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Methods for minimizing the formation of thioamide compounds using decoy agents during reactions, such as thionations of carbonyl compounds containing nitrile groups, are provided.



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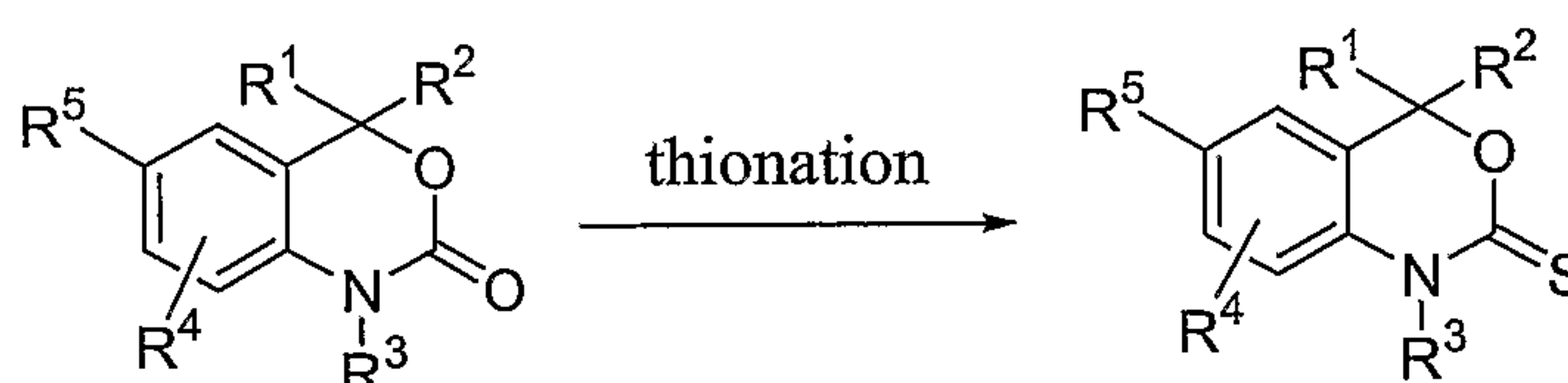
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METHODS FOR MINIMIZING THIOAMIDE IMPURITIES

BACKGROUND OF THE INVENTION

Progesterone receptor modulators can be prepared by thionation of carbonyl
5 compounds. The thionation of benzoxazin-2-ones using either 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) or phosphorous pentasulfide is known (US Patent No. 6,436,929). See, Scheme 1.

Scheme 1



10 Such compounds are useful for contraception, hormone replacement therapy, synchronization of estrus, and in the treatment of conditions including hormone neoplastic diseases, adenocarcinomas, and carcinomas.

However, certain impurities formed during thionation are difficult to remove. What is needed in the art are methods for reducing or eliminating the formation of
15 impurities.

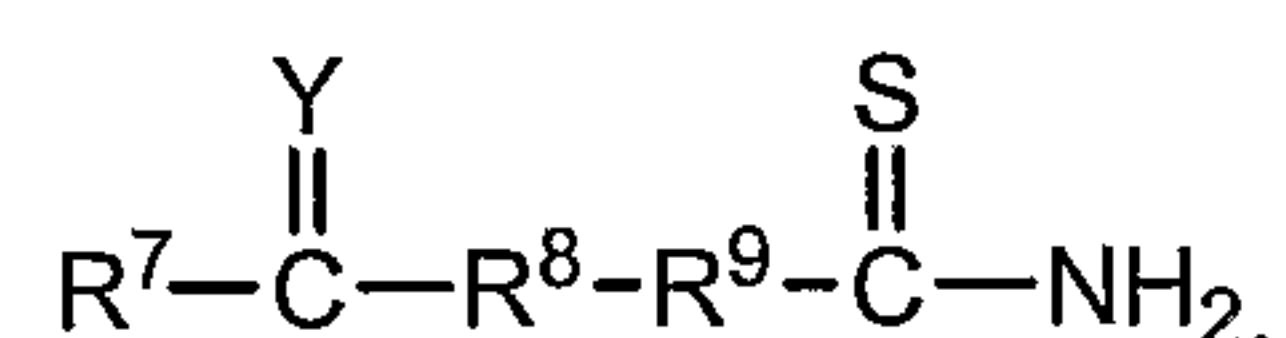
SUMMARY OF THE INVENTION

In one aspect, the present invention provides methods for preventing, reducing or minimizing the formation of thioamide impurities.

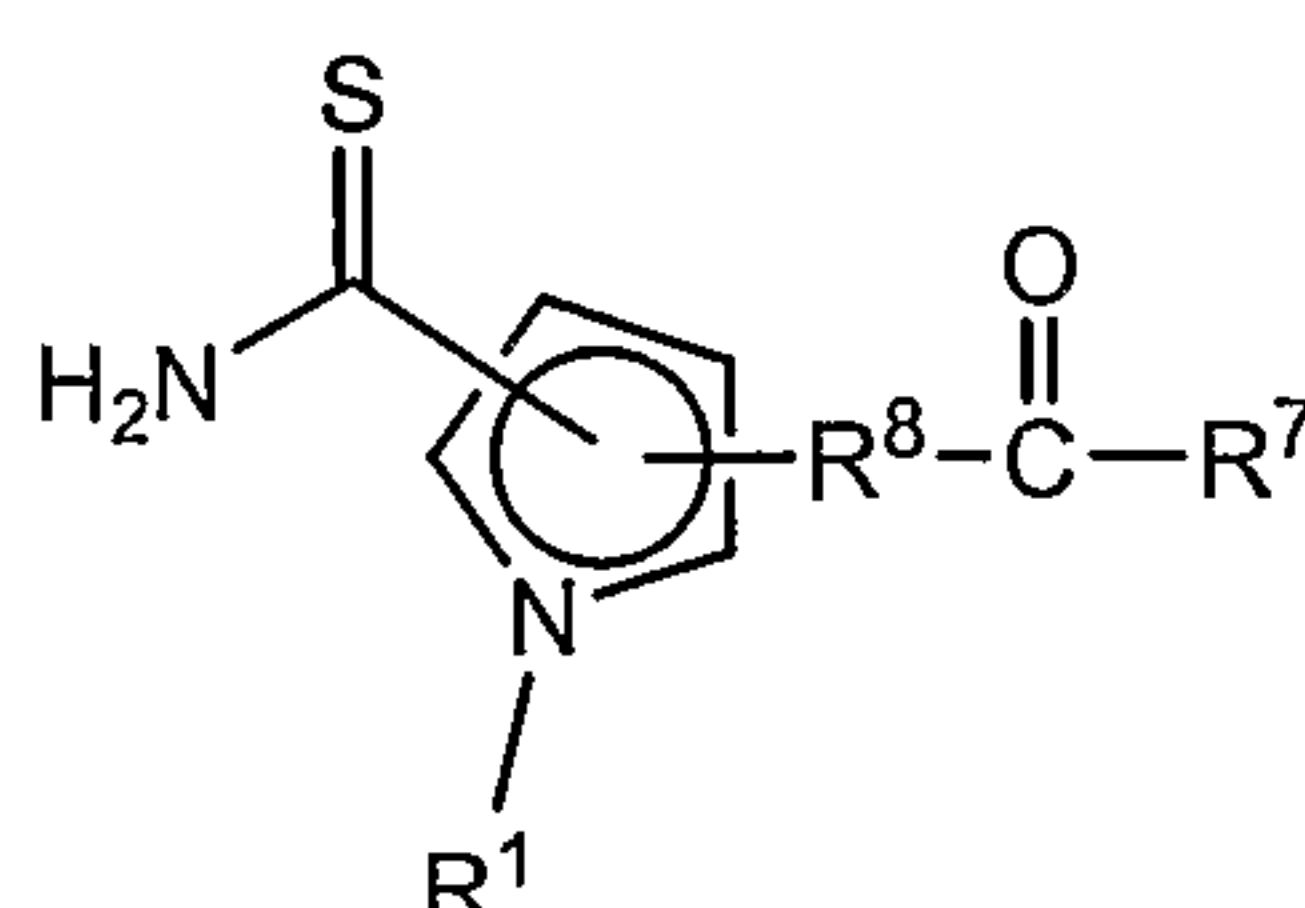
20 In another aspect, the present invention provides methods for preventing, reducing or minimizing the formation of thioamide impurities using a decoy agent.

In a further aspect, the present invention provides methods for preventing, reducing or minimizing the formation of thioamide impurities during thionation of a carbonyl compound comprising a nitrile group.

25 In yet another aspect, the present invention provides methods for preventing the formation of thioamide impurities of the structure, wherein Y, R⁷-R⁹ are defined below:

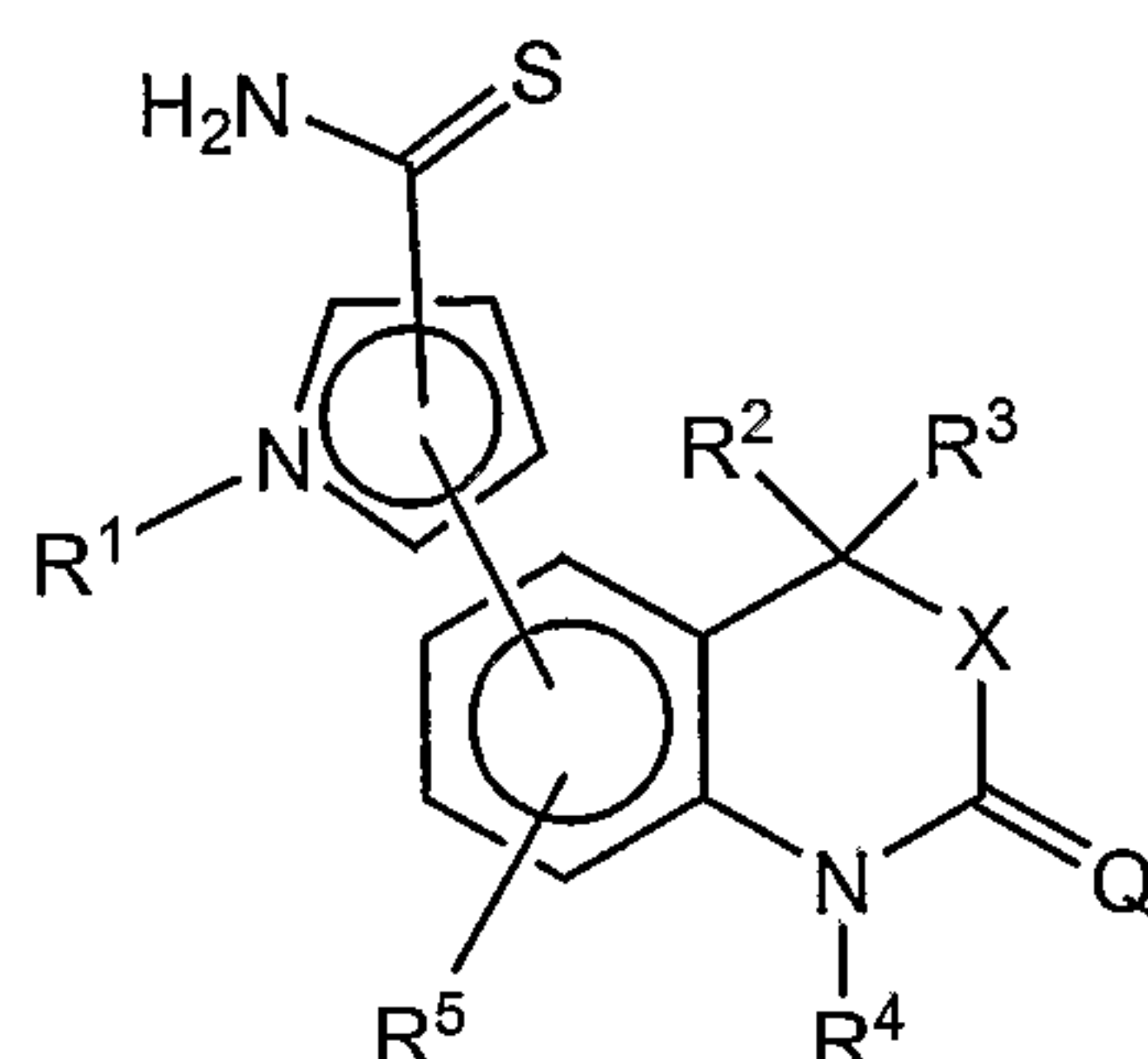


In still a further aspect, the present invention provides methods for preventing the formation of thioamide impurities of the structure, wherein R^1 , R^7 , and R^8 are defined below:



