyl
Dihydropyrimidinone	substituted cycloalkyl	amino
Tetrahydropyrimidinone	substituted cycloalkyl	hydroxy
Tetrahydropyrimidinone	substituted cycloalkyl	isobutylsulfonyl
Tetrahydropyrimidinone	substituted cycloalkyl	trifluoromethyl
Tetrahydropyrimidinone	substituted cycloalkyl	carboxamidobenzyl
Tetrahydropyrimidinone	substituted cycloalkyl	carboxamidobutyl-2-yl
Tetrahydropyrimidinone	substituted cycloalkyl	isobutyramido
Tetrahydropyrimidinone	substituted cycloalkyl	isobutoxy
Tetrahydropyrimidinone	substituted cycloalkyl	carboethoxy
Tetrahydropyrimidinone	substituted cycloalkyl	carboxyl
Tetrahydropyrimidinone	substituted cycloalkyl	amino
Dehydropiperidinedione	substituted cycloalkyl	hydroxy
Dehydropiperidinedione	substituted cycloalkyl	isobutylsulfonyl
Dehydropiperidinedione	substituted cycloalkyl	trifluoromethyl

TABLE 1		
Core	Z ₁	R ₄₄
Dehydropiperidinedione	substituted cycloalkyl	carboxamidobenzyl
Dehydropiperidinedione	substituted cycloalkyl	carboxamidobutyl-2-yl
Dehydropiperidinedione	substituted cycloalkyl	isobutyramido
Dehydropiperidinedione	substituted cycloalkyl	isobutoxy
Dehydropiperidinedione	substituted cycloalkyl	carboethoxy
Dehydropiperidinedione	substituted cycloalkyl	carboxyl
Dehydropiperidinedione	substituted cycloalkyl	amino
Dihydropyridazinone	substituted cycloalkyl	hydroxy
Dihydropyridazinone	substituted cycloalkyl	isobutylsulfonyl
Dihydropyridazinone	substituted cycloalkyl	trifluoromethyl
Dihydropyridazinone	substituted cycloalkyl	carboxamidobenzyl
Dihydropyridazinone	substituted cycloalkyl	carboxamidobutyl-2-yl
Dihydropyridazinone	substituted cycloalkyl	isobutyramido
Dihydropyridazinone	substituted cycloalkyl	isobutoxy
Dihydropyridazinone	substituted cycloalkyl	carboethoxy
Dihydropyridazinone	substituted cycloalkyl	carboxyl
Dihydropyridazinone	substituted cycloalkyl	amino
Dihydroisoxazinone	substituted cycloalkyl	hydroxy

TABLE 1		
Core	Z ₁	R ₄₄
Dihydroisoxazinone	substituted cycloalkyl	isobutylsulfonyl
Dihydroisoxazinone	substituted cycloalkyl	trifluoromethyl
Dihydroisoxazinone	substituted cycloalkyl	carboxamidobenzyl
Dihydroisoxazinone	substituted cycloalkyl	carboxamidobutyl-2-yl
Dihydroisoxazinone	substituted cycloalkyl	isobutyramido
Dihydroisoxazinone	substituted cycloalkyl	isobutoxy
Dihydroisoxazinone	substituted cycloalkyl	carboethoxy
Dihydroisoxazinone	substituted cycloalkyl	carboxyl
Dihydroisoxazinone	substituted cycloalkyl	amino
Tetrahydrotriazinedione	substituted cycloalkyl	hydroxy
Tetrahydrotriazinedione	substituted cycloalkyl	isobutylsulfonyl
Tetrahydrotriazinedione	substituted cycloalkyl	trifluoromethyl
Tetrahydrotriazinedione	substituted cycloalkyl	carboxamidobenzyl
Tetrahydrotriazinedione	substituted cycloalkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinedione	substituted cycloalkyl	isobutyramido
Tetrahydrotriazinedione	substituted cycloalkyl	isobutoxy
Tetrahydrotriazinedione	substituted cycloalkyl	carboethoxy
Tetrahydrotriazinedione	substituted cycloalkyl	carboxyl

TABLE 1		
Core	Z ₁	R ₄₄
Tetrahydrotriazinedione	substituted cycloalkyl	amino
Tetrahydrotriazinone	substituted cycloalkyl	hydroxy
Tetrahydrotriazinone	substituted cycloalkyl	isobutylsulfonyl
Tetrahydrotriazinone	substituted cycloalkyl	trifluoromethyl
Tetrahydrotriazinone	substituted cycloalkyl	carboxamidobenzyl
Tetrahydrotriazinone	substituted cycloalkyl	carboxamidobutyl-2-yl
Tetrahydrotriazinone	substituted cycloalkyl	isobutyramido
Tetrahydrotriazinone	substituted cycloalkyl	isobutoxy
Tetrahydrotriazinone	substituted cycloalkyl	carboethoxy
Tetrahydrotriazinone	substituted cycloalkyl	carboxyl
Tetrahydrotriazinone	substituted cycloalkyl	amino
Piperidine	substituted cycloalkyl	hydroxy
Piperidine	substituted cycloalkyl	isobutylsulfonyl
Piperidine	substituted cycloalkyl	trifluoromethyl
Piperidine	substituted cycloalkyl	carboxamidobenzyl
Piperidine	substituted cycloalkyl	carboxamidobutyl-2-yl
Piperidine	substituted cycloalkyl	isobutyramido
Piperidine	substituted cycloalkyl	isobutoxy

TABLE 1		
Core	Z ₁	R ₄₄
Piperidine	substituted cycloalkyl	carboethoxy
Piperidine	substituted cycloalkyl	carboxyl
Piperidine	substituted cycloalkyl	amino
Piperazine	substituted cycloalkyl	hydroxy
Piperazine	substituted cycloalkyl	isobutylsulfonyl
Piperazine	substituted cycloalkyl	trifluoromethyl
Piperazine	substituted cycloalkyl	carboxamidobenzyl
Piperazine	substituted cycloalkyl	carboxamidobutyl-2-yl
Piperazine	substituted cycloalkyl	isobutyramido
Piperazine	substituted cycloalkyl	isobutoxy
Piperazine	substituted cycloalkyl	carboethoxy
Piperazine	substituted cycloalkyl	carboxyl
Piperazine	substituted cycloalkyl	amino

In a preferred embodiment, the compounds correspond to any of Formulae A, B, C, or D and the core, Z₁ and R₄₄ are as identified in Table 2.

TABLE 2		
Core	Z ₁	R ₄₄
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy

TABLE 2		
Core	Z ₁	R ₄₄
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Piperidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl

TABLE 2		
Core	Z ₁	R ₄₄
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Dihydropyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Dihydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy

TABLE 2		
Core	Z ₁	R ₄₄
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Tetrahydro-pyrimidinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Dehydro-piperidine-dione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy

TABLE 2		
Core	Z ₁	R ₄₄
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Dihydro-pyridazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl

TABLE 2		
Core	Z ₁	R ₄₄
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Dihydro-isoxazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy

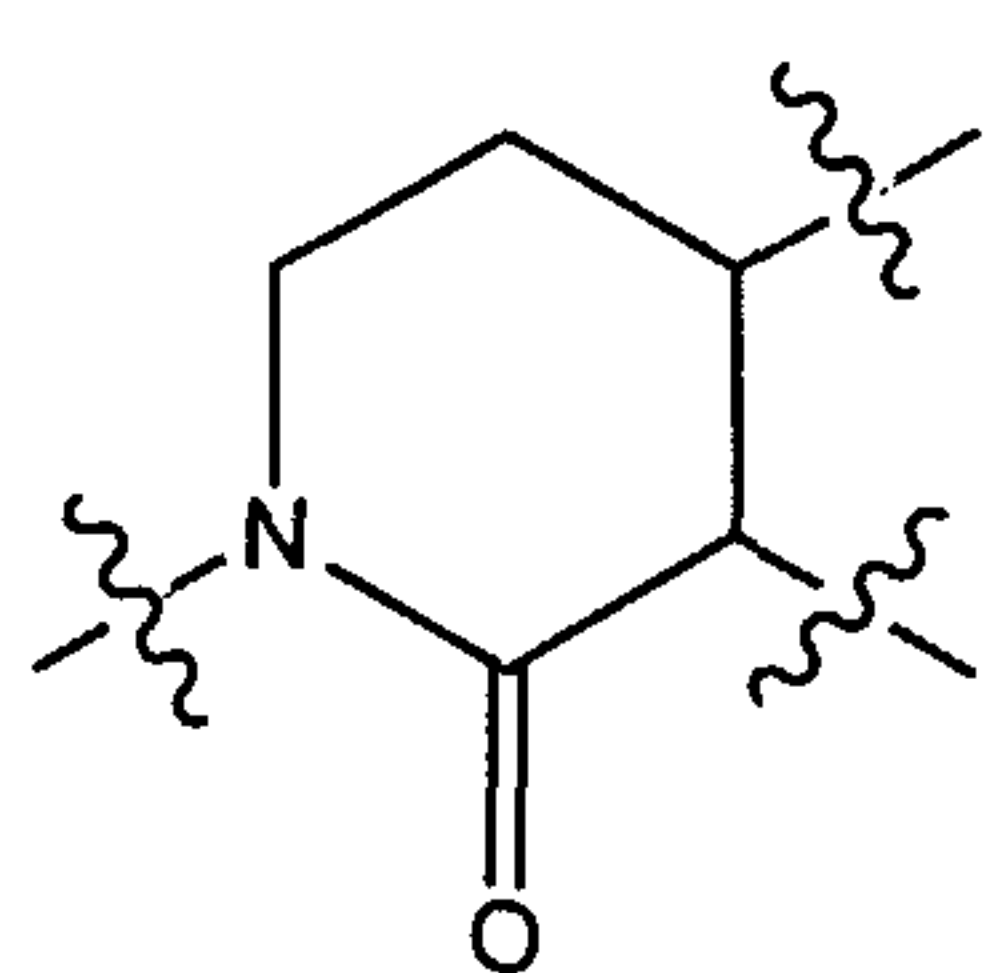
TABLE 2		
Core	Z ₁	R ₄₄
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Tetrahydro-triazinedione	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Tetrahydro-triazinone	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino

TABLE 2		
Core	Z ₁	R ₄₄
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Piperidine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	hydroxy
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutylsulfonyl
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	trifluoromethyl

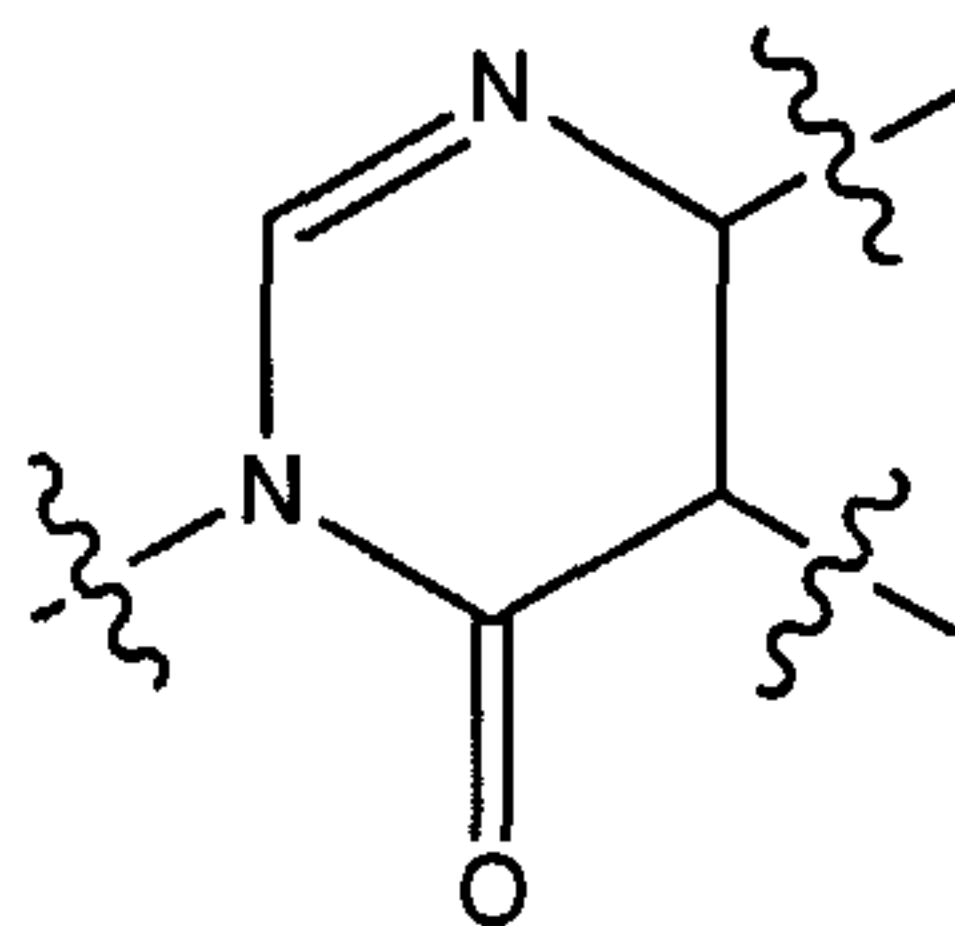
TABLE 2		
Core	Z ₁	R ₄₄
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobenzyl
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxamidobutyl-2-yl
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutyramido
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	isobutoxy
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboethoxy
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	carboxyl
Piperazine	methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or phenyl	amino

For convenience, each of the core heterocyclic rings and R₄₄ moieties identified in Tables 1 and 2 are set forth below.

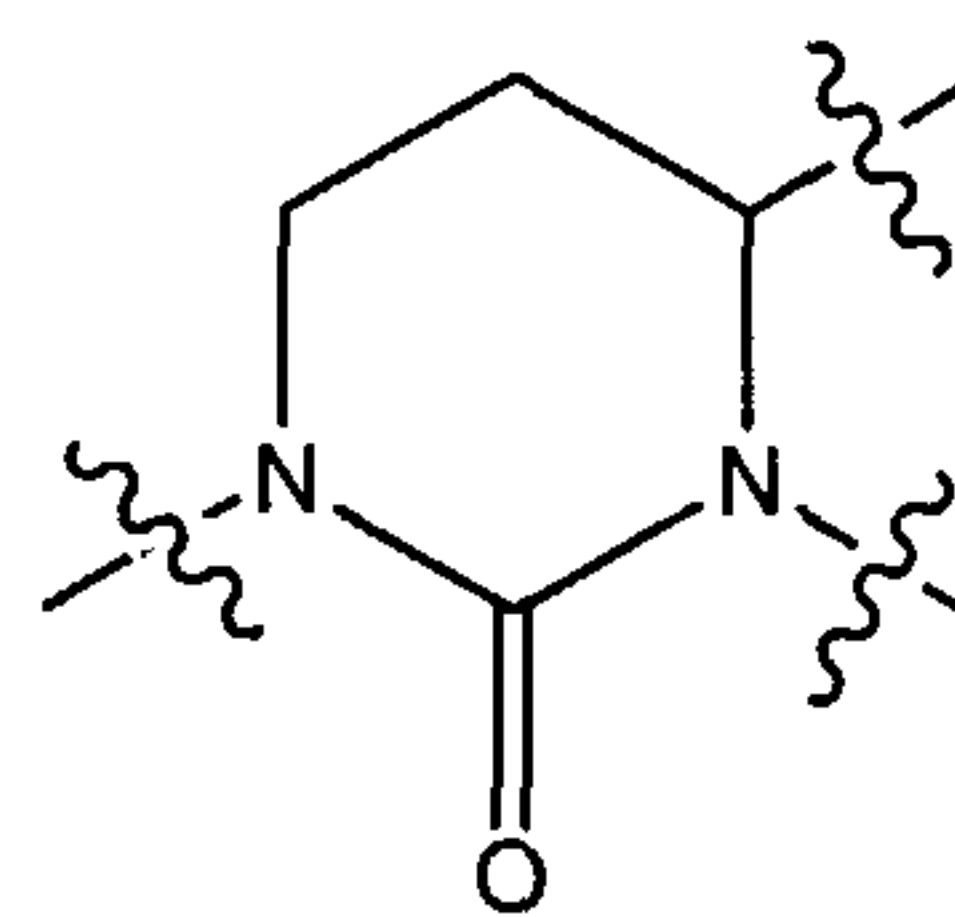
Heterocyclic Core Ring Structures



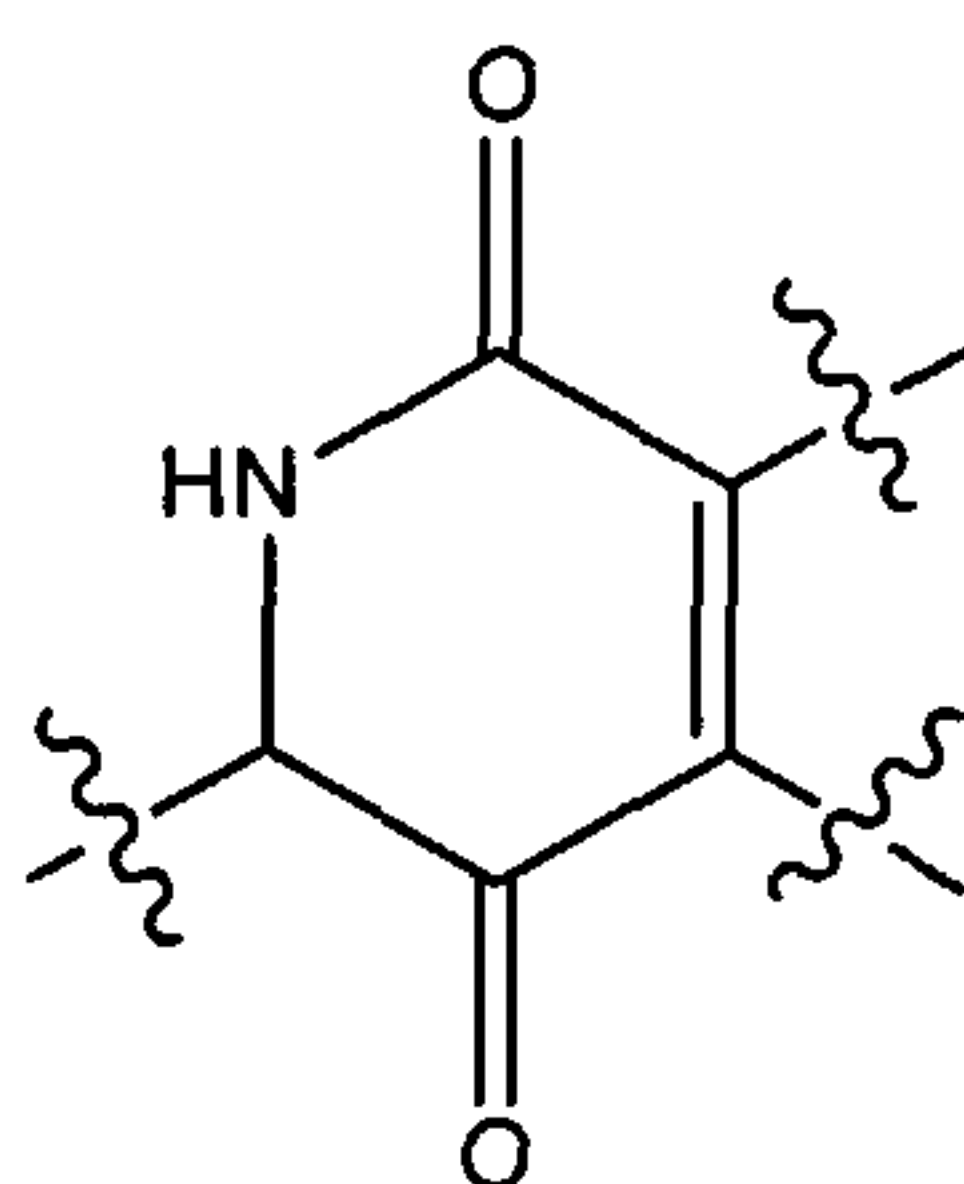
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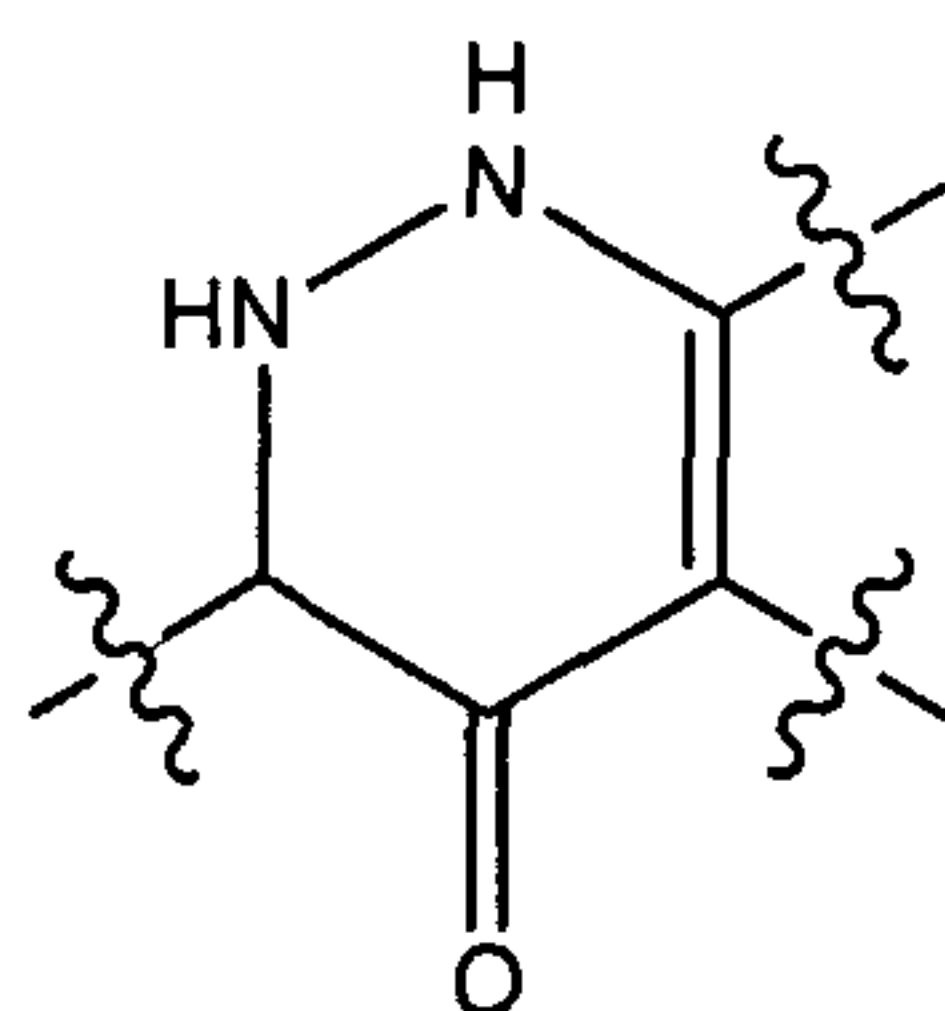
DIHYDROPYRIMIDONE



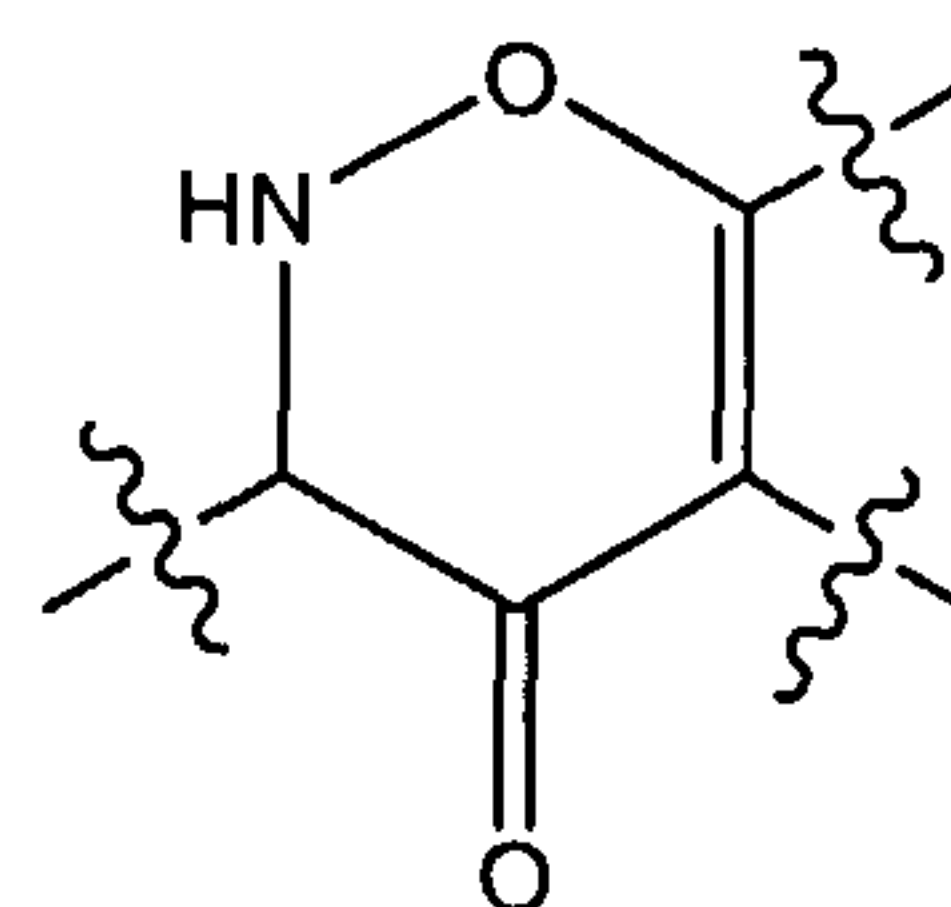
TETRAHYDROPYRIMIDINONE



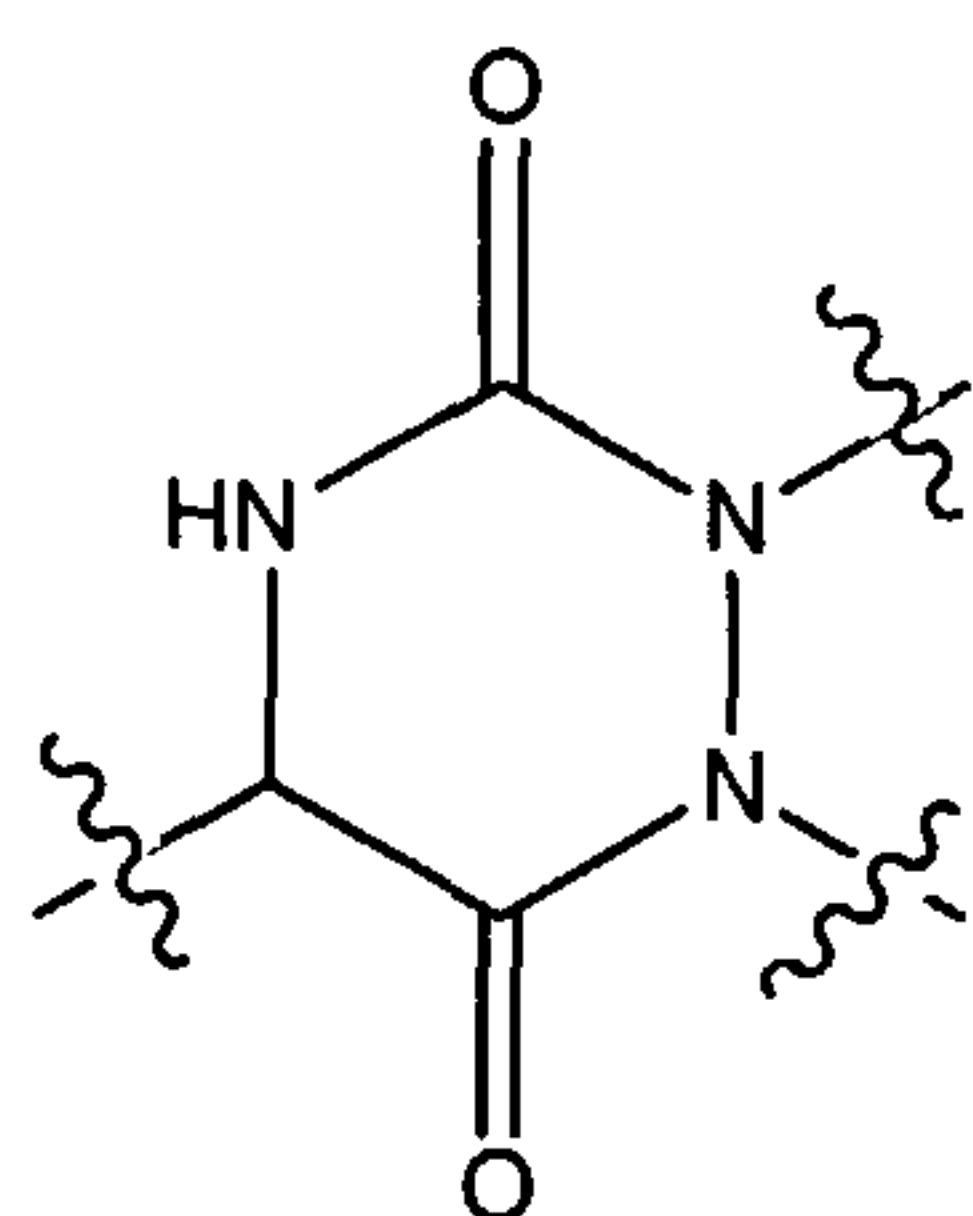
DEHYDROPIPERIDINEDIONE



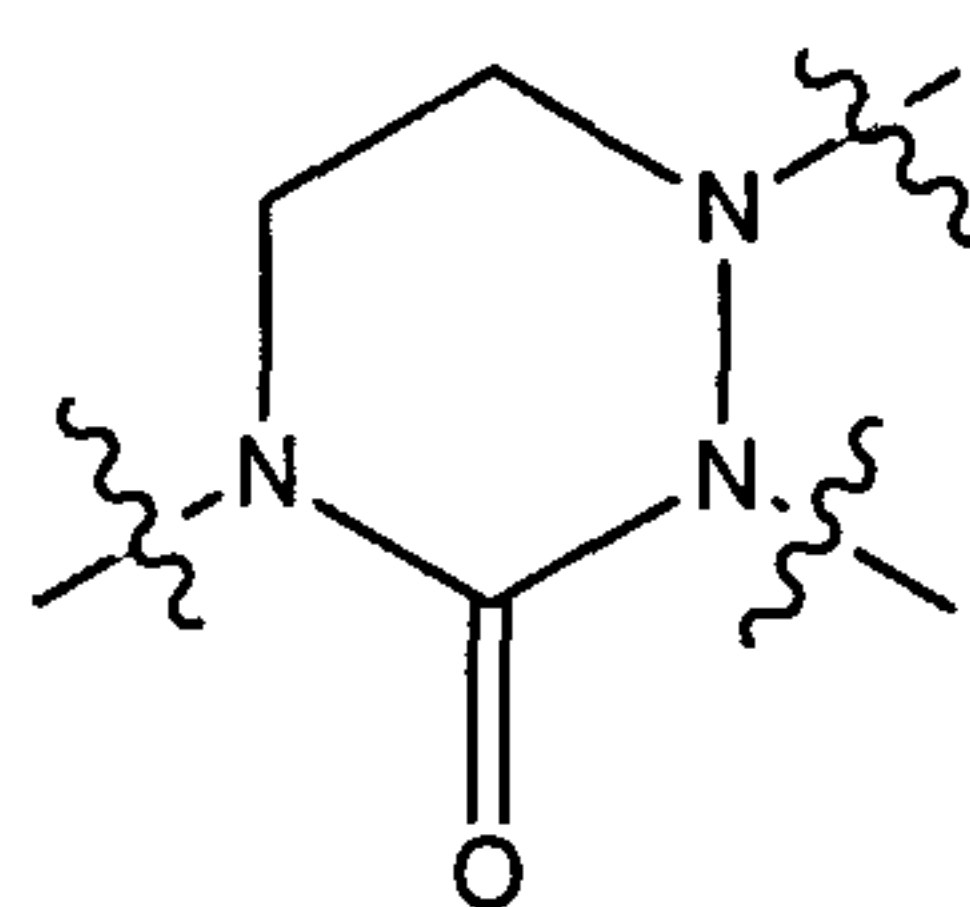
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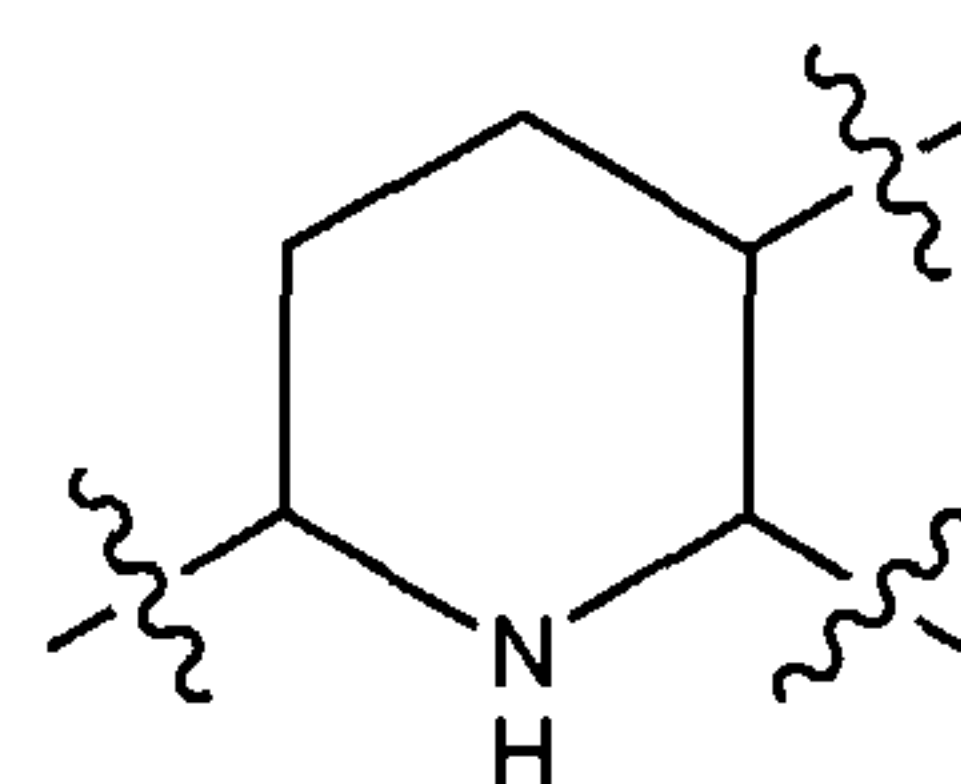
DIHYDROISOXAZINONE