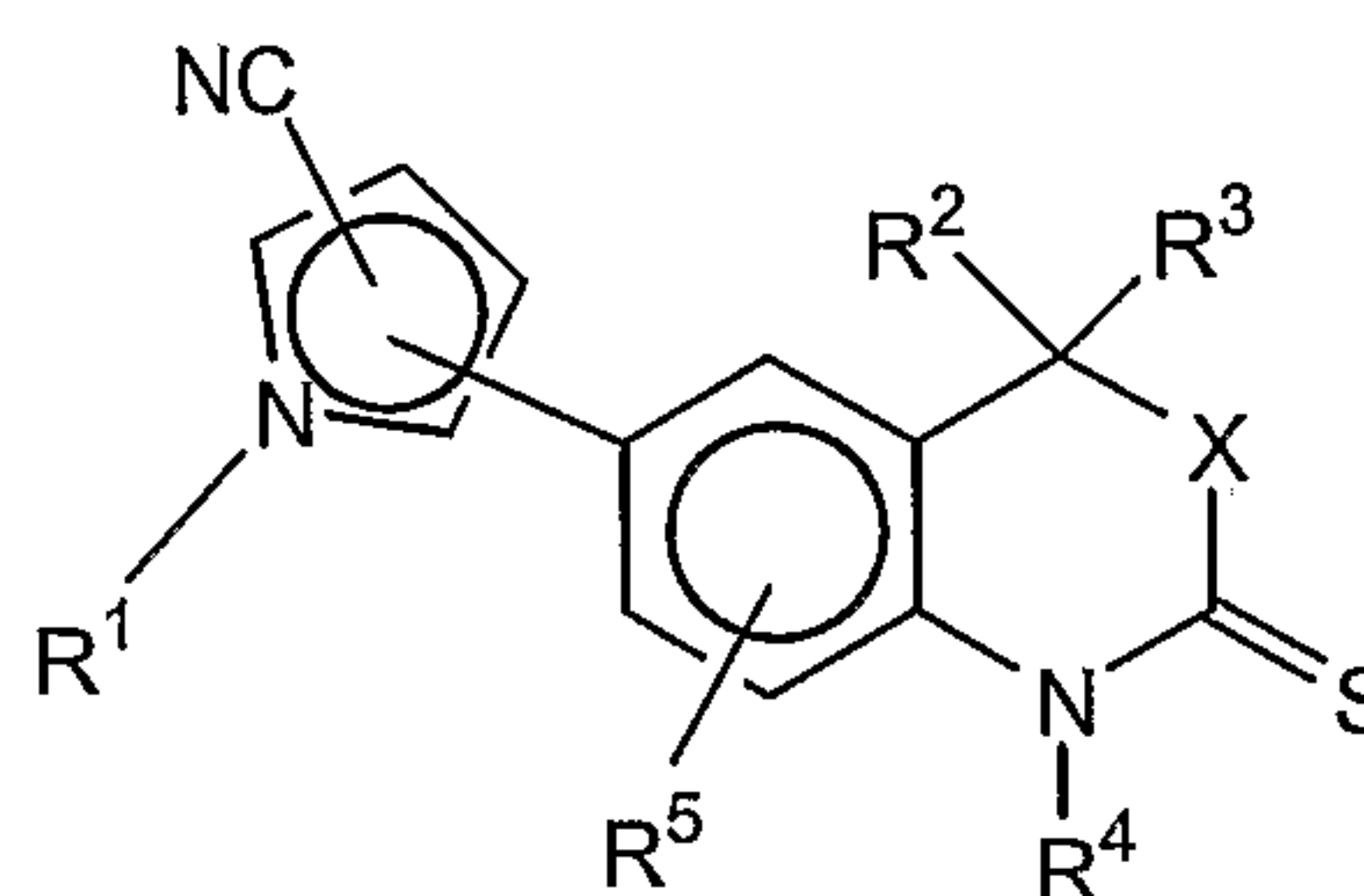
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In another aspect, the present invention provides methods for preventing the formation of thioamide impurities of the structure, wherein R^1 - R^5 are defined below:



10

In another aspect the invention provides for the use of a decoy agent containing a nitrile group in a method for preparing a compound having the formula:



wherein:

R^1 is C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

15

R^2 and R^3 are, independently, H, C_1 to C_6 alkyl, or substituted C_1 to C_6 alkyl;

or R^2 and R^3 are fused to form a ring comprising $-CH_2(CH_2)_nCH_2-$,

$-CH_2CH_2C(CH_3)_2CH_2CH_2-$, $-O(CH_2)_pCH_2-$, $-O(CH_2)_qO-$, $-CH_2CH_2OCH_2CH_2-$, or

$-CH_2CH_2NR^6CH_2CH_2-$;

n is 1 to 5;

p is 1 to 4;

q is 1 to 4;

R^4 is H, OH, NH_2 , CN, halogen, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, or substituted C_2 to C_6 alkynyl;

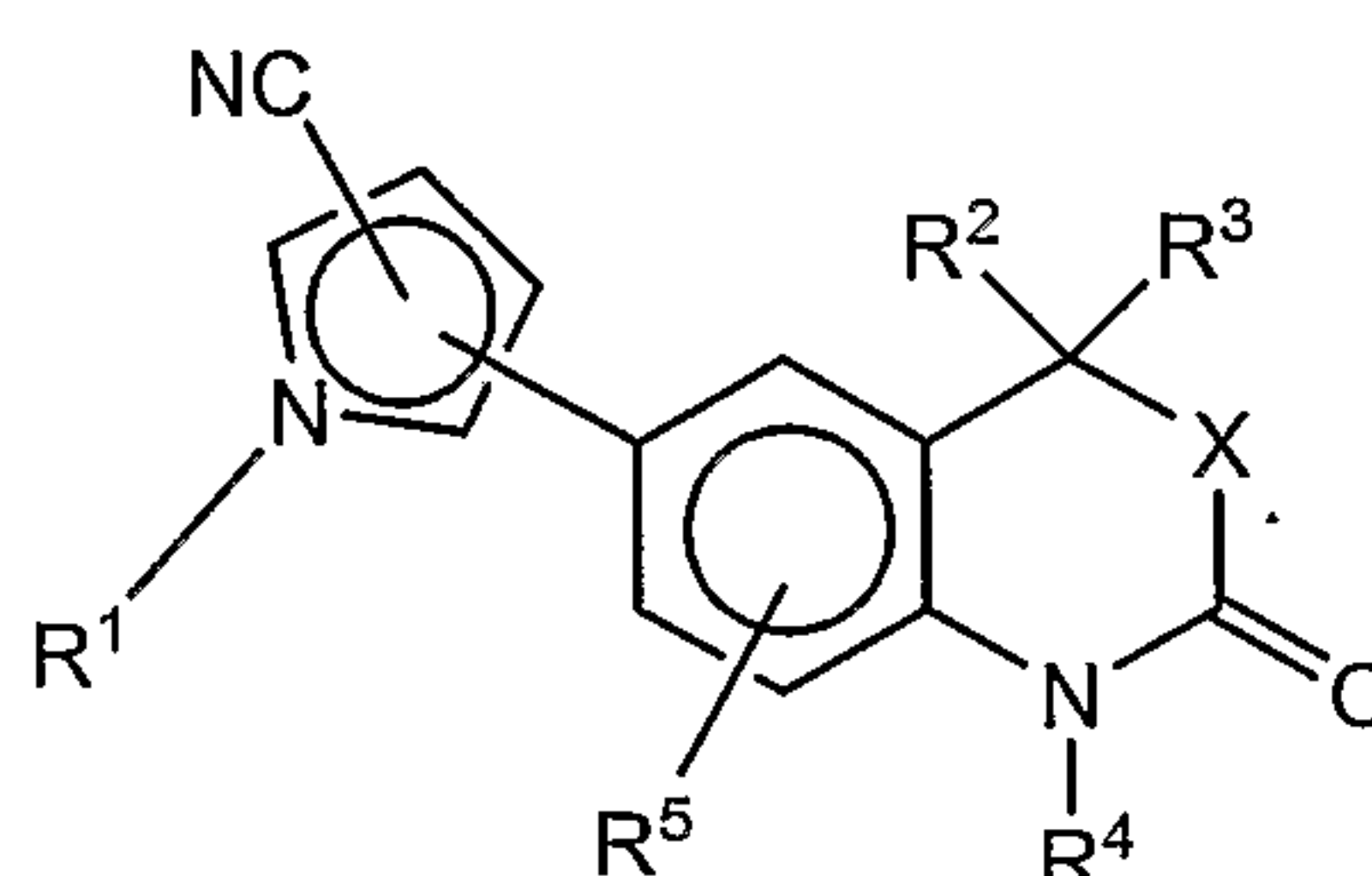
R^5 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^6 is H or C_1 to C_6 alkyl;

X is O, S, or absent;

or a pharmaceutically acceptable salt thereof;

the method comprising reacting a thionating agent with a carbonyl compound having the formula



wherein R^1 – R^6 , n, p, q, and X are as defined above;

wherein the decoy agent prevents or reduces thionation of the one or more nitrile groups present in the carbonyl compound.

The thionating agent may be selected from the group consisting of hydrogen sulfide, Lawesson's reagent, phosphorus pentasulfide, and diethyldithiophosphate.

The decoy agent may be an aryl nitrile selected from the group consisting of benzonitrile, p-chlorobenzonitrile, p-ethoxybenzonitrile, p-methoxybenzonitrile, o-nitrobenzonitrile, p-acetylbenzonitrile, p-methylbenzonitrile, p-fluorobenzonitrile, and 1,3-dicyanobenzene.

Alternatively the decoy agent may be a heteroaryl nitrile selected from the group consisting of N-methyl-2-pyrrolicarbonitrile, 2-thiophenecarbonitrile, 2-cyanopyridine, 3-cyanopyridine and 4-cyanopyridine.

The decoy agent may alternatively be an aliphatic nitrile selected from the group consisting of acetonitrile, propionitrile, butyronitrile, isobutyronitrile, chloroacetonitrile, trichloroacetonitrile and malononitrile.

In one embodiment the molar ratio of said decoy agent to said carbonyl
5 compound is greater than 1:1.

In a further embodiment the thionation reaction can be carried out in a solvent selected from the group consisting of tetrahydrofuran, 1,2-dimethoxyethane, methylene chloride, and toluene.

Other aspects and advantages of the present invention are described further in
10 the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for minimizing the formation of thioamide compounds using decoy agents. Specifically, the present invention
15 provides methods for adding decoy agents to avoid undesirable side reactions.

I. Definitions

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having 1 to about 10 carbon atoms, and
20 desirably 1 to about 8 carbon atoms. The term "alkenyl" is used herein to refer to both straight- and branched-chain alkyl groups having one or more carbon-carbon double bonds and containing about 2 to about 10 carbon atoms. Desirably, the term alkenyl refers to an alkyl group having 1 or 2 carbon-carbon double bonds and having 2 to about 6 carbon atoms. The term "alkynyl" group is used herein to refer to both
25 straight- and branched-chain alkyl groups having one or more carbon-carbon triple bond and having 2 to about 8 carbon atoms. Desirably, the term alkynyl refers to an alkyl group having 1 or 2 carbon-carbon triple bonds and having 2 to about 6 carbon atoms.

The term "cycloalkyl" is used herein to refer to an alkyl group as previously
30 described that is cyclic in structure and has about 4 to about 10 carbon atoms, and desirably about 5 to about 8 carbon atoms.

The terms “substituted alkyl”, “substituted alkenyl”, “substituted alkynyl”, and “substituted cycloalkyl” refer to alkyl, alkenyl, alkynyl, and cycloalkyl groups, respectively, having one or more substituents the same or different including, without limitation, halogen, CN, OH, NO₂, amino, aryl, heterocyclic, alkoxy, aryloxy, alkylcarbonyl, alkylcarboxy, and arylthio which groups are optionally substituted. These substituents can be attached to any carbon of an alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term “aryl” as used herein as a group or part of a group refers to an aromatic system which can include a single ring or multiple aromatic rings fused or linked together where at least one part of the fused or linked rings forms the conjugated aromatic system e.g. having 6 to 14 carbon atoms. The aryl groups can include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl, indene, benzonaphthyl, fluorenyl, and carbazolyl.

The term “substituted aryl” refers to an aryl group which is substituted with one or more substituents the same or different including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkyloxy, alkylcarbonyl, alkylcarboxy, aminoalkyl, and arylthio, which groups can be optionally substituted. Desirably, a substituted aryl group is substituted with 1, 2, 3 or 4 substituents.

The term “heterocyclic” or “heteroaryl” as used herein refers to a stable 4- to 10-membered monocyclic or multicyclic heterocyclic ring which is saturated, partially unsaturated, or wholly unsaturated. The heterocyclic ring has carbon atoms and one or more heteroatoms including nitrogen, oxygen, and sulfur atoms. Desirably, the heterocyclic ring has 1 to about 4 heteroatoms in the backbone of the ring. When the heterocyclic ring contains nitrogen or sulfur atoms in the backbone of the ring, the nitrogen or sulfur atoms can be oxidized. The term “heterocyclic” also refers to multicyclic rings in which a heterocyclic ring is fused to an aryl ring e.g. of 6 to 14 carbon atoms. The heterocyclic ring can be attached to the aryl ring through a heteroatom or carbon atom provided the resultant heterocyclic ring structure is chemically stable.

A variety of heterocyclic or heteroaryl groups are known in the art and include, without limitation, oxygen-containing rings, nitrogen-containing rings, sulfur-containing rings, mixed heteroatom-containing rings, fused heteroatom

containing rings, and combinations thereof. Oxygen-containing rings include, but are not limited to, furyl, tetrahydrofuranyl, pyranyl, pyronyl, and dioxinyl rings.

Nitrogen-containing rings include, without limitation, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, piperidiny, 2-oxopiperidiny, pyridazinyl, pyrimidinyl, pyrazinyl,

5 piperazinyl, azepinyl, triazinyl, pyrrolidinyl, and azepinyl rings. Sulfur-containing rings include, without limitation, thienyl and dithiolyl rings. Mixed heteroatom containing rings include, but are not limited to, oxathiolyl, oxazolyl, thiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxazinyl, oxathiazinyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, oxepinyl, thiepinyl, and
10 diazepinyl rings. Fused heteroatom-containing rings include, but are not limited to, benzofuranyl, thionaphthene, indolyl, benazazolyl, purindinyl, pyranopyrrolyl, isoindazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzopyranyl, quinolinyl, isoquinolinyl, benzodiazonyl, naphthylridinyl, benzothieryl, pyridopyridinyl, benzoxazinyl, xanthenyl, acridinyl, and purinyl rings.

15 The term “substituted heterocyclic” or “substituted heteroaryl” as used herein refers to a heterocyclic group having one or more substituents the same or different including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkyloxy, alkylcarbonyl, alkylcarboxy, aminoalkyl, and arylthio, which groups can be optionally substituted. Desirably, a substituted heterocyclic group is
20 substituted with 1, 2, 3 or 4 substituents.

The term “alkoxy” as used herein refers to the O(alkyl) group, where the point of attachment is through the oxygen-atom and the alkyl group is optionally substituted.

25 The term “aryloxy” as used herein refers to the O(aryl) group, where the point of attachment is through the oxygen-atom and the aryl group is optionally substituted.

The term “alkyloxy” includes hydroxyalkyl and as used herein refers to the alkylOH group, where the point of attachment is through the alkyl group.

30 The term “arylthio” as used herein refers to the S(aryl) group, where the point of attachment is through the sulfur-atom and the aryl group can be optionally substituted.

The term "alkylcarbonyl" as used herein refers to the C(O)(alkyl) group, where the point of attachment is through the carbon-atom of the carbonyl moiety and the alkyl group is optionally substituted.

The term "alkylcarboxy" as used herein refers to the C(O)O(alkyl) group, where the point of attachment is through the carbon-atom of the carboxy moiety and the alkyl group is optionally substituted.

The term "aminoalkyl" includes alkylamino and as used herein refers to both secondary and tertiary amines where the point of attachment is through the nitrogen-atom and the alkyl groups are optionally substituted. The alkyl groups can be the same or different.

The term "thioalkoxy" or "thioalkyl" as used herein refers to the S(alkyl), where the point of attachment is through the sulfur-atom and the alkyl group is optionally substituted.

The term "halogen" as used herein refers to Cl, Br, F, or I groups.

The term "amide" as used herein refers to the C(O)NH₂ group, where the point of attachment is through the carbon-atom. Similarly, the term "thioamide" as used herein refers to a C(S)NH₂ substituent.

The term "nitrile" or "cyano" as used herein refers to a CN group.

The term "ketone" as used herein refers to the C(O) group, where the points of attachment are through the carbon-atom. Similarly, the term "aldehyde" as used herein refers to the C(O)H, where the point of attachment is through the carbon-atom.

The term "lactone" as used herein refers to a ring having an ester moiety in the backbone of the ring. The lactone ring can be optionally substituted with any substituent that forms a stable bond to the ring.

The terms "carbamate" and "urethane" are used herein interchangeably to refer to a N-C(O)O group, where the point of attachments are through the nitrogen and oxygen atoms.

The term "carbonate" is used herein to refer to a O-C(O)-O group.

The term "enone" is used therein to refer to a molecule that contains an alkene group, i.e., -C=C-, and a ketone group. Desirably, the enone is C=C-C(O), where the point of attachments are through the carbon-atom of the alkene and the carbon-atom of the carbonyl.

The term “enaminone” is used herein to refer to a molecule that contains the -N-C=C-C(O) group, where the point of attachments are through the carbon-atom of the alkene and the carbon-atom of the carbonyl.

The term “purified” or “pure” as used herein refers to a compound that contains less than about 10% impurity. Desirably, the term “purified” or “pure” refers to a compound that contains less than about 5% impurity, more desirably, less than about 2% impurity, and most desirably less than 1% impurity. The term “purified” or “pure” can also refer to a compound that contains about 0% impurity. In one embodiment, the impurity is a thioamide.

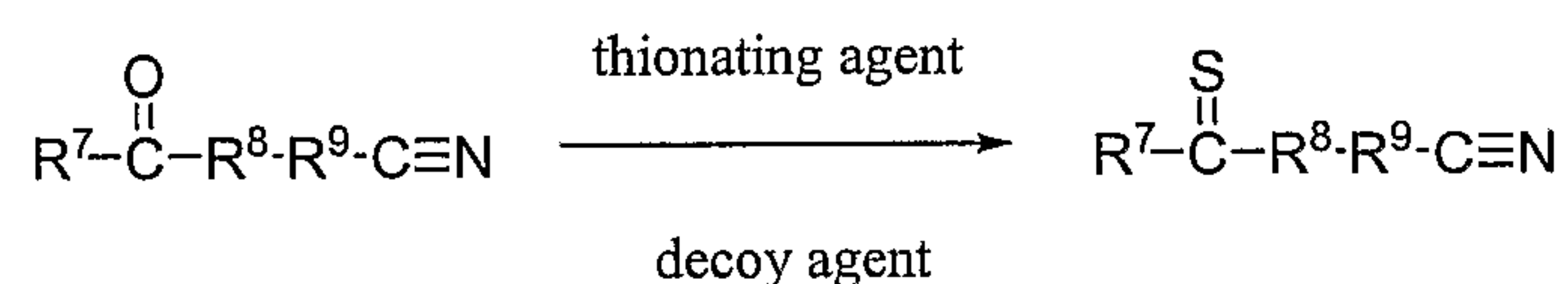
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II. The Decoy Agent

Methods are provided for preventing or minimizing the formation of impurities such as thioamides. Desirably, the present invention provides methods for preventing or minimizing the formation of thioamide impurities during thionations of carbonyl compounds containing nitrile groups. The method utilizes a decoy agent containing a nitrile group. See, Scheme 2.

15

Scheme 2

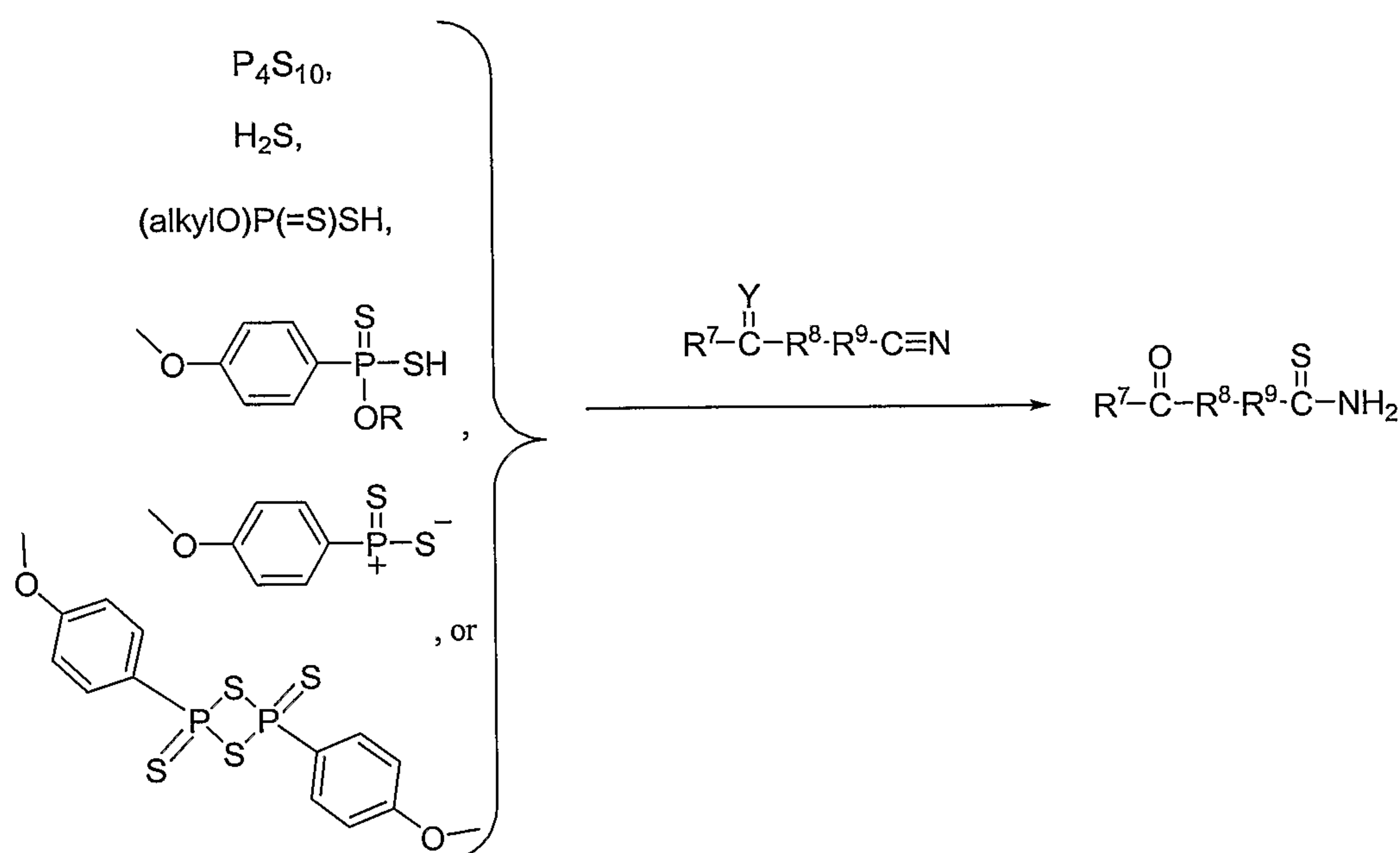


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Without wishing to be bound by theory, the inventors have hypothesized that thioamide impurities are formed by addition of hydrogen sulfide (H₂S), a H₂S by-product, or a dithiaphosphetane by-product such as a Lawesson’s reagent by-product, among others, to a nitrile moiety. See, Scheme 3. Therefore, the inventors have found that the addition of a decoy agent in the reaction mixture that prevents or minimizes the formation of the thioamide impurity is advantageous.

25

Scheme 3



The decoy agent used in the present invention competes with the nitrile
 5 substituent of the carbonyl compound during thionation. In one embodiment, the
 decoy agent competes with the nitrile substituent for reaction with H_2S , an H_2S by-
 product formed during the reaction, or a Lawesson's agent by-product formed during
 thionation of a carbonyl compound having a nitrile compound attached thereto.
 However, the decoy agent desirably reacts only minimally or does not react with
 10 actual thionating reagent.

The term "decoy agent" as used herein is distinguishable from "scavengers",
 "trapping agents" or "mopping reagents". As known to those of skill in the art,
 scavengers, trapping agents or mopping reagents are used to remove excess reagents,
 products, or other formed impurities. For example, H_2S can be scavenged with lead
 15 acetate, trapped with molecular sieves, or mopped with water. A decoy agent,
 however, is intentionally added to redirect any side reactions and is a sacrificial
 reagent which protects the product from being a source of a contaminant.

One of skill in the art would readily be able to select a suitable decoy agent
 depending on the reaction conditions, cost of decoy agent, reactivity of the decoy
 20 agent, reactivity of the carbonyl compound, and reactivity of the carbonyl group of

the carbonyl compound. Desirably, the decoy agent is similar in structure to the nitrile group of the carbonyl compound.

Electron withdrawing substituents attached to the decoy agent can increase the reactivity of the decoy agent, and specifically, the reactivity of a nitrile group on the
5 decoy agent. Desirably, the electron withdrawing substituent includes a halogen, and more desirably chlorine. Desirably, the decoy agent is chloroacetonitrile (ClCH_2CN), trichloroacetonitrile, or 1,3-dicyanobenzene.