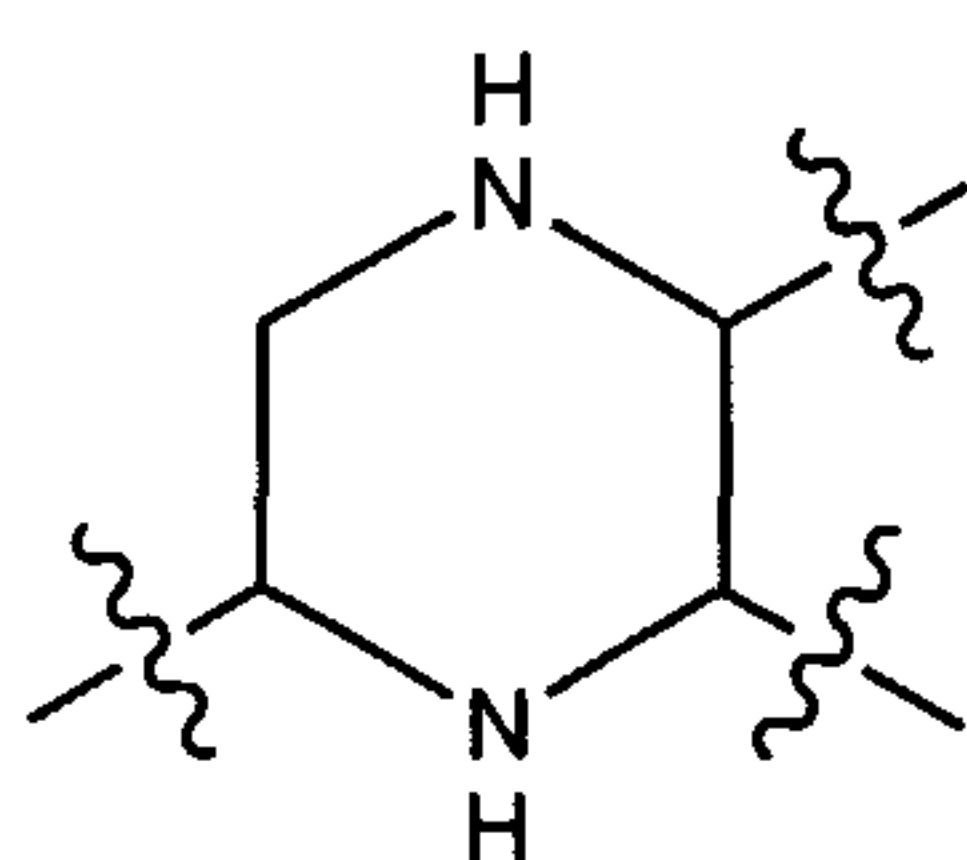
TETRAHYDROTRIAZINEDIONE



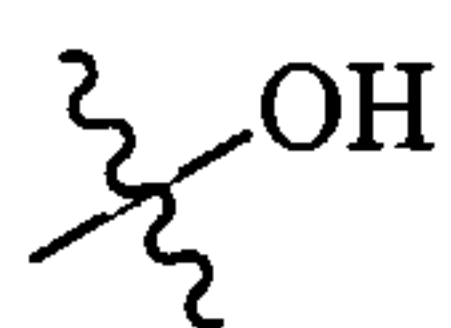
TETRAHYDROTRIAZINONE



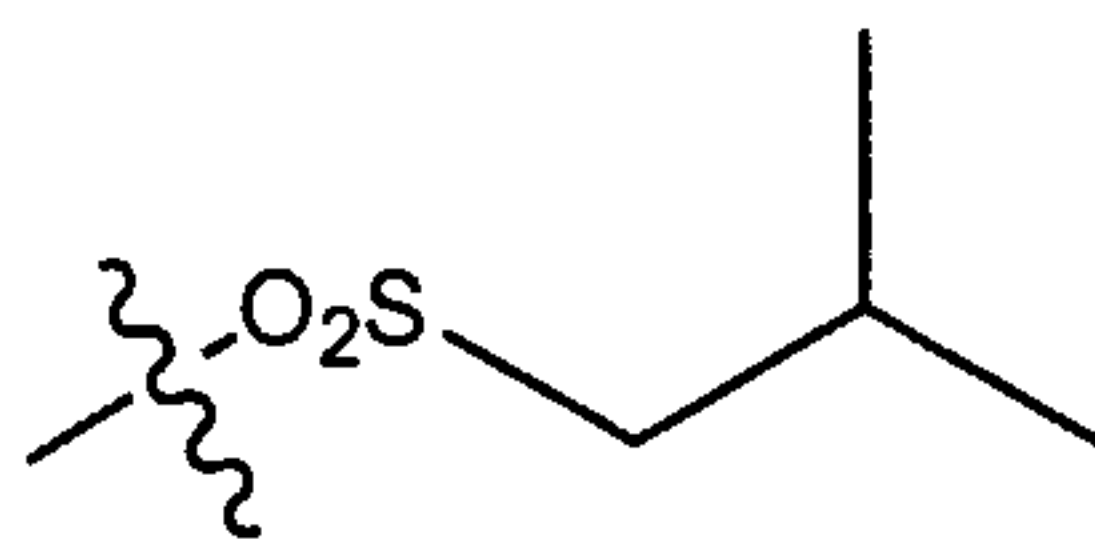
PIPERIDINE



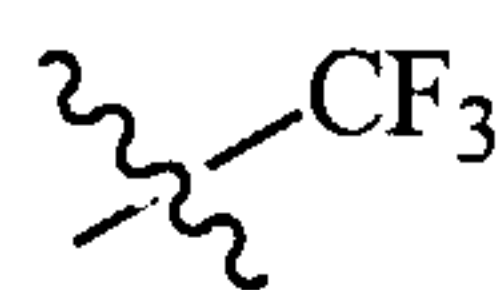
PIPERAZINE

R₄₄ Moieties

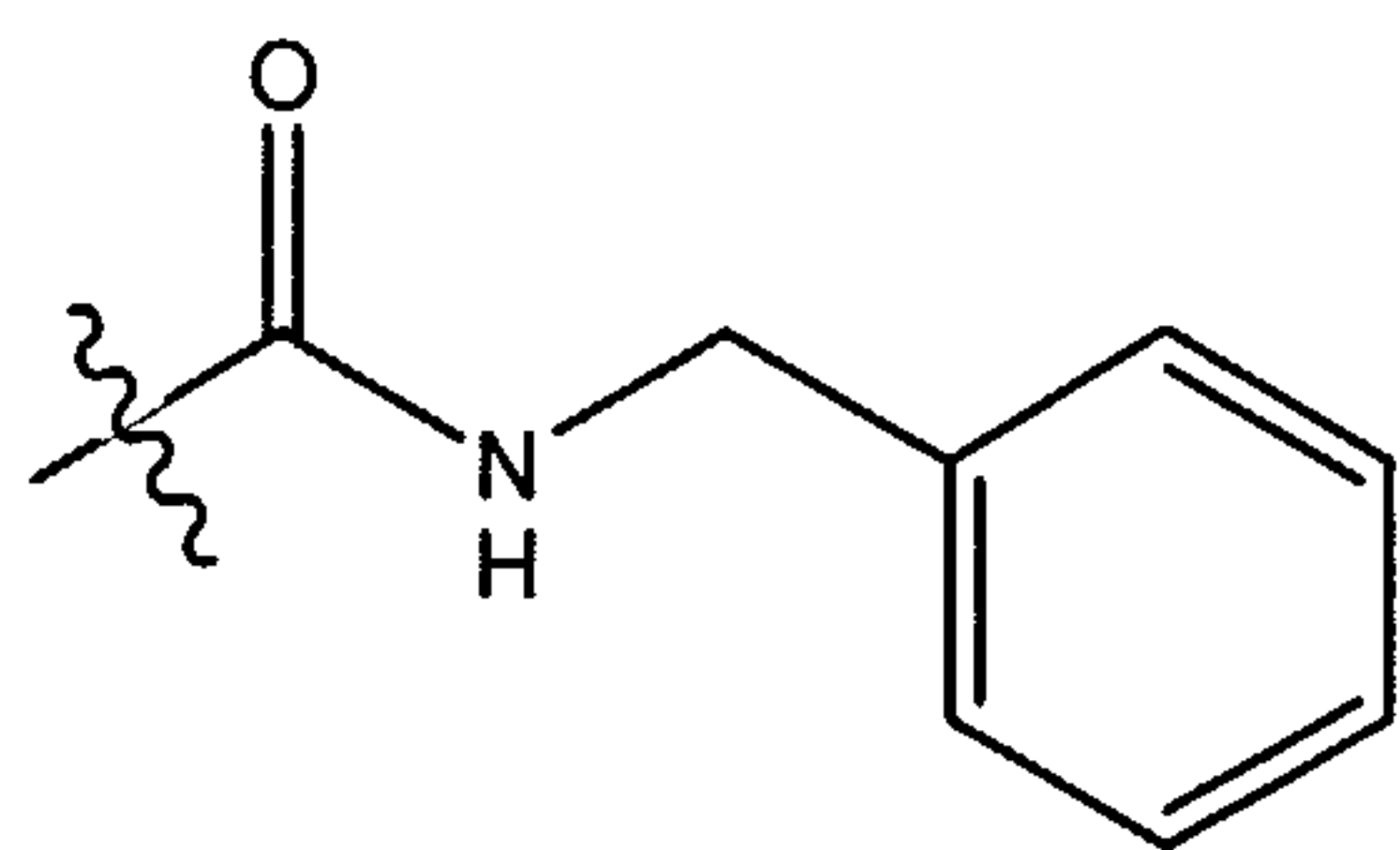
hydroxy



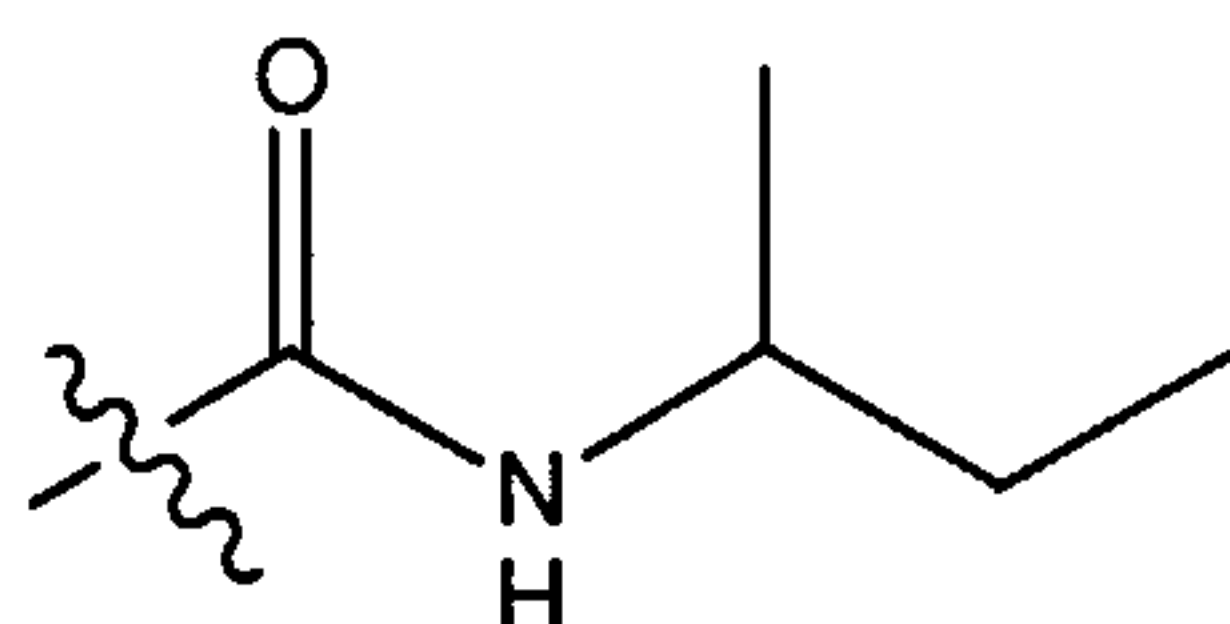
isobutylsulfonyl



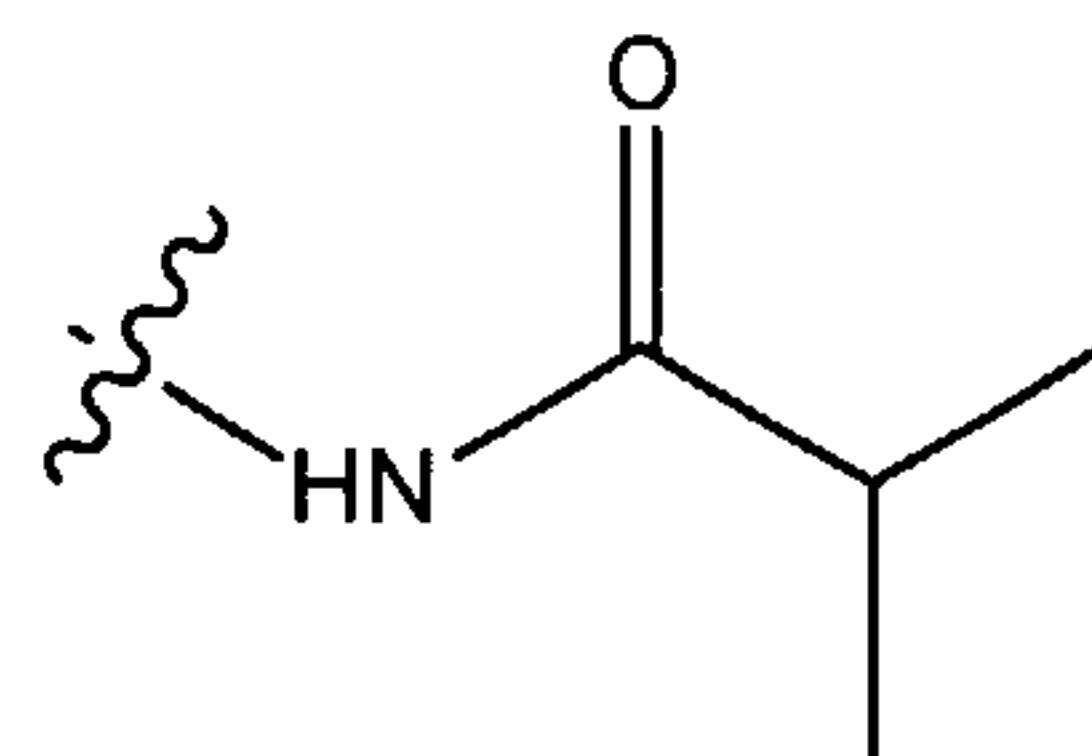
trifluoromethyl



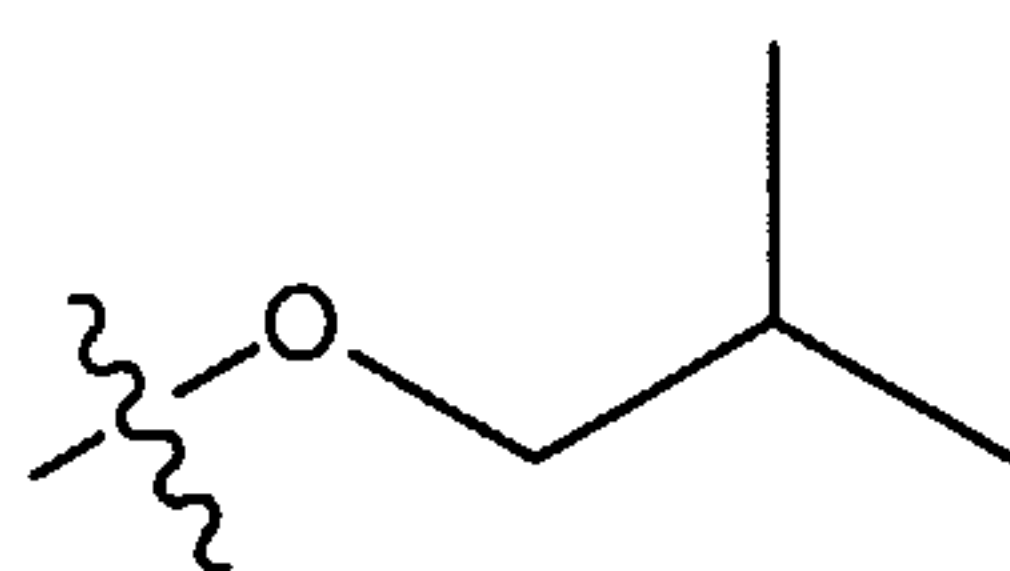
carboxamidobenzyl



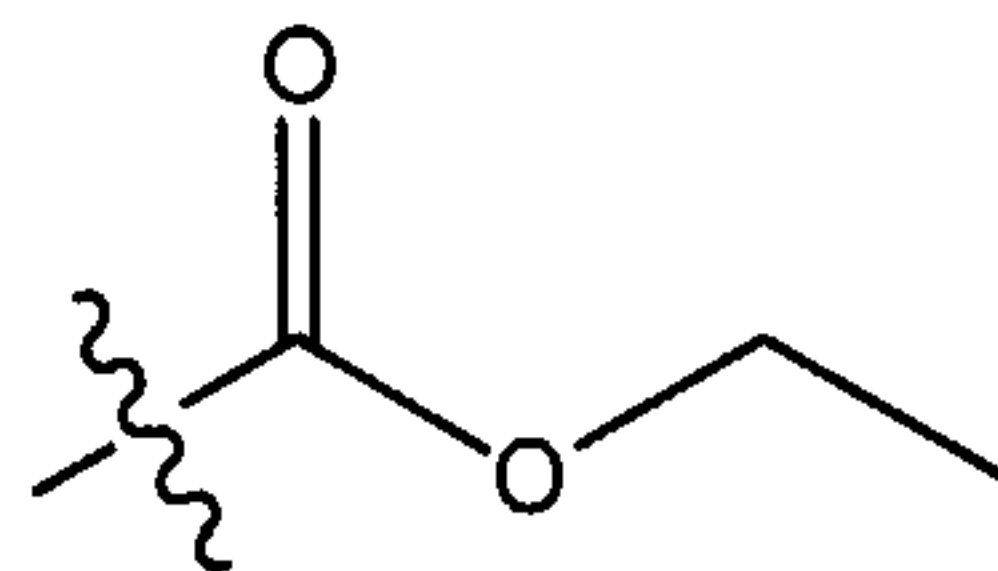
carboxamidobutyl-2-yl



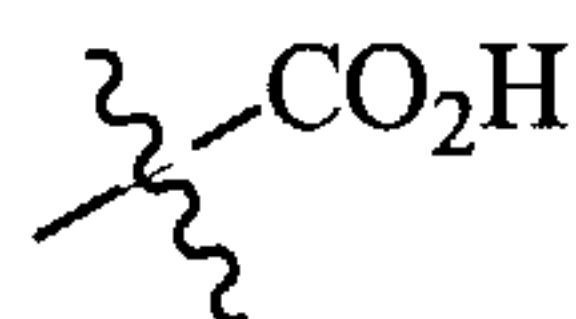
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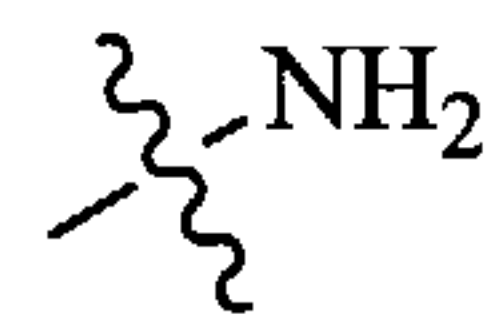
isobutoxy



carboethoxy



carboxyl

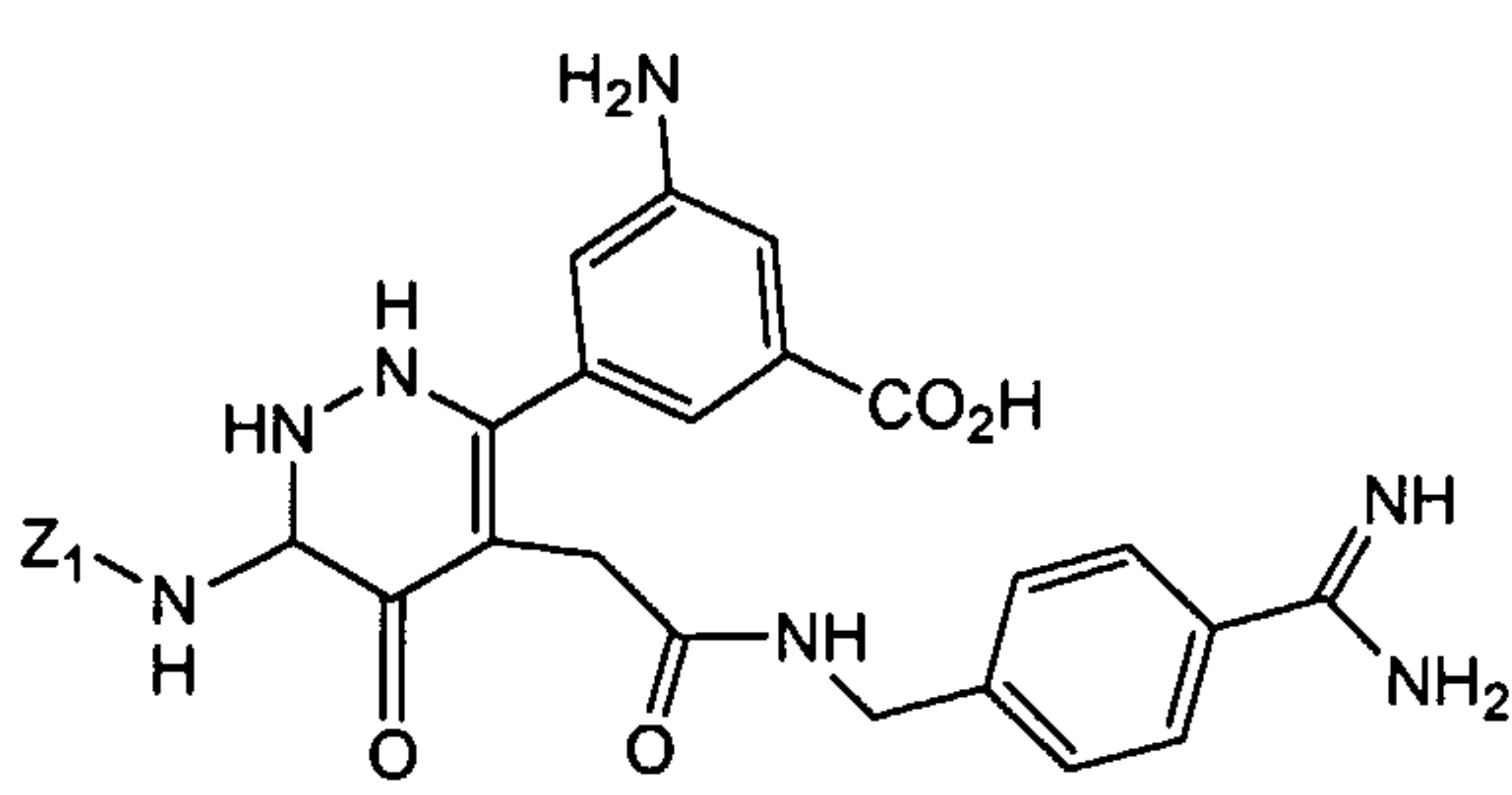


amino

In another preferred embodiment, the compounds corresponding to either of formulas (1) and (2) are selected from the group of compounds illustrated in Table 3 below wherein for any given compound, Z₁ is isopropyl, cyclopropyl, cyclobutyl, trifluoroethyl, or carboxymethyl.

TABLE 3	
Compound No.	Compound
1	
2	
3	
4	

TABLE 3	
Compound No.	Compound
5	
6	
7	
8	
9	

TABLE 3	
Compound No.	Compound
10	

Any prodrug compound of the present invention having one or more prodrug moieties as part of the molecule, can be converted under physiological conditions to the biologically active drug by a number of chemical and biological mechanisms. In general terms, as detailed above, these prodrug conversion mechanisms are hydrolysis, reduction, oxidation, and elimination. For illustrative purposes, the following paragraphs detail prodrugs in which the prodrug moiety is covalently bonded to the amidine group on Z_3 .

In one embodiment, conversion of the prodrug to the biologically active drug can be accomplished by hydrolysis of the prodrug moiety provided the prodrug moiety is chemically or enzymatically hydrolyzable with water. The reaction with water typically results in removal of the prodrug moiety and liberation of the biologically active drug. By way of example, a hydrolyzable prodrug derivative at the amidine group may be a carbonyl derivative such as N-acyl. Hydrolysis results in freeing the amidine group of the drug by removal of the acyl as carbon acid. Other suitable hydrolyzable prodrug derivatives include carbonyl, thiocarbonyl, imine, enamine, and oxygenated sulfur.

Yet another aspect of the invention provides conversion of the prodrug to the biologically active drug by reduction of the prodrug moiety. Typically in this embodiment, the prodrug moiety is reducible under physiological conditions in the presence of a reducing

enzymatic process. The reduction preferably results in removal of the prodrug moiety and liberation of the biologically active drug. An example of a reducible prodrug derivative at the amidine group is an oxygen containing group in which an oxygen is directly attached to the amidine. Reduction results in freeing the amidine group of the drug by removal of oxygen as water or an alcohol. Generally speaking, other suitable reducible prodrug derivatives include a nitrogen containing group, and a sulfur containing group, provided both nitrogen and sulfur are each preferably in their most reduced state.

In another aspect of the invention, conversion of the prodrug to the biologically active drug can also be accomplished by oxidation of the prodrug moiety. Typically in this embodiment, the prodrug moiety is oxidizable under physiological conditions in the presence of an oxidative enzymatic process. The oxidation preferably results in removal of the prodrug moiety and liberation of the biologically active drug. An example of an oxidizable prodrug derivative at the amidine group is a hydrocarbyl containing unsaturation in the carbon beta to the carbon directly connected to the amidine group. Oxidation results in forming an oxygenated intermediate that breaks down, thereby freeing the amidine group of the drug with concurrent hydrolysis of the oxygenated hydrocarbyl residue. Other suitable oxidizable prodrug derivatives of the amidine include saturated hydrocarbyl, unsaturated substituted hydrocarbyl, aryl, and aralkyl.

A further aspect of the invention encompasses conversion of the prodrug to the biologically active drug by elimination of the prodrug moiety. Generally speaking, in this embodiment the prodrug moiety is removed under physiological conditions with a chemical or biological reaction. The elimination results in removal of the prodrug moiety and liberation of the biologically active drug. By way of example, an eliminateable prodrug

derivative at the amidine group is a hydrocarbyl containing an unsaturated electron withdrawing group bonded to the carbon beta to the carbon directly connected to the amidine. More specifically, for illustration purposes and exemplification, the hydrocarbyl group could have a cyano group beta to the carbon directly bonded to the amidino group. Elimination results in the freeing of the amidine group of the drug with concurrent removal of the unsaturated hydrocarbyl residue derived from the prodrug moiety. Other suitable eliminateable prodrug derivatives of the amidine include a hydrocarbyl substituted at the beta carbon with carbonyl, alkoxycarbonyl, amidocarbonyl, nitro, or sulfonyl or an alkyl group substituted with oxygen, nitrogen or sulfur at the carbon directly bonded to the amidine group.

Any prodrug compound of the present invention may undergo any combination of the above detailed mechanisms to convert the prodrug to the biologically active compound. For example, a particular compound may undergo hydrolysis, oxidation, elimination, and reduction to convert the prodrug to the biologically active compound. Equally, a particular compound may undergo only one of these mechanisms to convert the prodrug to the biologically active compound.

As a further embodiment, compounds of the present invention or a pharmaceutically-acceptable salt thereof, comprise a treatment and prophylaxis for thrombotic events resulting from coronary artery disease, cerebrovascular disease and other coagulation cascade related disorders in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of compounds of the present invention or a pharmaceutically-acceptable salt thereof.

In another aspect of the invention, the compounds may also be used whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole

blood and to prevent coagulation in other biological samples for testing or storage. Thus coagulation inhibitors of the present invention can be added to or contacted with stored whole blood and any medium containing or suspected of containing plasma coagulation factors and in which it is desired that blood coagulation be inhibited, e.g. when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of the invention are capable of inhibiting activity of serine proteases related to the coagulation cascade, and thus could be used in the manufacture of a medicament, a method for the prophylactic or therapeutic treatment of diseases mediated by coagulation cascade serine proteases, such as inhibiting the formation of blood platelet aggregates, inhibiting the formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, in blood, in blood products, and in mammalian organs. The compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The compounds also can be used to study the mechanism of action of coagulation cascade serine proteases to enable the design of better inhibitors and development of better assay methods. The compounds would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Also included in the family of compounds are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salt" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not

critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of formulas (1), (2), or (3) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of formulas (1), (2), or (3) include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chlorprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound of the present invention.

The present invention also comprises a pharmaceutical composition comprising a therapeutically-effective amount of the compound in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent. Pharmaceutical compositions of the present invention can comprise the active compounds in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention

may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, ocularly, or topically. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other silicon containing polymers.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid,

polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacrylates and cross linked or amphitpathic block copolymers of hydrogels.

For oral administration, the pharmaceutical composition may be in the form of, for example, tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, liquids including syrups, and emulsions. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to

15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the

oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

For therapeutic purposes, the active compounds of the present invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided

in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

In practicing the methods of the present invention for the treatment and prevention of a variety of thrombotic conditions resulting from coronary artery and cerebrovascular disease, the compounds and pharmaceutical compositions of the present invention are administered alone or in combination with one another, or in combination with other therapeutics or in vivo diagnostic agents. The coagulation cascade inhibitors of the present invention can also be co-administered with suitable anti-platelet aggregation agents, including, but not limited to ticlopidine, clopidogrel, or aspirin, fibrinogen receptor antagonists (e.g., to treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), anti-coagulants such as warfarin or heparins, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various pathologies, lipid lowering agents including antihypercholesterolemics (e.g., HMG CoA reductase inhibitors such as mevastatin, lovastatin, simvastatin, pravastatin, and fluvastatin, HMG CoA synthetase inhibitors, etc.), anti-diabetic drugs, or other cardiovascular agents (loop diuretics, thiazide type diuretics, nitrates, aldosterone antagonists (i.e.,

spironolactone and eplerenone), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, antiarrhythmics, anti-hypertension agents, and calcium channel blockers) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and coagulation cascade inhibitors of the present invention. Also, coagulation cascade inhibitors could enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion.

Typical doses of coagulation cascade inhibitors of the present invention with other suitable anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents may be the same as those doses of coagulation cascade inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, or may be substantially less than those doses of coagulation cascade inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, depending on a patient's therapeutic needs.

Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention.

The terms "cis" and "trans", as used herein, denote a

form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

The present novel methods preferably employ compounds which selectively inhibit human TF-VIIa over the inhibition of both human Thrombin II and human factor Xa. Preferably, the compounds have a human TF-VIIa IC_{50} of less than 0.5 μM and also have a selectivity ratio of TF-VIIa inhibition over both human Thrombin II and human factor Xa inhibition of at least 10, and more preferably at least 100. Even more preferably, the compounds have a human TF-VIIa IC_{50} of less than 0.1 μM and also have a selectivity ratio of TF-VIIa inhibition over both human Thrombin II and human factor Xa inhibition of at least 300, more preferably at least 1000, and most preferably at least 10,000.

All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Compounds containing multiple variations of the structural modifications illustrated in the Schemes are also contemplated. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

GENERAL SYNTHETIC PROCEDURES AND SPECIFIC EXAMPLES

The compounds of the present invention can be synthesized, for example, according to the following procedures and Schemes given below.

Abbreviations used in the schemes and tables include: "AA" represents amino acids, "AcCN" represents acetonitrile, "AcOH" represents acetic acid, "BINAP" represents 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, "BnOH" represents benzyl alcohol, "BnCHO" represents 2-phenylethanal, "BnSO₂Cl" represents benzylsulfonyl chloride, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino), "bu" represents butyl, "dba" represents dibenzylidene-acetone, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DCM" represents dichloromethane or methylene chloride, "DIBAH" or "DIBAL" represents diisobutylaluminum hydride, "DMF" represents dimethylformamide, "DMSO" represents dimethylsulfoxide, "DPPA" represents diphenylphosphoryl azide, "EDC" represents 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, "Ex. No." represents Example Number, "Fmoc" represents 9-fluorenylmethoxycarbonyl, "HOBt" represents hydroxybenzotriazole, "LDA" represents lithium diisopropylamide, "MW" represents molecular weight, "NMM" represents N-methylmorpholine, "Ph" represents phenyl or aryl, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxy-carbonyl, "PTC" represents a phase transfer catalyst, "py" represents pyridine, "RNH₂" represents a primary organic amine, "SEM" represents 2-(trimethylsilyl)ethoxy-methyl chloride, "p-TsOH" represents paratoluenesulfonic acid, "TBAF" represents tetrabutylammonium fluoride, "TBTU" represents 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, "TEA" represents triethylamine, "TFA" represents trifluoroacetic acid, "THF" represents tetrahydrofuran, "TMS" represents trimethylsilyl, "TMSCN"

represents trimethylsilyl cyanide, and "Cbz" or "Z" represents benzyloxycarbonyl.

A specific synthetic process, useful in the preparation of many of the heterocyclic compounds of the present invention, is the arylation or heteroarylation of an intermediate compound characterized by having a suitable leaving group on a sp^2 hybridized carbon of a heterocyclic ring or a cycloalkenyl ring. In the product of the reaction, the leaving group is replaced by an aryl group or a heteroaryl group. Suitable leaving groups for the reaction include chloro, bromo, iodo, methylthio, and triflates. The heterocyclic ring or the cycloalkenyl ring with the leaving group will preferably have an acetic acid group or a derivative thereof bonded to a ring atom alpha to the bromo and a substituted or unsubstituted amino group bonded to a ring atom that is both beta to the carbon having the acetic acid group and gamma to the bromo substituted ring carbon. The aryl group that is reacted at the sp^2 hybridized carbon is generally an aryl boronic acid or an ester of the aryl boronic acid; similarly, heteroaryl boronic acids or esters of these boronic acids can be used in the same manner as aryl boronates. The aryl and heteroaryl boronates may be substituted or unsubstituted. The aryl or heteroaryl becomes bonded to the sp^2 hybridized carbon at the point at which the boron was attached to the aryl or heteroaryl ring. Aryl and heteroaryl organoSn compounds can also be used instead of the corresponding boronates.

Suitable reaction conditions for carrying out this transformation include:

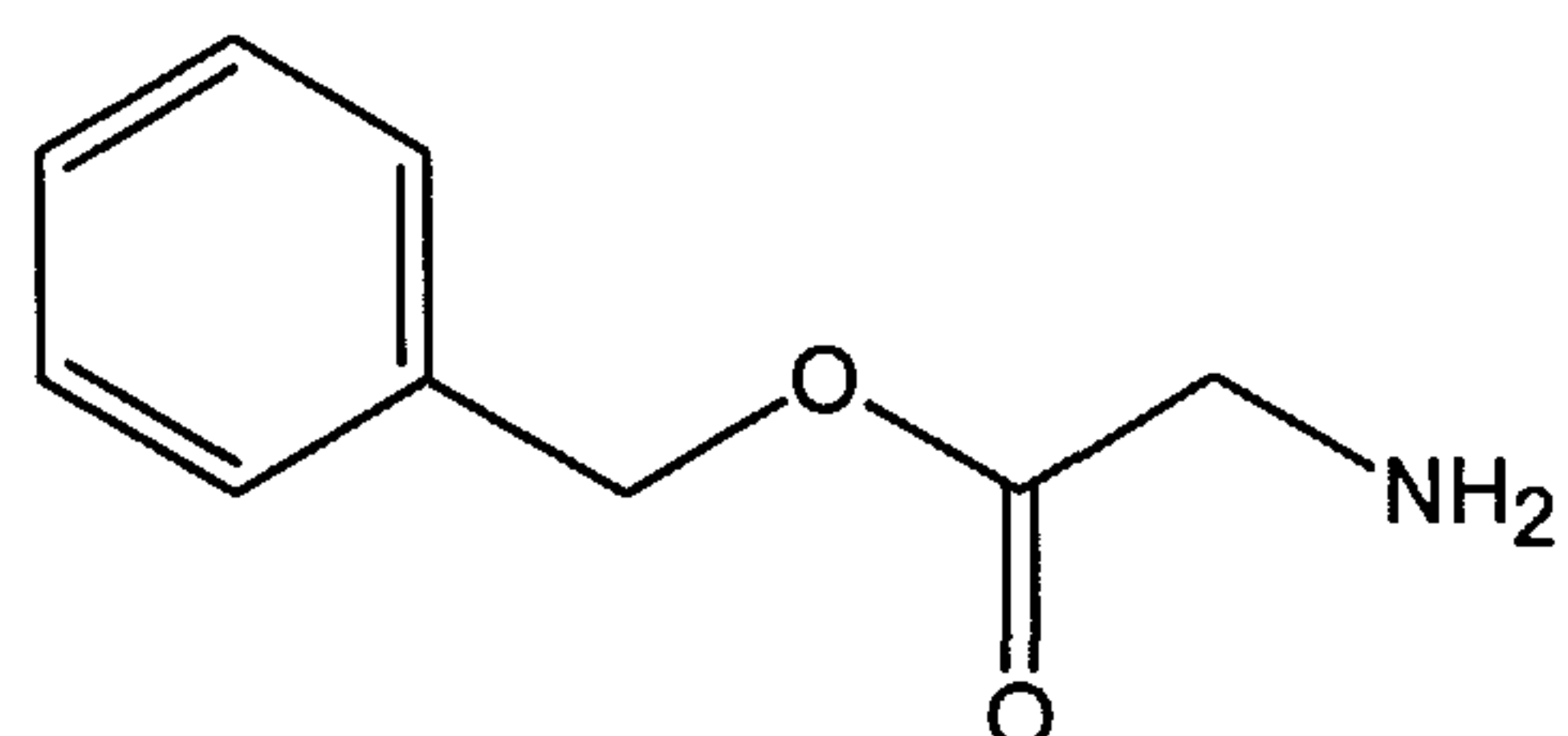
1. $Pd[P(phenyl)_3]_4$, 2M Na_2CO_3 , 60-75°C, dimethoxyethane (DME), H_2O , N_2 ;
2. $Pd[P(phenyl)_3]_4$, Cs_2CO_3 , dioxane, 100°C;
3. $Pd[P(phenyl)_3]_4$, Cu(I)-2-thiophenecarboxylate, 70-75°C, anhydrous THF, argon;

4. Z_4 -Sn(n-butyl)₃], Pd[P(phenyl)₃]₄, LiCl, anhydrous dioxane, 85°C, argon or N₂.

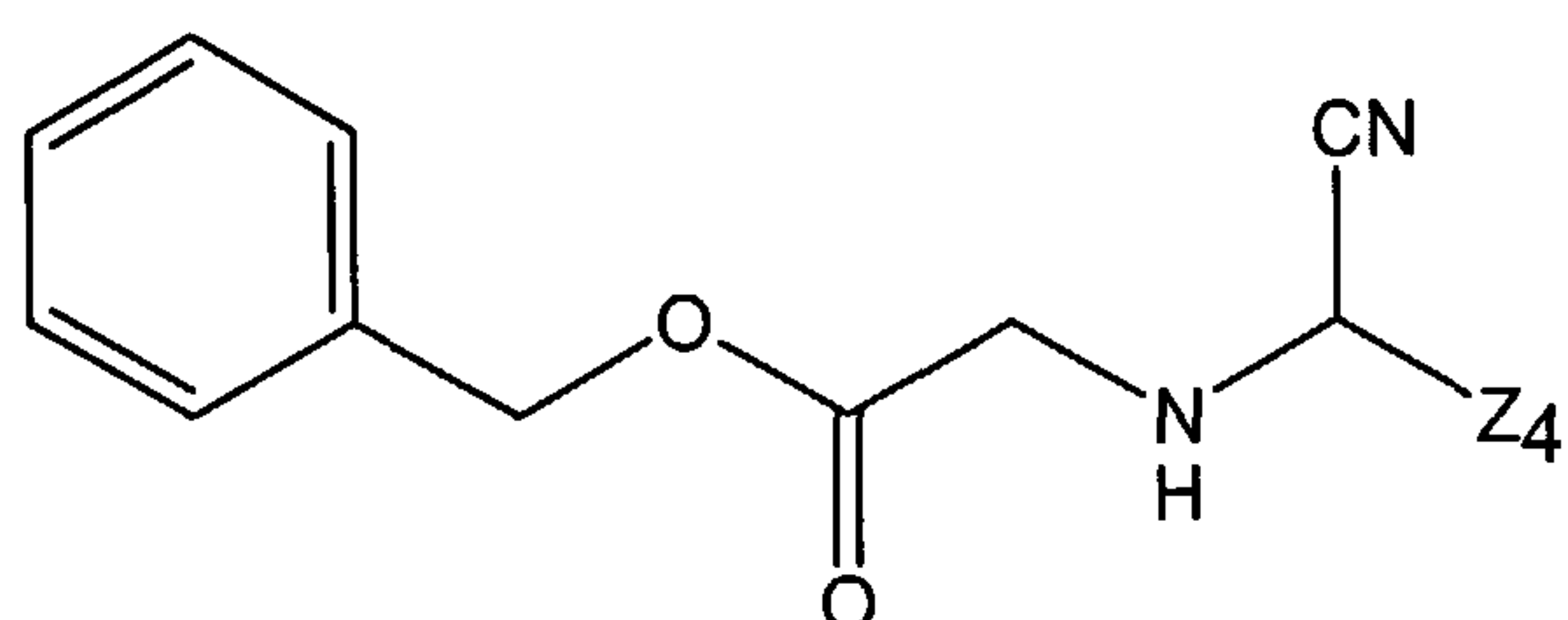
The organo palladium (Pd[P(phenyl)₃]₄) compound is used catalytically in a ratio of 1 to 40 mole %. The carbonate base is normally used in an excess of 1.2 to 2 molar equivalents. Suitable solvents include dimethoxyethane (DME), dioxane, 1-propanol, and tetrahydrofuran. The temperature of the reaction is normally in the range of from about 50 to 100°C. Cu(I)-2-thiophenecarboxylate (Cu(I)-TC) is normally used in a mole % of 110-150.

Schemes 2, 4, 5 and 6 show specific applications of this specific synthetic process. Procedures for preparing the intermediate heterocyclic or cycloalkenyl ring compounds having a suitable leaving group on sp² hybridized carbon and useful as suitable intermediates in this specific synthetic process are given in the schemes and examples listed above.

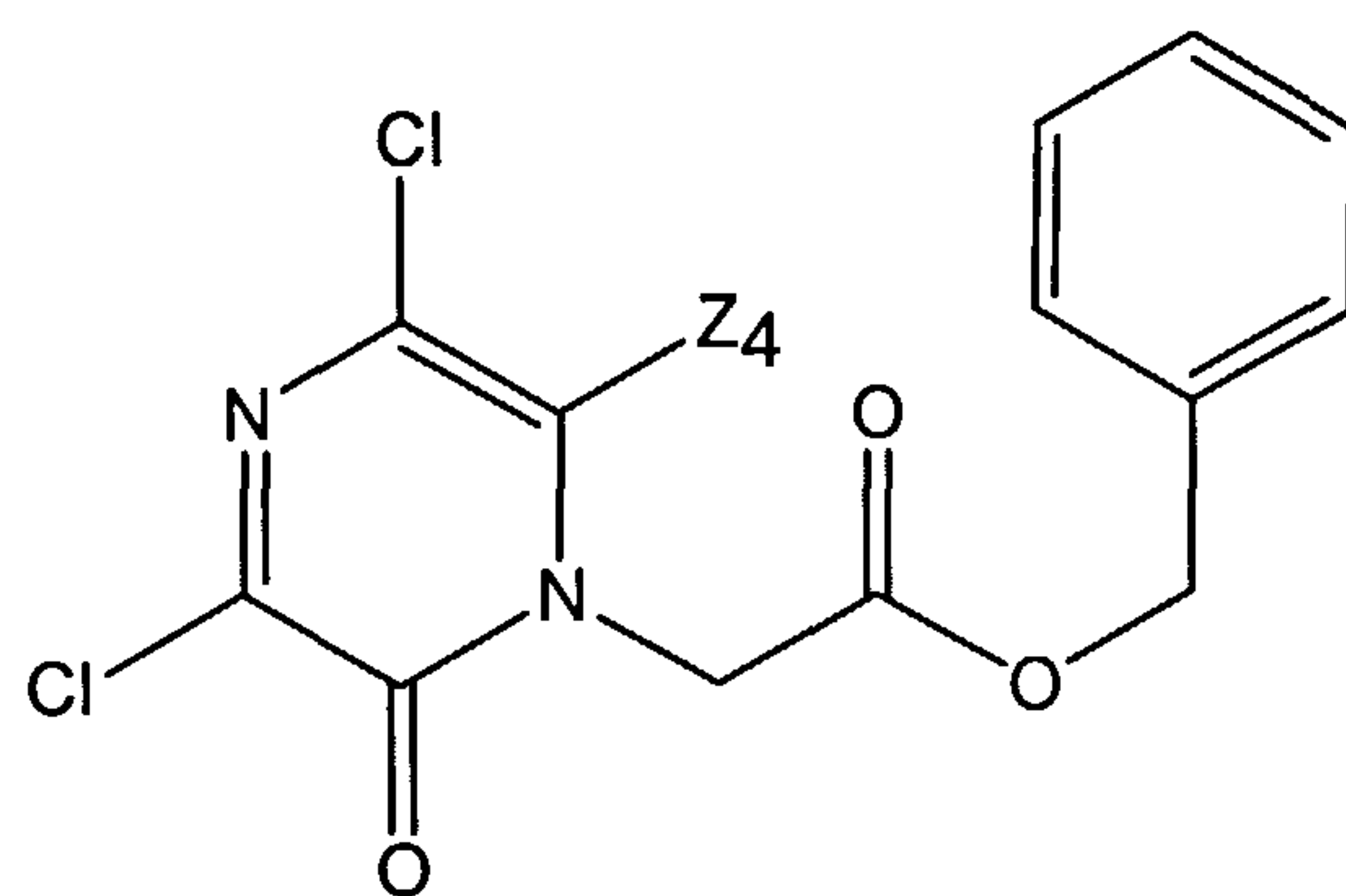
As used in the schemes and examples, L₃, Z₁, Z₃, Z₄, and R₄₄, along with any other variable depicted, encompass each group described for each particular variable for each embodiment of compounds having any of the formulas detailed herein. Further, Z₅ and Z₆ are independently hydrogen or halogen, R_{4a} and R_{4b} are hydrogen, and L₆ is a bond.

Scheme 1: Piperazine

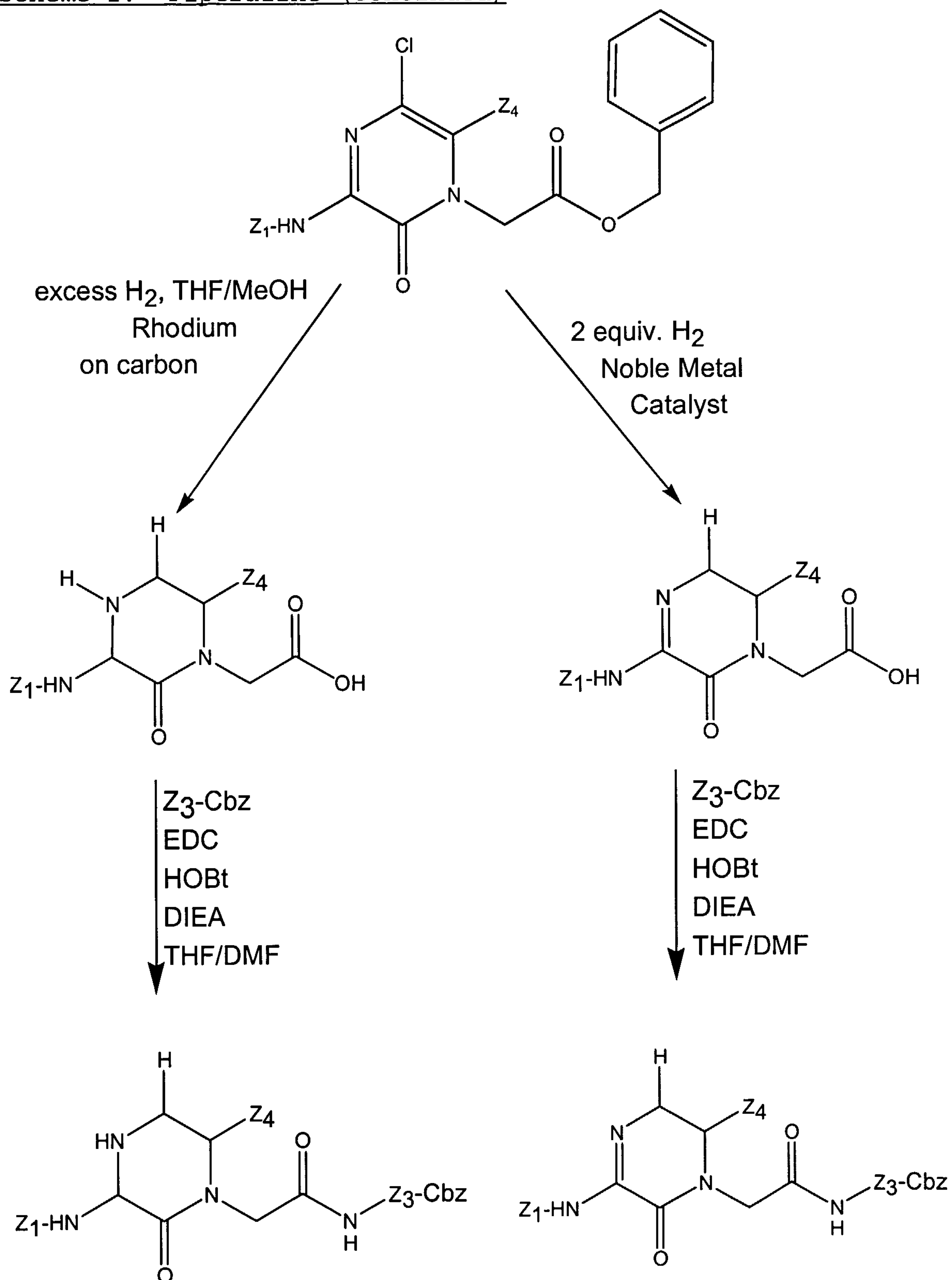
1. Z₄-CHO, TMSCN
CH₂Cl₂
2. HCl, EtOH

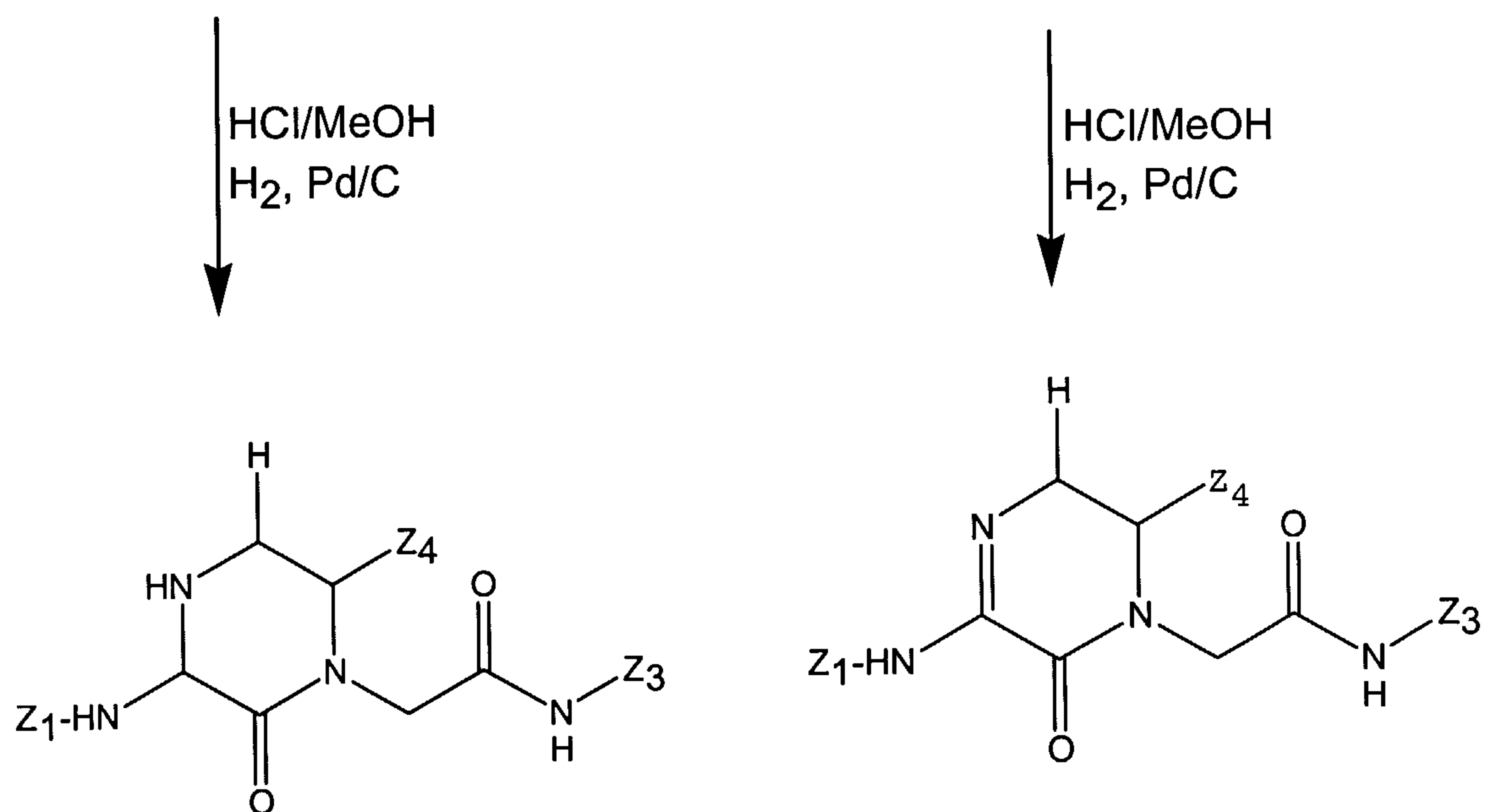


(ClCO)₂
C₆H₄Cl₂

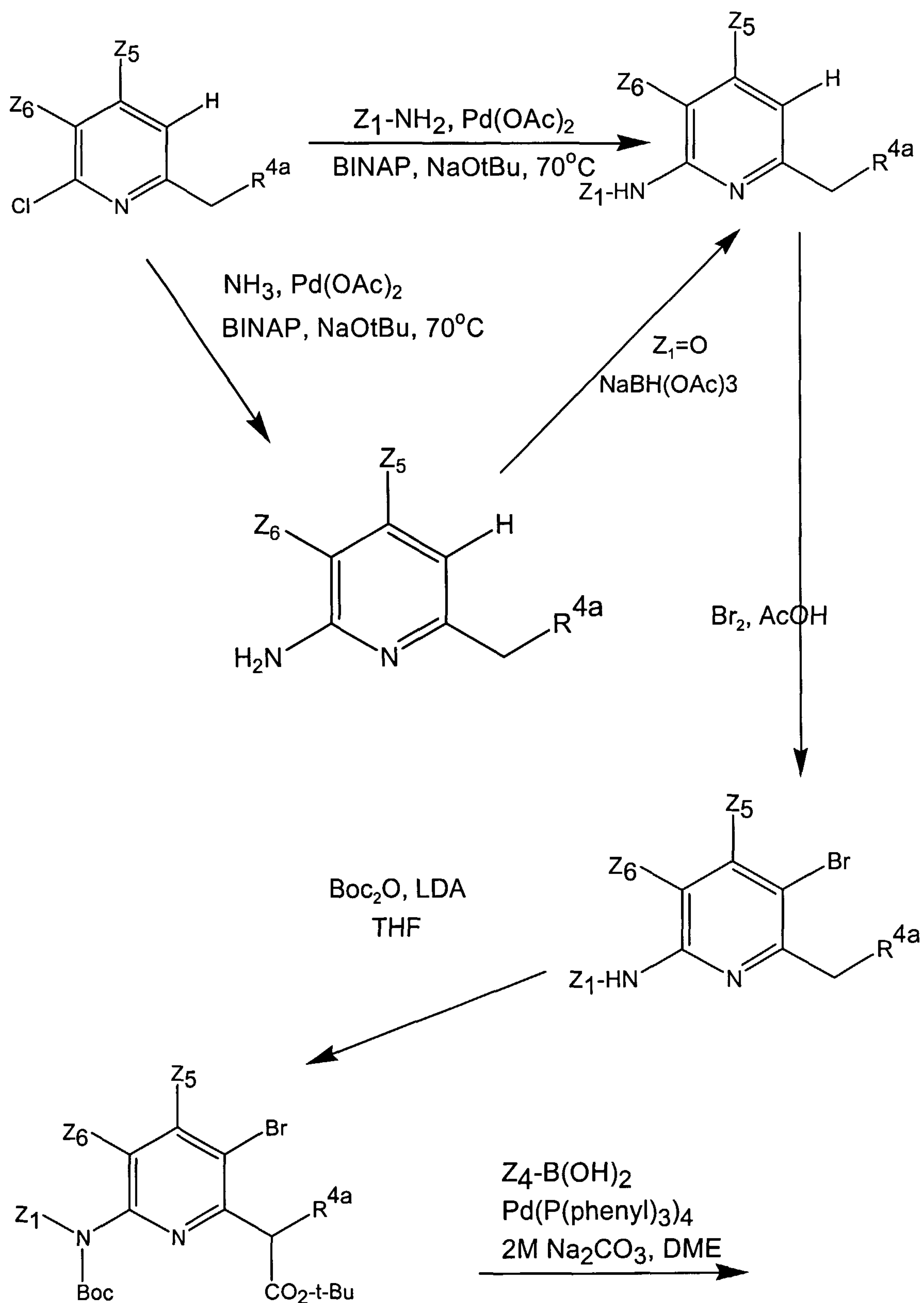


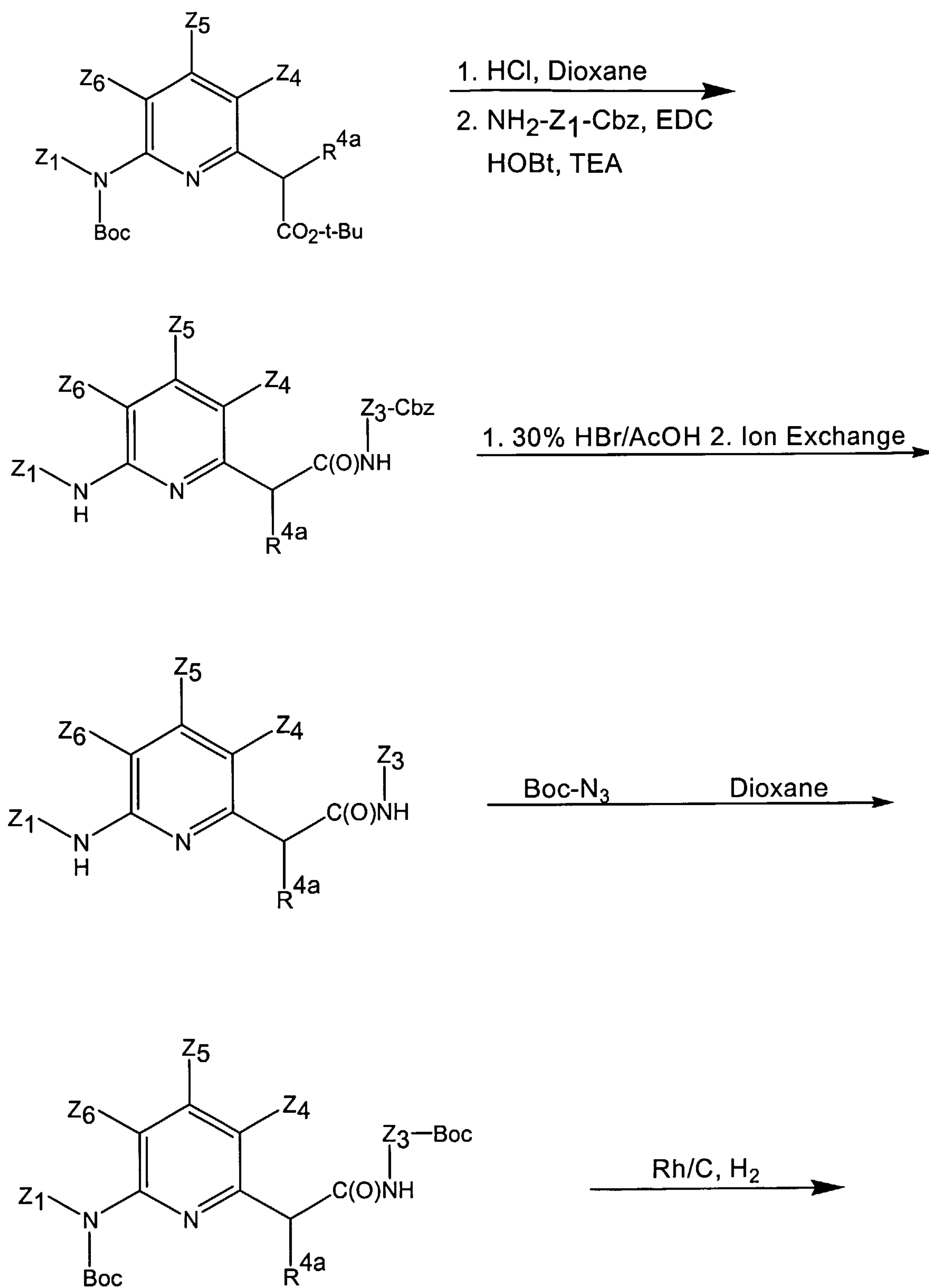
Z₁-NH₂
EtOAc

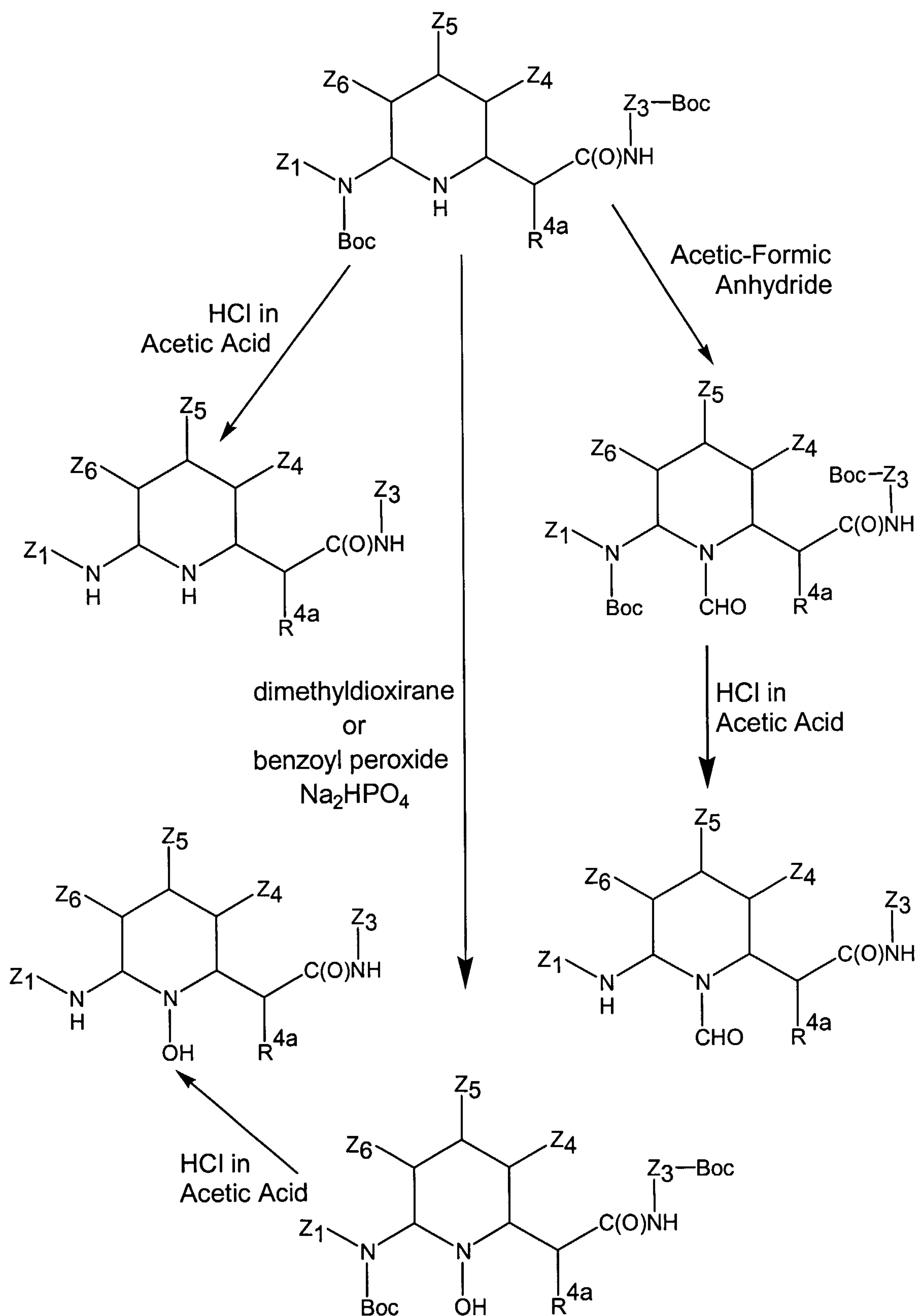
Scheme 1: Piperazine (continued)

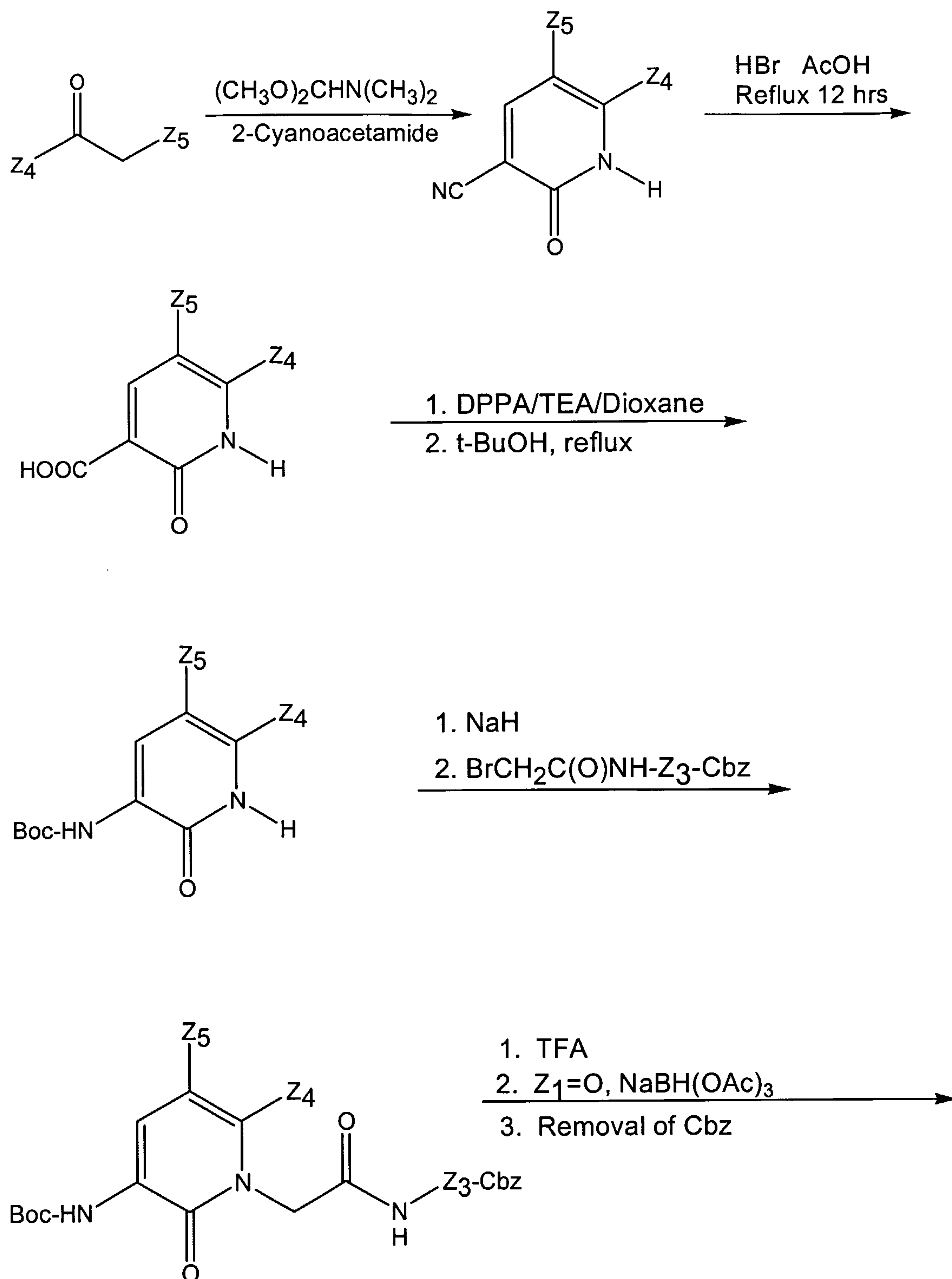
Scheme 1: Piperazine (continued)

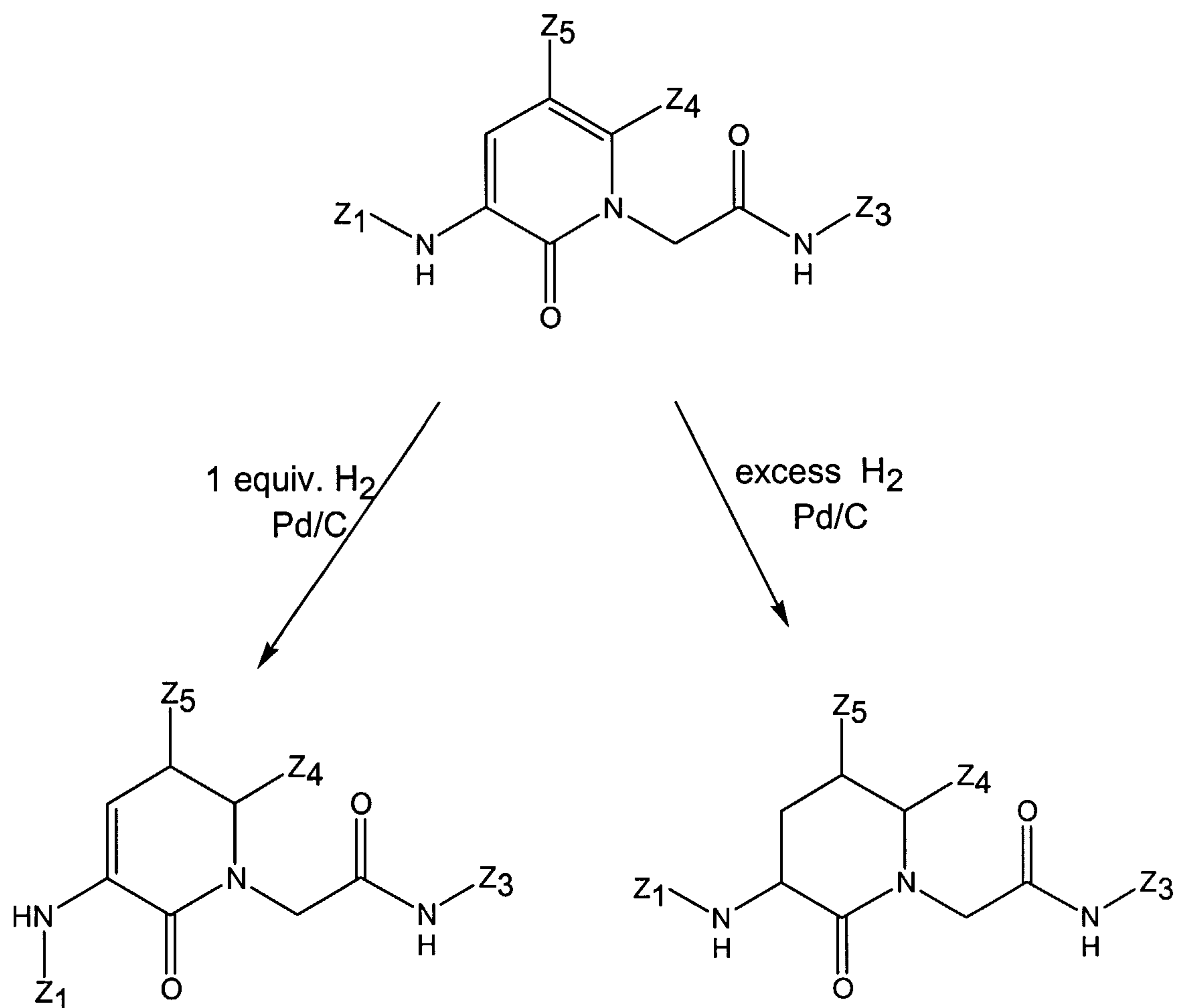
Scheme 2: Piperidine

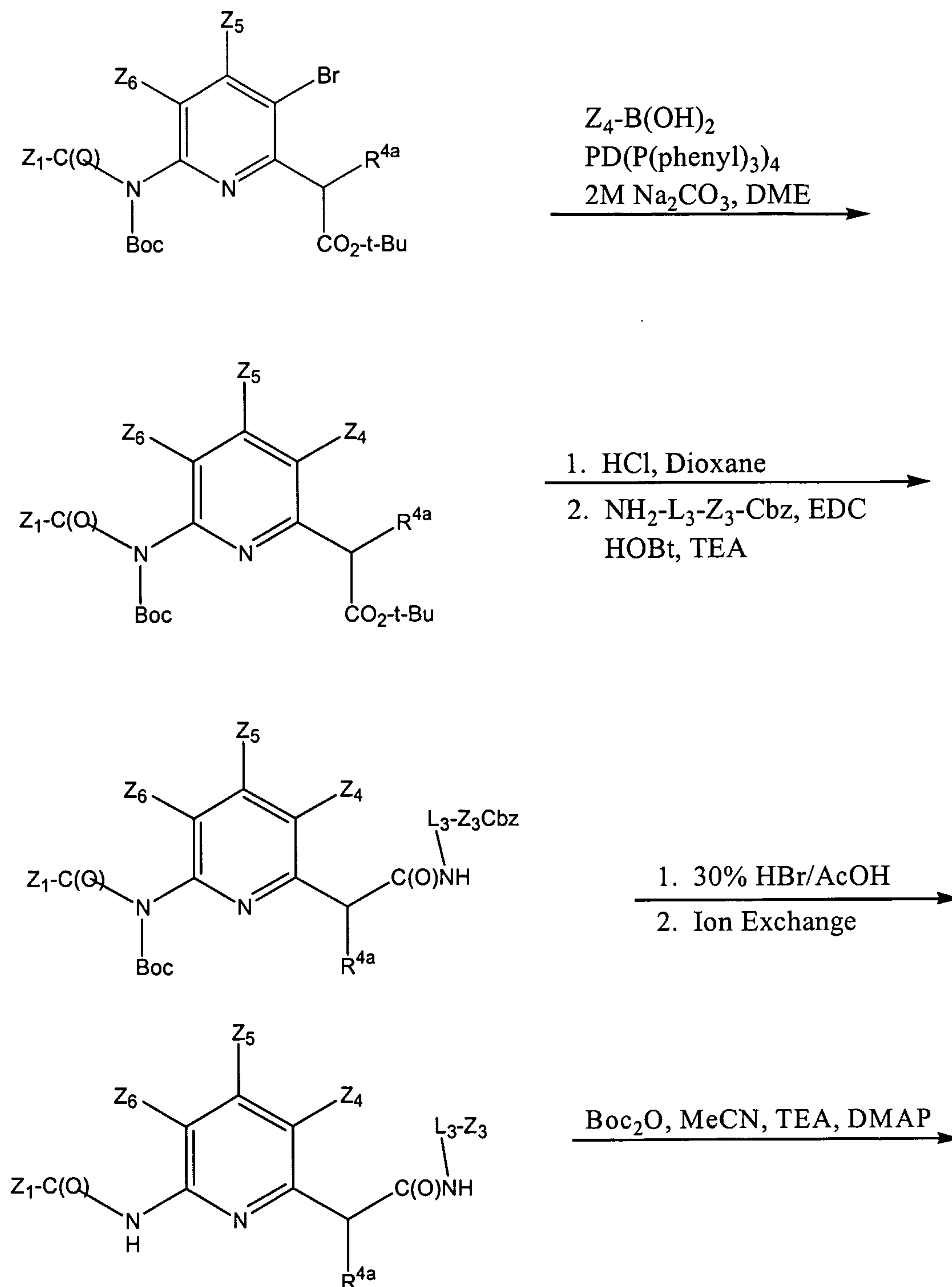


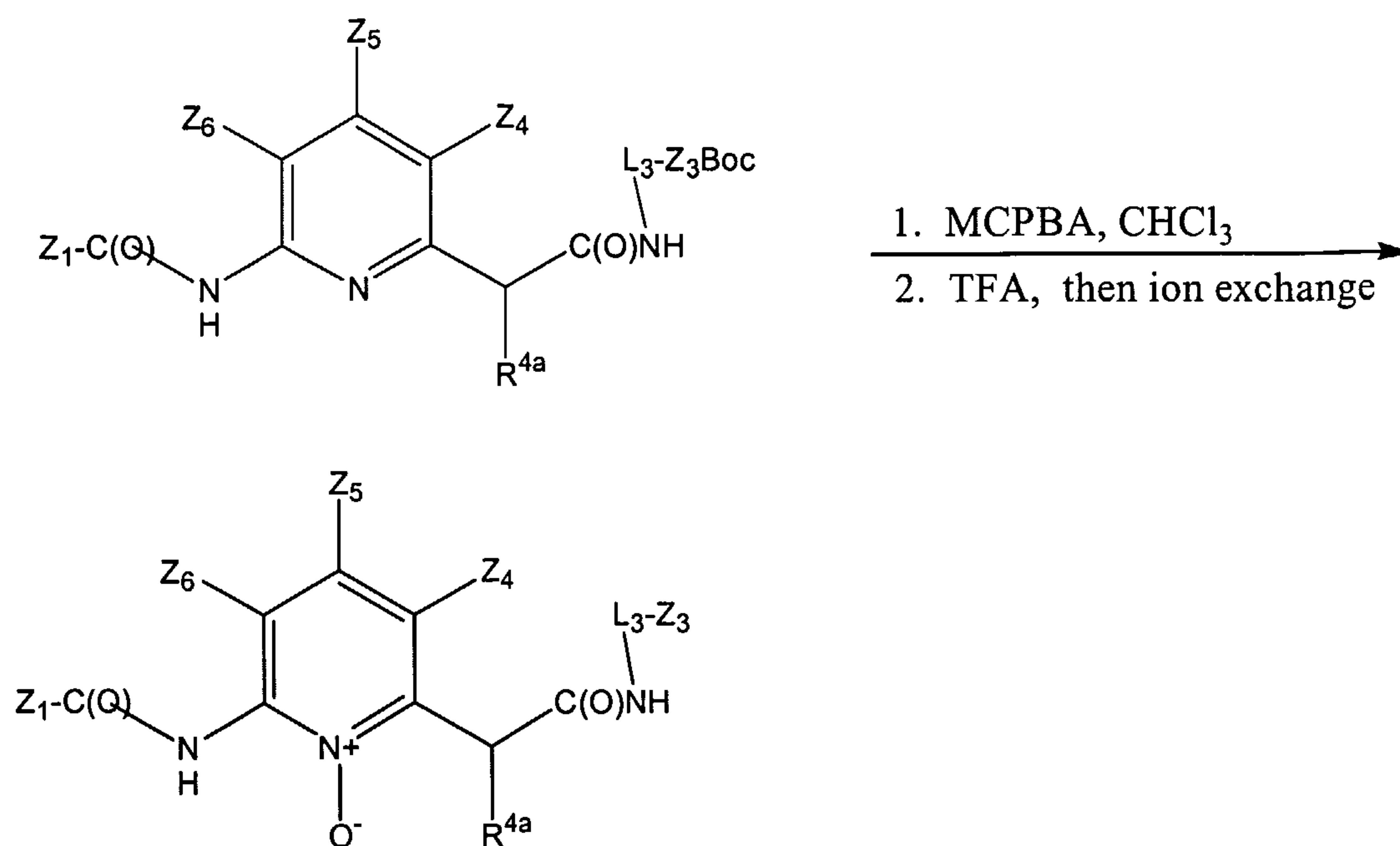
Scheme 2: Piperidine (continued)

Scheme 2: Piperidine (continued)

Scheme 3: Piperidinone

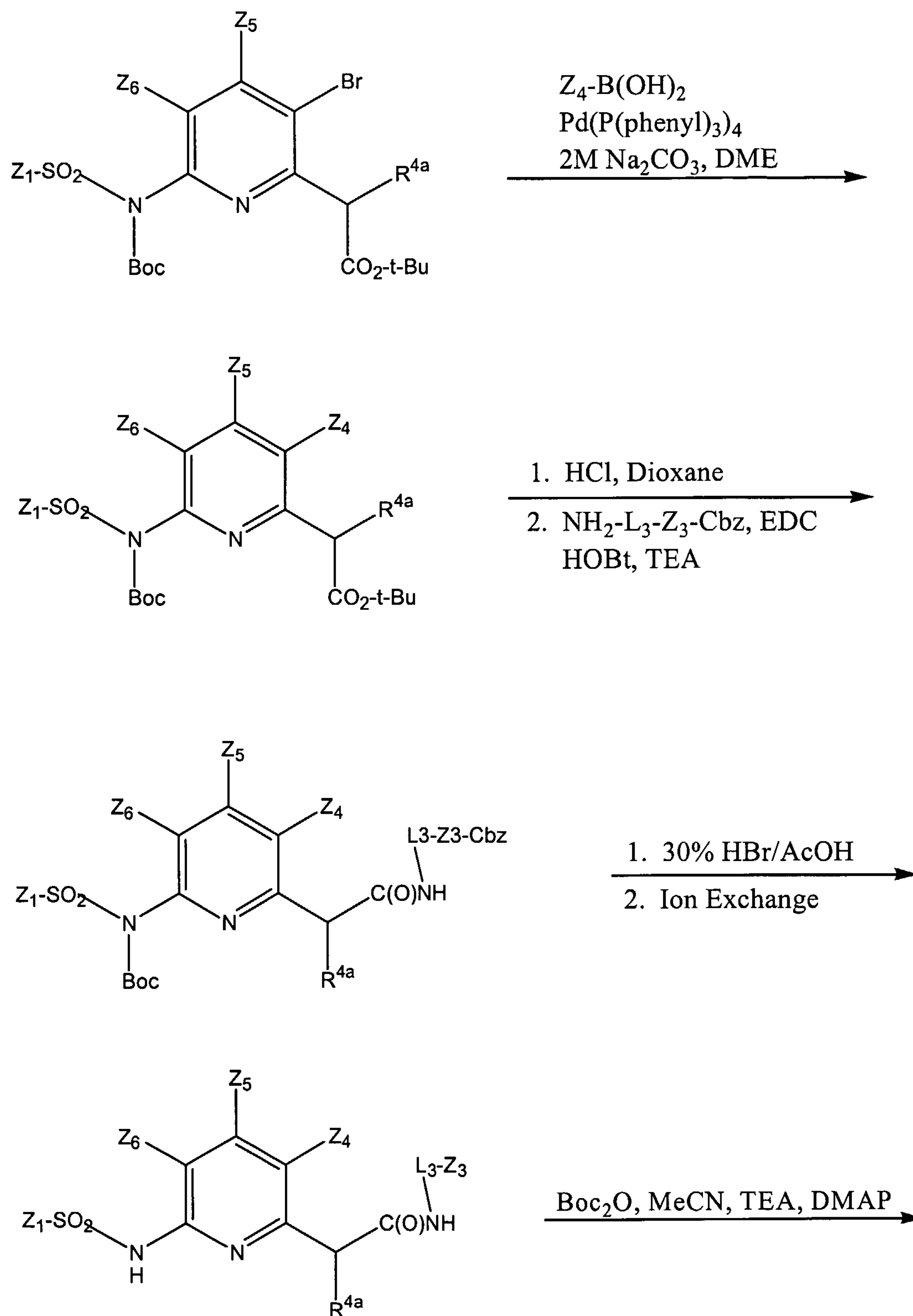
Scheme 3: Piperidinone (Continued)

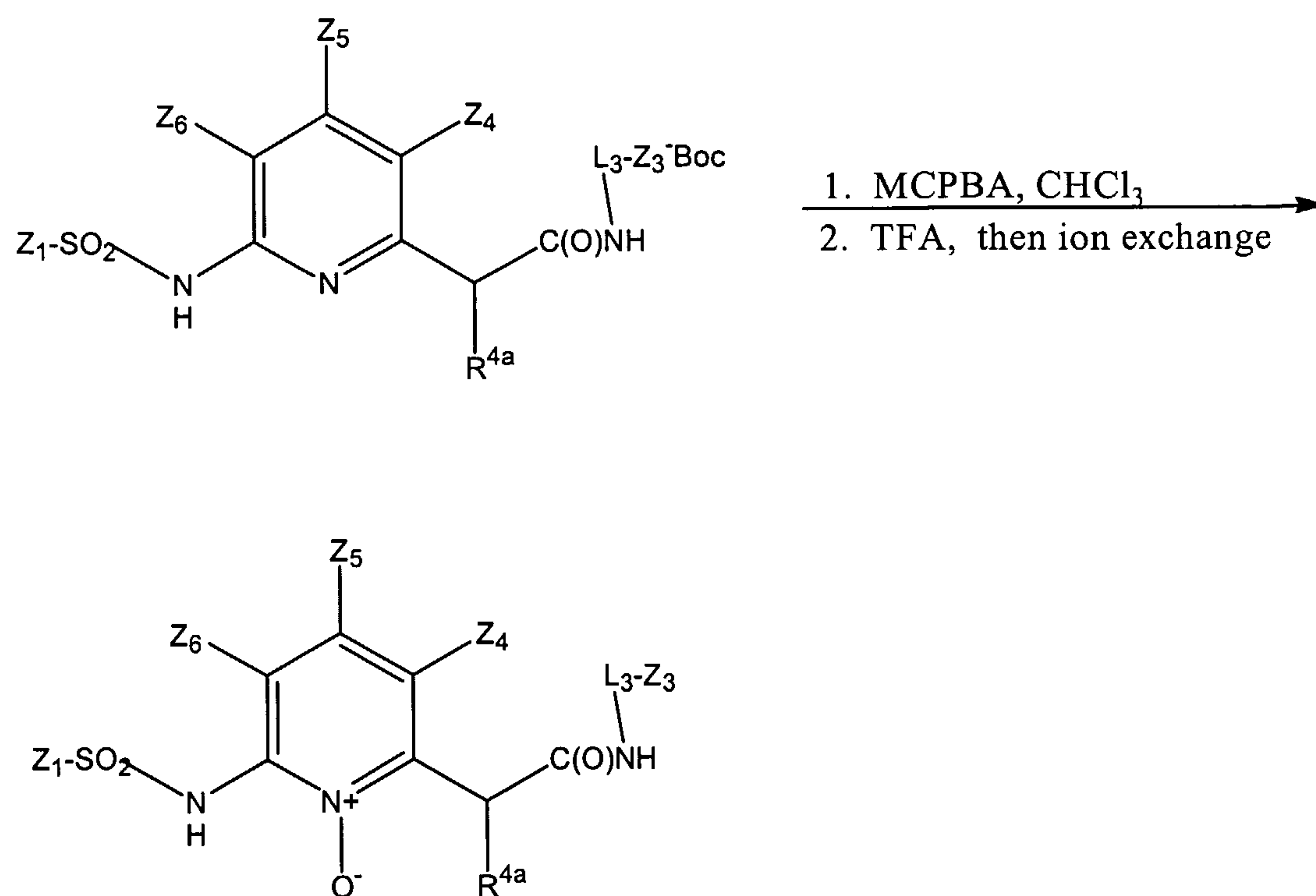
Scheme 4: General Synthesis of Pyridines (I)

Scheme 4: General Synthesis of Pyridines (I) (continued)

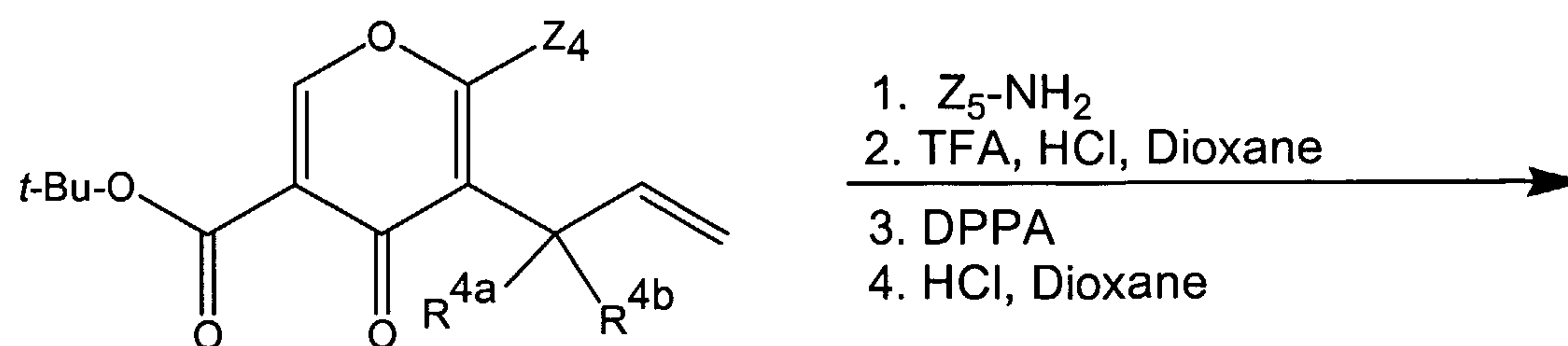
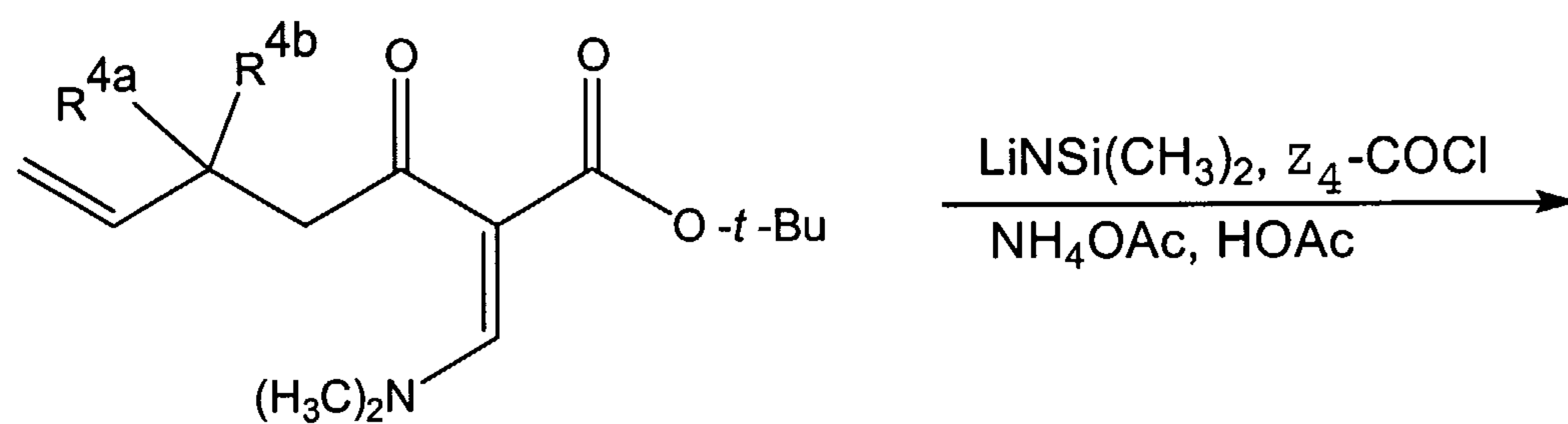
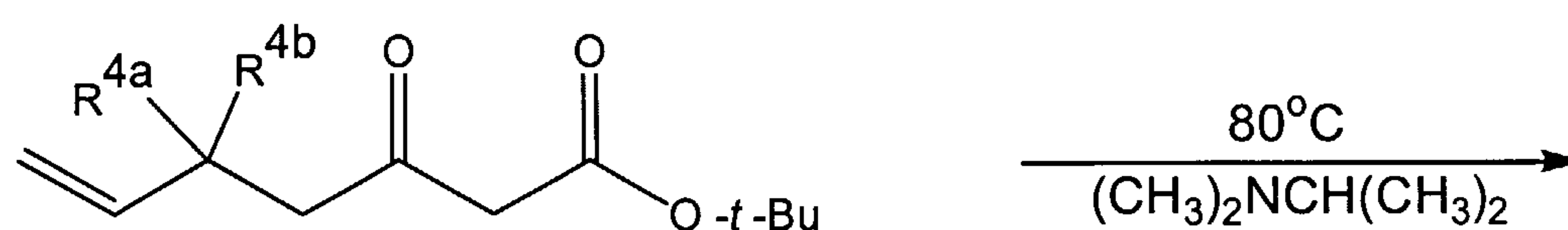
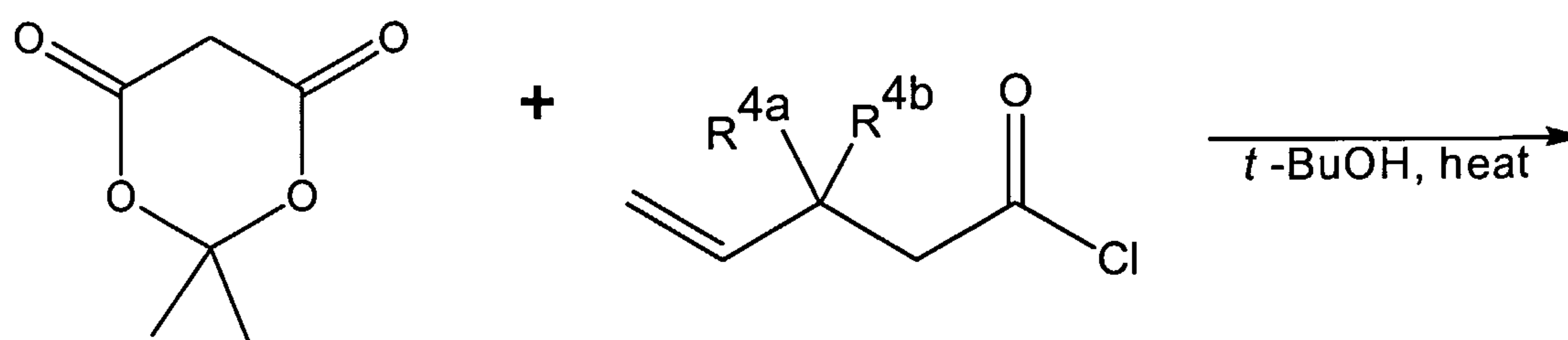
Note: Amino, thiol and hydroxygroups
in Z₄ and other groups will also be protected
as Boc derivatives.