In one embodiment, the carbonyl compound contains a very reactive carbonyl group and a less reactive nitrile group, whereby the carbonyl group easily reacts with
10 the thionating compound. In this case, a less reactive decoy agent can be utilized during the thionation reaction to prevent formation of the thioamide impurity. However, more reactive decoy agents can be utilized with reactive carbonyl compounds. Typically, acetonitrile is utilized if the carbonyl group of the carbonyl compound easily reacts with the thionating agent.

15 In another embodiment, the carbonyl compound contains a reactive carbonyl group and a reactive nitrile group. In this case, a moderately reactive decoy agent can be utilized during the thionation reaction to prevent formation of the thioamide impurity. Typically, moderately reactive decoy agents such as benzonitrile, p-chlorobenzonitrile, p-methylbenzonitrile, 1,3-dicyanobenzene, 3- and 4-
20 cyanopyridines and malononitrile can be utilized.

In a further embodiment, the carbon-containing compound contains a less reactive carbonyl group and a highly reactive nitrile. In this case, a highly reactive decoy agent can be utilized during the thionation reaction to prevent formation of the thioamide impurity. Typically, highly reactive decoy agents such as N-methyl-2-
25 pyrrolicarbonitrile, 2-thiophenecarbonitrile, 2-cyanopyridine, chloroacetonitrile and trichloroacetonitrile can be utilized.

Examples of decoy agents that can be used according to the present invention include, without limitation, aryl nitriles including benzonitrile, p-chlorobenzonitrile, p-ethoxybenzonitrile, p-methoxybenzonitrile, o-nitrobenzonitrile, p-
30 acetylbenzonitrile, p-methylbenzonitrile, p-fluorobenzonitrile, and 1,3-dicyanobenzene; aliphatic nitriles such as acetonitrile (CH_3CN), propionitrile, butyronitrile, isobutyronitrile, chloroacetonitrile, trichloroacetonitrile and

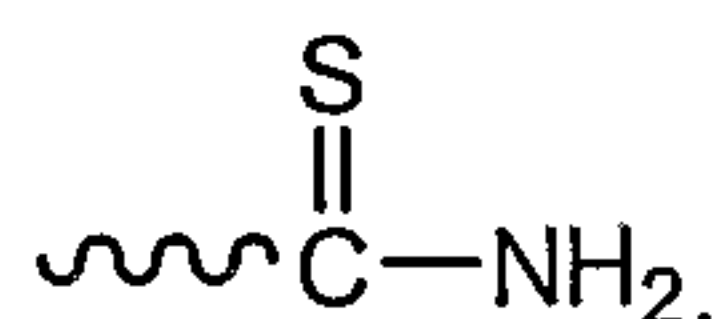
malononitrile; a nitrile compound having one or more electron withdrawing substituents; or heteroaryl nitriles including N-methyl-2-pyrrolicarbonitrile, 2-thiophenecarbonitrile, and 2-cyanopyridine. However, while some decoy agents may be utilized, it may be cost-prohibitive for the use thereof. For example, CH₃CN is an inexpensive, low-boiling, common reagent with twice the moles of nitrile groups as compared to N-methyl-2-pyrrolicarbonitrile. Further, while 2-thiophenecarbonitrile is twice as reactive as benzonitrile, it is considerably more expensive. More desirably, the decoy agent is similar in structure to N-methyl-2-pyrrolicarbonitrile and is acetonitrile or 2-thiophenecarbonitrile.

A molar excess of the decoy agent is typically added to the reaction mixture, where the reaction mixture contains a compound having a nitrile moiety, *i.e.*, moles of decoy agent are greater than moles of nitrile compound. However, less than a 1:1 ratio of decoy agent to the compound having a nitrile moiety, *i.e.*, moles of decoy agent are less than moles of nitrile compound, can also be utilized. In one embodiment, greater than an about 10 molar excess of decoy agent is utilized. In another embodiment, greater than an about 20 molar excess; in a further embodiment, greater than an about 40 molar excess; and in still another embodiment, greater than a 100 molar excess of decoy agent is utilized. In one embodiment, the decoy agent can be utilized as the solvent. One of skill in the art would readily be able to determine the amount of decoy agent required depending on the reaction being performed, reagents utilized, and reactivity of the decoy agent.

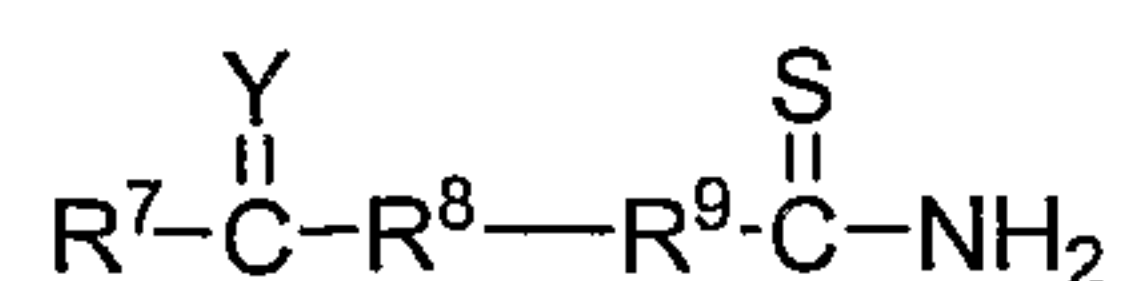
III. The Method of the Invention

The present invention thereby provides methods for preventing or minimizing the formation of thioamide impurities. Typically, the thioamide impurities formed according to the present invention include thioamide groups attached at any location on the backbone of the thioamide molecule.

In one embodiment, the thioamide impurity contains a thioamide group of the structure:

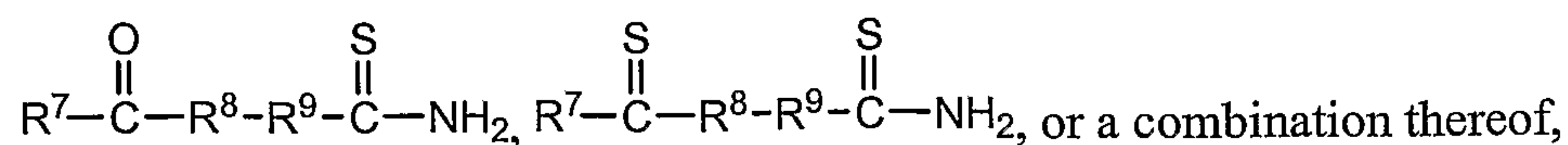


In another embodiment, the thioamide impurity is of the structure:



wherein Y is O or S; R⁷ is H, NH₂, NHR¹⁰, N(R¹⁰)₂, C(O)R¹⁰, C(S)R¹⁰, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R⁸ is C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or R⁷ and R⁸ are fused to form (i) a saturated carbon-based 4 to 8 membered ring; (ii) an unsaturated carbon-based 4 to 8 membered ring; or (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from among O, N, and S; wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from among H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁ to C₆ aminoalkyl, and substituted C₁ to C₆ aminoalkyl; R⁹ is absent, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R¹⁰ is selected from among H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, NH₂, NHR¹¹, and N(R¹¹)₂; and R¹¹ is selected from among H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, and NH₂.

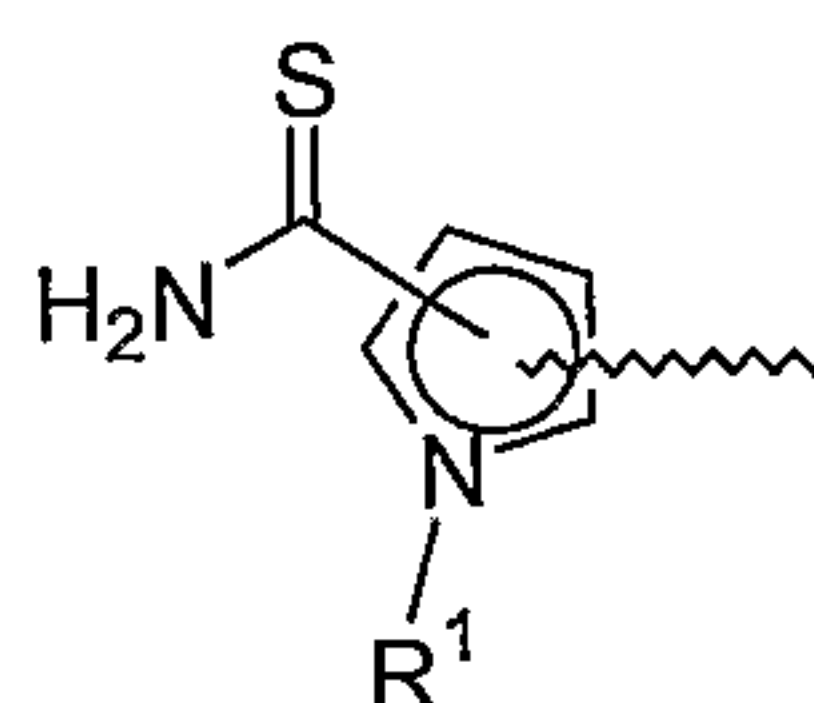
In a further embodiment, the thioamide impurity is of the structure:



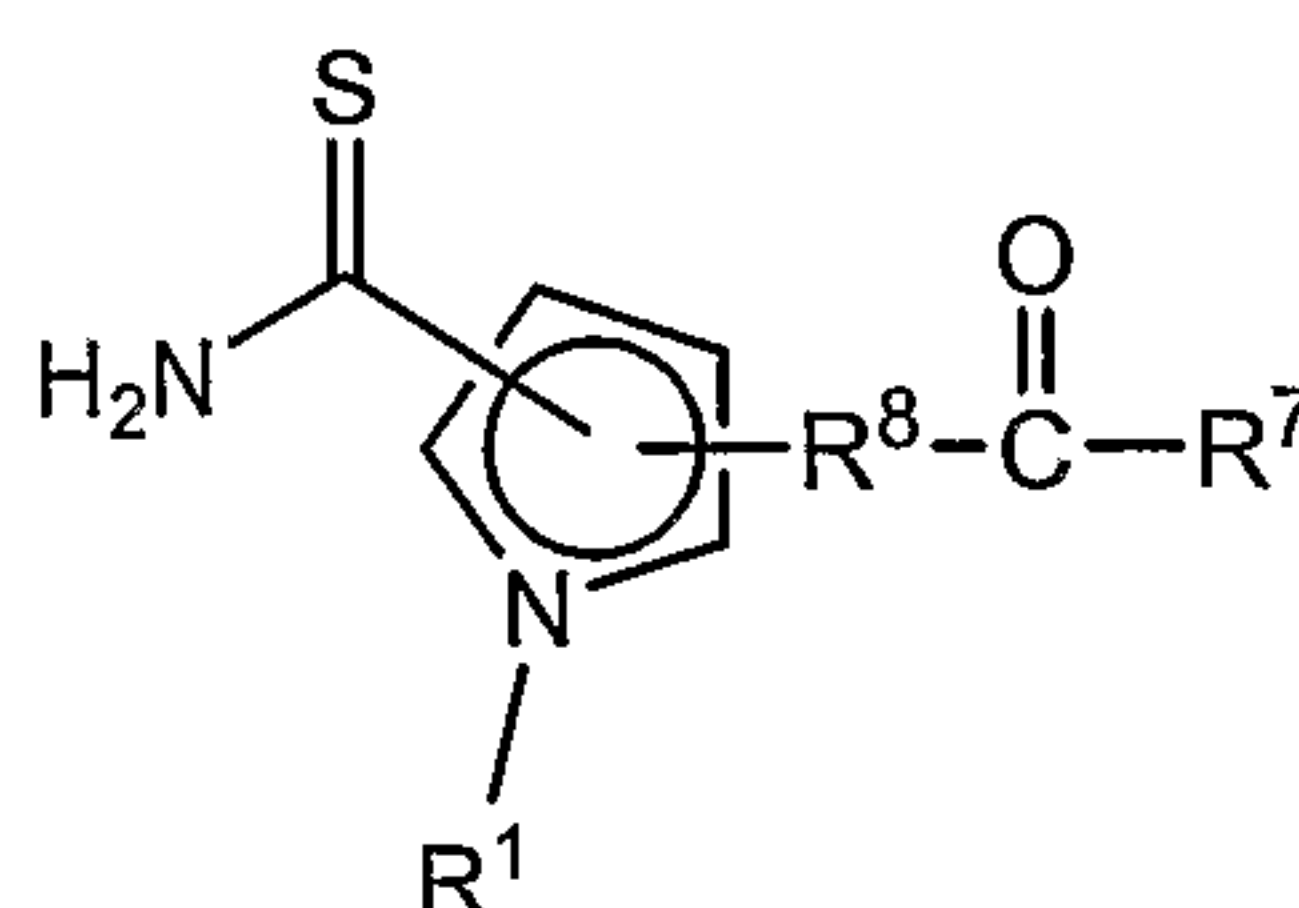
wherein, R^7 is H, NH_2 , NHR^{10} , $N(R^{10})_2$, $C(O)R^{10}$, $C(S)R^{10}$, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R^8 is C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or R^7 and R^8 are fused to form (i) a saturated carbon-based 4 to 8 membered ring; (ii) an unsaturated carbon-based 4 to 8 membered ring; or (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected among O, N, and S; wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from among H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_1 to C_6 aminoalkyl, and substituted C_1 to C_6 aminoalkyl; R^9 is absent, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R^{10} is selected from among H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, substituted C_1 to C_6 aminoalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, NH_2 , NHR^{11} , and $N(R^{11})_2$; and R^{11} is selected from among H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, substituted C_1 to C_6 aminoalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, and NH_2 .

In still a further embodiment, the thioamide impurity contains a thioamide group that is attached to a pyrrole ring or to a substituent of a pyrrole ring. The

thioamide impurity can therefore have the following thioamide substituent, where R^1 is C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl.



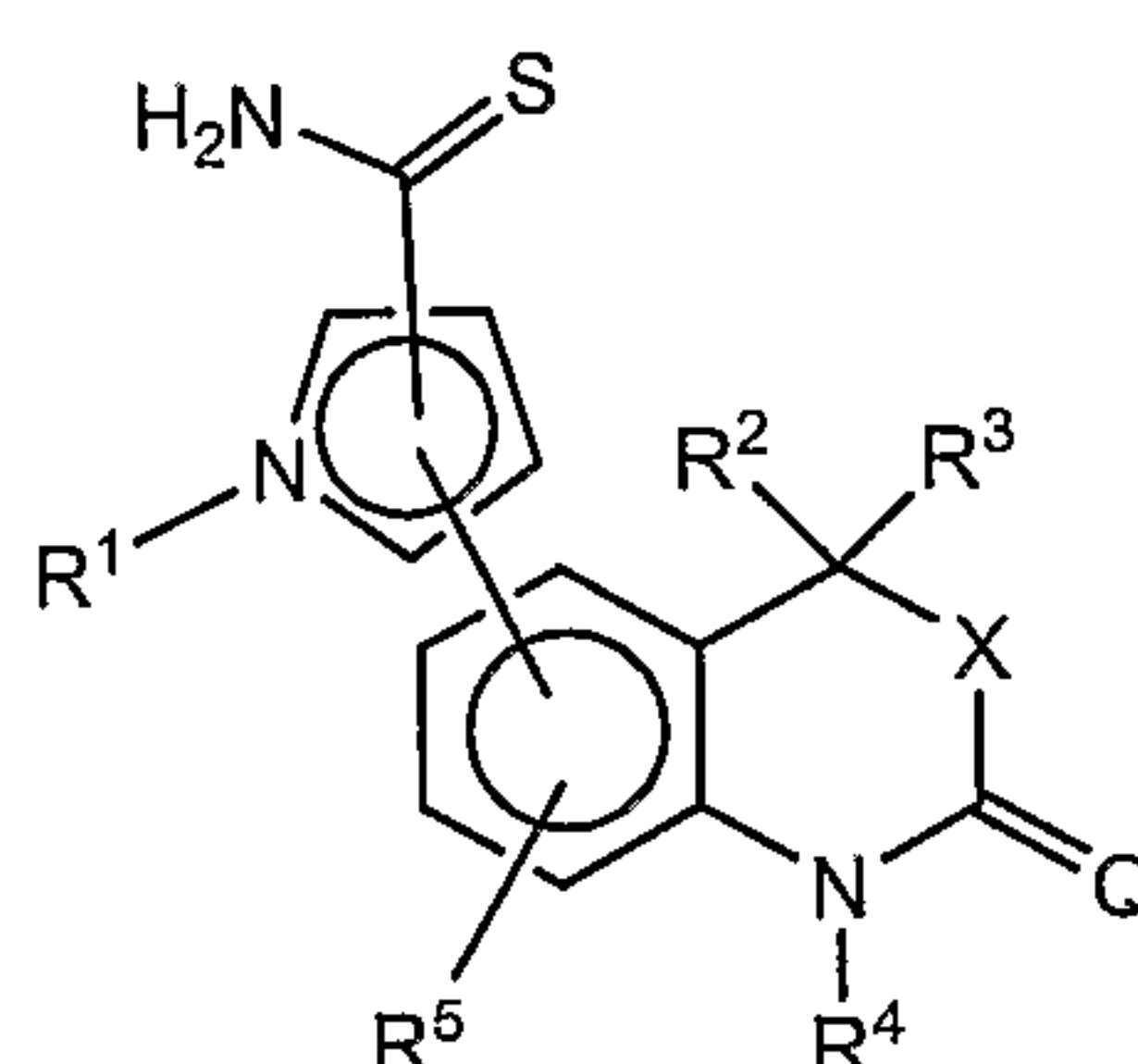
In another embodiment, the thioamide impurity is of the structure:



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wherein, R^1 is selected from among C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl. and R^7 and R^8 are defined above.

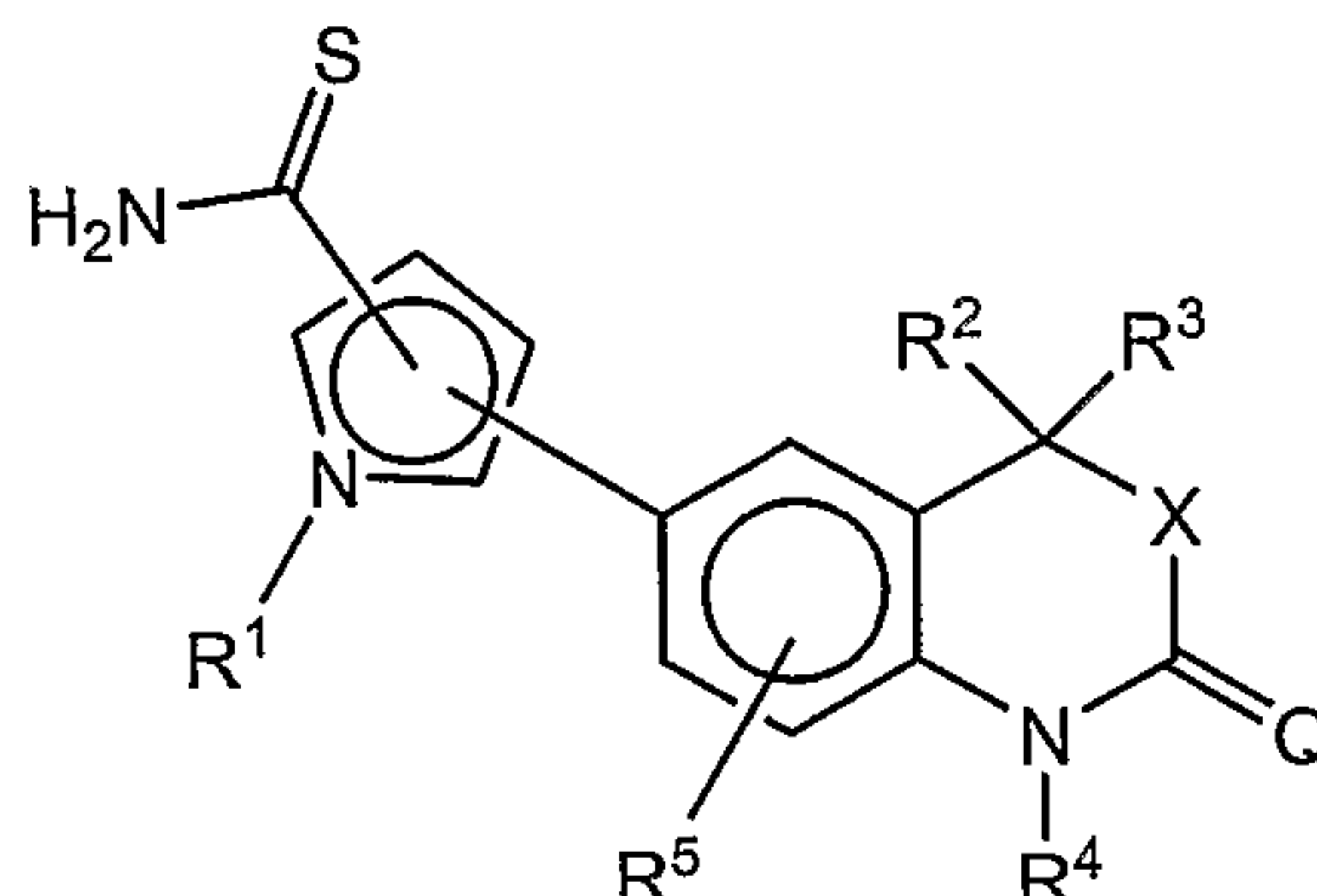
In still a further embodiment, the thioamide impurity is of the structure:



I

10 wherein, R^1 is selected from among C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl. R^2 and R^3 are independently selected from among H, C_1 to C_6 alkyl, or substituted C_1 to C_6 alkyl; or R^2 and R^3 are fused to form a ring including $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $-\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{NR}^6\text{CH}_2\text{CH}_2-$, n is 1, 2, 3, 4, or 5, p is 1, 2, 3, or 4, and q is 1, 2, 3, or 4; R^4 is
 15 selected from among H, OH, NH_2 , CN, halogen, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, or substituted C_2 to C_6 alkynyl; R^5 is selected from among H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl; R^6 is selected from among H or C_1 to C_6 alkyl; Q is selected
 20 from among O or S; and X is absent or is selected from among O or S.

In still a further embodiment, the thioamide impurity is of the structure:



wherein, R^1 - R^5 , X, and Q are defined above.

The carbonyl compound containing a nitrile group utilized in the present invention contains at least one carbonyl and at least one nitrile group. The present invention also provides for carbonyl compounds having more than 1 carbonyl group, e.g., 2, 3, 4, 5, or 5 carbonyl groups and more, more than 1 nitrile group, e.g., 2, 3, 4, or 5 nitrile groups and more, or a combination thereof.

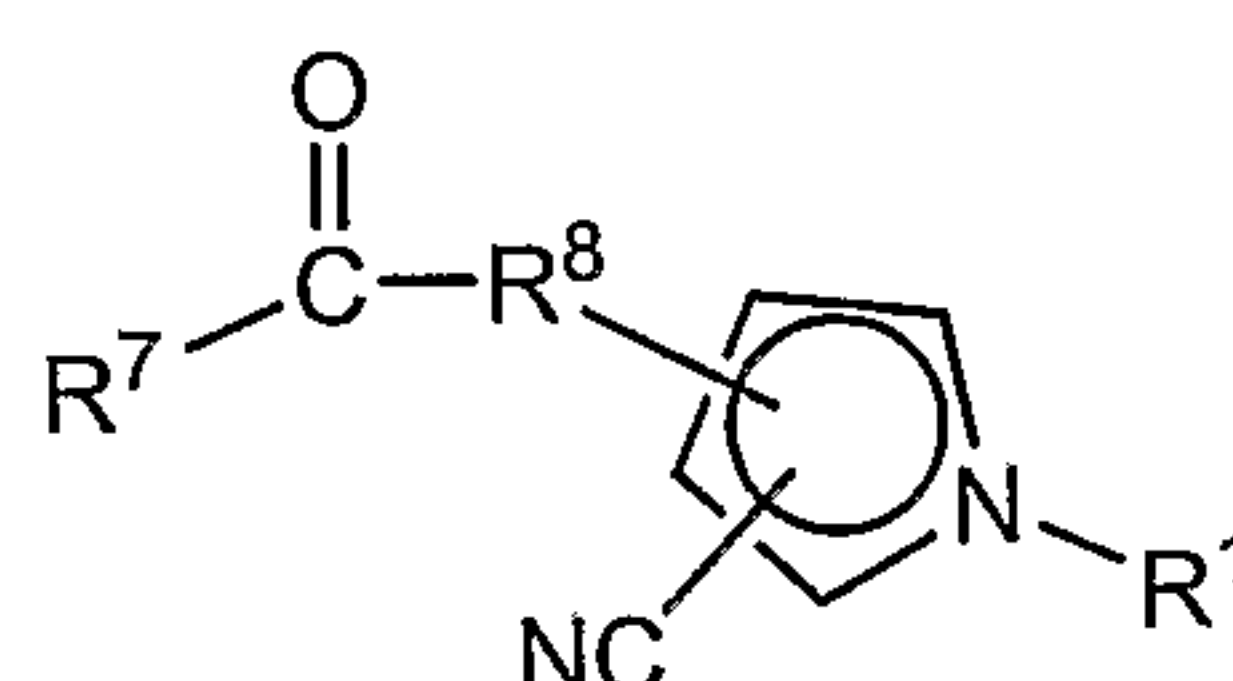
In one embodiment, the carbonyl compound is of the structure:



wherein, R^7 is H, NH_2 , NHR^{10} , $N(R^{10})_2$, $C(O)R^{10}$, $C(S)R^{10}$, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R^8 is C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or R^7 and R^8 are fused to form (i) a saturated carbon-based 4 to 8 membered ring; (ii) an unsaturated carbon-based 4 to 8 membered ring; or (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from among O, N, and S; wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from among H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