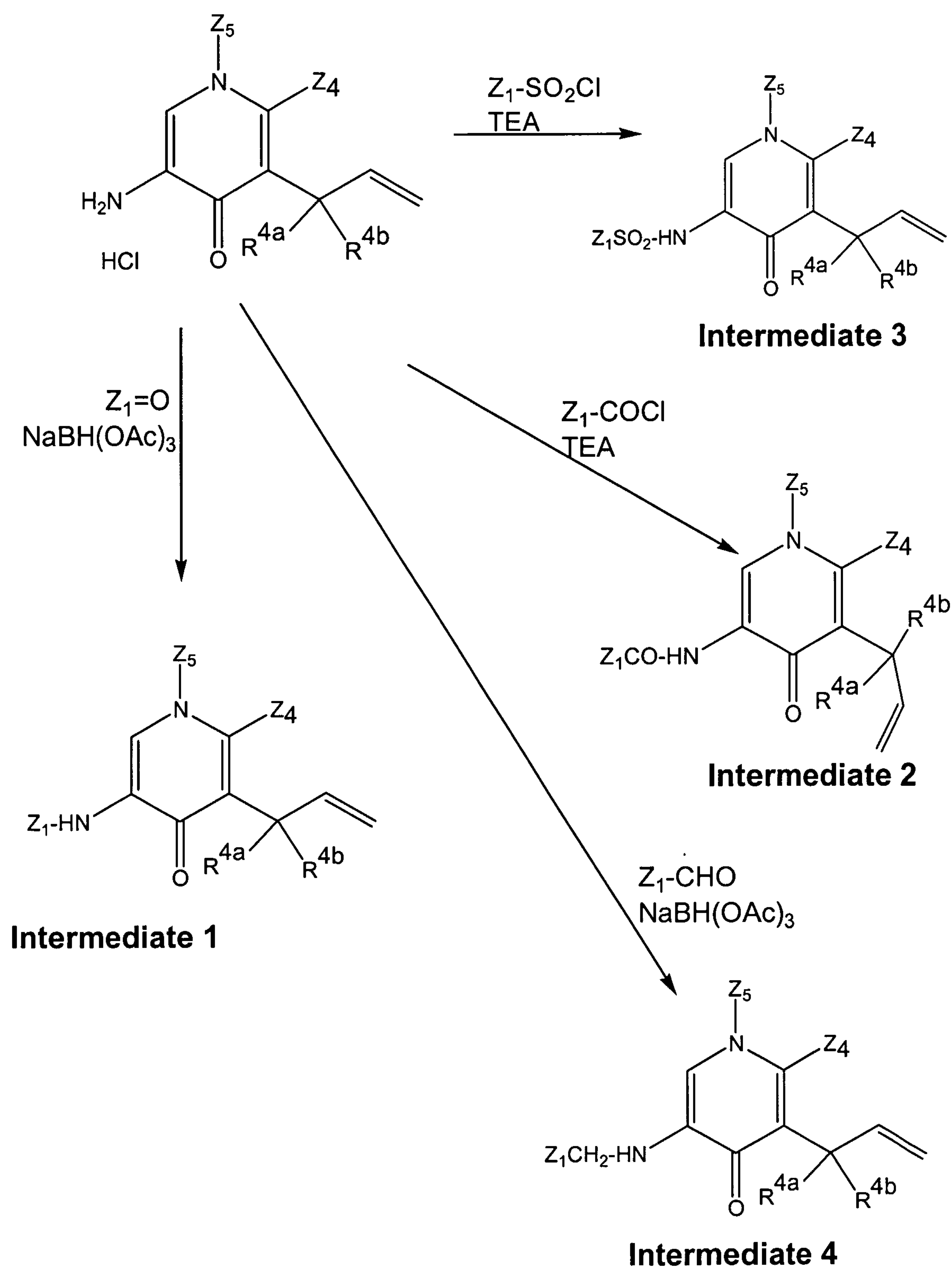
Scheme 5: General Synthesis of Pyridines (II)

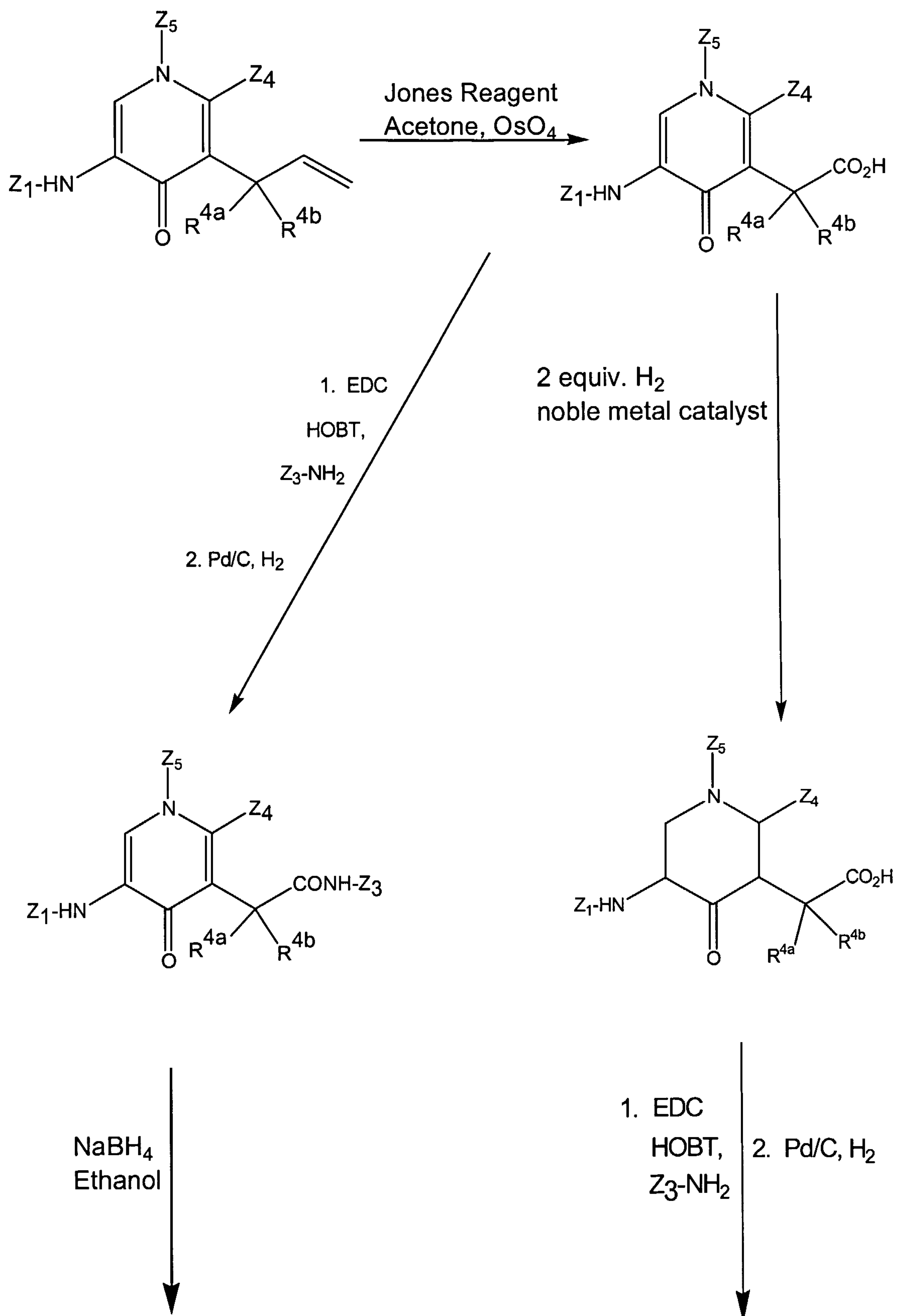


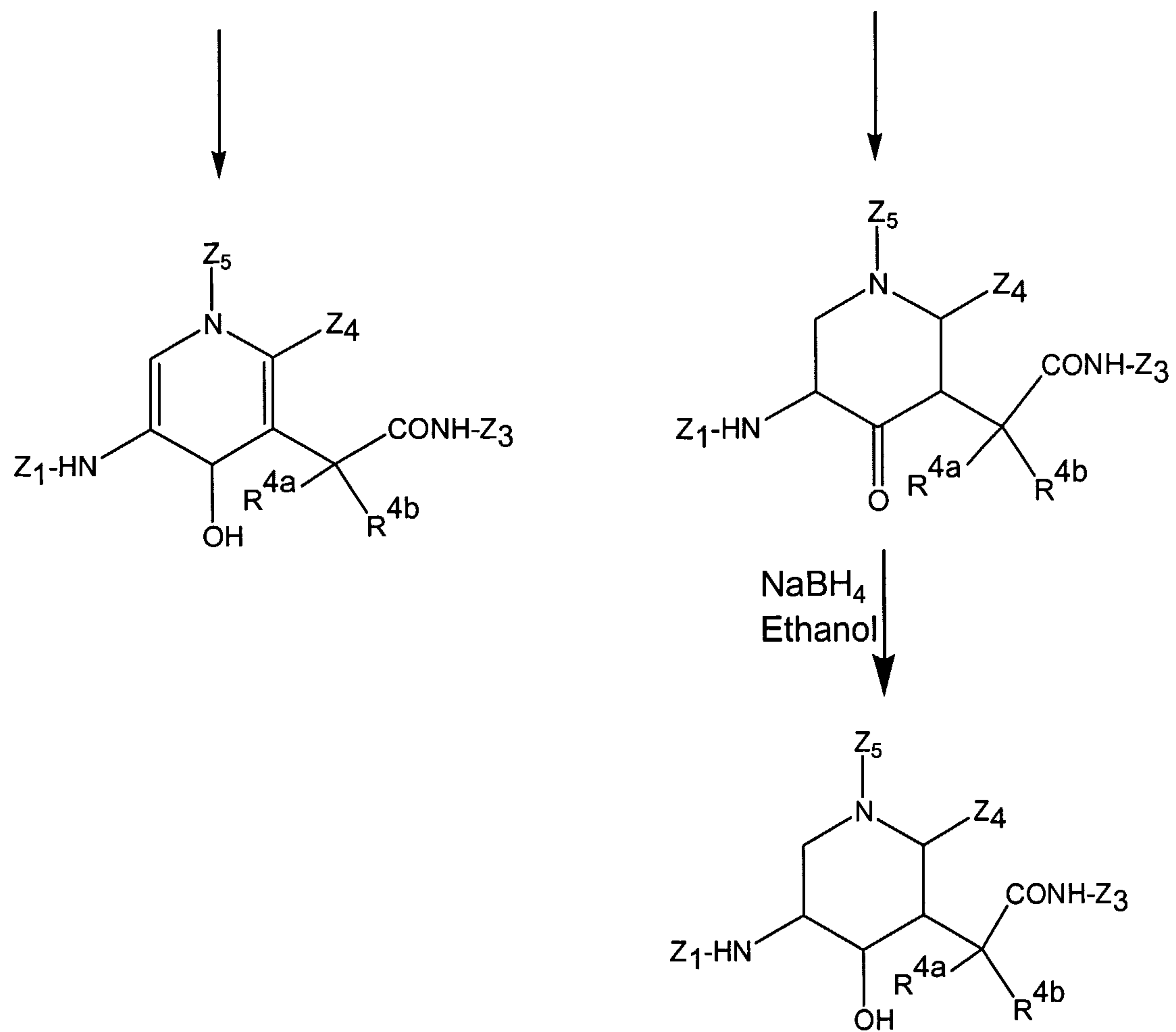
Scheme 5: General Synthesis of Pyridines (II) (continued)

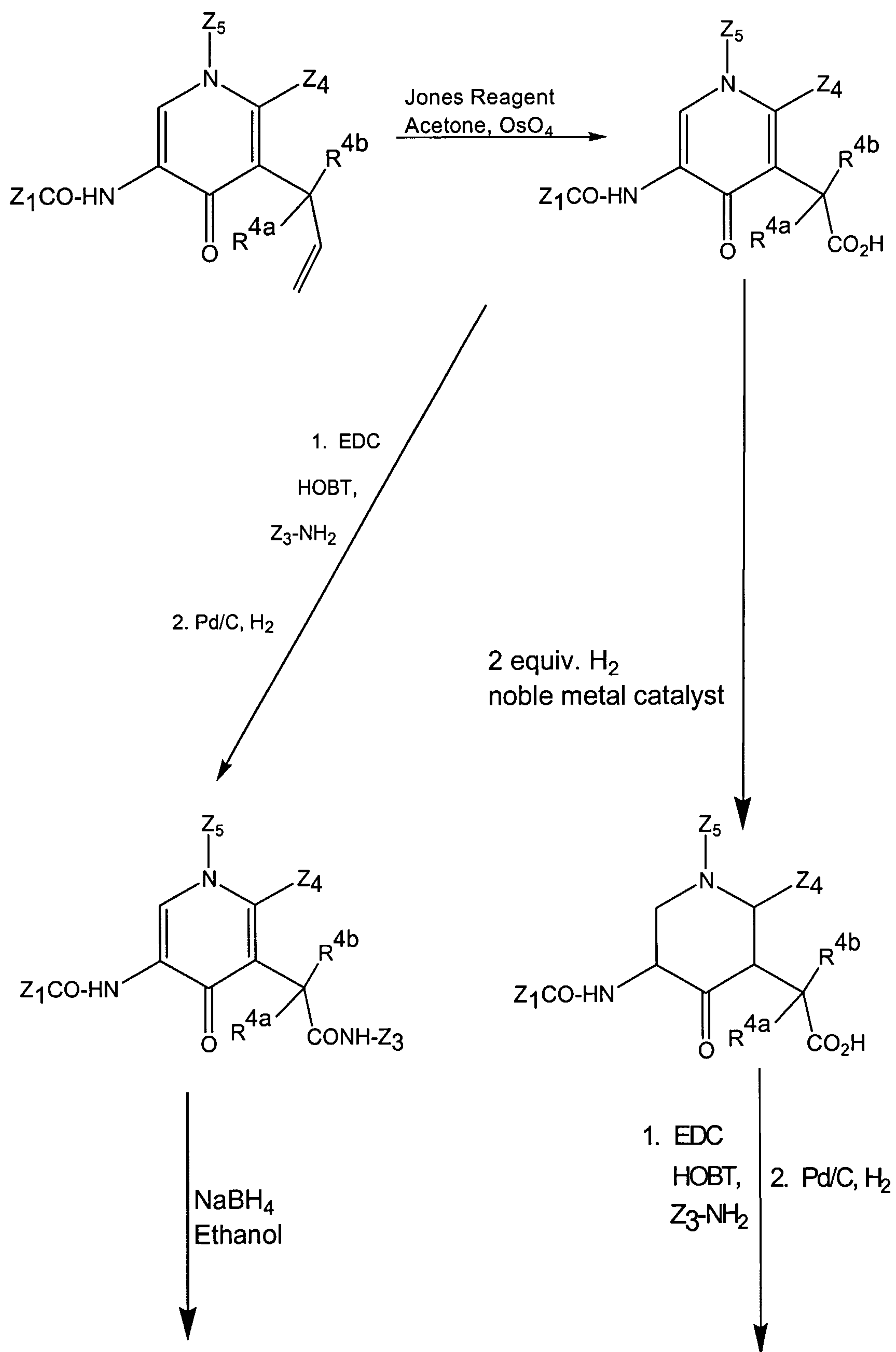
Note: Amino, thiol and hydroxygroups
in Z₄ and other groups will also be protected
as Boc derivatives.

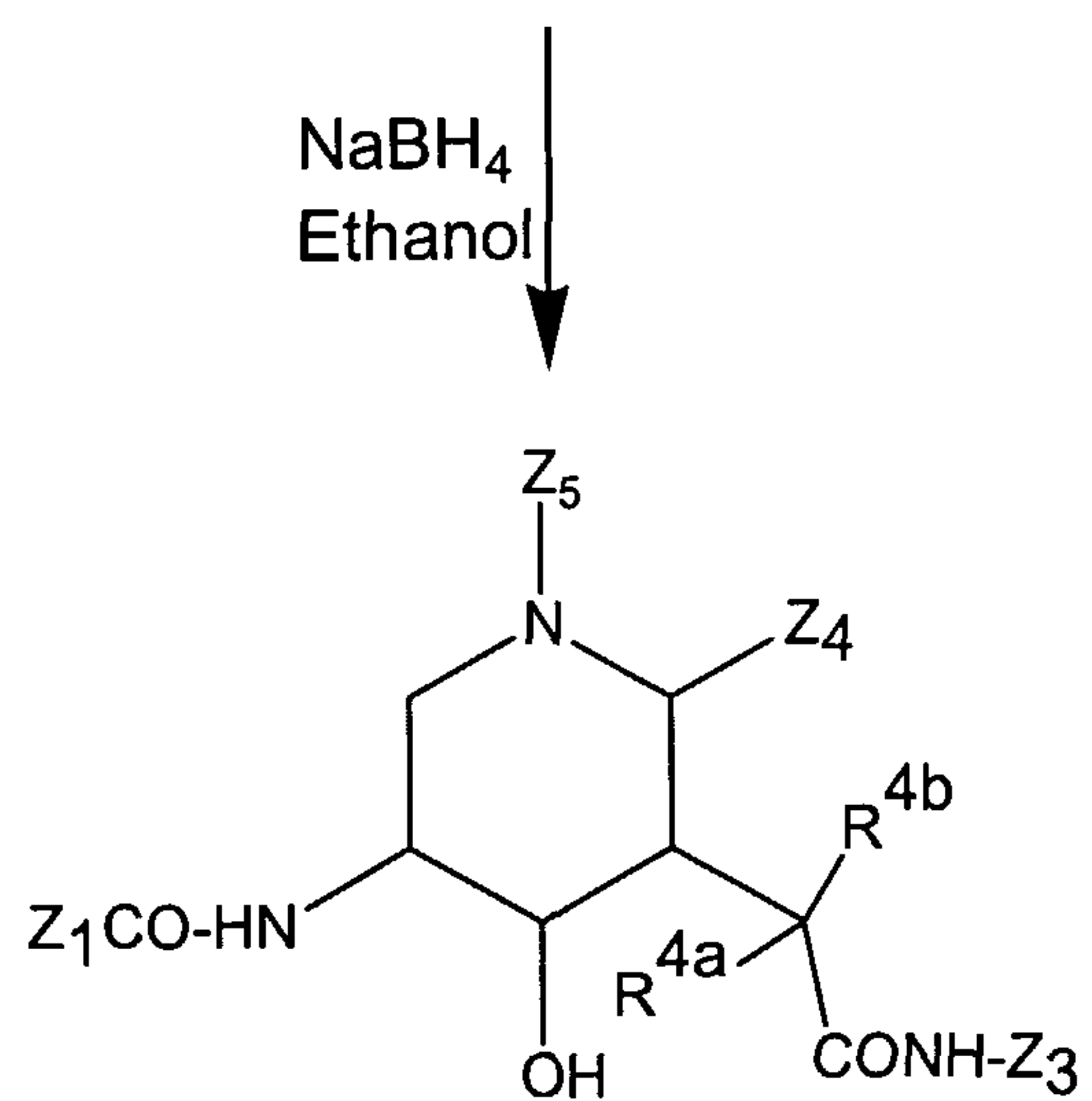
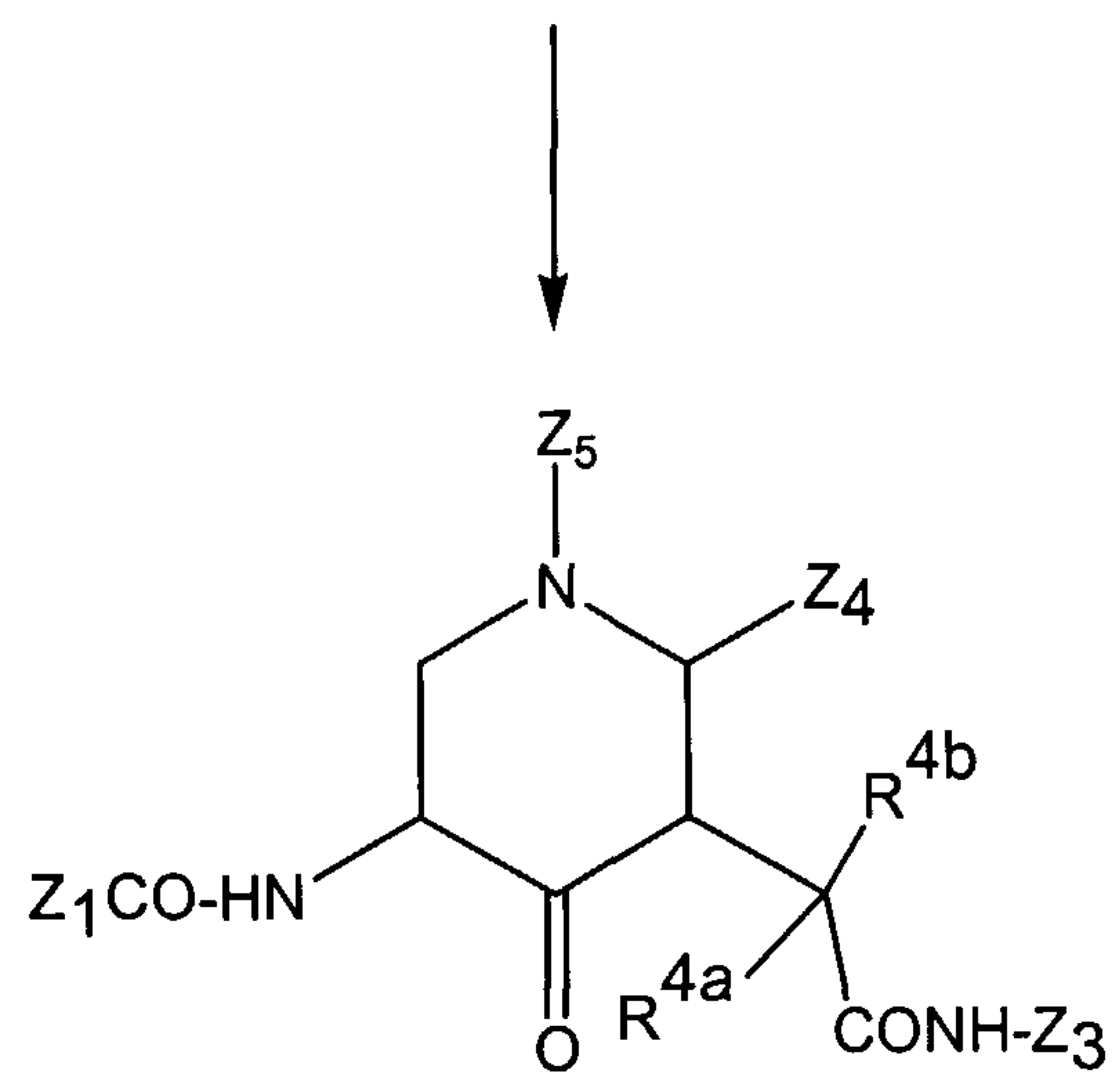
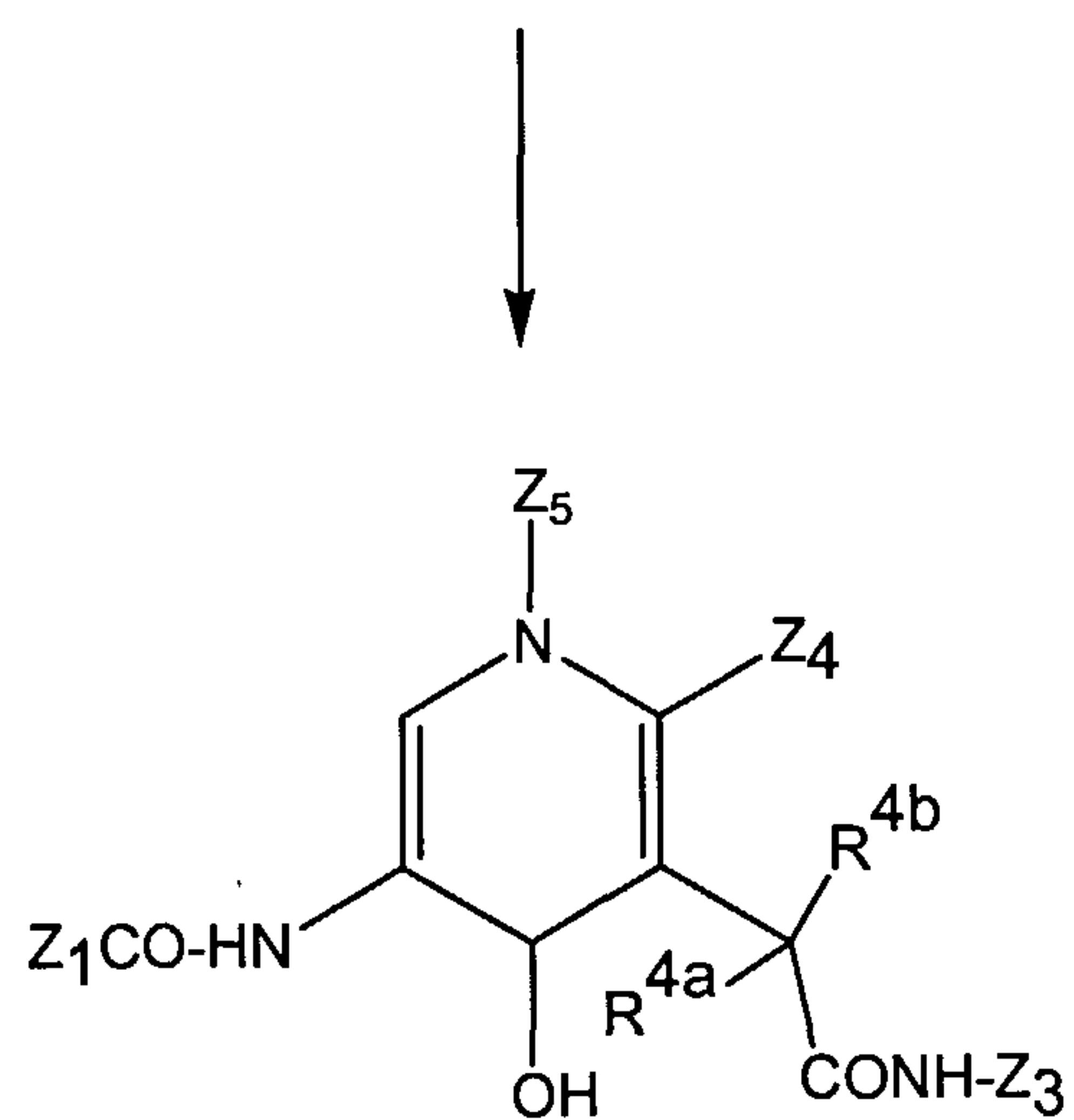
Scheme 6: 4-Piperdinone

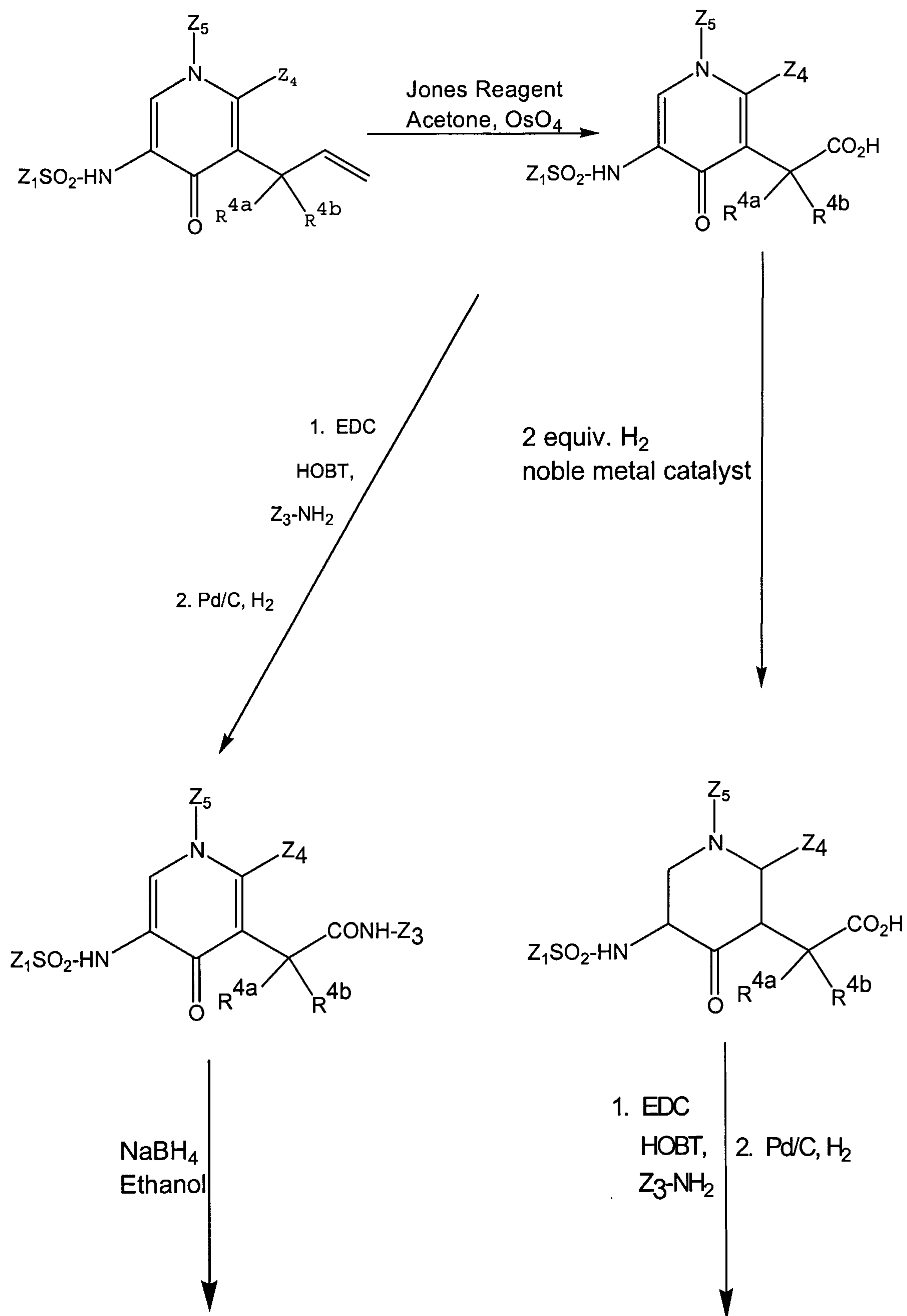
Scheme 6: 4-Piperdinone (continued)

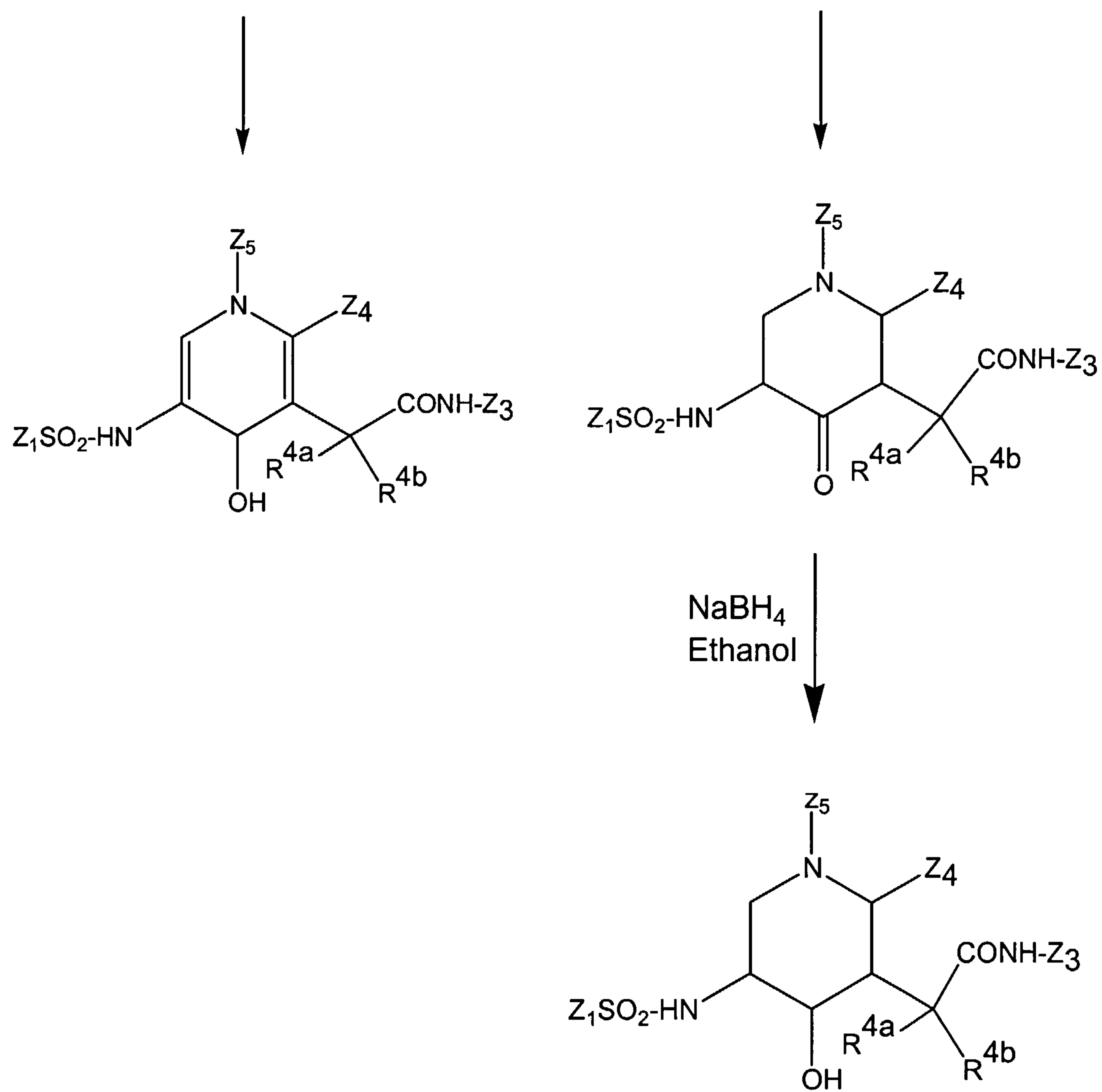
Scheme 6: 4-Piperidinone (Intermediate 1)

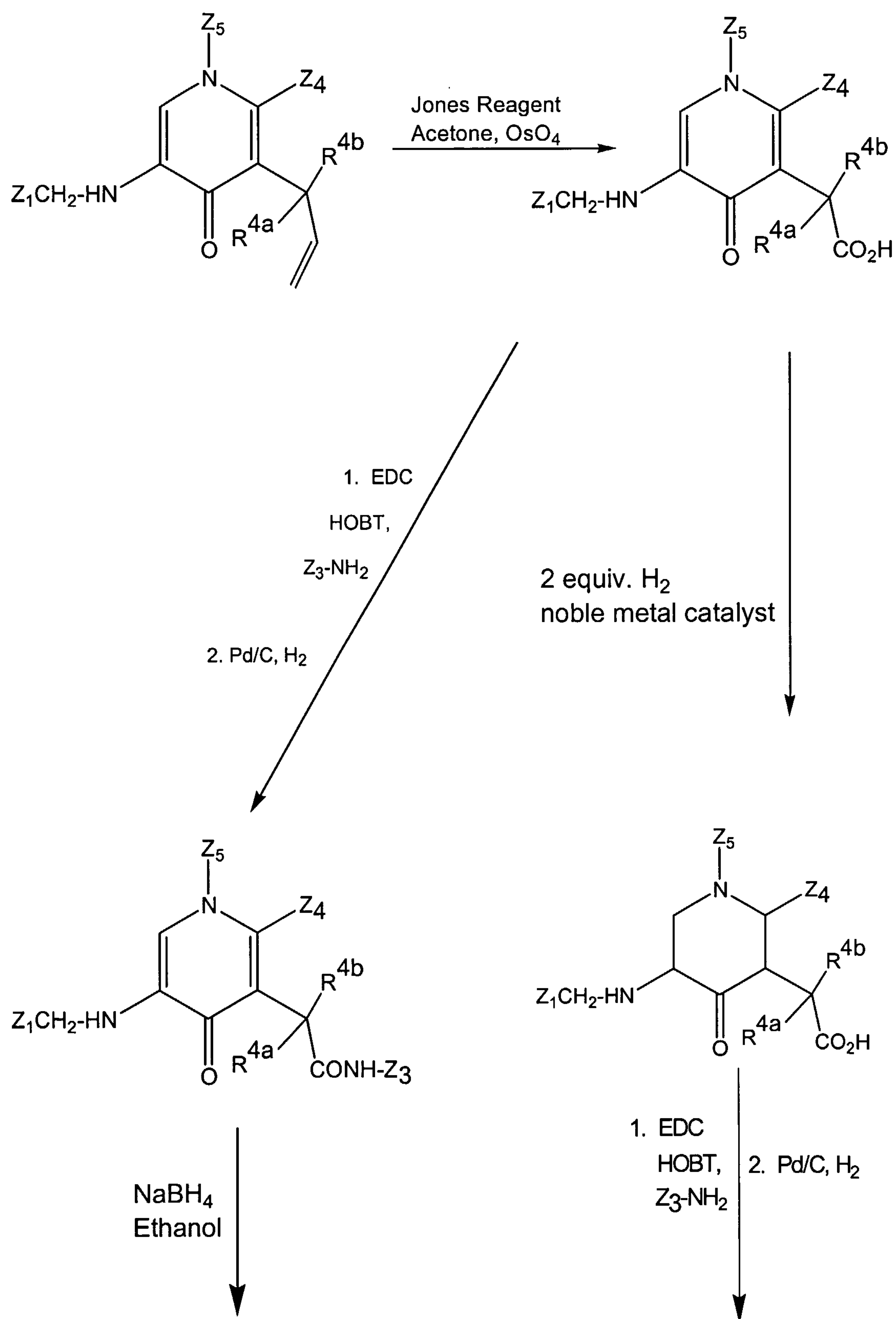
Scheme 6: 4-Piperidinone (Intermediate 1) (continued)

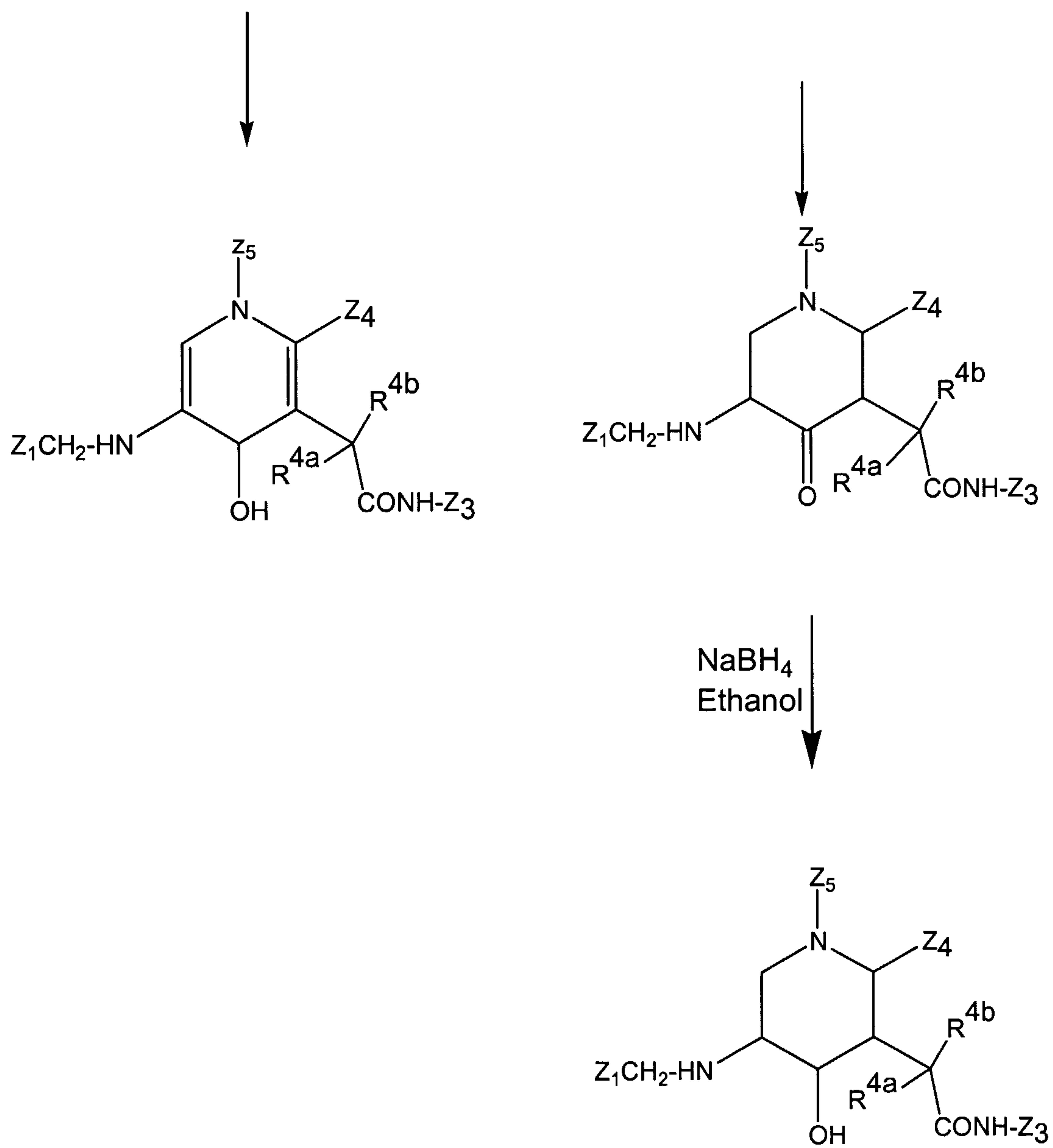
Scheme 6: 4-Piperidinone (Intermediate 2)

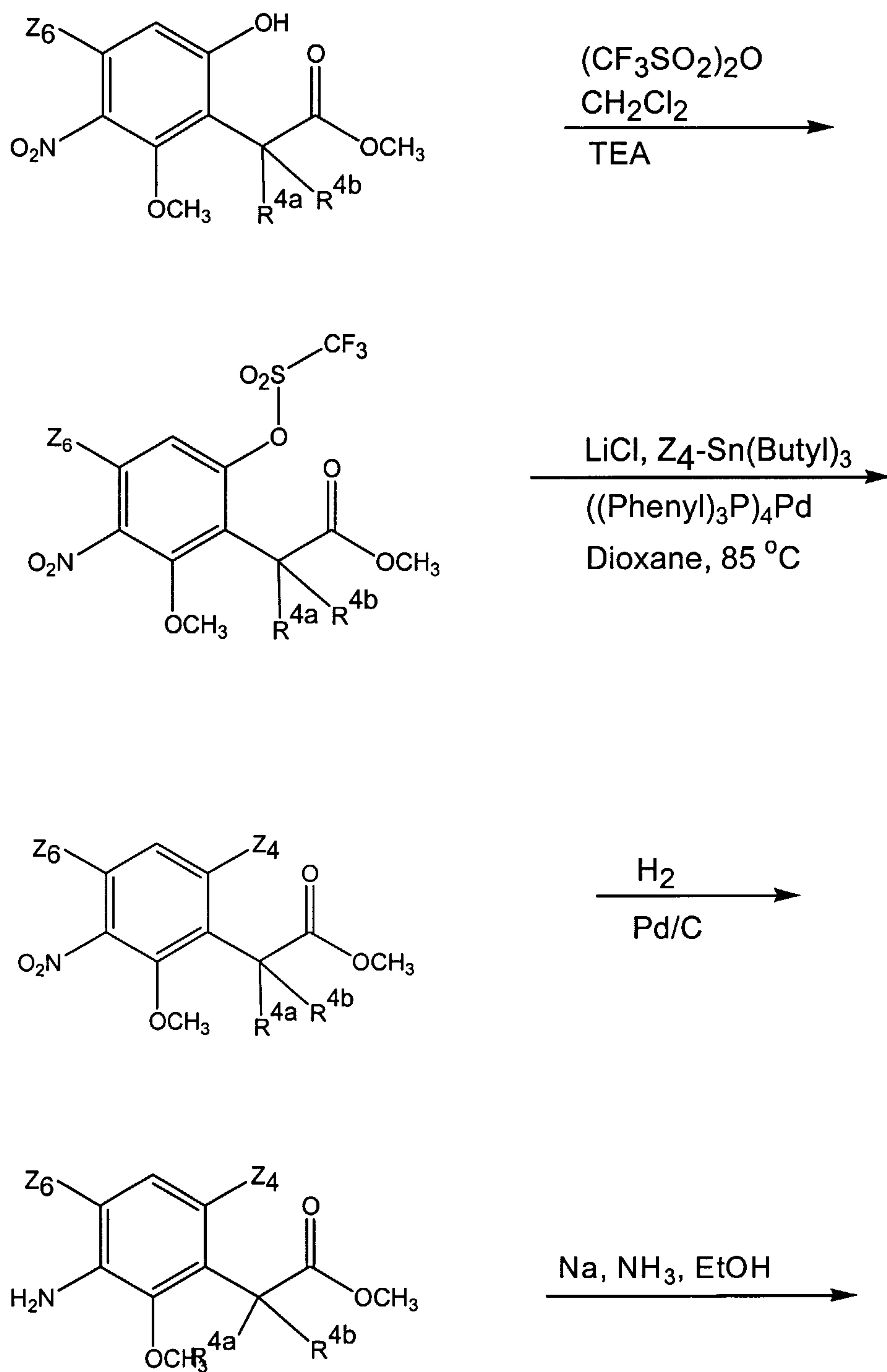
Scheme 6: 4-Piperidinone (Intermediate 2) (Continued)

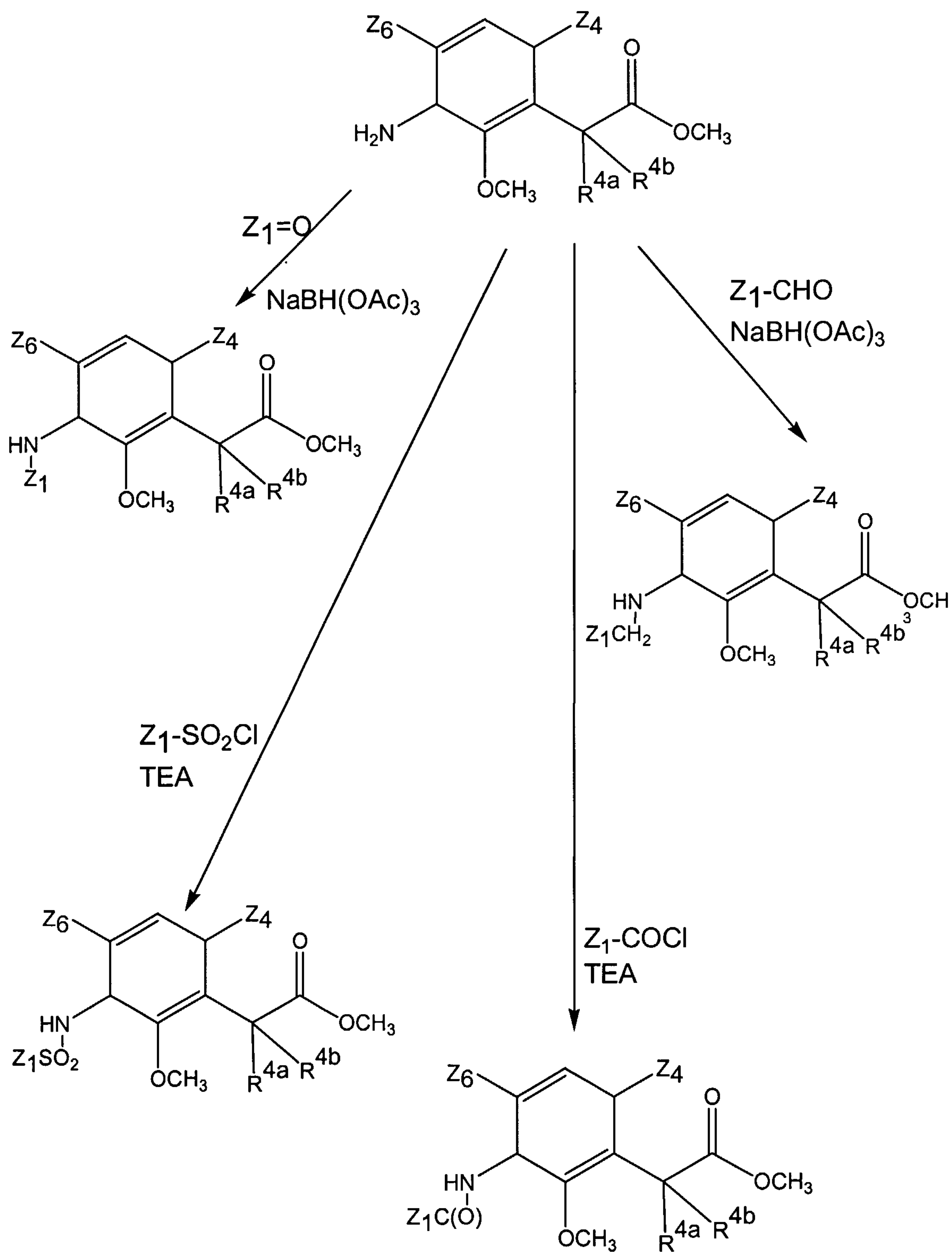
Scheme 6: 4-Piperidinone (Intermediate 3)

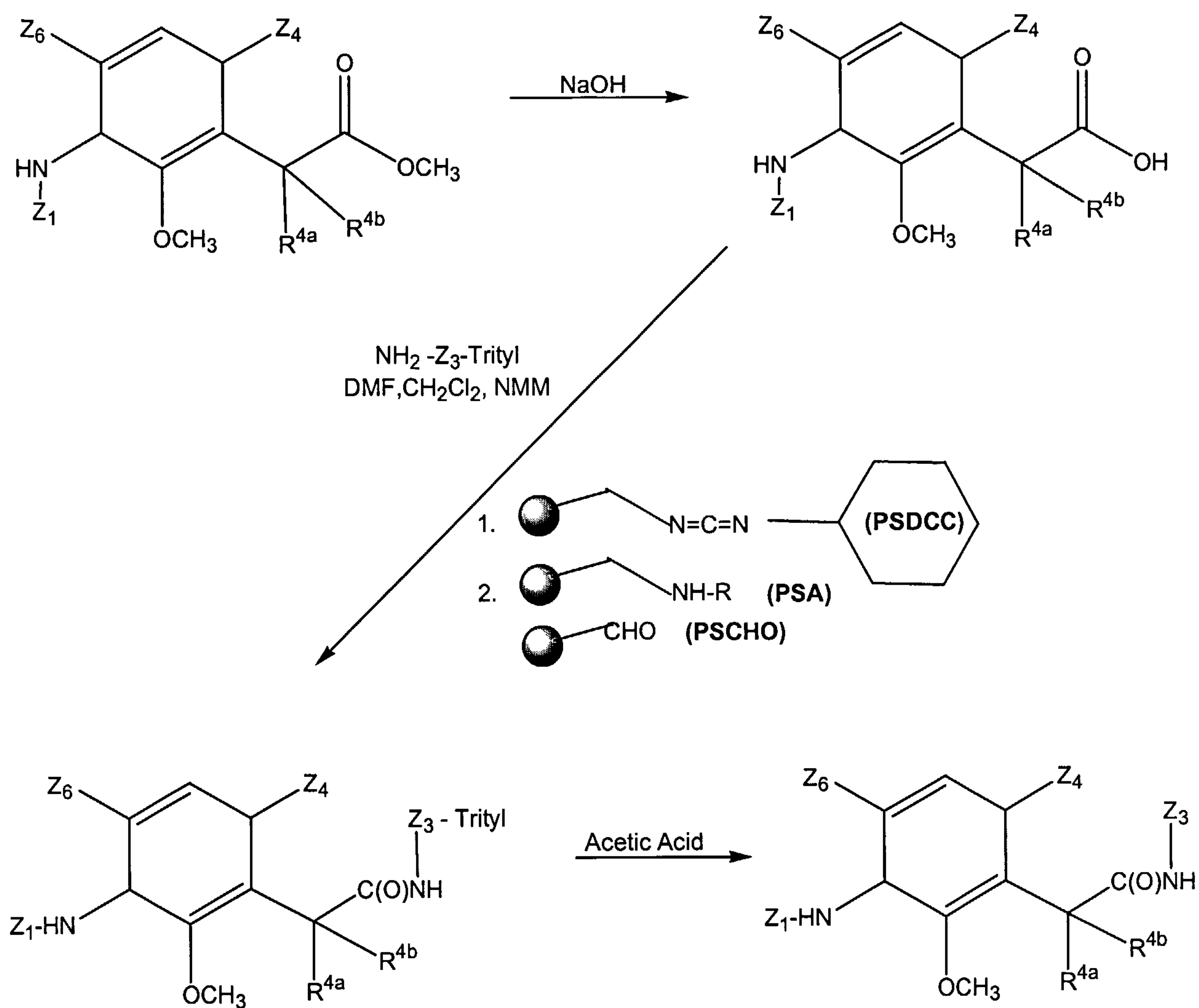
Scheme 6: 4-Piperidinone (Intermediate 3) (continued)

Scheme 6: 4-Piperidinone (Intermediate 4)

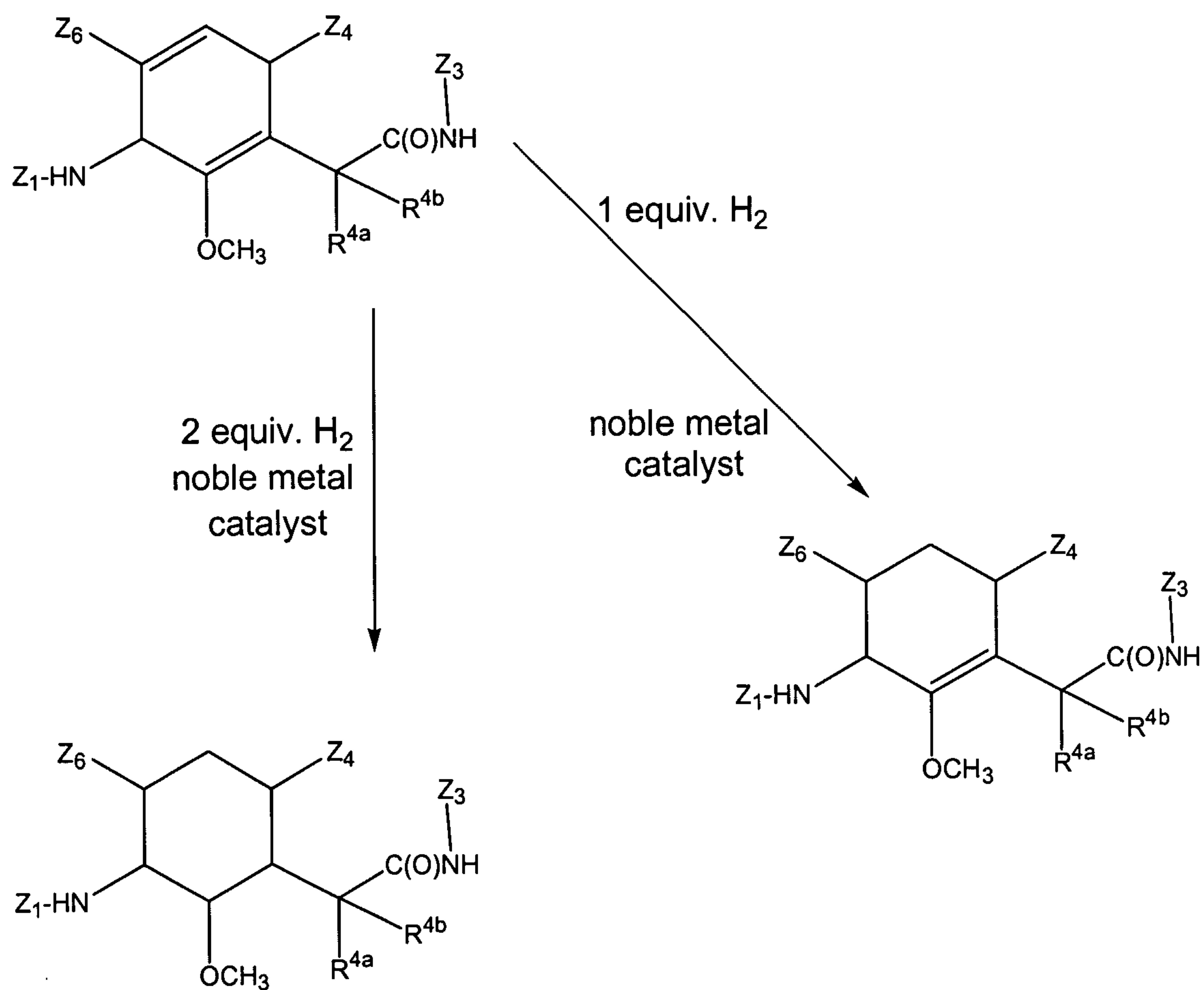
Scheme 6: 4-Piperidinone (Intermediate 4) (Continued)

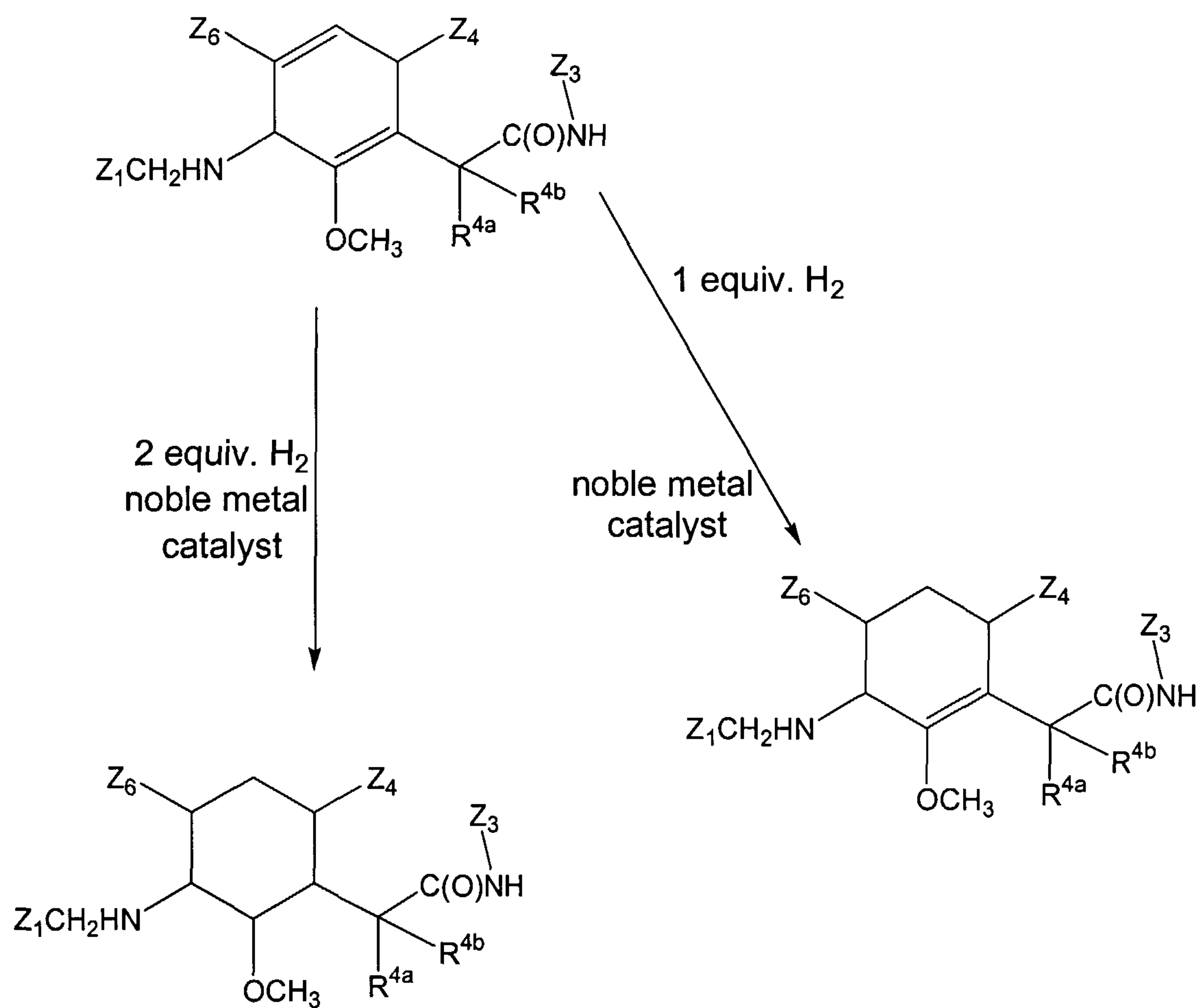
Scheme 7: Cycloalkyl

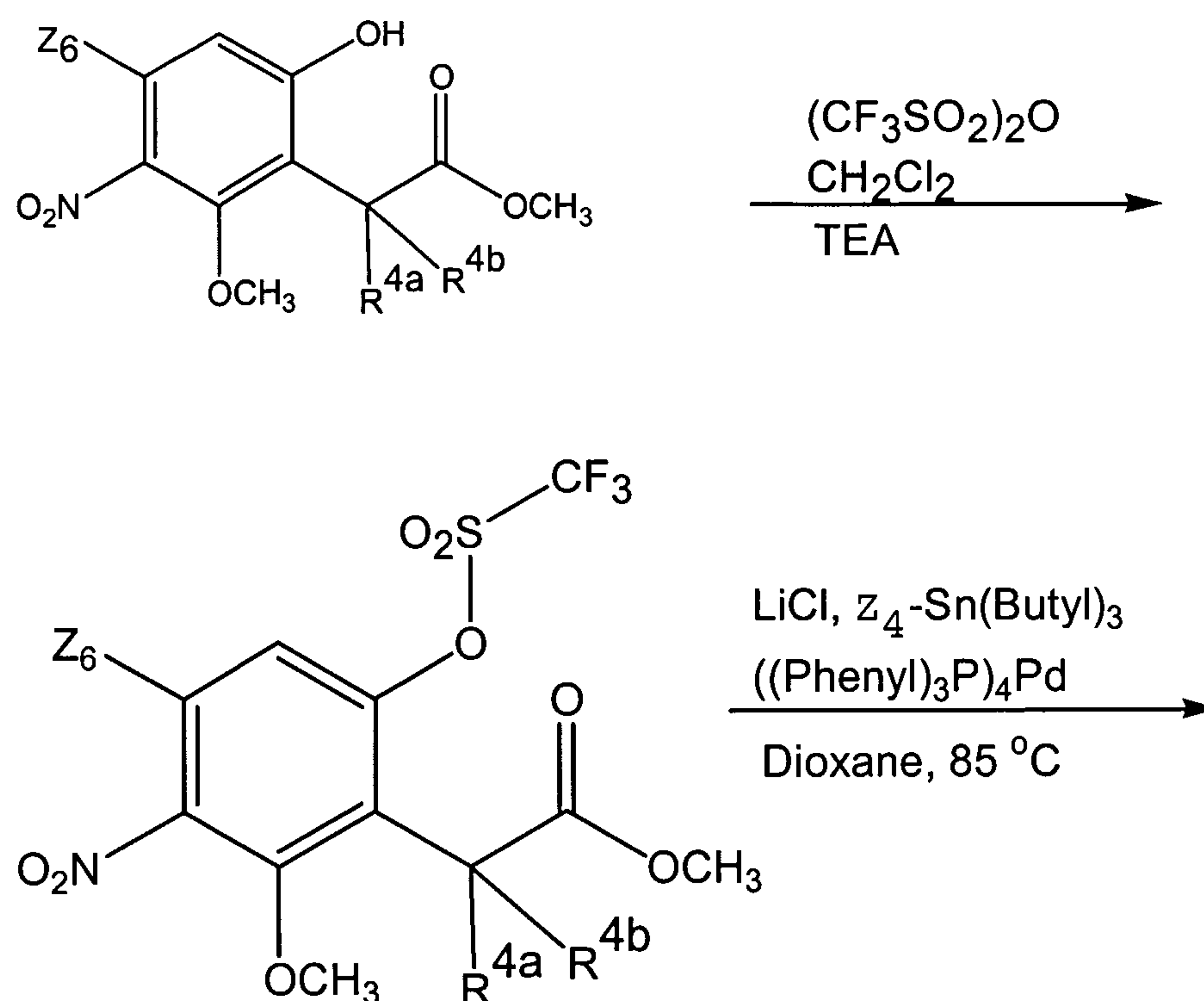
Scheme 7: Cycloalkyl (continued)

Scheme 7: Cycloalkyl (continued)

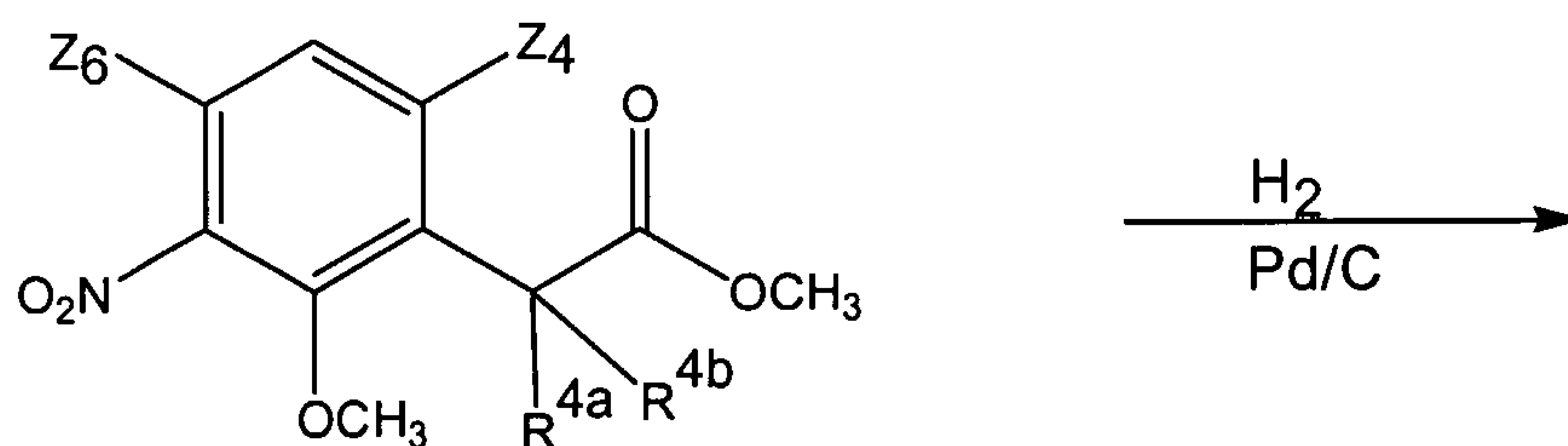
Note: Intermediates derived from the use of Z_1 -CHO, Z_1 -SO₂Cl, and Z_1 -COCl can substitute for the one from $Z_1=O$ illustrated in this scheme

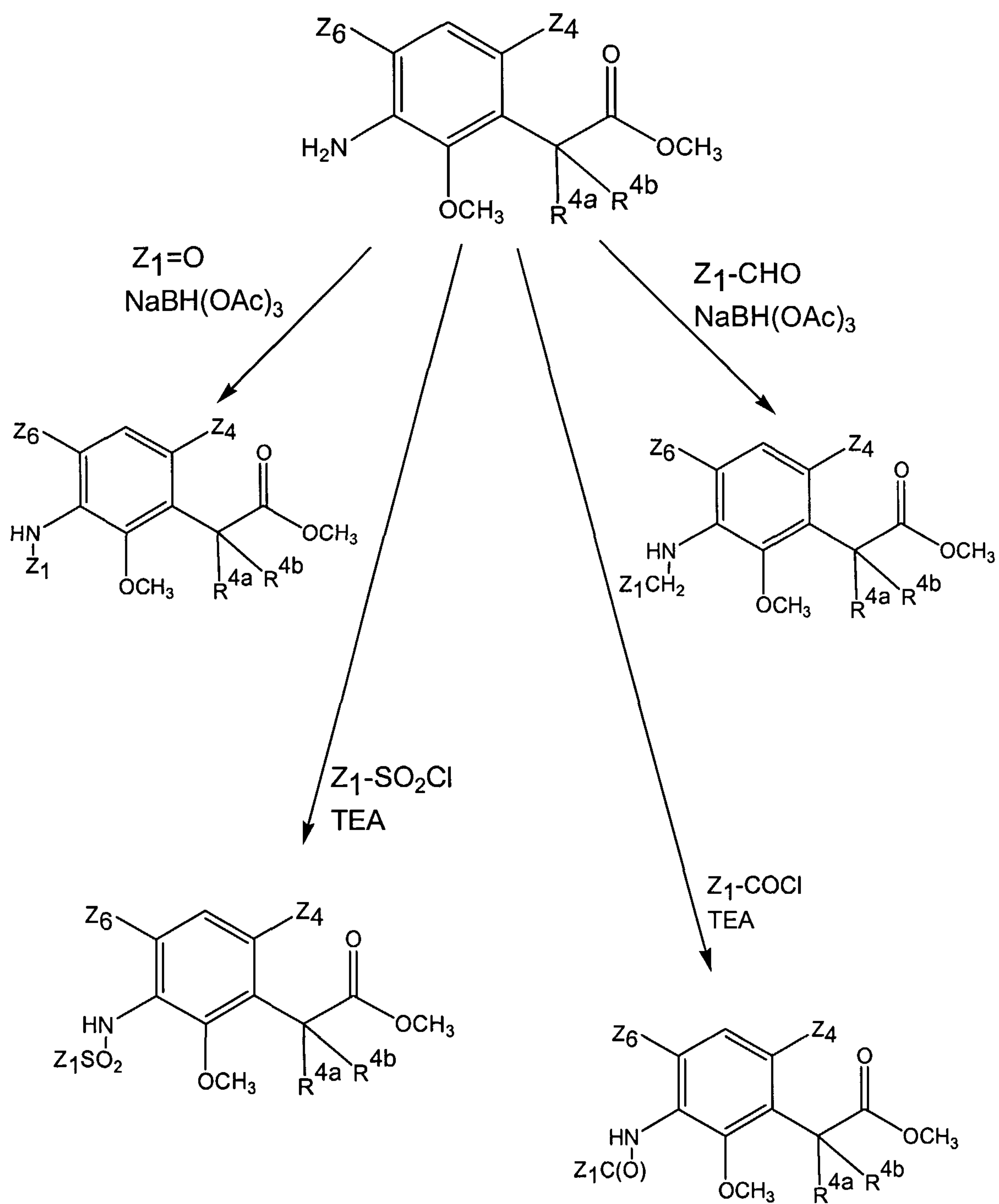
Scheme 7: Cycloalkyl (continued)

Scheme 7: Cycloalkyl (continued)

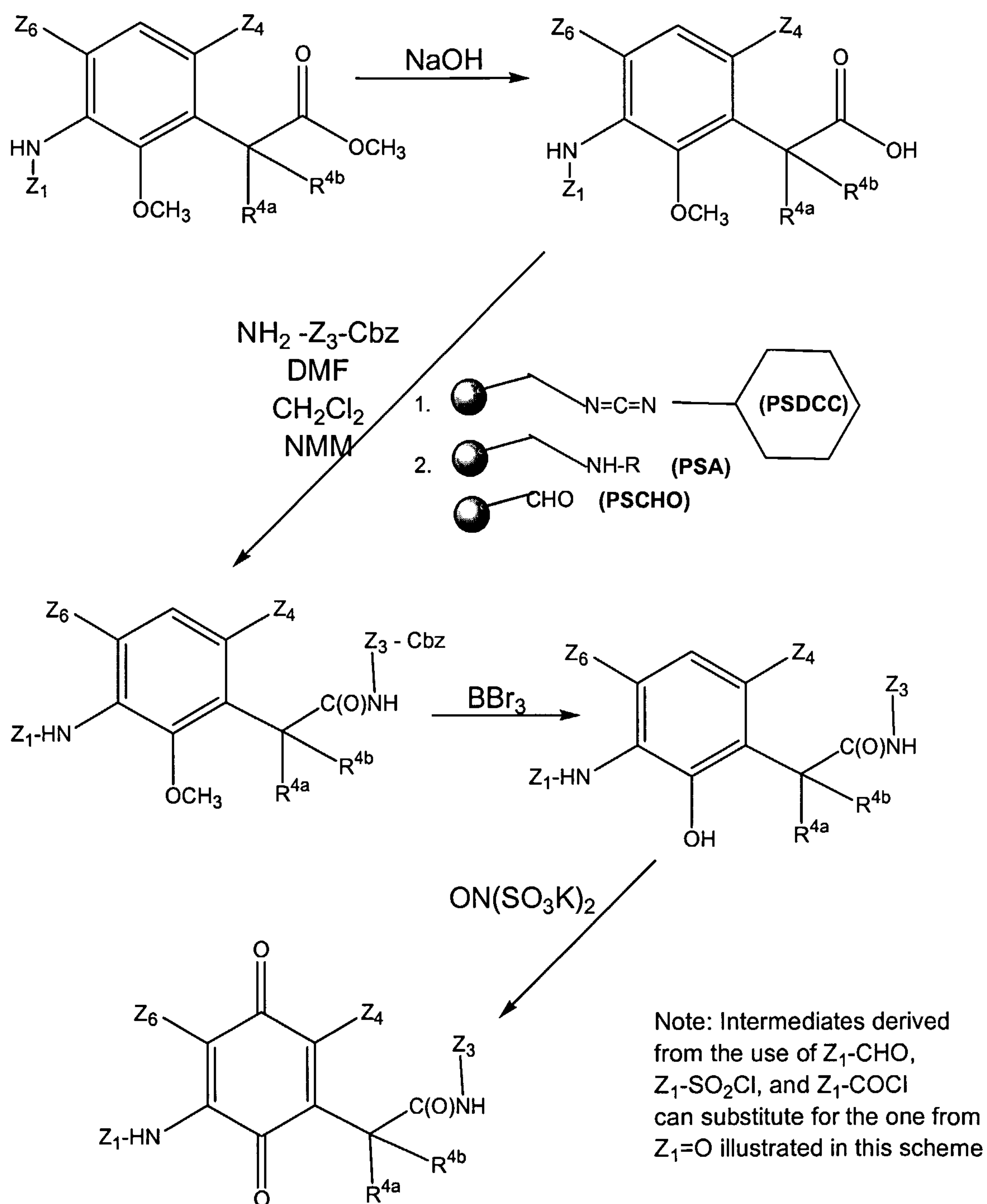
Scheme 8: Reduced Quinone

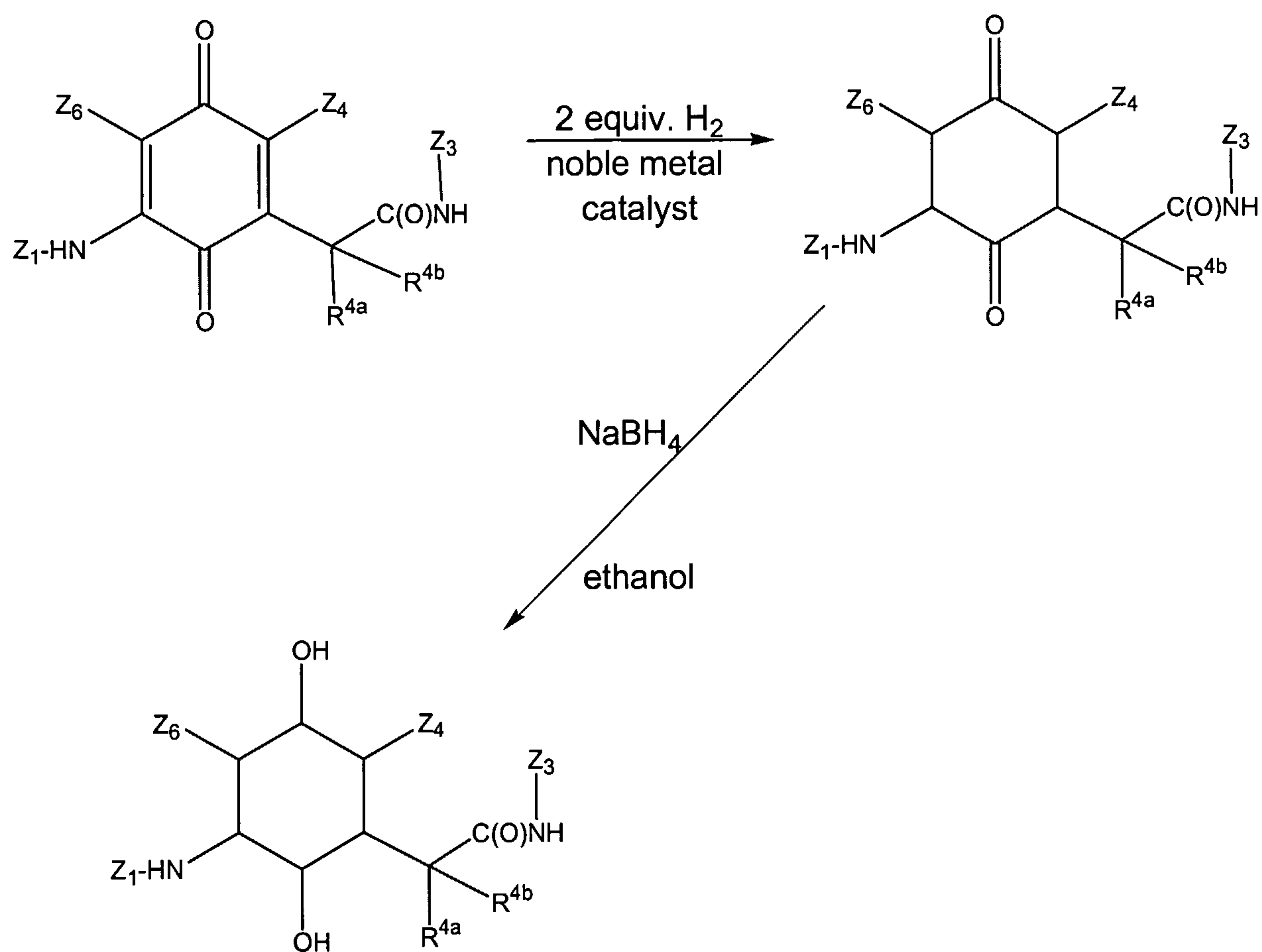
Z_4 is selected from the group consisting of aryl (for example, phenyl) and heteroaryl each of which may be optionally substituted.