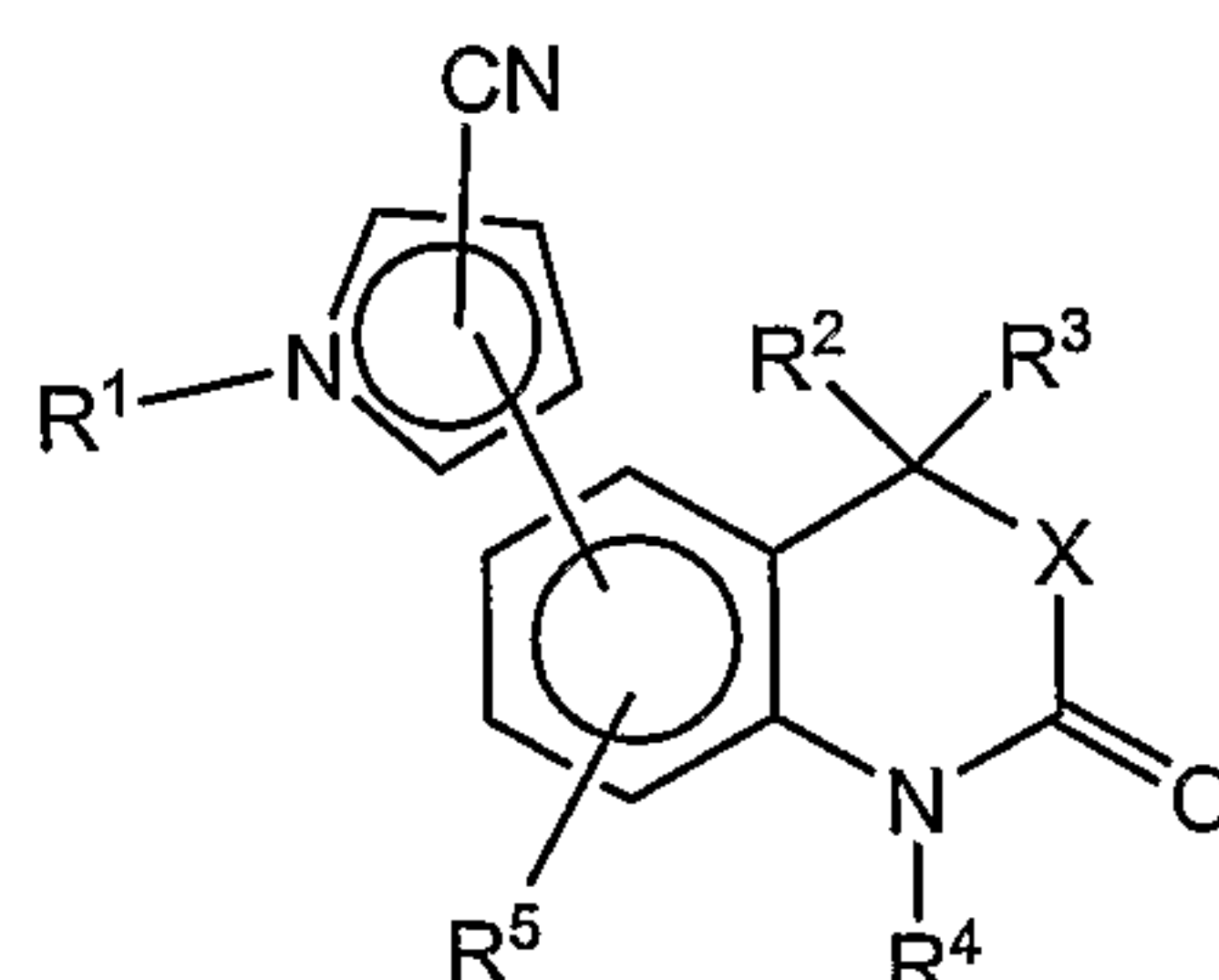
C₁ to C₆ aminoalkyl, and substituted C₁ to C₆ aminoalkyl; R⁹ is absent, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; R¹⁰ is selected from among H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, NH₂, NHR¹¹, and N(R¹¹)₂; and R¹¹ is selected from among H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, and NH₂.

In a further embodiment, the carbonyl compound is of the structure:



wherein, R¹ is C₁ to C₆ alkyl or substituted C₁ to C₆ alkyl; R⁷ and R⁸ are defined above.

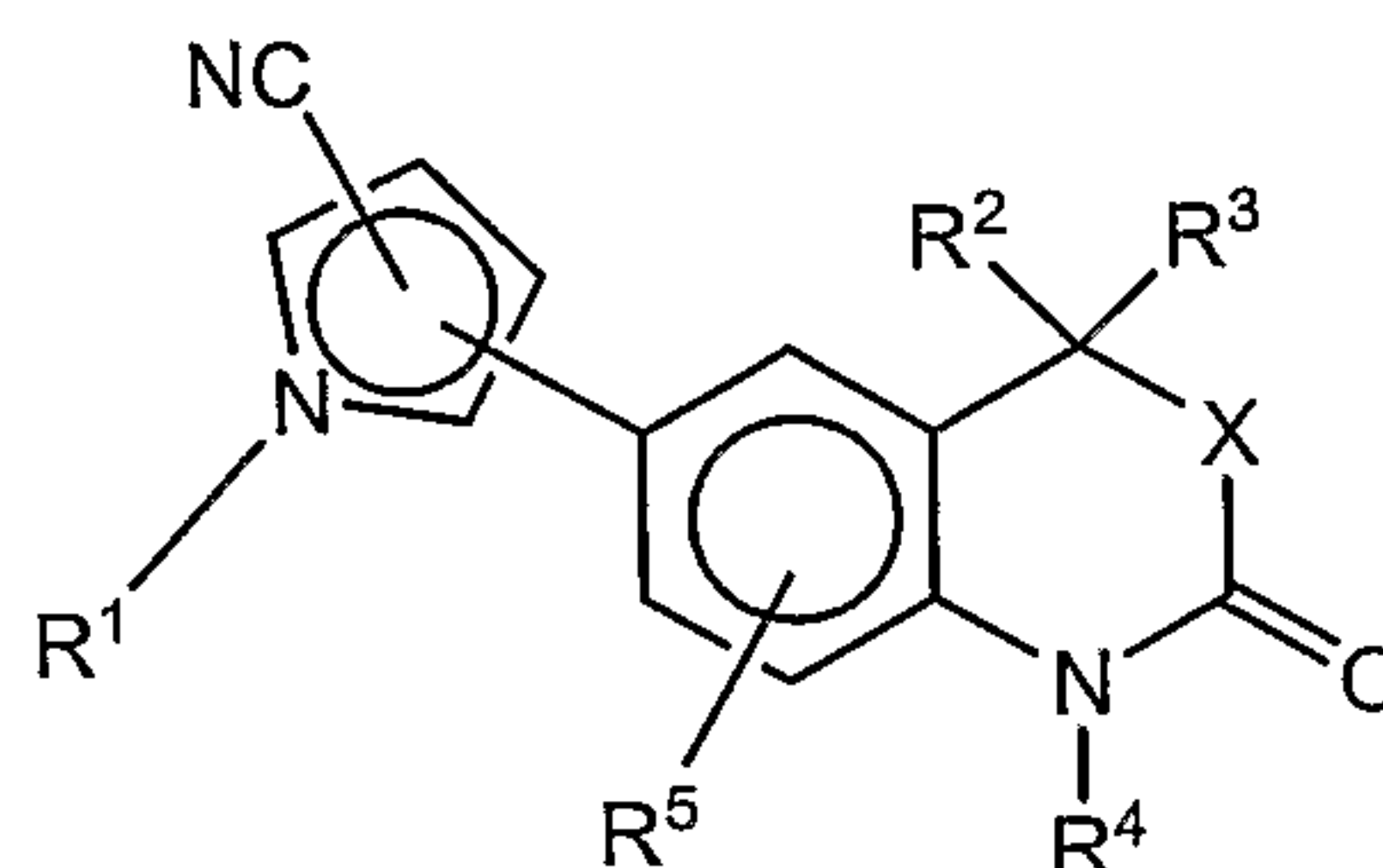
In yet another embodiment, the carbonyl compound is of the structure:



wherein, R¹ is C₁ to C₆ alkyl or substituted C₁ to C₆ alkyl; R² and R³ are, independently, H, C₁ to C₆ alkyl, or substituted C₁ to C₆ alkyl; or R² and R³ are fused to form a ring comprising -CH₂(CH₂)_nCH₂-, -CH₂CH₂C(CH₃)₂CH₂CH₂-, -O(CH₂)_pCH₂-, -O(CH₂)_qO-, -CH₂CH₂OCH₂CH₂-, or -CH₂CH₂NR⁶CH₂CH₂-, n is 1 to 5; p is 1 to 4; q is 1 to 4; R⁴ is H, OH, NH₂, CN, halogen, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, or substituted C₂ to C₆ alkynyl; R⁵ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆

aminoalkyl; R^6 is H or C_1 to C_6 alkyl; X is O, S, or absent; or a pharmaceutically acceptable salt thereof.

In still a further embodiment, the carbonyl compound is of the structure:



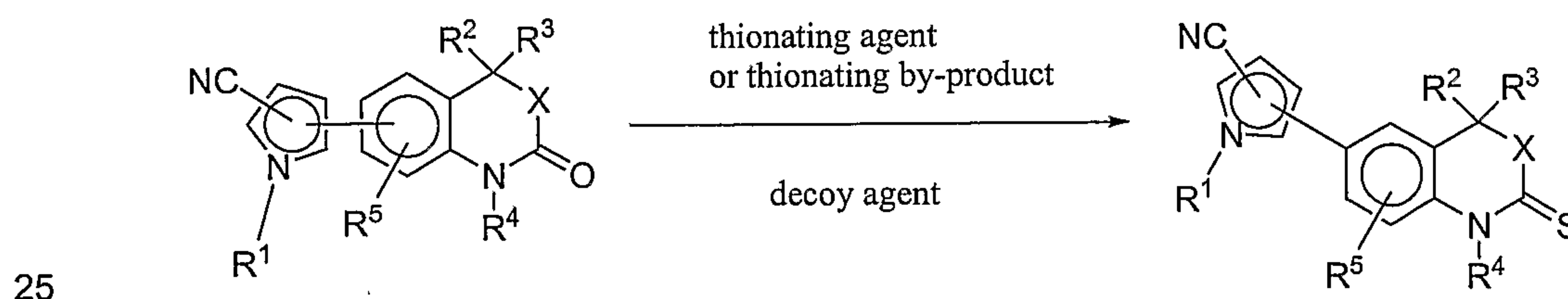
5 wherein, R^1 - R^5 and X are defined above.

Typically, the decoy agent utilized is in the presence of a solvent. One of skill in the art would readily be able to select a suitable solvent for use with the decoy agent depending on the other reagents utilized and reaction conditions, among others. Desirably, the solvent does not react with any of the reagents utilized in the reaction and does not contain any peroxides. In one embodiment, the solvent includes tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), toluene, and methylene chloride, among others.

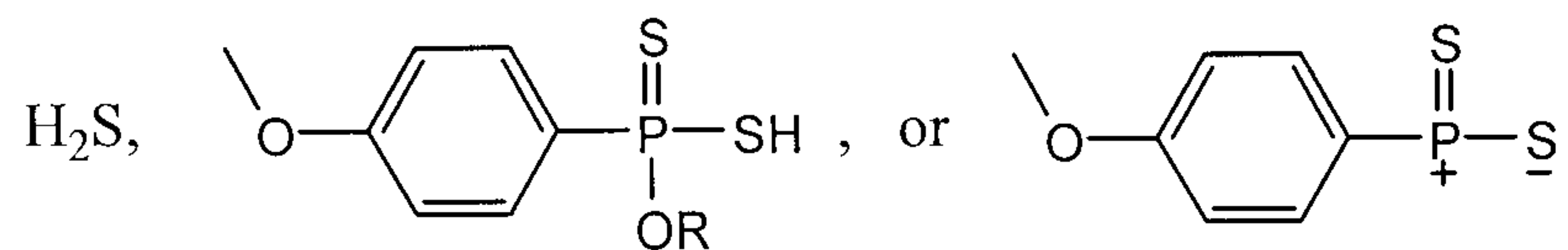
The decoy agent can be utilized at any temperature that facilitates the reaction and can readily be determined by one of skill in the art. Desirably, the decoy agent is utilized at least room temperature, and more desirably at the boiling point of the solvent.