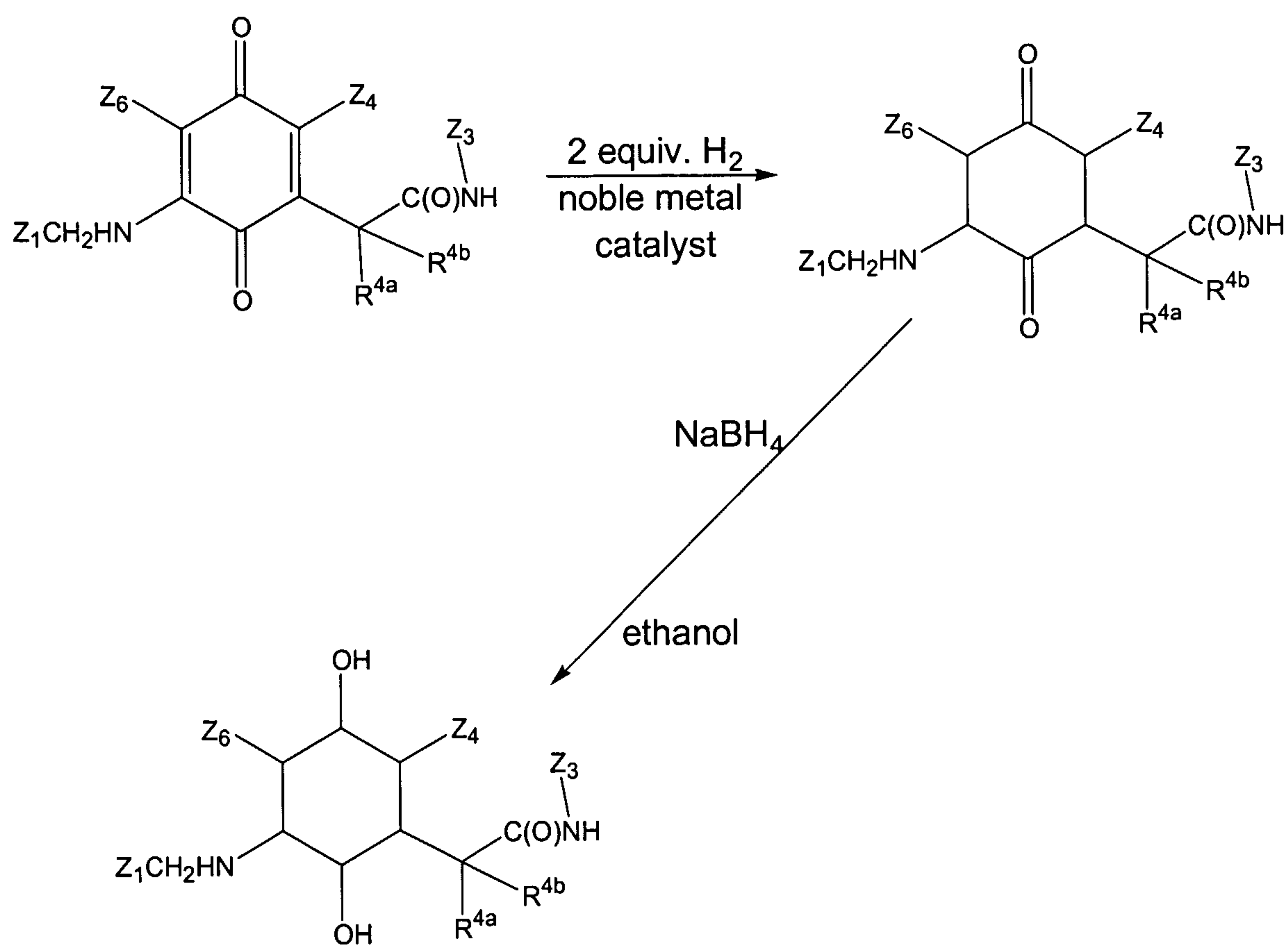


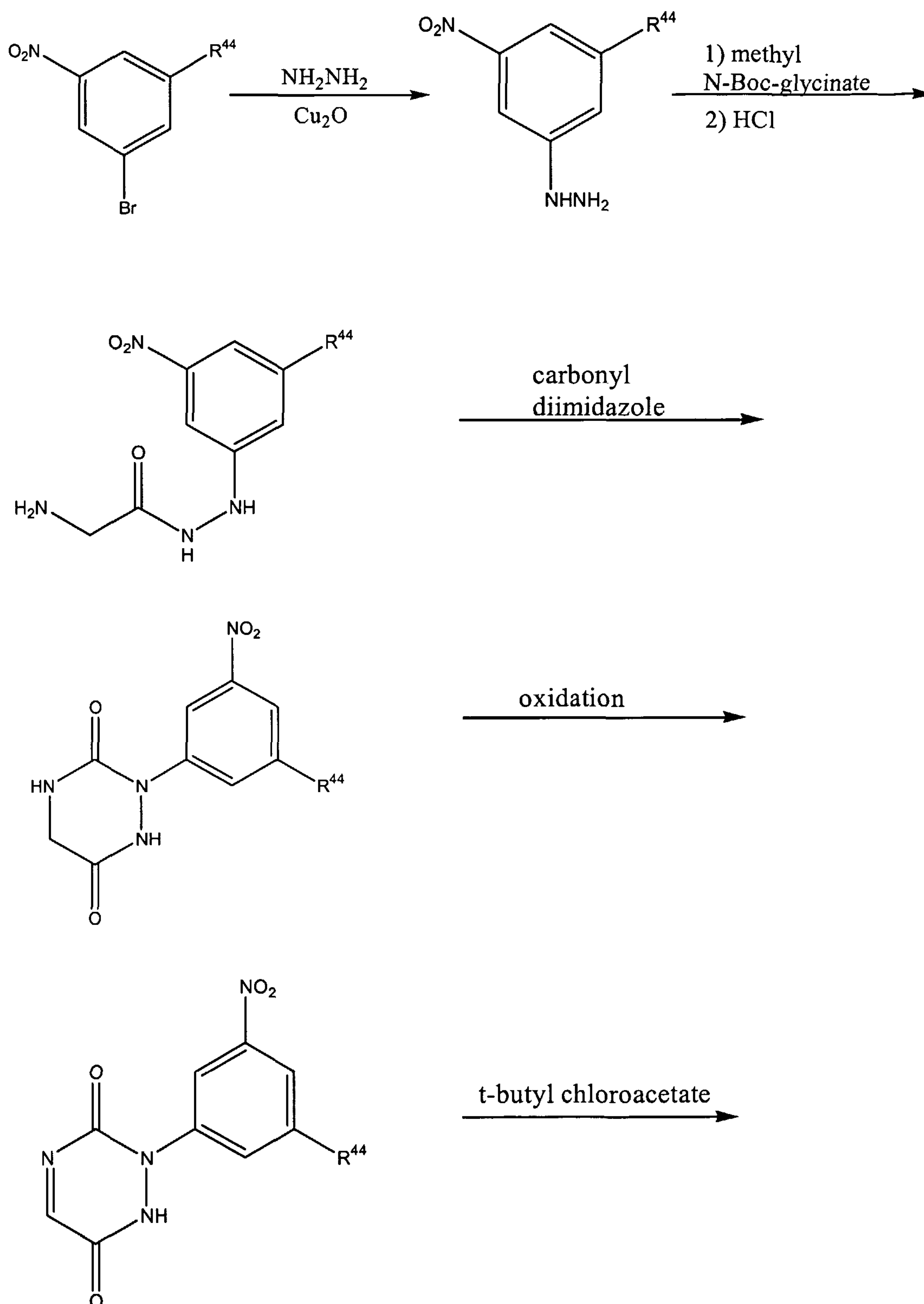
Scheme 8: Reduced Quinone (continued)

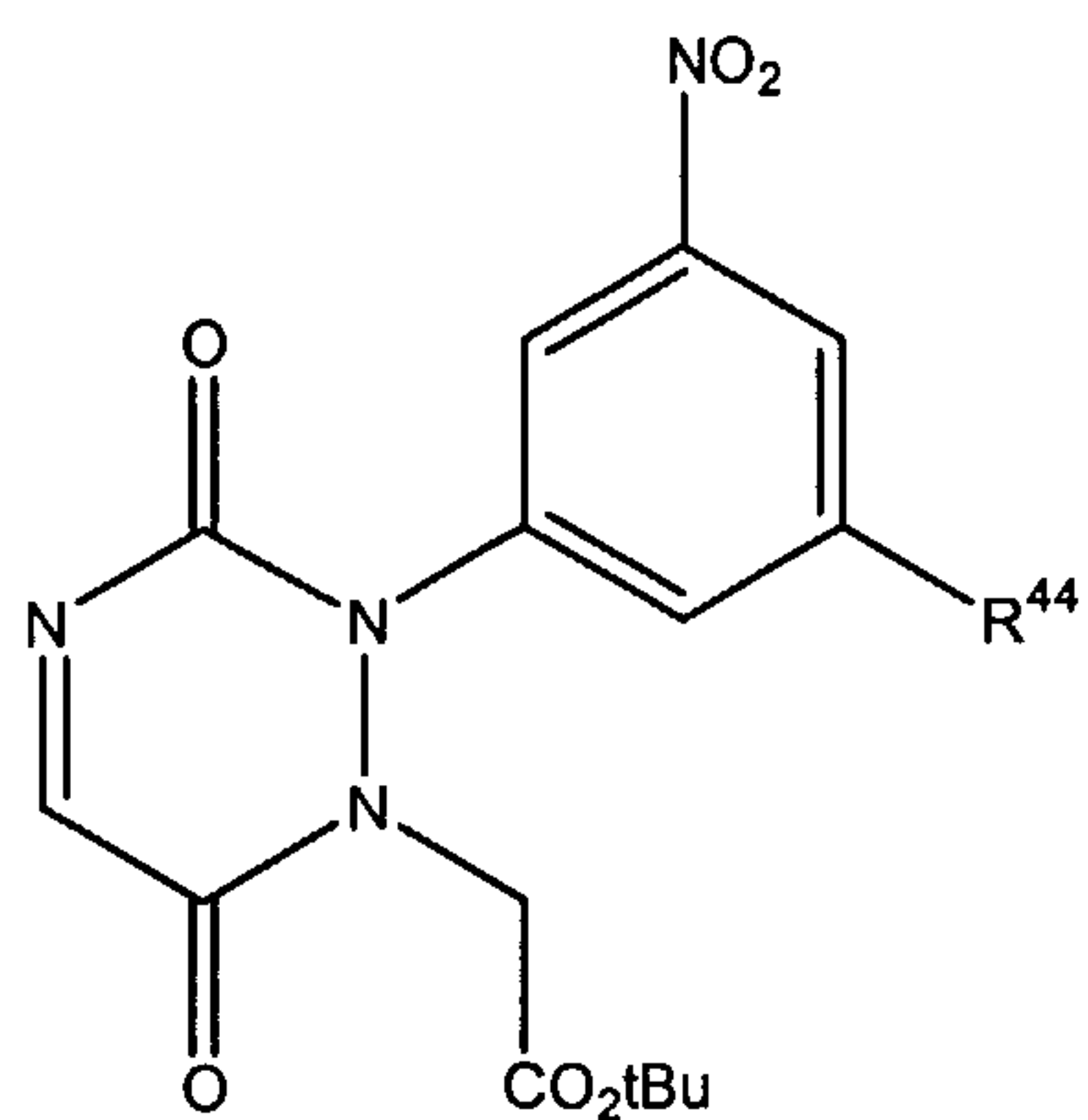
Scheme 8: Reduced Quinone (continued)



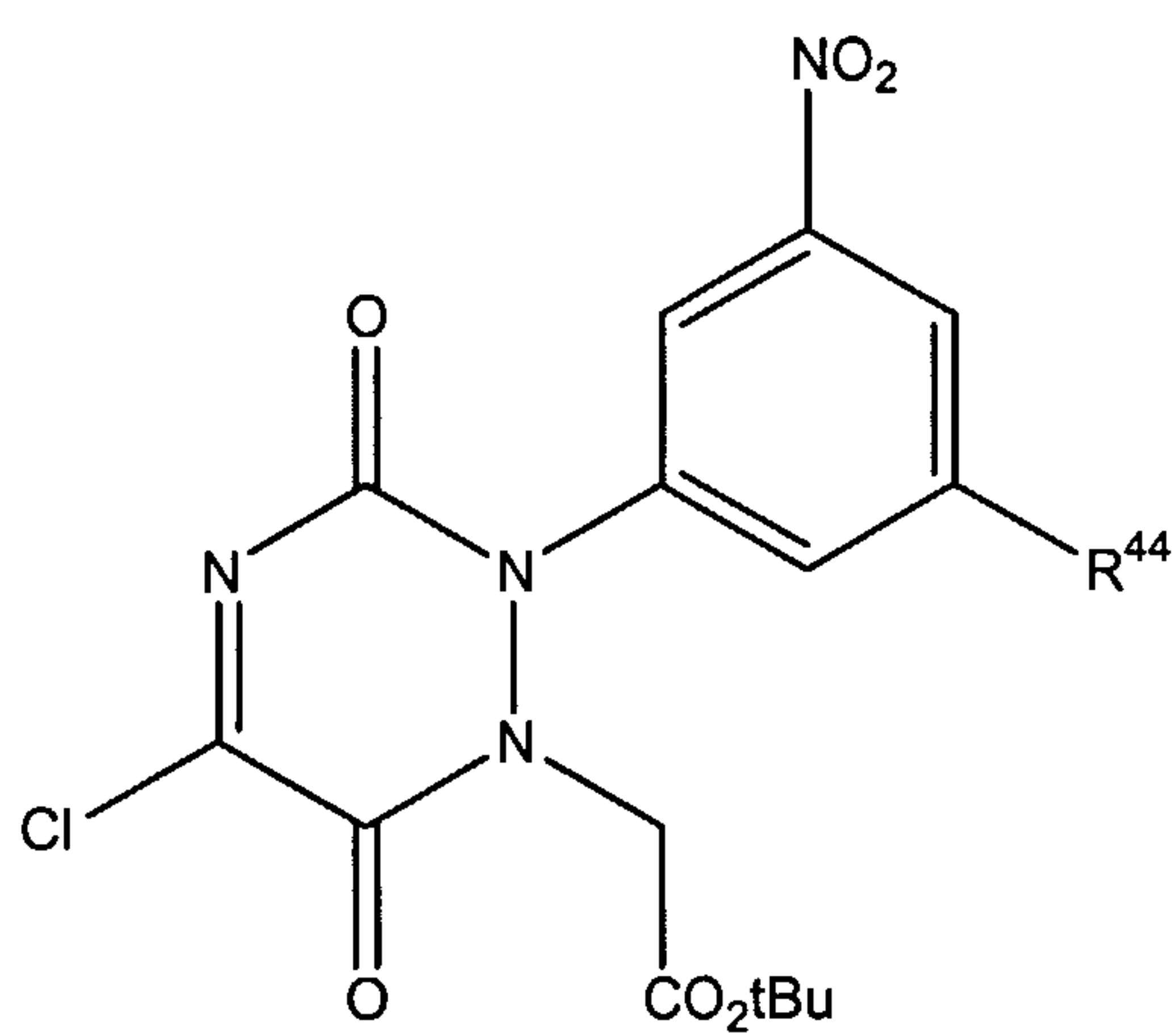
Scheme 8: Reduced Quinone (continued)

Scheme 8: Reduced Quinone (continued)

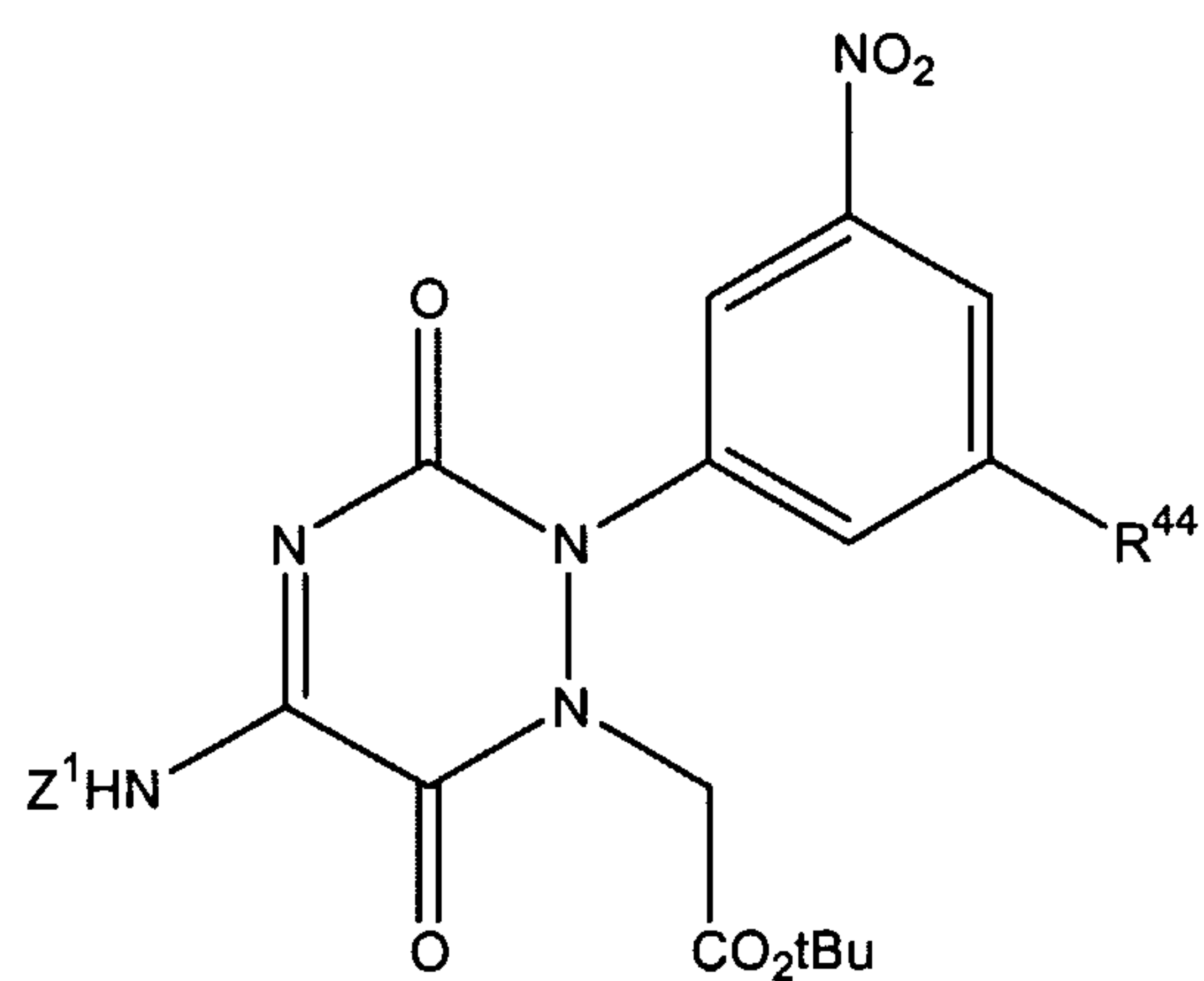
Scheme 9:

Scheme 9: (continued)

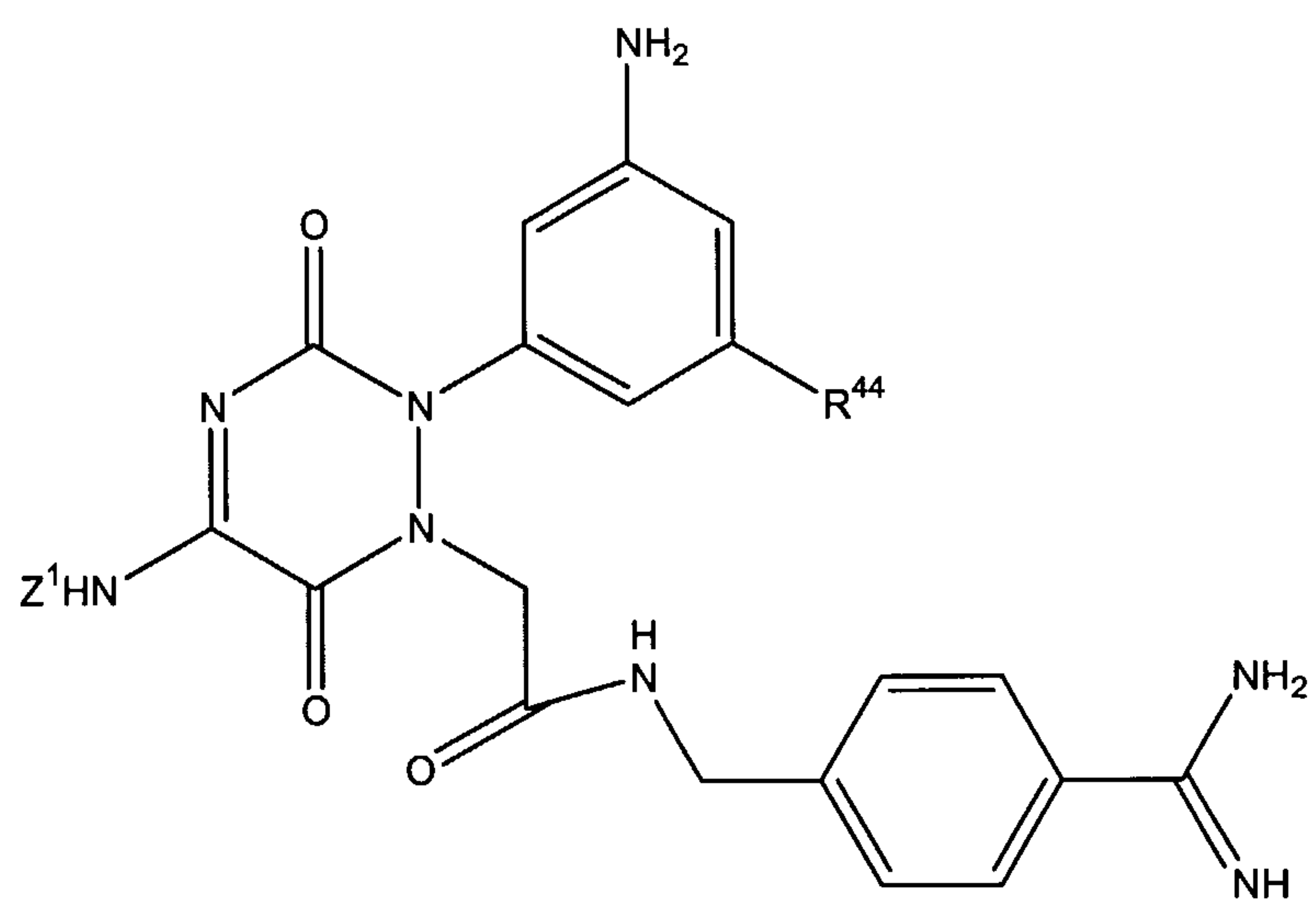
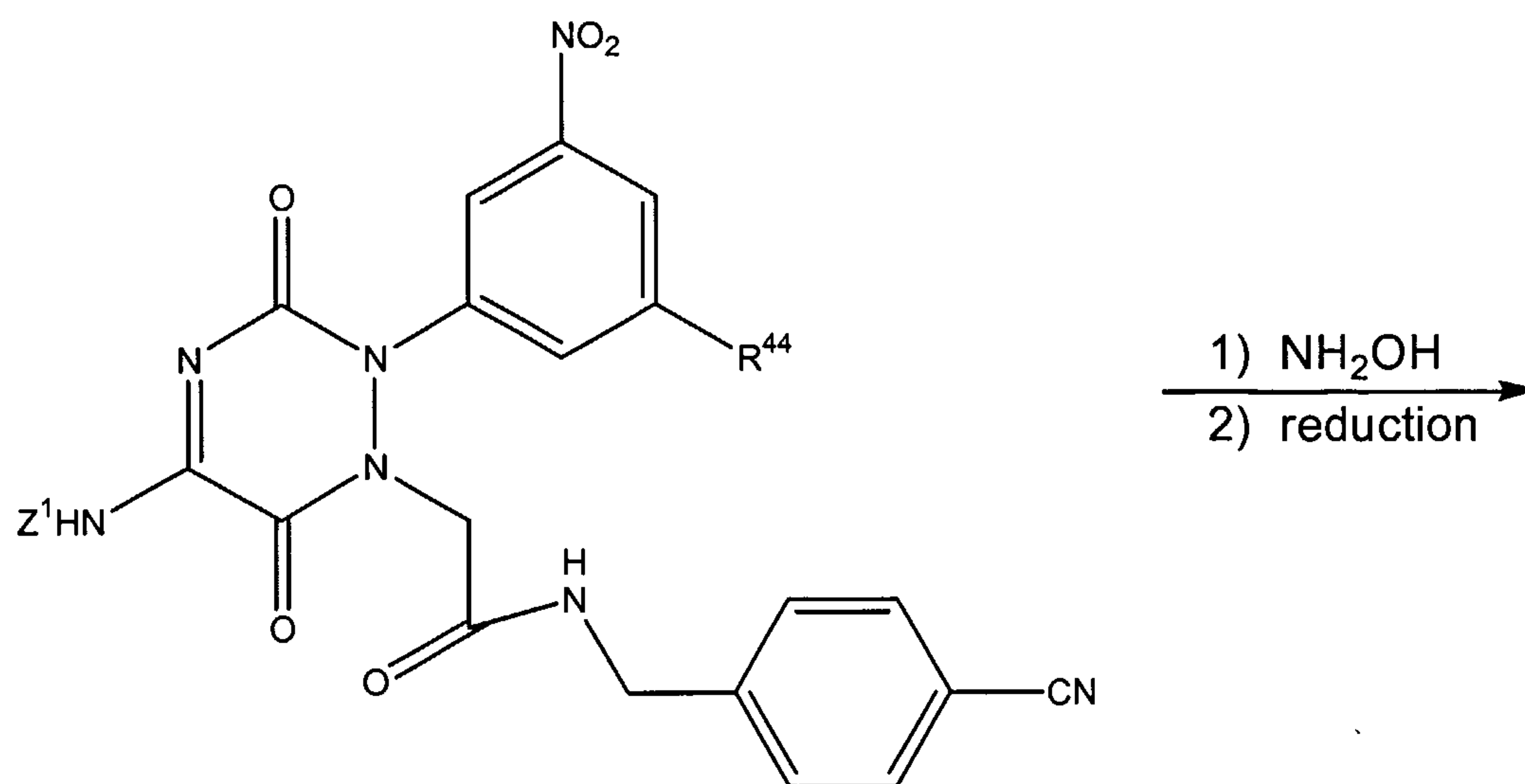
halogenation →



Z₁NH₂ →

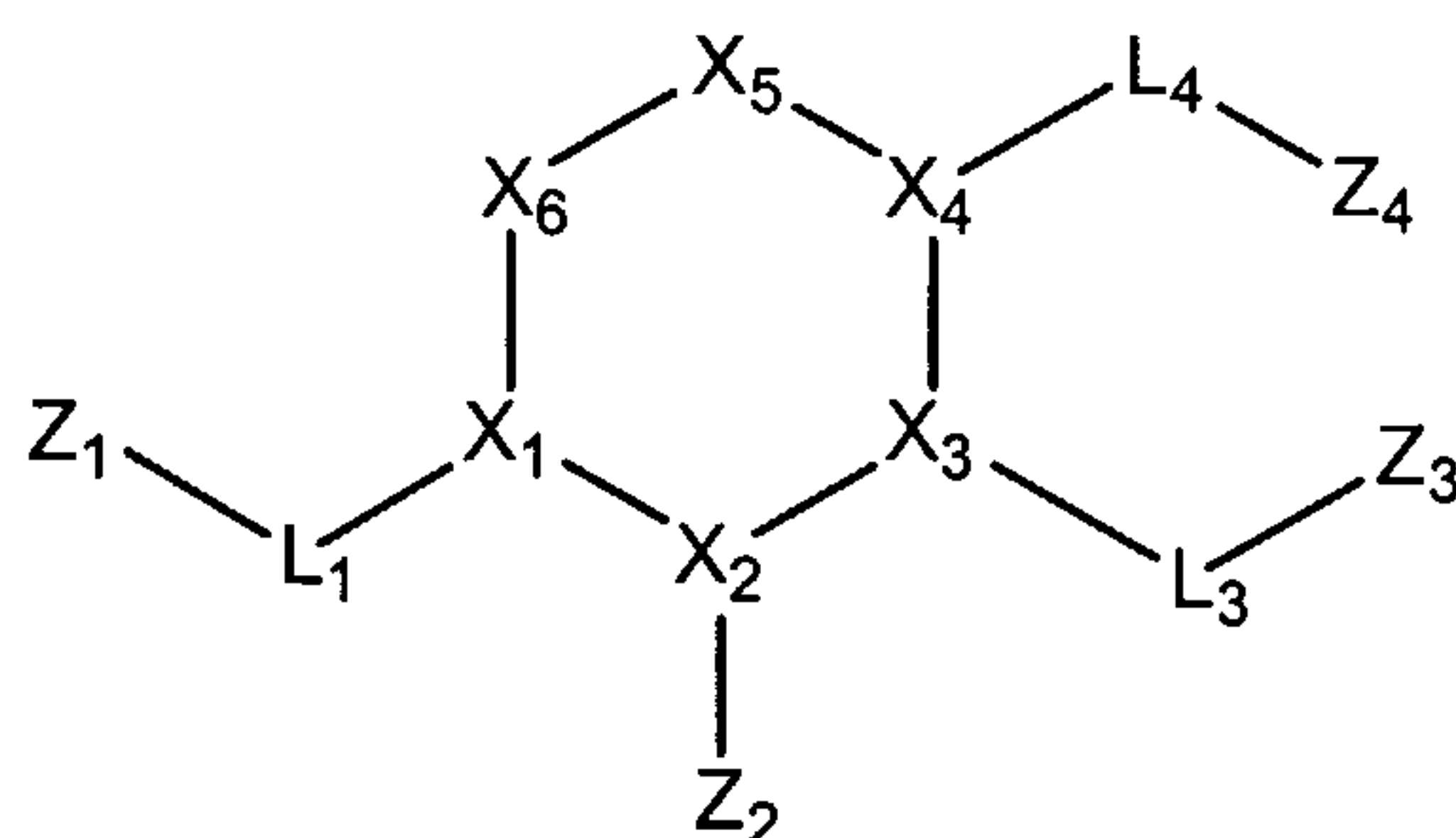


1) HCl
2) p-cyano
benzylamine →

Scheme 9: (continued)

Claims:

1. A compound having the structure:



wherein

X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are each ring atoms defining a 6-membered heterocyclic ring;

X_1 , X_3 , and X_4 are independently carbon or nitrogen;

X_2 , X_5 , and X_6 are independently carbon, nitrogen, oxygen or sulfur where X_5 and X_6 are optionally substituted with a halogen;

provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

L_1 , L_3 and L_4 are linkages through which Z_1 , Z_3 , and Z_4 , respectively, are covalently bonded to different ring atoms of the 6-membered heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 , wherein Z_1 is covalently bonded to X_1 , Z_3 is covalently bonded to X_3 , and Z_4 is covalently bonded to X_4 , each of L_1 , L_3 and L_4 independently being a covalent bond or comprising one or more atoms through which Z_1 , Z_3 , and Z_4 are covalently bonded to X_1 , X_3 and X_4 , respectively;

Z_1 is hydrocarbyl or substituted hydrocarbyl;

Z_2 is hydrogen, an electron pair, or a hydrogen bond acceptor covalently or datively bonded to X_2 ;

Z_3 comprises a 5- or 6-membered heterocyclic or aromatic ring substituted with an amidine or a derivatized amidine group, the ring atoms of the 5- or 6-membered heterocyclic or aromatic ring of Z_3 being carbon, sulfur, nitrogen, or oxygen, wherein the 5- or 6-membered ring is optionally substituted at any position with halogen,

hydroxy, haloalkyl, alkyl, carboxy, alkoxycarbonyl, or hydrocarbyloxy; and

Z₄ comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of the 5- or 6-membered heterocyclic or carbocyclic ring of Z₄ being carbon, nitrogen, oxygen, or sulfur.

2. The compound of claim 1 wherein Z₂ is a hydrogen bond acceptor covalently or datively bonded to X₂;

Z₃ comprises a 5- or 6-membered heterocyclic or aromatic ring substituted with an amidine or derivatized amidine group, the ring atoms of the 5- or 6-membered heterocyclic or aromatic ring of Z₃ being carbon, sulfur, nitrogen, or oxygen, wherein the 5- or 6-membered ring is optionally substituted at any position with halogen, hydroxy, haloalkyl, or alkyl; and

X₁, X₂, X₃, X₄, X₅, X₆, L₁, L₃, L₄, Z₁, and Z₄ are as defined in claim 1.

3. The compound of claim 1 wherein X₁, X₂, X₃, X₄, X₅, and X₆ are independently selected from carbon and nitrogen provided at least one of X₁, X₂, X₃, X₄, X₅, and X₆ is nitrogen.

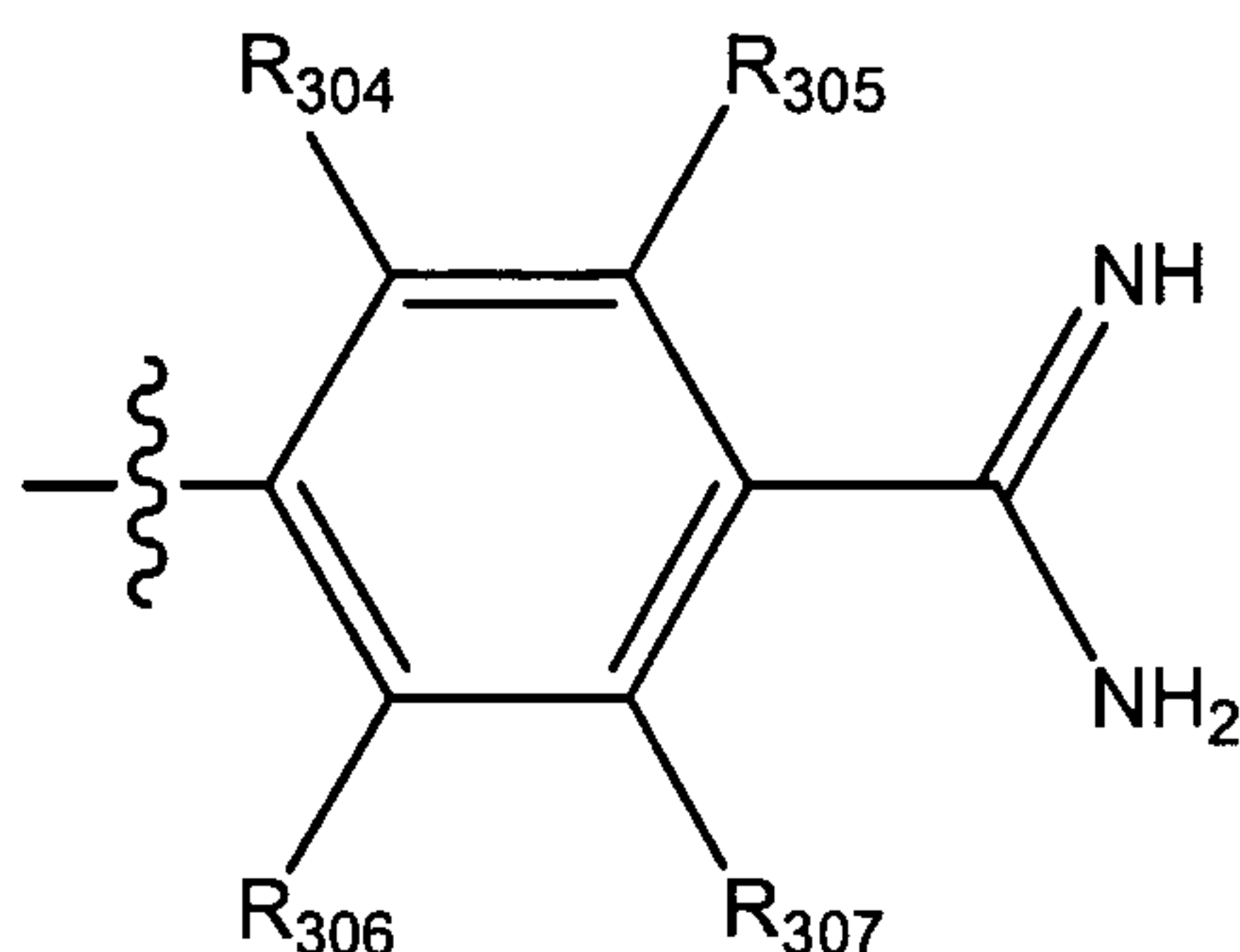
4. The compound of claims 1 or 2 wherein X₁, X₂, X₃, X₄, X₅, X₆, and Z₂ are selected to provide a heterocyclic ring selected from the group consisting of piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, dehydropiperidinedione, dihydropyridazinone, dihydroisoxazinone, tetrahydrotriazinedione, tetrahydrotriazinone, piperidine, and piperazine.

5. The compound of claims 1 or 2 wherein L₁ is covalently bonded directly to X₆ to form a fused ring.

6. The compound of claims 1 or 2 wherein L_1 is X_9NH , wherein X_9 is covalently bonded to Z_1 , and X_9 is a bond or $(CH_2)_m$, wherein m is 1 to 5.
7. The compound of claim 6 wherein X_9 is a bond.
8. The compound of claims 1 or 2 wherein L_3 is selected from the group consisting of a glycine derivative, an alanine derivative, an amino derivative, and a sulfonyl derivative.
9. The compound of claim 8 wherein L_3 is $CH_2CONHCH_2$.
10. The compound of claim 1 wherein L_4 is selected from the group consisting of a bond, methylene, ethylene, or an optionally substituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus.
11. The compound of claim 10 wherein L_4 is a bond.
12. The compound of claim 1 wherein Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.
13. The compound of claims 1 or 2 wherein the 5- or 6-membered heterocyclic or aromatic ring comprising Z_3 is substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination yields an amidine group.
14. The compound of claim 1 wherein Z_3 comprises a substituted phenyl, thienyl, or furanyl ring, the phenyl, thienyl or furanyl ring being substituted with an amidine or a derivatized amidine group, and optionally further

substituted at any substitutable position with fluorine, hydroxy, carboxy, alkoxycarbonyl, or hydrocarbyloxy;

15. The compound of claim 14 wherein Z_3 is



wherein

R_{304} and R_{306} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, carboxy, hydrocarbyloxy and alkoxycarbonyl; and

R_{305} and R_{307} are independently selected from the group consisting of hydrogen, fluorine, methoxy, hydroxy and carboxy.

16. The compound of claim 2 wherein the 5- or 6-membered heterocyclic or aromatic ring comprising Z_3 is optionally substituted at any position with fluorine, methyl or hydroxy.

17. The compound of claim 1 wherein Z_4 comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of Z_4 being Z_{40} , Z_{41} , Z_{42} , Z_{44} and Z_{45} when Z_4 is a 5-membered ring and Z_{40} , Z_{41} , Z_{42} , Z_{43} , Z_{44} and Z_{45} when Z_4 is a 6-membered ring, Z_{40} , Z_{41} , Z_{42} , Z_{43} , Z_{44} and Z_{45} , being carbon, nitrogen, oxygen or sulfur, Z_{40} being the ring atom through which Z_4 is attached to the heterocyclic core ring, Z_{41} and Z_{45} each being in an alpha position relative to Z_{40} , Z_{42} and Z_{44} each being in a beta position relative to Z_{40} , Z_{43} being in the gamma position relative to Z_{40} when Z_4 is a 6-

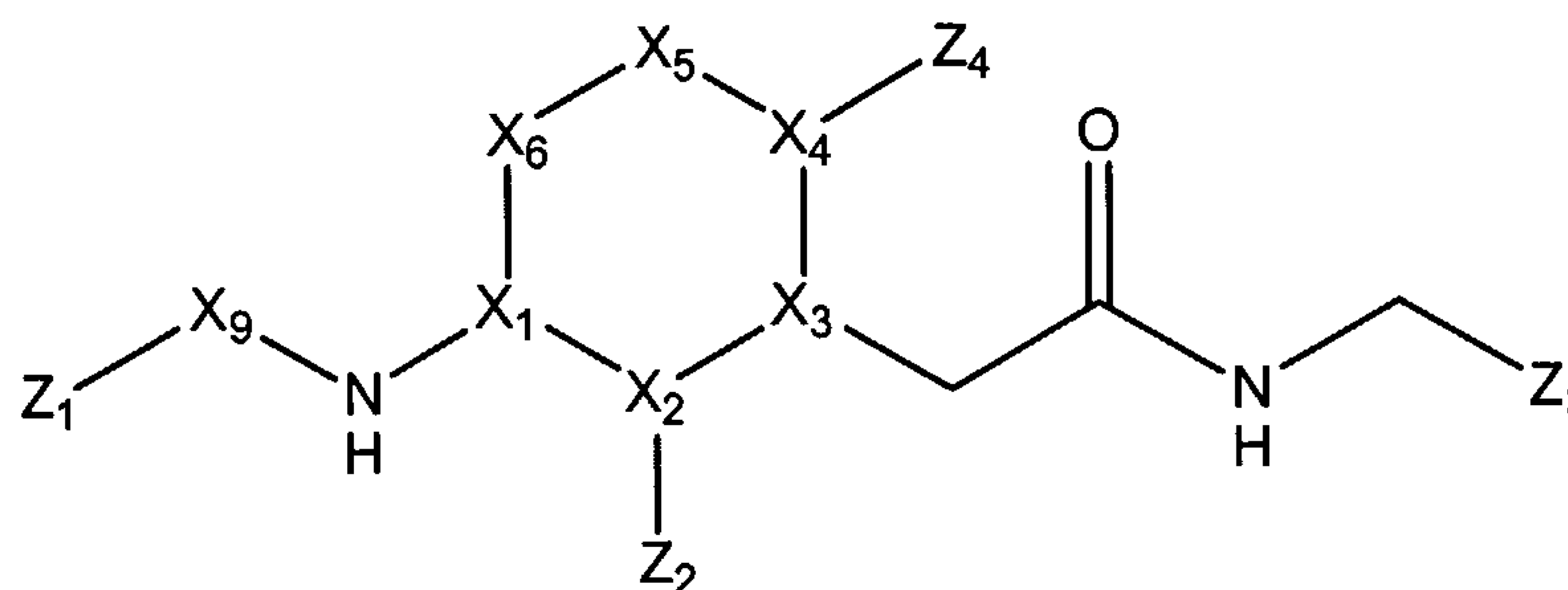
membered ring, Z_4 having a substituent R_{42} covalently attached to Z_{42} , and a second substituent bonded to one of Z_{41} , Z_{43} , Z_{44} , or Z_{45} , the substituent being R_{41} when bonded to Z_{41} , the substituent being R_{43} when bonded to Z_{43} , the substituent being R_{44} when bonded to Z_{44} , and the substituent being R_{45} when bonded to Z_{45} ;

R_{42} is amino; and

R_{41} , R_{43} , R_{44} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclo, halogen, or a substituted or unsubstituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus, provided at least one of R_{41} , R_{43} , R_{44} or R_{45} is other than hydrogen.

18. The compound of claim 17 wherein R_{44} is selected from the group consisting of hydrogen, hydrocarbyl, substituted hydrocarbyl, heteroaryl, heterocyclo, halogen, acetamido, guanidino, hydroxy, nitro, amino, amidosulfonyl, acylamido, hydrocarbyloxy, substituted hydrocarbyloxy, hydrocarbylthio, substituted hydrocarbylthio, hydrocarbylsulfonyl, and substituted hydrocarbylsulfonyl.

19. The compound of claim 1 wherein the compound has the structure:



wherein

X_9 is a bond or $(CH_2)_m$ wherein m is 1 or 2; and

X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , Z_1 , Z_2 , Z_3 , and Z_4 are as defined in claim 1.

20. The compound of claim 19 wherein X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are independently selected from carbon and nitrogen, and at least one of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 is nitrogen.

21. The compound of claims 1 or 19 wherein X_2 is carbon and Z_2 is hydrogen, fluorine, oxygen, or sulfur.

22. The compound of claims 1 or 19 wherein X_2 is nitrogen, oxygen or sulfur and Z_2 is hydrogen, an electron pair, or a hydrogen bond acceptor.

23. The compound of claims 1 or 19 wherein X_2 is nitrogen and Z_2 is hydrogen, oxygen, amino, or acyl.

24. The compound of claims 1 or 19 wherein X_3 is nitrogen.

25. The compound of claims 1 or 19 wherein X_2 is carbon and X_3 is nitrogen.

26. The compound of claim 19 wherein X_9 is a bond.

27. The compound of claim 26 wherein Z_1 is C_1 - C_5 alkyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.

28. The compound of claim 19 wherein Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.

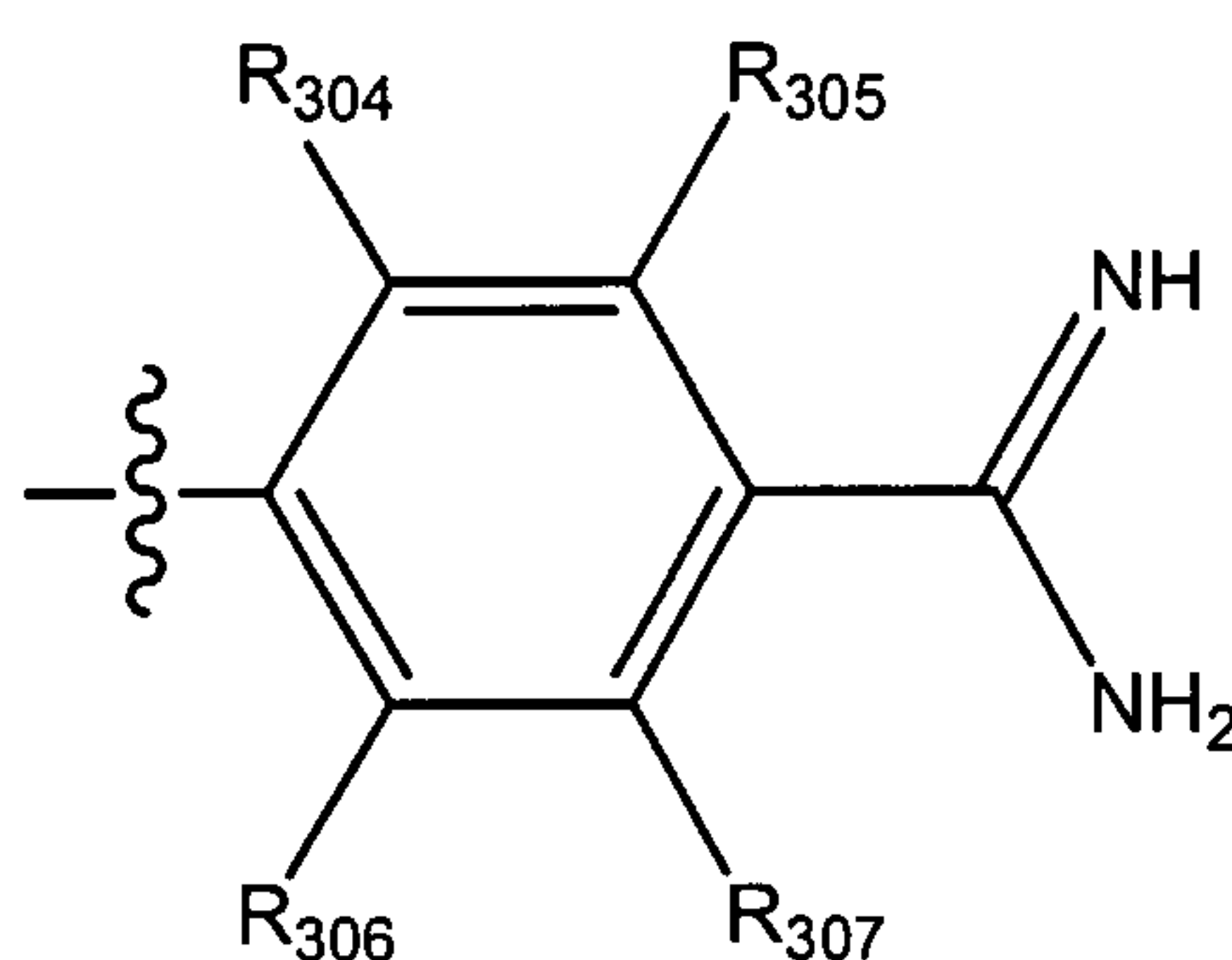
29. The compound of claim 19 wherein the 5- or 6-membered heterocyclic or aromatic ring comprising Z_3 is substituted with a derivatized amidine which, upon

hydrolysis, oxidation, reduction or elimination, or any combination thereof, yields an amidine group.

30. The compound of 19 wherein Z_3 is phenyl substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination, or any combination thereof, under physiological conditions yields an amidine group.

31. The compound of claim 19 wherein Z_3 comprises a substituted phenyl, thienyl, or furanyl ring, the phenyl, thienyl or furanyl ring being substituted with an amidine or a derivatized amidine group, and optionally further substituted at any substitutable position with fluorine, hydroxy, carboxy, alkoxycarbonyl, or hydrocarbyloxy

32. The compound of claim 31 wherein Z_3 is



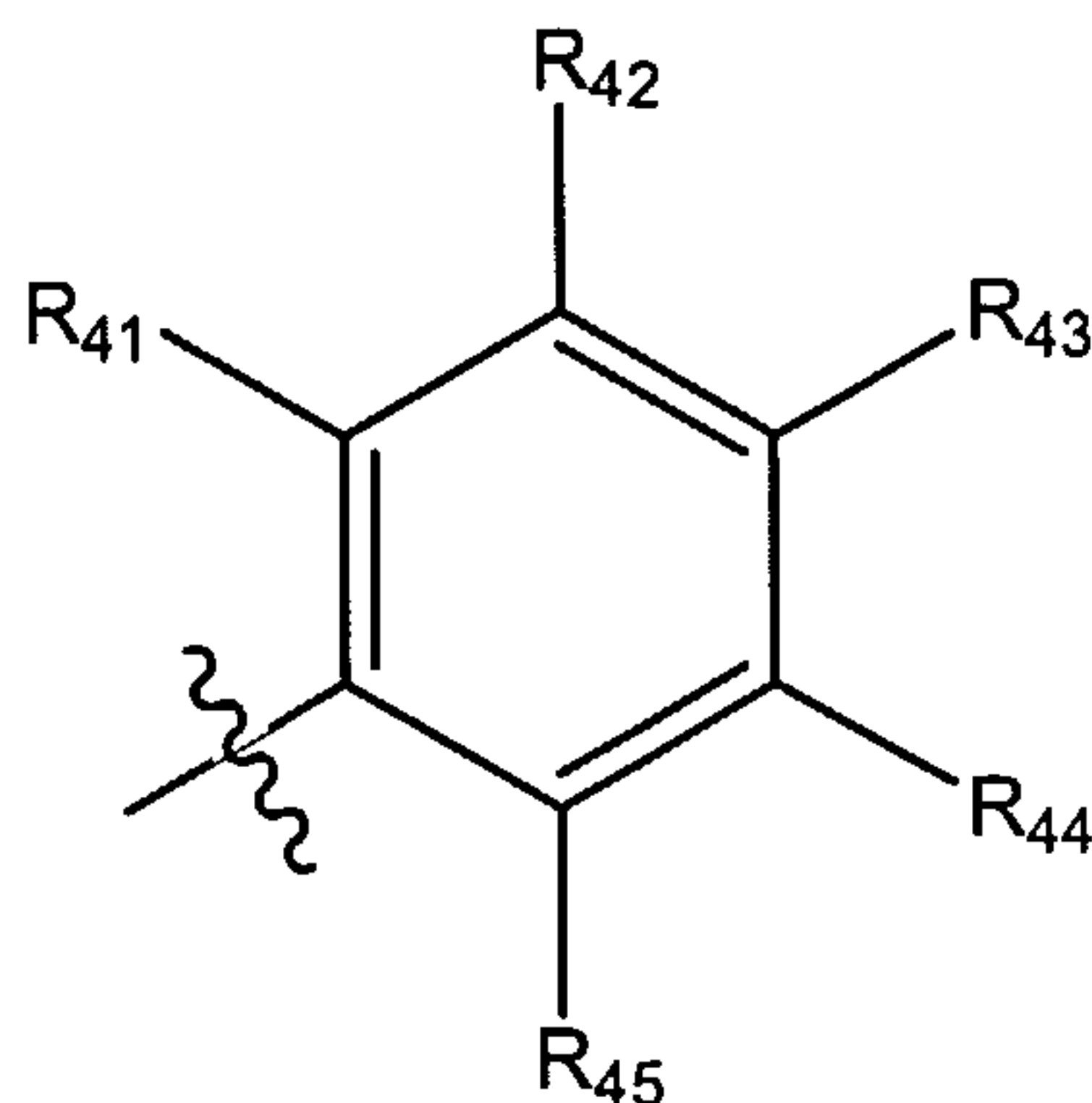
wherein

R_{304} and R_{306} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, carboxy, hydrocarbyloxy and alkoxycarbonyl; and

R_{305} and R_{307} are independently selected from the group consisting of hydrogen, fluorine, methoxy, hydroxy and carboxy.

33. The compound of claims 1 or 19 wherein Z_4 is a substituted, 6-membered, carbocyclic aromatic ring.

34. The compound of claim 19 wherein Z_4 is



wherein:

R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} , R_{43} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

35. The compound of claim 34 wherein R_{41} , R_{43} and R_{45} are independently hydrogen, halogen, alkoxy, or alkyl, optionally substituted with halogen or alkoxy and R_{42} and R_{44} are as defined in claim 34.

36. The compound of claim 34 wherein R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, acetamidyl, alkoxy, hydroxy, amino, alkylsulfonyl, haloalkoxy, haloalkylthio, alkoxycarbonyl, carboxy, sulfonamido, carboxamido and sulfonamidyl, optionally substituted with fluorine.

37. The compound of claim 36 wherein R_{44} is selected from the group consisting of hydroxy, carboxy, carboxamido, alkoxy, alkylsulfonyl, sulfonamido, or alkoxycarbonyl.

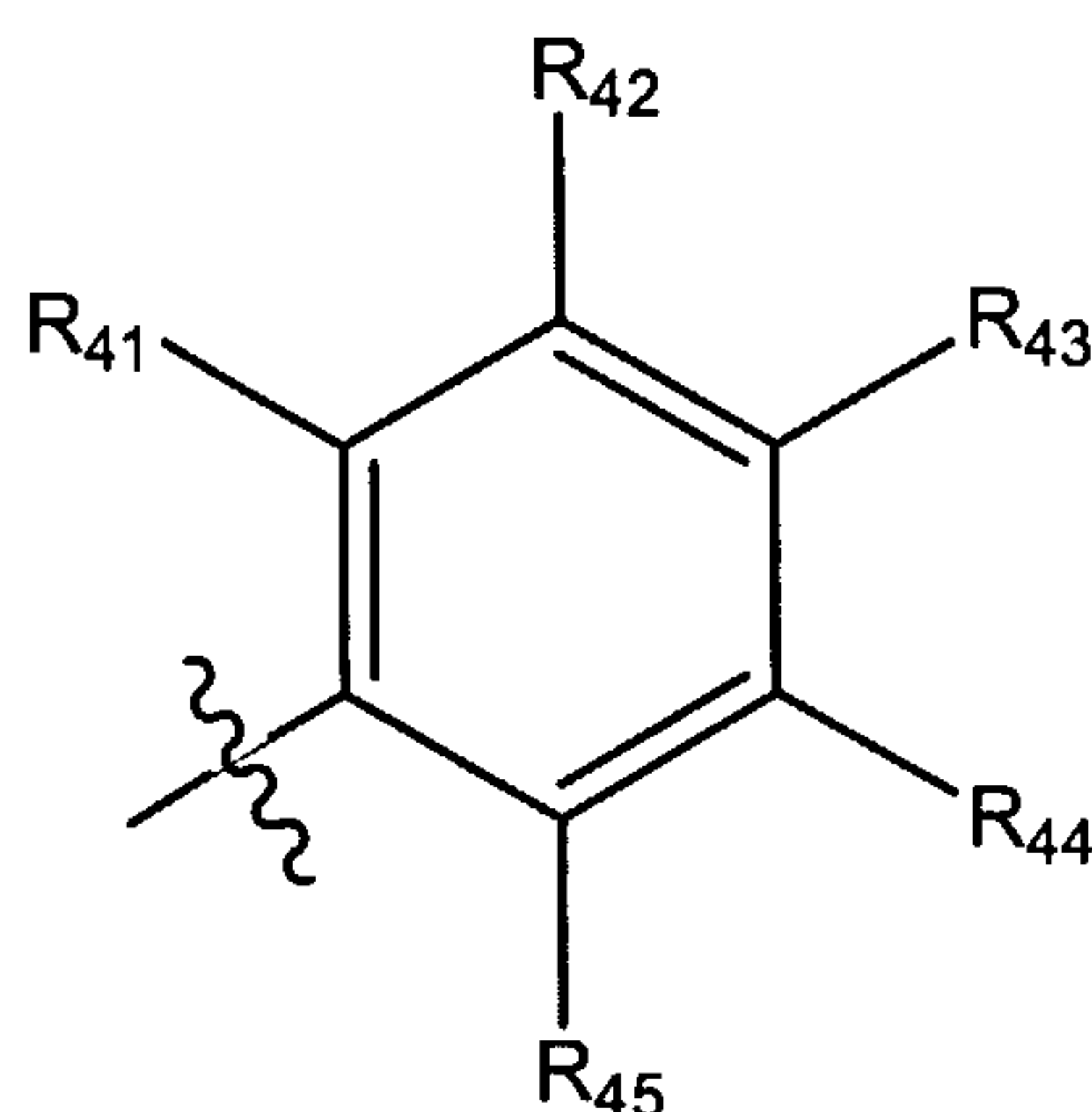
38. The compound of claim 37 wherein R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy.

39. The compound of claim 34 wherein R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, acetamido, alkoxy, hydroxy, amino, alkylsulfonyl, haloalkyl, haloalkoxy, haloalkylthio, carboalkoxy, carboxy, carboxamidoalkyl, and carboxamidoalkylaryl.

40. The compound of claim 39 wherein each of R_{41} , R_{43} and R_{45} is hydrogen.

41. The compound of claim 36 wherein Z_{41} , Z_{43} or Z_{45} is substituted with fluorine or chlorine.

42. The compound of claim 19 wherein Z_4 is



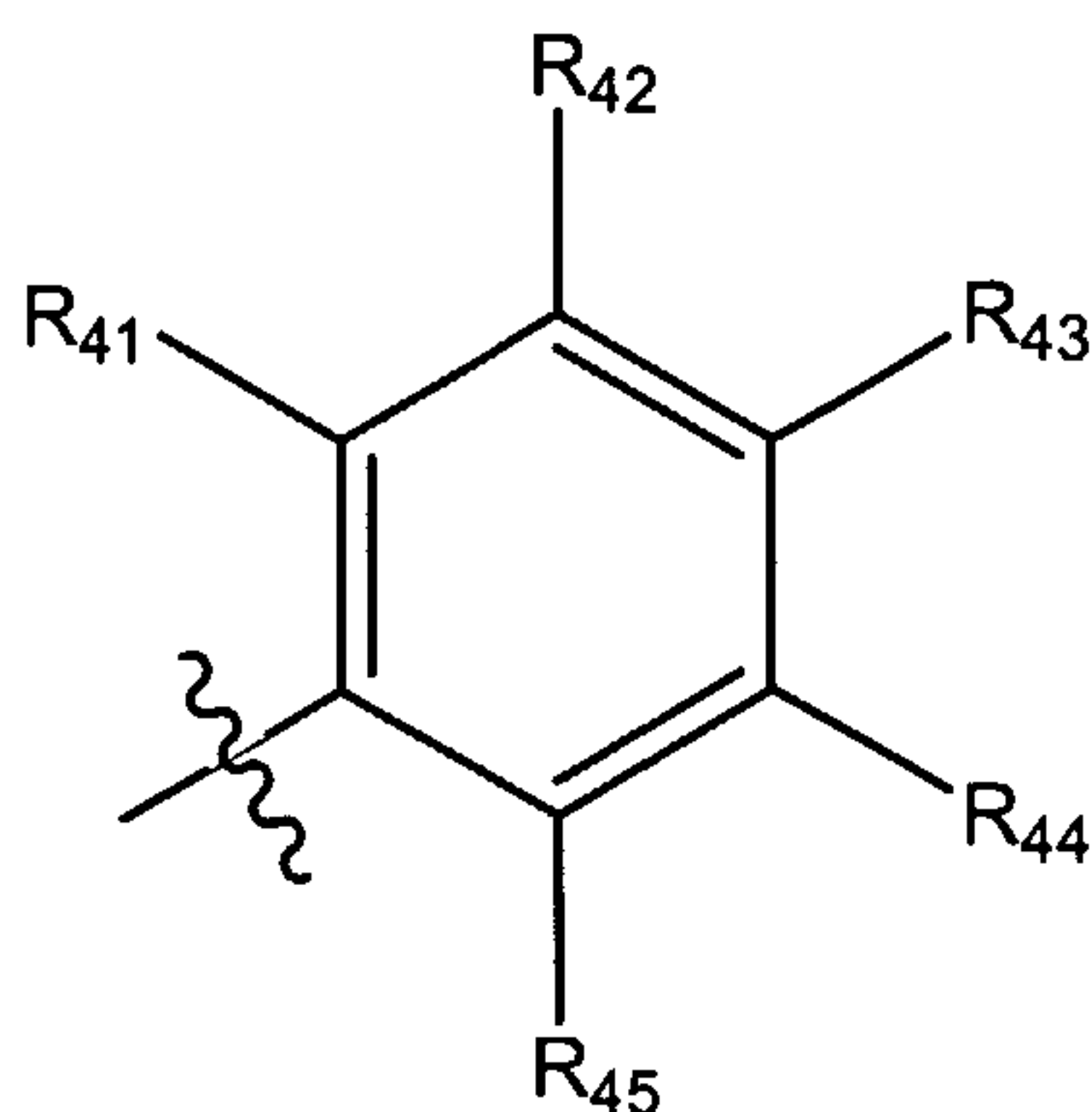
wherein

R_{42} is amino;

R_{43} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} , R_{44} and R_{45} are independently hydrogen, halogen or alkoxy.

43. The compound of claim 19 wherein Z_4 is



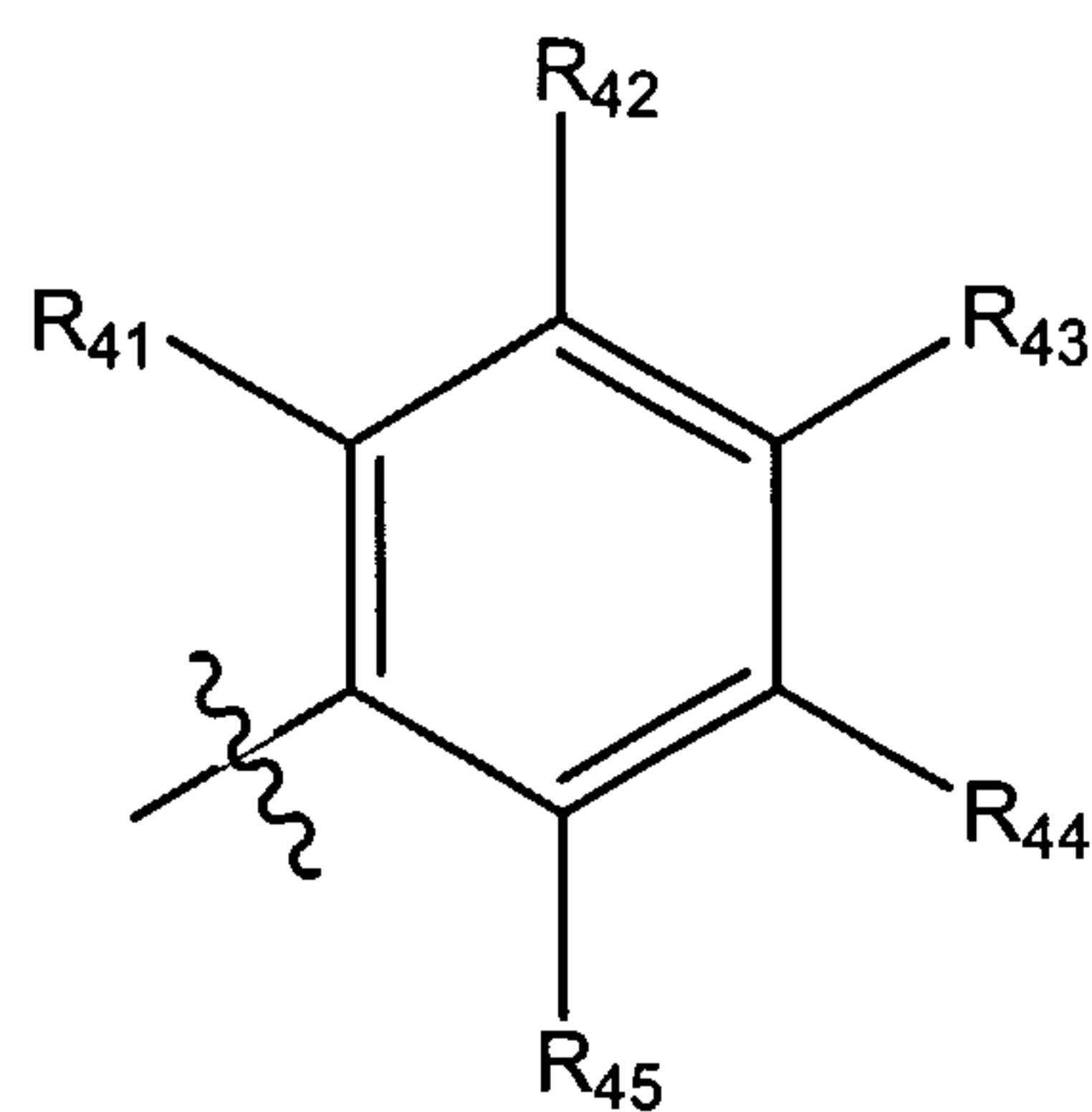
wherein

R_{42} is amino;

R_{45} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} , R_{43} and R_{44} are independently hydrogen, halogen or alkoxy.

44. The compound of claim 19 wherein Z_4 is



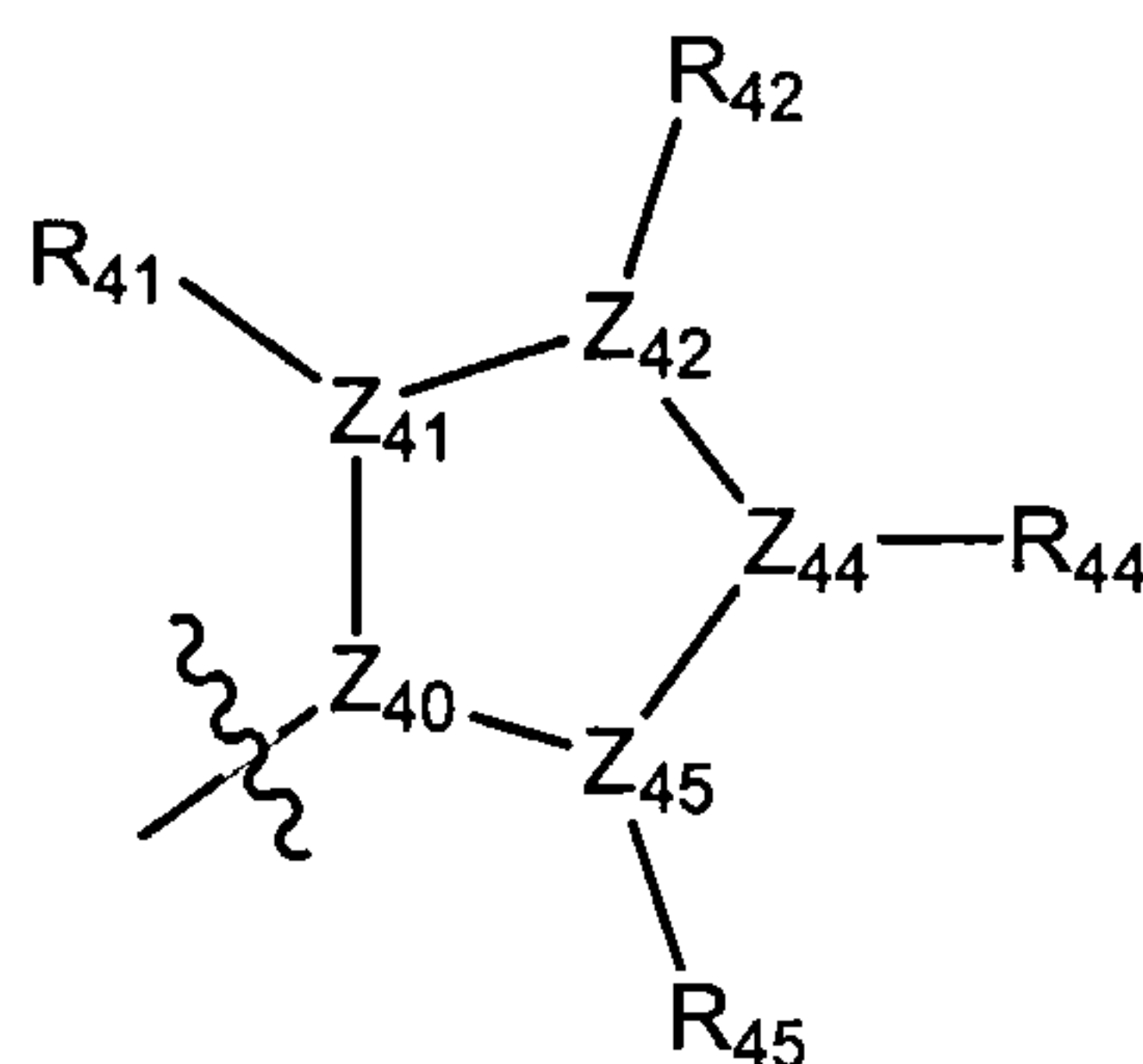
wherein

R_{42} is amino;

R_{41} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{43} , R_{44} and R_{45} are independently hydrogen, halogen or alkoxy.

45. The compound of claim 19 wherein Z_4 has the following structure:



wherein

Z_{40} , Z_{41} , Z_{42} , Z_{44} , and Z_{45} are independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

46. The compound of claim 45 wherein R_{41} and R_{45} are independently hydrogen, halogen, alkoxy, or alkyl, optionally substituted with halogen or alkoxy and R_{42} and R_{44} are as defined in claim 45.

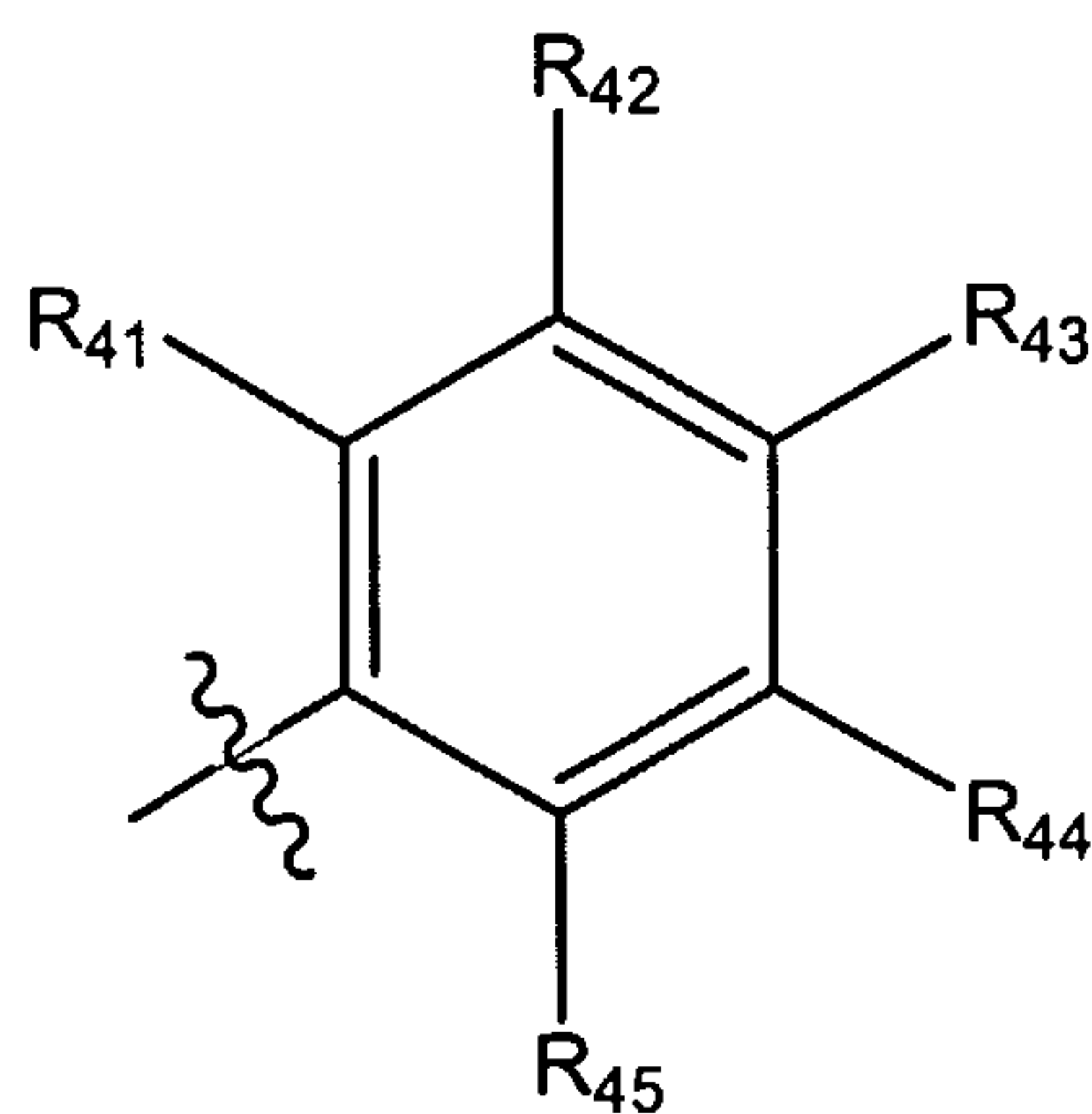
47. The compound of claim 45 wherein R_{44} is selected from the group consisting of hydroxy, carboxy, carboxamido, alkoxy, alkylsulfonyl, sulfonamido, or alkoxycarbonyl.

48. The compound of claim 47 wherein R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy.

49. The compound of claims 1 or 19 wherein X_9 is a bond, Z_1 is selected from the group consisting of cyclopropyl, isopropyl, cyclobutyl, isobutyl, sec-butyl, methyl, ethyl, and phenyl, and Z_3 is phenyl substituted with an amidine group.

50. The compound of claims 1 or 19 wherein X_9 is a bond, Z_4 is a substituted, 6-membered, carbocyclic aromatic ring, Z_3 is phenyl substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination under physiological conditions yields an amidine group, and Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, sec-butyl, and phenyl.

51. The compound of claims 1 or 19 wherein X_9 is a bond, Z_1 is selected from the group consisting of optionally substituted C_1 - C_6 cycloalkyl, C_1 - C_6 alkyl and phenyl, Z_3 is phenyl substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination under physiological conditions yields an amidine group, and Z_4 is



wherein

R_{42} is amino;

R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, halogen and an

optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} , R_{43} and R_{45} are independently selected from the group consisting of hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen and an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

52. The compound of claim 51 wherein R_{44} is selected from the group consisting of hydroxy, alkylsulfonyl, haloalkyl, haloalkoxy, haloalkylthio, carboxamidoalkyl, and carboxamidoalkylaryl.

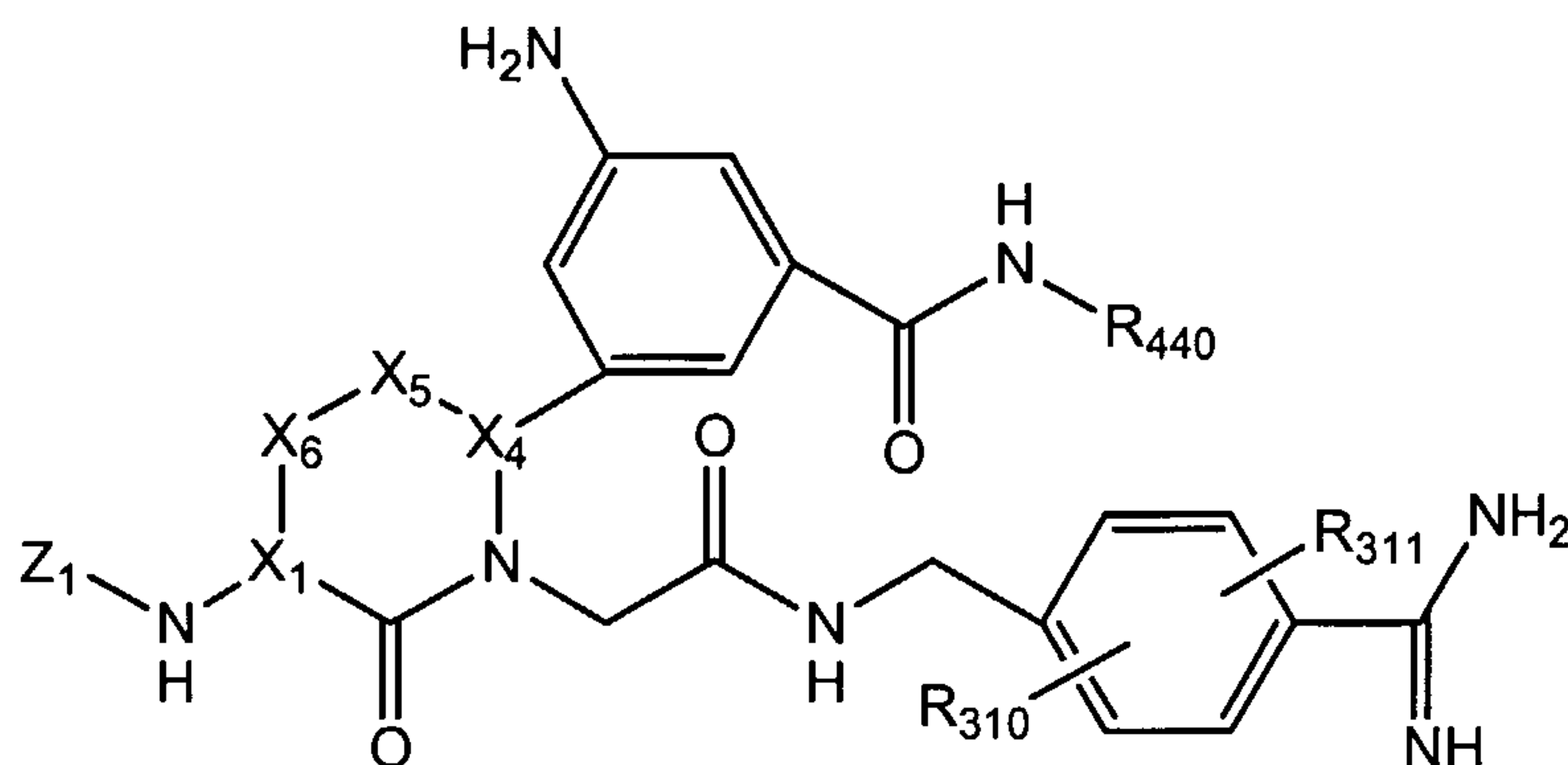
53. The compound of claim 51 wherein each of R_{41} , R_{43} and R_{45} is hydrogen.

54. The compound of claim 51 wherein R_{44} is selected from the group consisting of hydrocarbyl, substituted hydrocarbyl, acetamidyl, alkoxy, hydroxy, amino, alkylsulfonyl, haloalkoxy, haloalkylthio, alkoxycarbonyl, carboxy, sulfonamido, carboxamido and sulfonamidyl, optionally substituted with fluorine; and each of Z_{41} , Z_{43} and Z_{45} is optionally substituted with fluorine or chlorine.

55. The compound of claim 54 wherein R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy.

56. The compound of any of claims 1 or 19 wherein the 6-membered heterocyclic ring defined by X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , and Z_2 is selected from the group consisting of piperidinone, dihydropyrimidinone, tetrahydropyrimidinone, tetrahydrotriazinone, piperidine, and piperazine.