When the decoy agent is utilized in a thionation reaction, the reaction is performed using a thionating agent. Several thionating agents that replace O-atoms with S-atoms are known in the art and include, without limitation, phosphorus pentasulfide (P_4S_{10}), hydrogen sulfide, Lawesson's reagent, and dialkyldithiophosphates such as diethyldithiophosphate (See, Phosphorous and Sulfur 1985, 25, 297). See, Scheme 4.

Scheme 4



Desirably, the thionating agent does not react with the decoy reagent. The thionation can also be performed with thionating by-products that agents are formed during the reaction and include:



5 In one embodiment, the present invention provides a method for preventing or minimizing the formation of thioamide impurities during thionation of a nitrile compound containing a carbonyl group including performing the thionation in the presence of a decoy agent having a nitrile group.

10 In another embodiment, the present invention provides a product prepared by the method of the present invention.

The resulting compounds of the present invention can be formulated in a physiologically compatible carrier and used as PR modulators as described in US Patent Nos. 6,509,334; 6,391,907; 6,417,214; and 6,407,101. The invention further provides kits comprising the product.

15 The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

20 EXAMPLES

EXAMPLE 1 - REACTIVITY OF DECOY AGENTS

One mmol of the aromatic nitrile decoy agents set forth in Table 1 were reacted at reflux with the thionating agent diethyl dithiophosphate (0.2 mL) in wet THF (6 mL) to give the respective thioamides.

25

Table 1

Nitrile	% Conversion to Thioamide*
2-thiophenecarbonitrile	100
benzonitrile	55
p-chlorobenzonitrile	67
p-methoxybenzonitrile	45
o-nitrobenzonitrile	25
p-acetylbenzonitrile	57
p-methylbenzonitrile	52
p-fluorobenzonitrile	68

*% conversion as determined by gas chromatography/mass spectroscopy (GC/MS)

- 5 This example illustrates that 2-thiophenecarbonitrile was the most reactive with the thionating agent.

EXAMPLE 2 - USE OF DECOY AGENT DURING THIONATION

Acetonitrile (21 kg, 512 mol) was utilized as decoy agent in a thionation of 5-
 10 (4,4-dimethyl-2-oxo-1,4-dihydro-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile (34 kg, 126 mol), *i.e.*, a 4:1 molar ratio, using Lawesson's reagent (28.3 kg, 70 mol) in DME (505 kg) at reflux to give 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile (26.7 kg; 74% yield).

The crude reaction mixture of 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-
 15 benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile contained only about 2.6% of 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-benzoxazine)-1-methyl-pyrrole-2-thioamide impurity. After recrystallization, the purified 5-(4,4-dimethyl-2-thioxo-1,4-dihydro-benzoxazin-6-yl)-1-methyl-1H-pyrrole-2-carbonitrile was about 99.90% pure.

When the reaction was performed in the absence of the decoy agent, the
 20 thioamide impurity was present at about 11 to about 12%.

EXAMPLE 3 - COMPETITION BETWEEN 2-THIOPHENECARBONITRILE AND ALKYL NITRILES

2-Thiophenecarbonitrile (1 mmol) was reacted at reflux with diethyl
 25 dithiophosphate (200 μ L) in wet THF (6 mL) and in the presence of the aliphatic

nitriles (1 mmol) set forth in Table 2. The conversion of the undesired thiophene-2-carbothioic acid amide was then measured.

Table 2

Nitrile	% Conversion to Thioamide*
None	75
Trichloroacetonitrile	46
Chloroacetonitrile	40
Malononitrile	54
Acetonitrile	71

* Technical grade of diethyldithiophosphate was utilized.

5

This example illustrates that conversion of a reactive nitrile, such as 2-thiophene carbonitrile, to the thioamide impurity is high when no decoy agent is utilized. However, conversion to the thioamide impurity is decreased when decoy agents are utilized.

10

EXAMPLE 4 - COMPETITION BETWEEN 2-THIOPHENECARBONITRILE AND ACETONITRILE

2-Thiophenecarbonitrile (1 mmol) was reacted at reflux with diethyl dithiophosphate (200 μ L) in wet THF and acetonitrile using the molar equivalents set forth in Table 3. The conversion of the undesired thiophene-2-carbothioic acid amide was then measured.

15

Table 3

Molar Equivalent of Acetonitrile	% Conversion to Thioamide
1	71
10	53
20	37
40	25
120**	19

20

*Volume of THF and MeCN retained at 6 mL by adjusting the amount of MeCN and THF.

**Neat acetonitrile (no THF solvent present)

This example illustrates that conversion to the thioamide impurity decreased as the amount of acetonitrile increased.

5 EXAMPLE 5 - EFFECT OF ACETONITRILE ON THE FORMATION OF THIOAMIDE IMPURITIES

The nitrile set forth in Table 4 was reacted at reflux with diethyl dithiophosphate (200 μ L) in wet THF (5 mL) and acetonitrile (1 mL = 20 molar equivalents). The control set contained 6 mL THF and no acetonitrile. After 5 hours at 66 °C, the mixtures were subjected to GC/MS analysis to detect the presence of
10 thioamide impurity.

Table 4

Nitrile	% Conversion to Thioamide	
	<i>with acetonitrile</i>	<i>without acetonitrile</i>
2-thiophenecarbonitrile	33	78
benzonitrile	11	43
p-acetylbenzonitrile	11	45
p-methoxybenzonitrile	2	38
p-chlorobenzonitrile	13	51
1,4-dicyanobenzene	34	67

This example illustrates that conversion to the thioamide impurity was suppressed in samples containing acetonitrile. Further, samples containing
15 acetonitrile and p-methoxybenzonitrile had very little conversion to the thioamide impurity.

EXAMPLE 6 – USE OF DECOY AGENT DURING THIONATION

20 A 2-L flask was charged with 1,2-dimethoxyethane (2.1 L) and 5-(spiro[cyclohexane-1,3'-[3H]indole]-2'-oxo-5'-yl)-1H-pyrrole-1-methyl-2-carbonitrile (150 g, 0.49 mol), followed by Lawesson's reagent (119 g, 0.295 mol) and acetonitrile (0.3 L, 5.75 mol), *i.e.*, a 12:1 molar ratio of decoy agent to nitrile compound. The suspension was heated to reflux and kept for 1 hour. Upon cooling to
25 ambient temperature, water (2.51 L) was added to the suspension at a rate to maintain the temperature below 30 °C. The yellow-greenish precipitate was filtered on a fritted funnel. The solid was transferred back to the reaction flask and slurried in water (0.75

L) overnight. The yellow suspension was filtered, washed with water (0.45 L) and dried to give 154 g (98% yield, 99.0% purity by HPLC area, mp 269-271.5 °C, 0.60% thioamide impurity) of 5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-1H-pyrrole-2-carbonitrile.

5

EXAMPLE 7 – USE OF DECOY AGENT DURING THIONATION (SCALE-UP)

In this example, a larger scale production of [5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-1H-pyrrole-2-carbonitrile] was performed.

A 100-gal vessel was charged with 1,2-dimethoxyethane (155.1 kg, 178.8 L) and 5-(spiro[cyclohexane-1,3'-[3H]indole]-2'-oxo-5'-yl)-1H-pyrrole-1-methyl-2-carbonitrile (12.78 kg), followed by Lawesson's reagent (10.14 kg) and acetonitrile (20.1 kg, 25.6 L). The contents of the vessel was heated to reflux and kept for 1 hour.

The orange-brown solution was cooled to 70 °C and a sample was withdrawn for the reaction completion test that showed less than 0.2% of the starting material. The batch was cooled to ambient temperature and water (213.9 kg) was charged at a rate to maintain temperature between 23 and 29 °C. The yellow-greenish suspension was filtered on a 0.3 SQM PSL filter/dryer. The solids were slurried in water (63.9 kg) on the filter/dryer for 15 minutes. The yellow suspension was transferred into a 100-gal vessel and the filter was rinsed with water (2 x 10 kg) into the vessel. The slurry was stirred at 18-26 °C for 12 hours, filtered on a 0.3 SQM PSL filter/dryer and washed with water (2 x 19.2 kg). The solids were dried in a vacuum oven at initially 20-30 °C and then at 45 °C to give 12.8 kg of crude 5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-1H-pyrrole-2-carbonitrile (95% yield, 0.45% thioamide impurity).

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

30

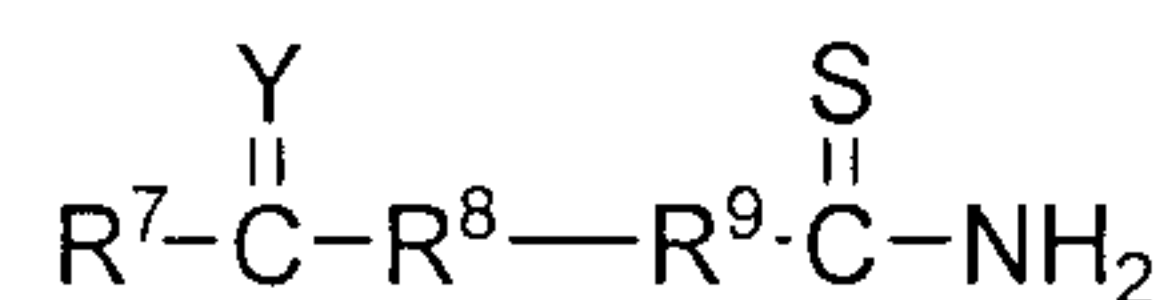
WHAT IS CLAIMED IS:

1. A method for preventing, reducing or minimizing the formation of thioamide impurities during thionation of a carbonyl compound comprising a nitrile group, comprising performing said thionation in the presence of a decoy agent comprising a nitrile group.

2. The method according to claim 1, wherein the moles of said decoy agent is greater than the moles of said carbonyl compound.

3. The method according to claim 1, wherein the moles of said decoy agent is less than the moles of said carbonyl compound.

4. The method according to any one of claims 1 to 3, wherein said thioamide impurity is of the structure:



wherein:

Y is O or S;

R⁷ is H, NH₂, NHR¹⁰, N(R¹⁰)₂, C(O)R¹⁰, C(S)R¹⁰, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R⁸ is C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

R⁷ and R⁸ are fused to form:

- (i) a saturated carbon-based 4 to 8 membered ring;
- (ii) an unsaturated carbon-based 4 to 8 membered ring; or

(iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from the group consisting of O, N, and S;

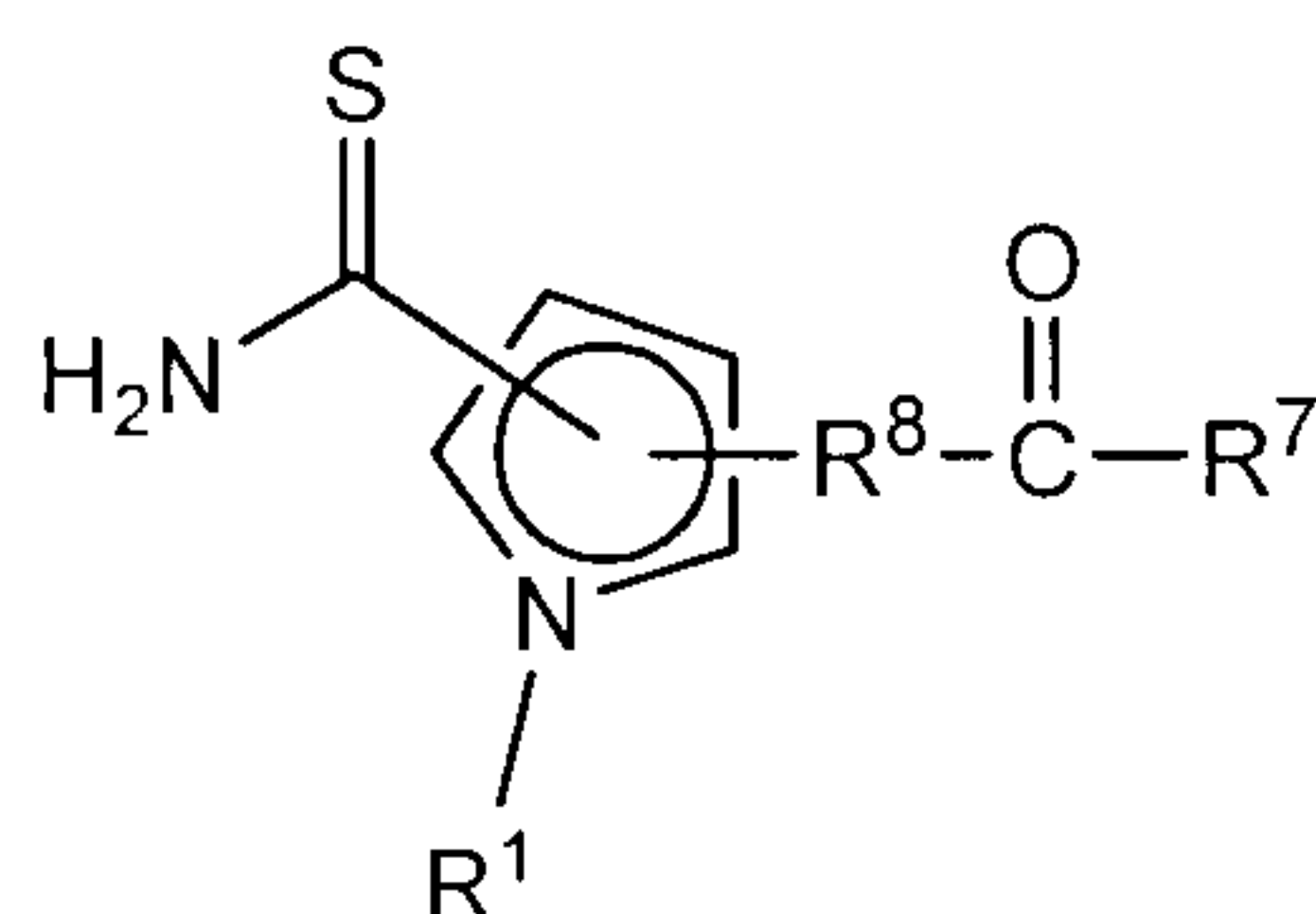
wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁ to C₆ aminoalkyl, and substituted C₁ to C₆ aminoalkyl;

R⁹ is absent, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R¹⁰ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, NH₂, NHR¹¹, and N(R¹¹)₂; and

R¹¹ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, and NH₂.