57. The compound of claim 1 having the structure:



wherein

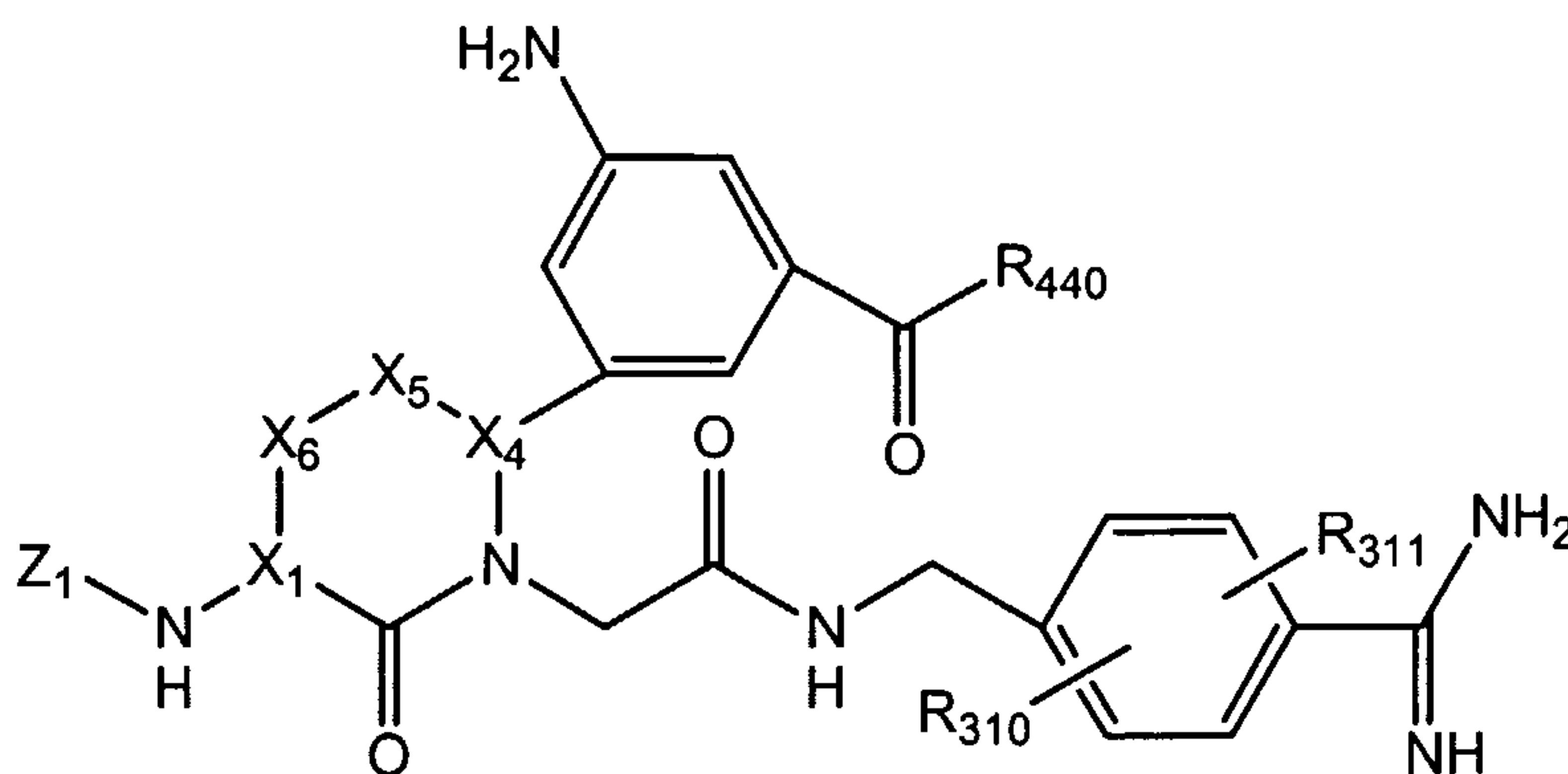
X_1 , X_4 , X_5 and X_6 are independently carbon or nitrogen;

Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted with fluorine, hydroxy, carboxy, or alkoxycarbonyl;

R_{440} is C_1 - C_6 alkyl, aryl, aralkyl, carboxy, or carboxyalkyl, wherein said alkyl, aryl, aralkyl, carboxy, or carboxyalkyl is optionally further substituted by fluorine; and

R_{310} and R_{311} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, alkoxy, and carboxy.

58. The compound of claim 1 having the structure:



wherein

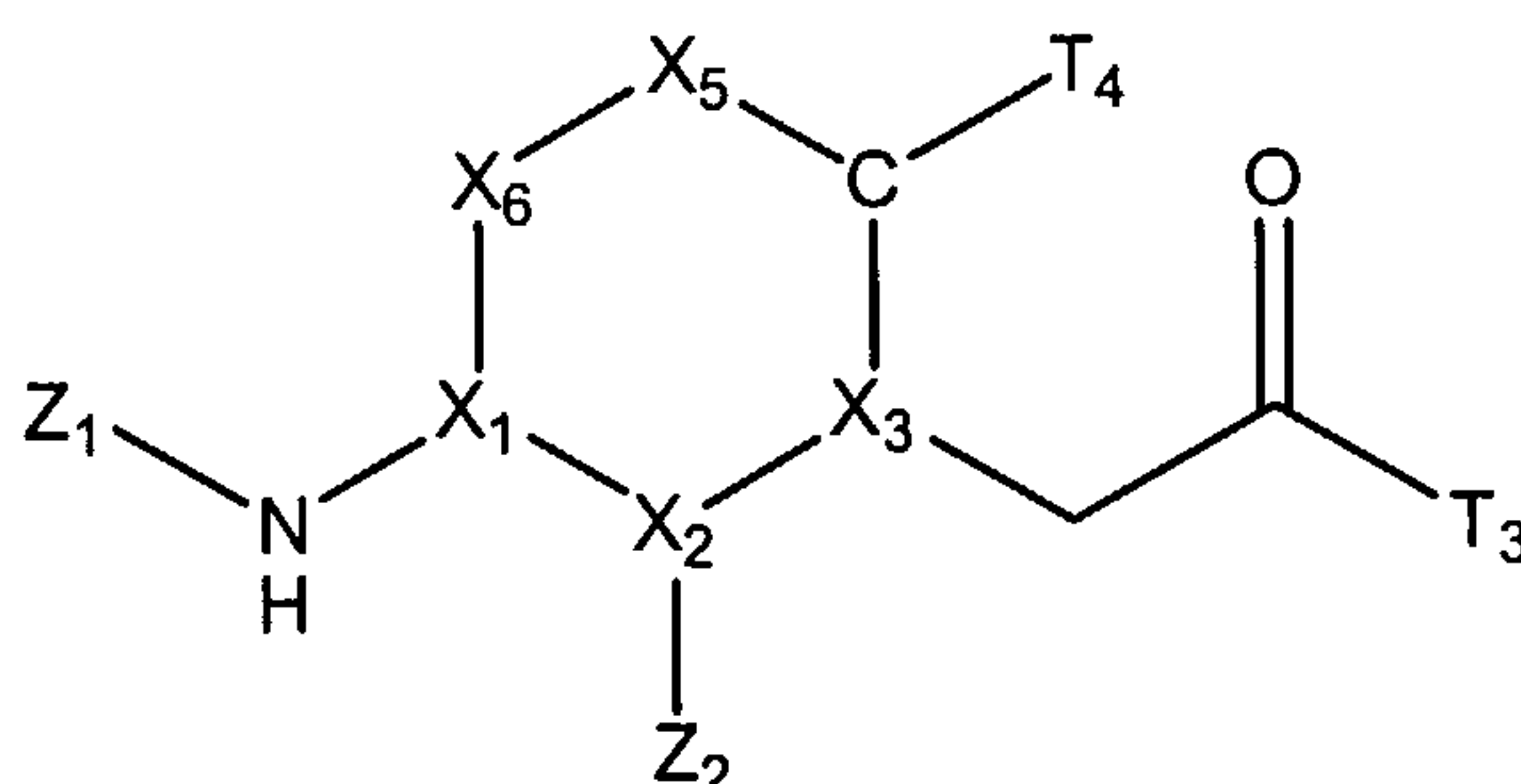
X_1 , X_4 , X_5 and X_6 are independently carbon or nitrogen;

Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted with fluorine, hydroxy, carboxy, or alkoxycarbonyl;

R_{440} is C_1 - C_6 alkyl, aryl, aralkyl, carboxy, or carboxyalkyl, wherein said alkyl, aryl, aralkyl, carboxy, or carboxyalkyl is optionally further substituted by fluorine; and

R_{310} and R_{311} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, alkoxy, and carboxy.

59. A compound having the structure:



wherein

X_1 , X_2 , X_5 , and X_6 are members of a heterocyclic ring;

X_1 , X_2 and X_3 are independently carbon or nitrogen;

X_5 and X_6 are independently selected from the group consisting of nitrogen, oxygen, sulfur, carbon, $C(F)$ and $C(Br)$;

provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

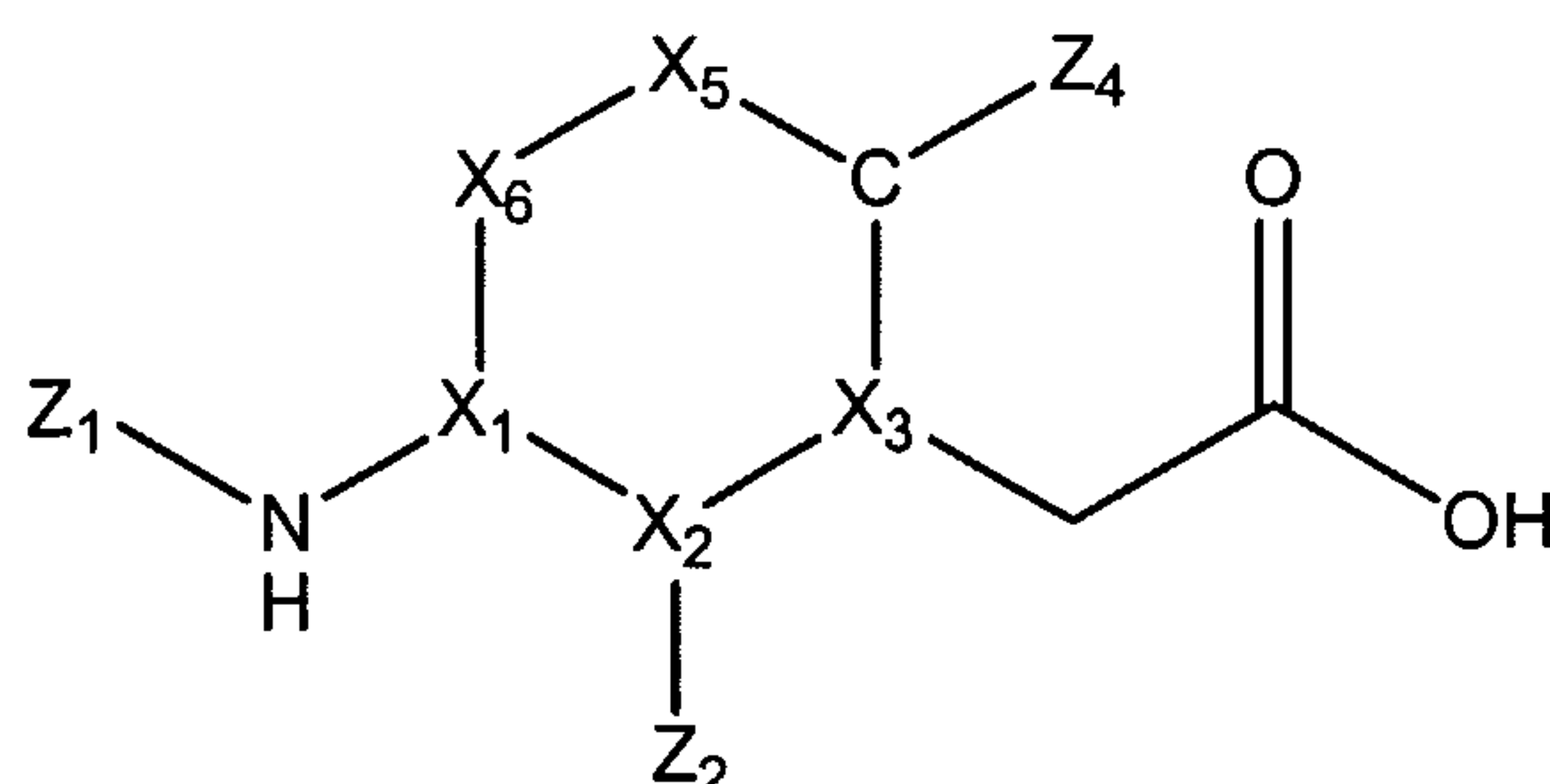
T_3 is selected from the group consisting of hydroxy, alkoxy, substituted alkoxy, and substituted amino;

T_4 is selected from the group consisting of $-Cl$, $-Br$, $-I$, $-S(CH_3)$, and $-OSO_2(CF_3)$;

Z_1 is hydrocarbyl, or substituted hydrocarbyl; and

Z_2 is a hydrogen bond acceptor covalently or datively bonded to X_2 .

60. A compound having the structure:



wherein

X_1 , X_2 , X_5 , and X_6 are members of a heterocyclic ring;

X_1 , X_2 and X_3 are independently carbon or nitrogen;

X_5 and X_6 are independently selected from the group consisting of nitrogen, oxygen, sulfur, carbon, C(F) and C(Br);

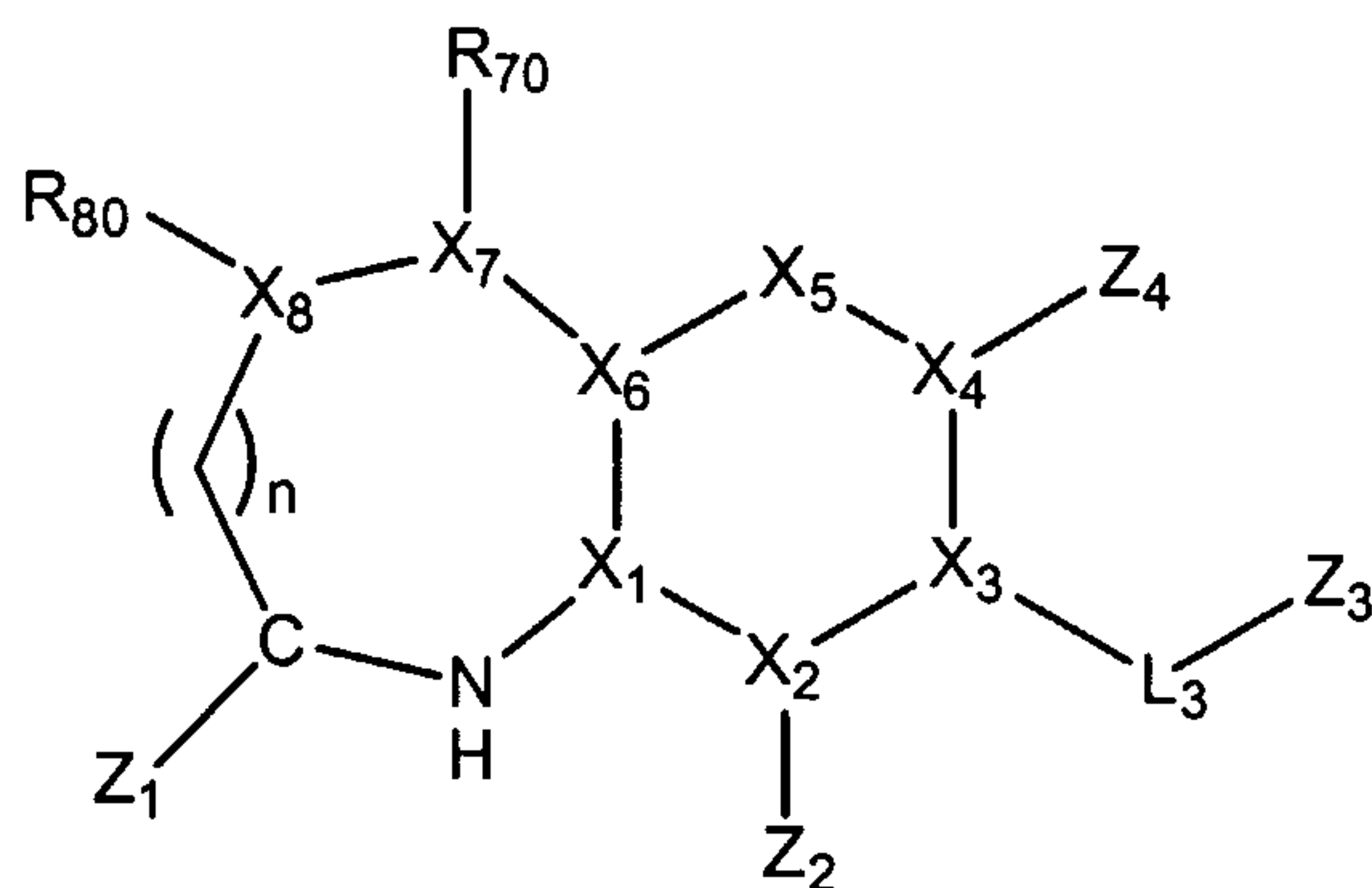
provided no more than 4 of X_1 , X_2 , X_3 , X_4 , X_5 , and X_6 are sp^2 hybridized;

Z_4 comprises hydrocarbyl, substituted hydrocarbyl or a 5 or 6 membered heterocyclic or carbocyclic ring, the ring atoms of the 5 or 6 membered heterocyclic or carboxylic ring of Z_4 being carbon, nitrogen, oxygen, or sulfur;

Z_1 is hydrocarbyl, or substituted hydrocarbyl; and

Z_2 is a hydrogen bond acceptor covalently or datively bonded to X_2 .

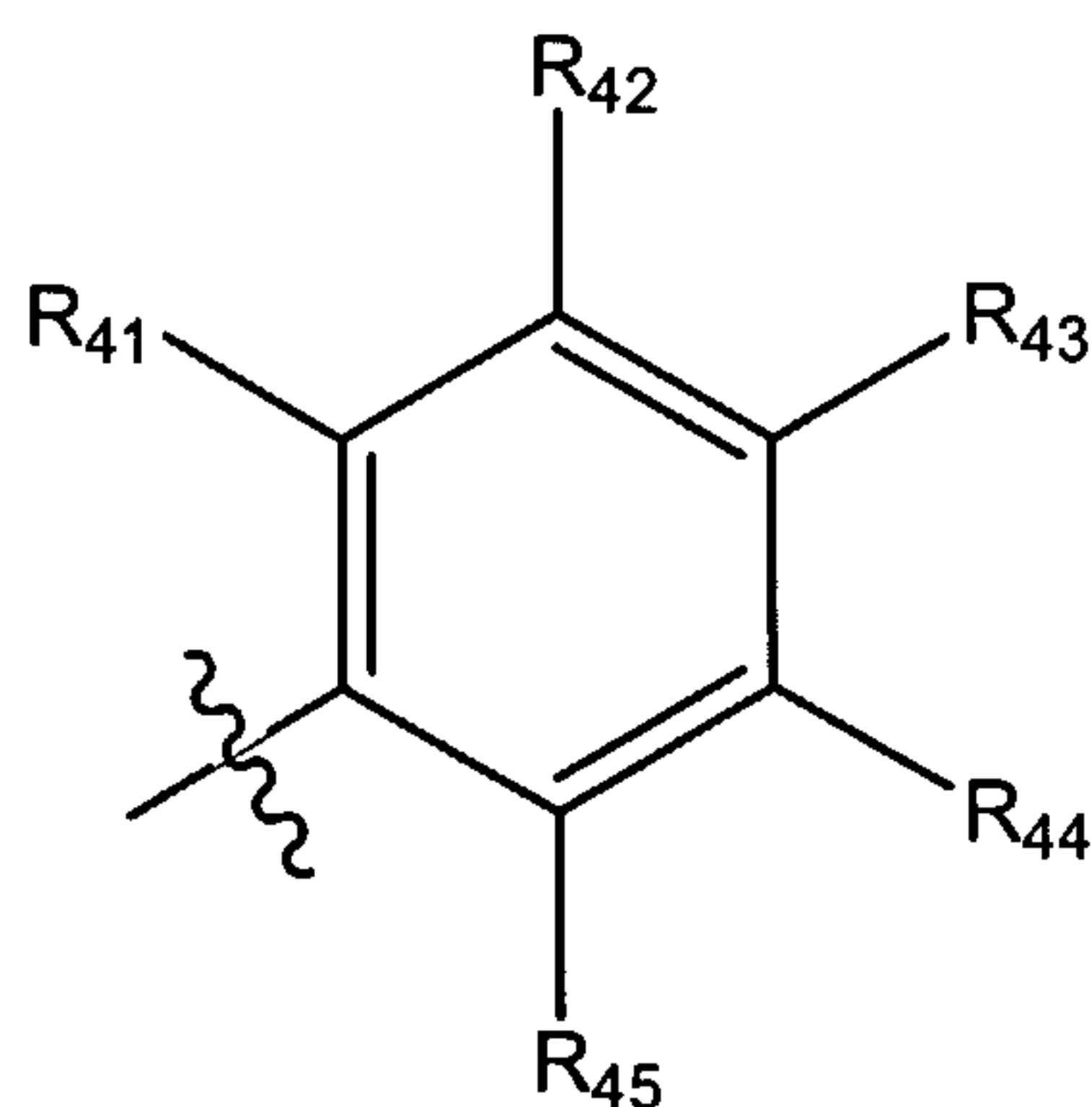
61. The compound of claim 1 having the structure:



n is 0 to 2.

137

64. The compound of claim 62 wherein Z_4 is



wherein:

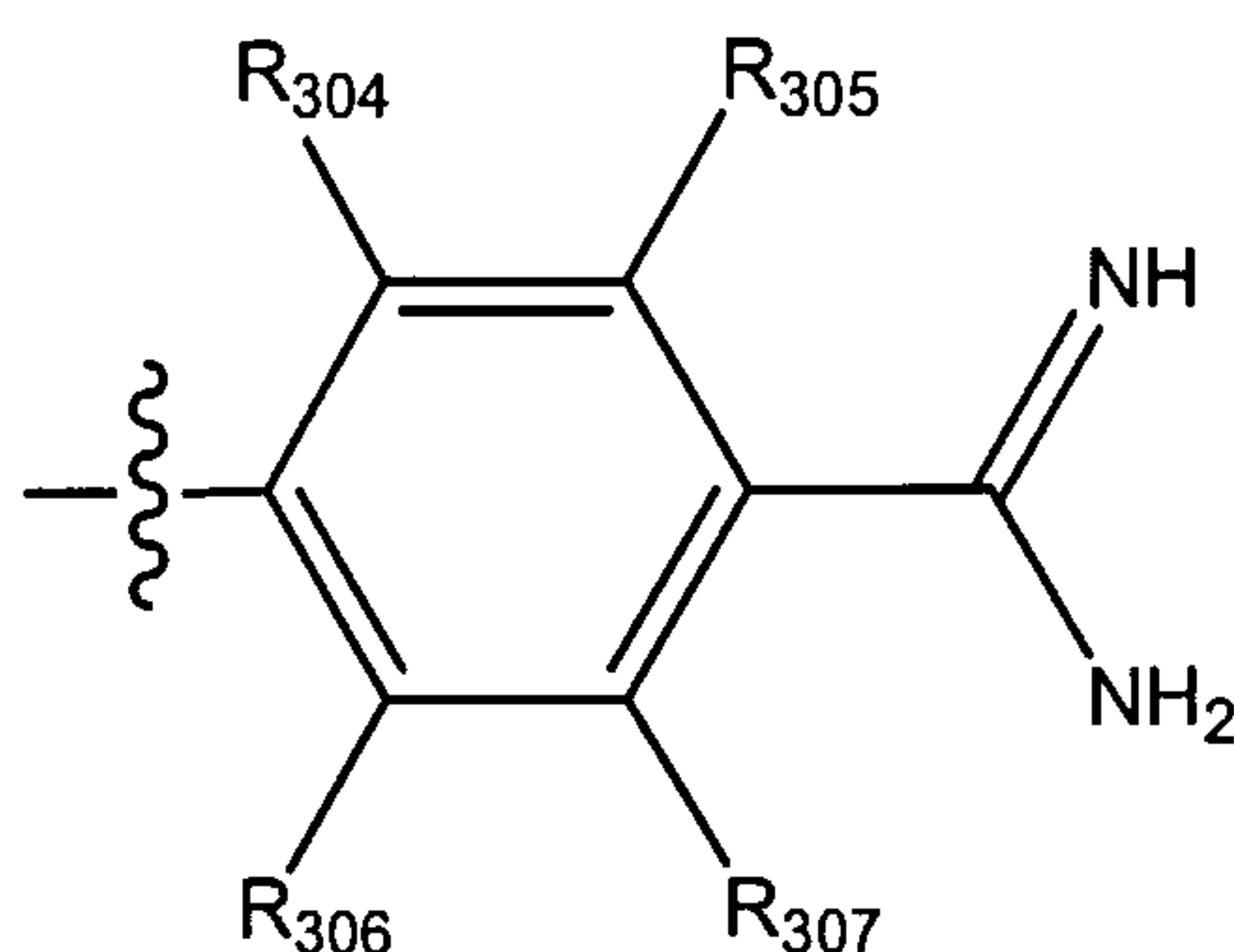
R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} , R_{43} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

65. The compound of claim 62 wherein Z_1 is methyl, ethyl, isopropyl, cyclopropyl, sec-butyl, tert-butyl, and cyclobutyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.

66. The compound of claim 62 wherein Z_3 is



wherein

R_{304} and R_{306} are independently selected from the group

R_{305} and R_{307} are independently selected from the group consisting of hydrogen, fluorine, methoxy, hydroxy, and carboxy.

N1C(=O)N(CCC(=O)N)C2CCN1C2

Z₁ is selected from the group consisting of an optionally substituted C₂ to C₈ alkyl, optionally substituted C₃ to C₆ cycloalkyl and optionally substituted phenyl;

Z_4 comprises a 5- or 6-membered heterocyclic or carbocyclic ring, the ring atoms of Z_4 being Z_{40} , Z_{41} , Z_{42} , Z_{44} and Z_{45} when Z_4 is a 5-membered ring and Z_{40} , Z_{41} , Z_{42} , Z_{43} , Z_{44} and Z_{45} when Z_4 is a 6-membered ring, Z_{40} , Z_{41} , Z_{42} , Z_{43} , Z_{44} and Z_{45} , being carbon, nitrogen, oxygen or sulfur, Z_{40} being the ring atom through which Z_4 is attached to the heterocyclic core ring, Z_{41} and Z_{45} each being in an alpha position relative to Z_{40} , Z_{42} and Z_{44} each being in a beta position relative to Z_{40} , Z_{43} being in the gamma position relative to Z_{40} when Z_4 is a 6-membered ring, Z_4 having a

substituent R_{42} covalently attached to Z_{42} , and a second substituent bonded to one of Z_{41} , Z_{43} , Z_{44} , or Z_{45} , the substituent being R_{41} when bonded to Z_{41} , the substituent being R_{43} when bonded to Z_{43} , the substituent being R_{44} when bonded to Z_{44} , and the substituent being R_{45} when bonded to Z_{45} ;

R_{42} is amino; and

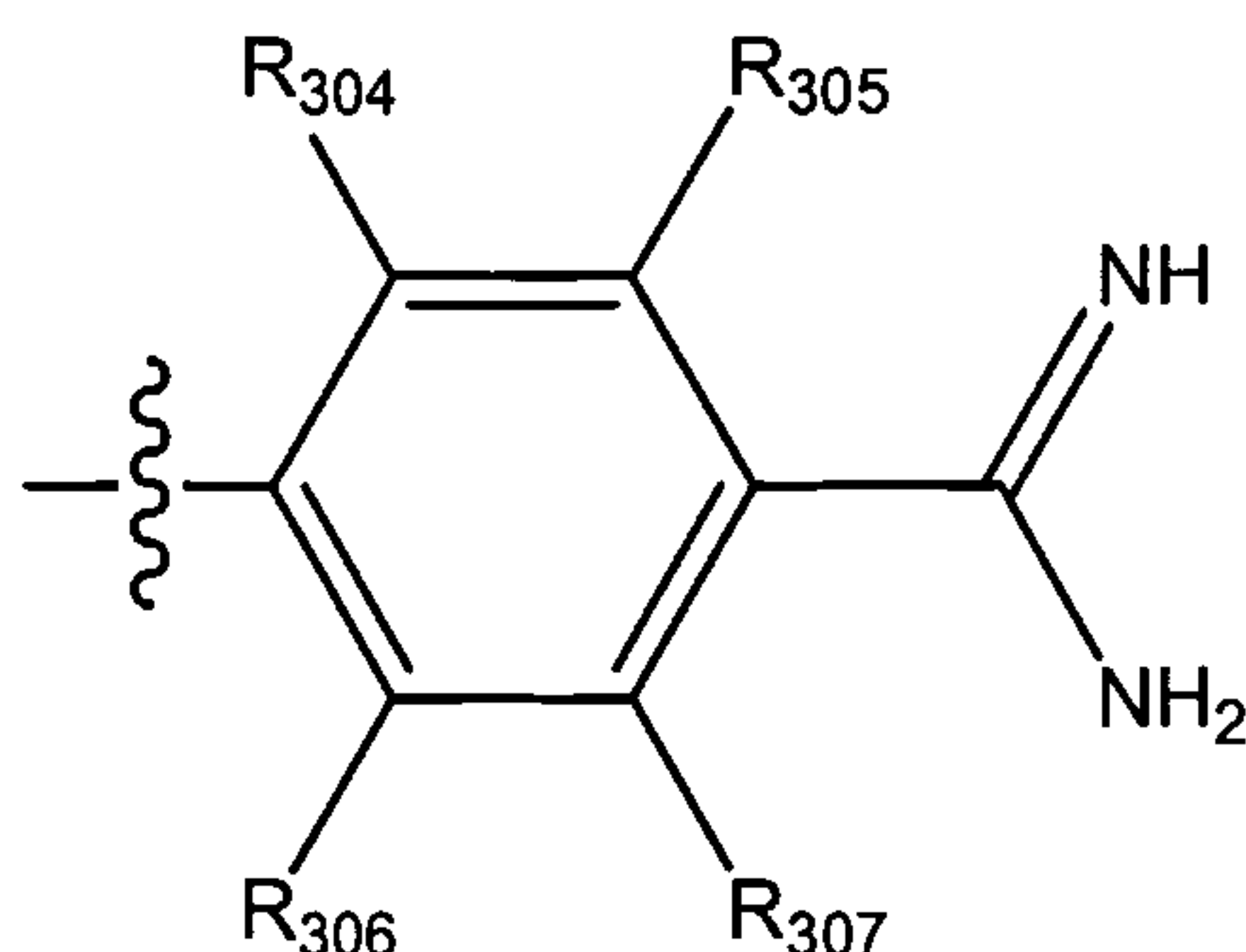
R_{41} , R_{43} , R_{44} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclo, halogen, or a substituted or unsubstituted heteroatom selected from nitrogen, oxygen, sulfur and phosphorus, provided at least one of R_{41} , R_{43} , R_{44} or R_{45} is other than hydrogen.

68. The compound of claim 67 wherein Z_1 is selected from the group consisting of cyclopropyl, isopropyl, methyl, ethyl, cyclobutyl, isobutyl, tert-butyl, sec-butyl, and phenyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.

69. The compound of claim 68 wherein Z_1 is cyclopropyl or isopropyl optionally substituted at any substitutable position with fluorine, hydroxy, carboxy or alkoxycarbonyl.

70. The compound of claim 67 wherein Z_3 comprises a substituted phenyl, thienyl, or furanyl ring, the phenyl, thienyl or furanyl ring being substituted with an amidine or a derivatized amidine group, and optionally further substituted at any substitutable position with fluorine, hydroxy, carboxy, alkoxycarbonyl, or hydrocarbyloxy.

71. The compound of claim 70 wherein Z_3 is



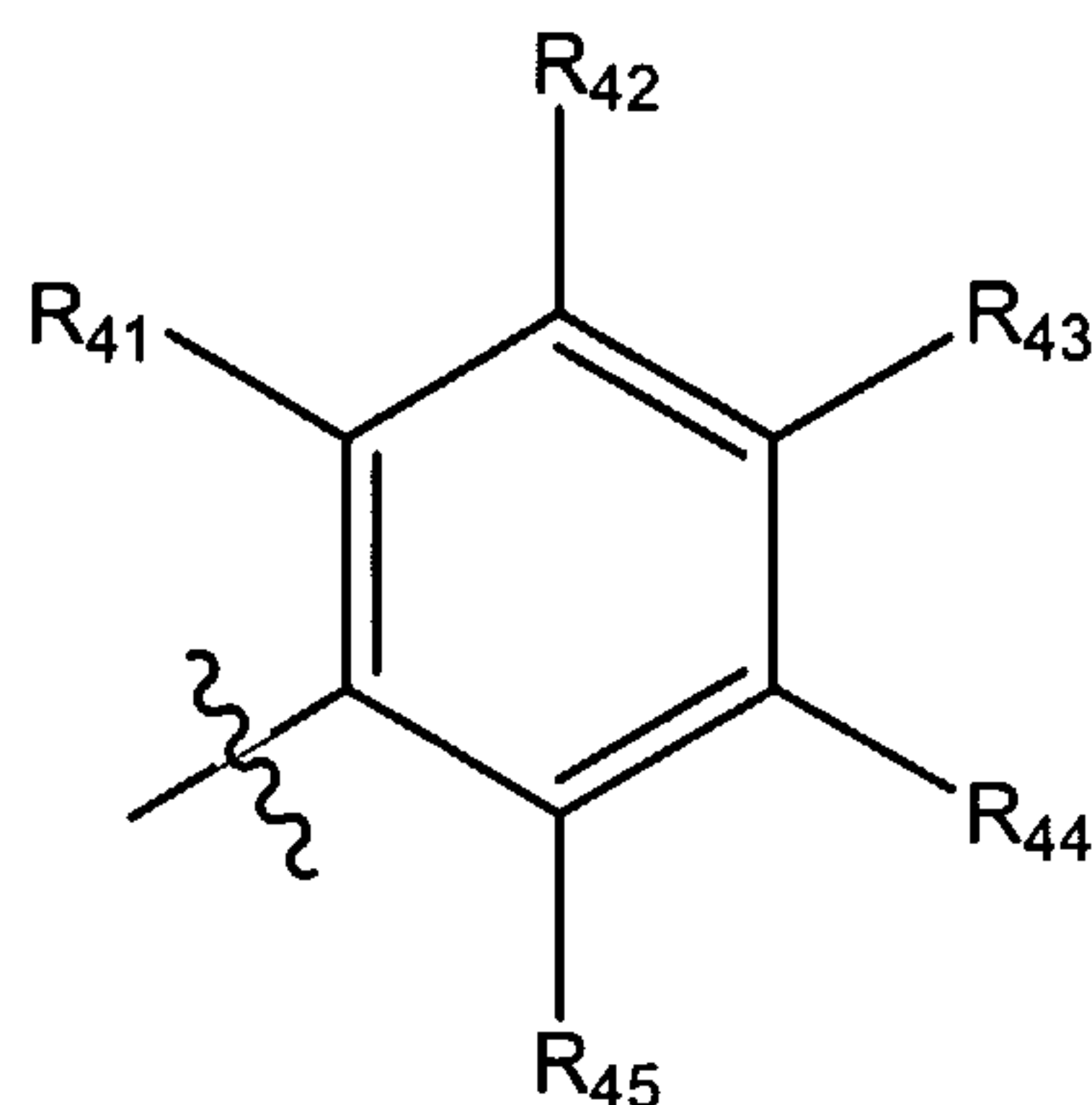
wherein

R_{304} and R_{306} are independently selected from the group consisting of hydrogen, fluorine, hydroxy, carboxy, hydrocarbyloxy and alkoxy carbonyl; and

R_{305} and R_{307} are independently selected from the group consisting of hydrogen, fluorine, methoxy, hydroxy and carboxy.

72. The compound of claim 70 wherein the 5- or 6-membered heterocyclic or aromatic ring comprising Z_3 is substituted with a derivatized amidine which, upon hydrolysis, oxidation, reduction or elimination, or any combination thereof, yields an amidine group.

73. The compound of claim 67 wherein Z_4 has the following structure:



wherein

R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

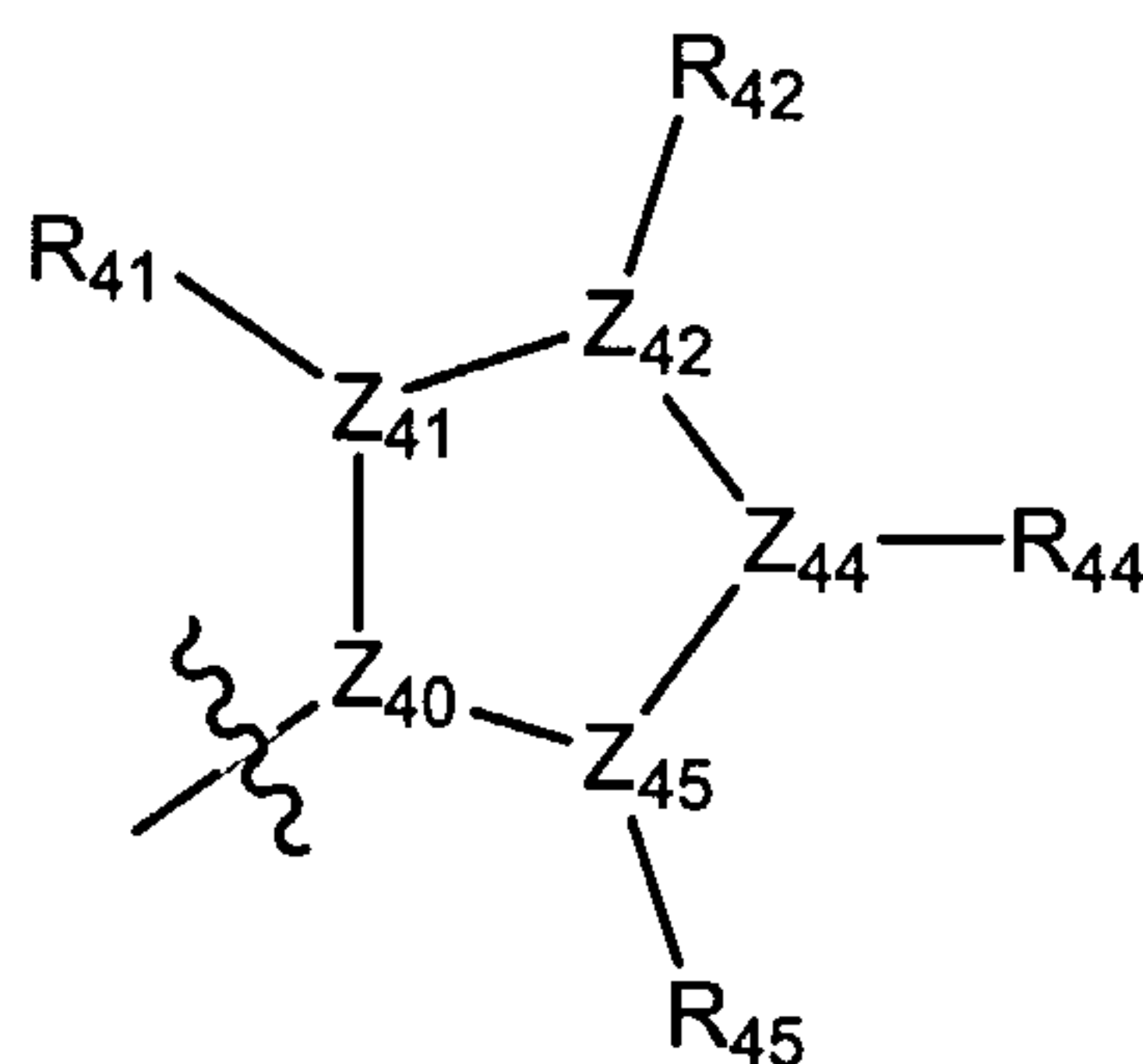
R_{41} , R_{43} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

74. The compound of claim 73 wherein R_{41} , R_{43} and R_{45} are independently hydrogen, halogen, alkoxy, or alkyl, optionally substituted with halogen or alkoxy and R_{42} and R_{44} are as defined in claim 73.

75. The compound of claim 73 wherein R_{44} is selected from the group consisting of hydroxy, carboxy, carboxamido, alkoxy, alkylsulfonyl, sulfonamido, or alkoxycarbonyl.

76. The compound of claim 75 wherein R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy.

77. The compound of claim 67 wherein Z_4 has the following structure:



wherein Z_{40} , Z_{41} , Z_{42} , Z_{44} , and Z_{45} are independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R_{42} is amino;

R_{44} is hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur; and

R_{41} and R_{45} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen or an optionally substituted heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur.

78. The compound of claim 77 wherein R_{41} and R_{45} are independently hydrogen, halogen, alkoxy, or alkyl, optionally substituted with halogen or alkoxy and R_{42} and R_{44} are as defined in claim 77.

79. The compound of claim 77 wherein R_{44} is selected from the group consisting of hydroxy, carboxy, carboxamido, alkoxy, alkylsulfonyl, sulfonamido, or alkoxycarbonyl.

80. The compound of claim 79 wherein R_{44} is sec-butylamide, carboxy, ethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isopropylamide or hydroxy.

81. A composition for substantially inhibiting thrombotic conditions in blood comprising a compound of claims 1 or 19 and a pharmaceutically acceptable carrier.

82. A method for substantially inhibiting thrombotic conditions in blood comprising adding to blood a therapeutically effective amount of the composition of claim 81.

83. A method for substantially inhibiting formation of blood platelet aggregates in blood comprising adding to blood a therapeutically effective amount of the composition of claim 81.

84. A method for substantially inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of the composition of claim 81.

85. A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

86. A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

87. A method for treating or preventing cardiogenic thromboembolism in a mammal comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

88. A method for treating or preventing thromboembolic stroke in mammals comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

89. A method for treating or preventing thrombosis associated with cancer and cancer chemotherapy in mammals comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

90. A method for treating or preventing unstable angina in mammals comprising administering to the mammal a therapeutically effective amount of the composition of claim 81.

91. A method for substantially inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of the composition of claim 81 with a therapeutically effective amount of fibrinogen receptor antagonist.

92. The method of any of claims 85-91 wherein the mammal is a human.