5. The method according to claim 4, wherein said thioamide impurity is of the structure:



wherein:

R¹ is C₁ to C₆ alkyl or substituted C₁ to C₆ alkyl;

R⁷ is H, NH₂, NHR¹⁰, N(R¹⁰)₂, C(O)R¹⁰, C(S)R¹⁰, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl,

substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R⁸ is C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

R⁷ and R⁸ are fused to form:

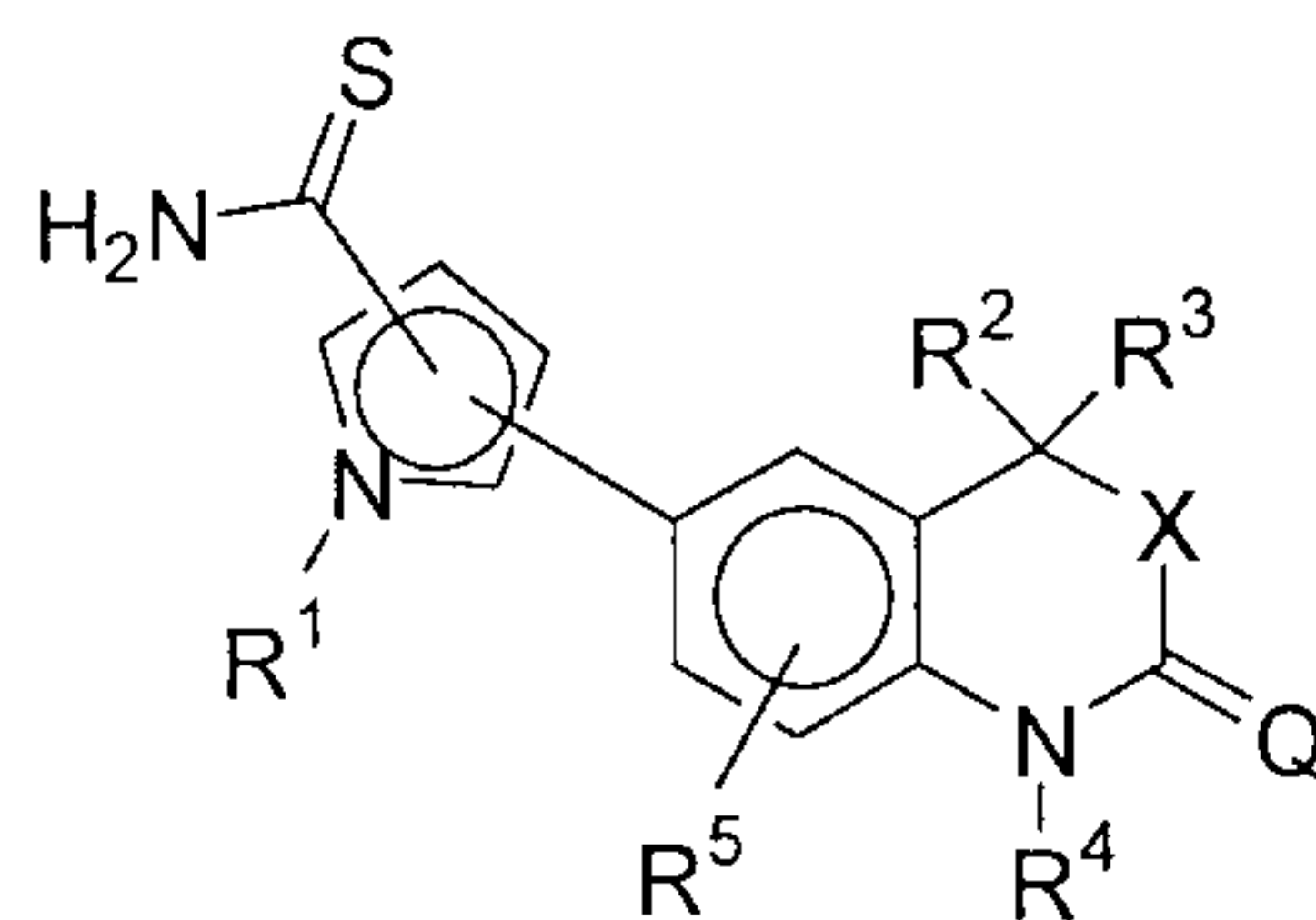
- (i) a saturated carbon-based 4 to 8 membered ring;
- (ii) an unsaturated carbon-based 4 to 8 membered ring; or
- (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from the group consisting of O, N, and S;

wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁ to C₆ aminoalkyl, and substituted C₁ to C₆ aminoalkyl;

R¹⁰ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, NH₂, NHR¹¹, and N(R¹¹)₂; and

R¹¹ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, and NH₂.

6. The method according to claim 4, wherein said thioamide impurity is of the structure:



I

wherein:

R^1 is C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^2 and R^3 are, independently, H, C_1 to C_6 alkyl, or substituted C_1 to C_6 alkyl;

or R^2 and R^3 are fused to form a ring comprising $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$,

$-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $-\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, or

$-\text{CH}_2\text{CH}_2\text{NR}^6\text{CH}_2\text{CH}_2-$;

n is 1 to 5;

p is 1 to 4;

q is 1 to 4;

R^4 is H, OH, NH_2 , CN, halogen, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, or substituted C_2 to C_6 alkynyl;

R^5 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^6 is H or C_1 to C_6 alkyl;

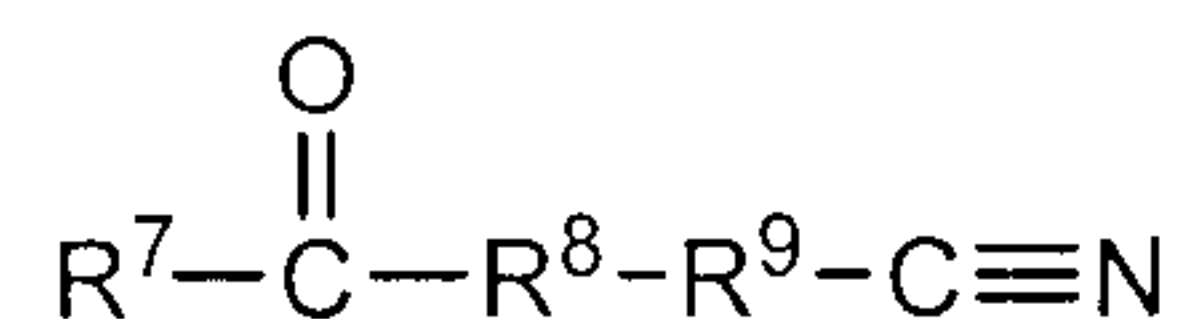
Q is O or S;

X is O, S, or absent;

or a pharmaceutically acceptable salt thereof.

7. The method according to any one of claims 1 to 3, wherein said carbonyl compound is a ketone, enone, aldehyde, ester, lactone, amide, carbamate, carbonate, or enaminone.

8. The method according to claim 7, wherein said carbonyl compound is of the structure:



wherein:

R^7 is H, NH_2 , NHR^{10} , $\text{N}(\text{R}^{10})_2$, $\text{C}(\text{O})\text{R}^{10}$, $\text{C}(\text{S})\text{R}^{10}$, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^8 is C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

R^7 and R^8 are fused to form:

- (i) a saturated carbon-based 4 to 8 membered ring;
- (ii) an unsaturated carbon-based 4 to 8 membered ring; or
- (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from the group consisting of O, N, and S;

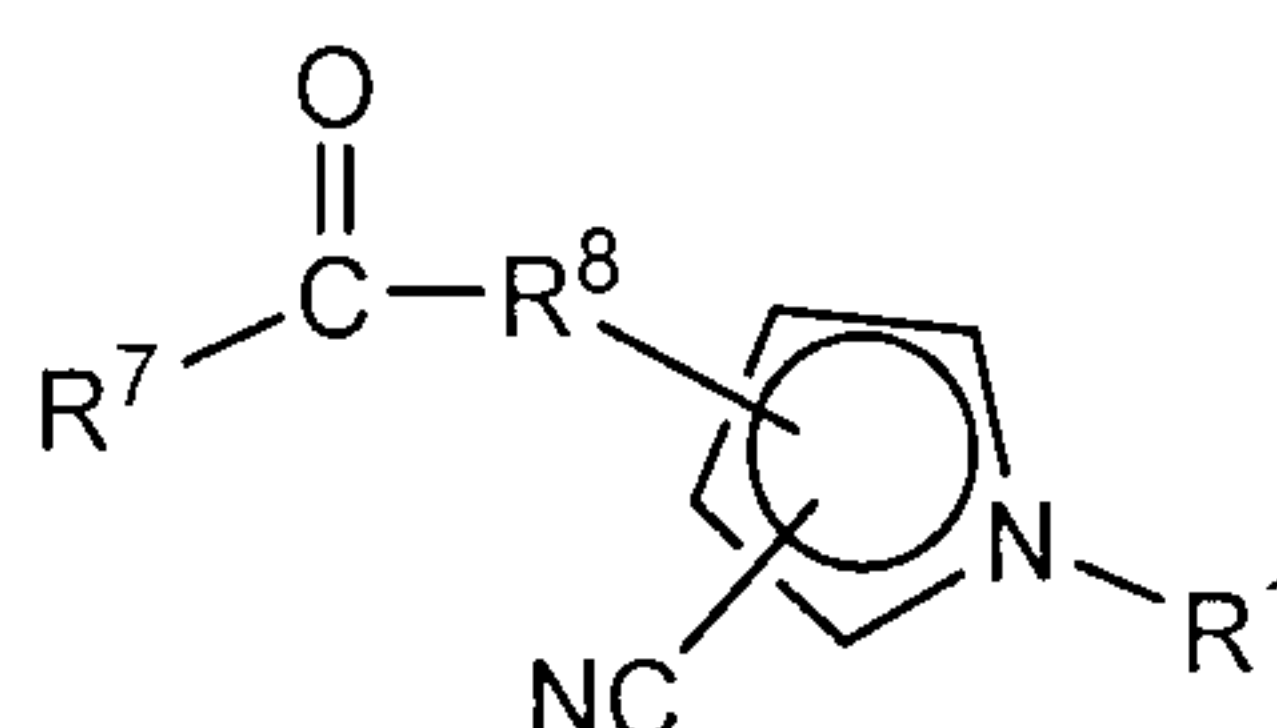
wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_1 to C_6 aminoalkyl, and substituted C_1 to C_6 aminoalkyl;

R^9 is absent, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^{10} is selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, substituted C_1 to C_6 aminoalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, NH_2 , NHR^{11} , and $\text{N}(\text{R}^{11})_2$; and

R^{11} is selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, substituted C_1 to C_6 aminoalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, and NH_2 .

9. The method according to claim 7, wherein said carbonyl compound is of the structure:



wherein:

R^1 is C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^7 is H, NH_2 , NHR^{10} , $N(R^{10})_2$, $C(O)R^{10}$, $C(S)R^{10}$, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 thioalkyl, substituted C_1 to C_6 thioalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^8 is C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

R^7 and R^8 are fused to form:

- (i) a saturated carbon-based 4 to 8 membered ring;
- (ii) an unsaturated carbon-based 4 to 8 membered ring; or
- (iii) a 4 to 8 heterocyclic ring containing 1 to 3 heteroatoms selected from the group consisting of O, N, and S;

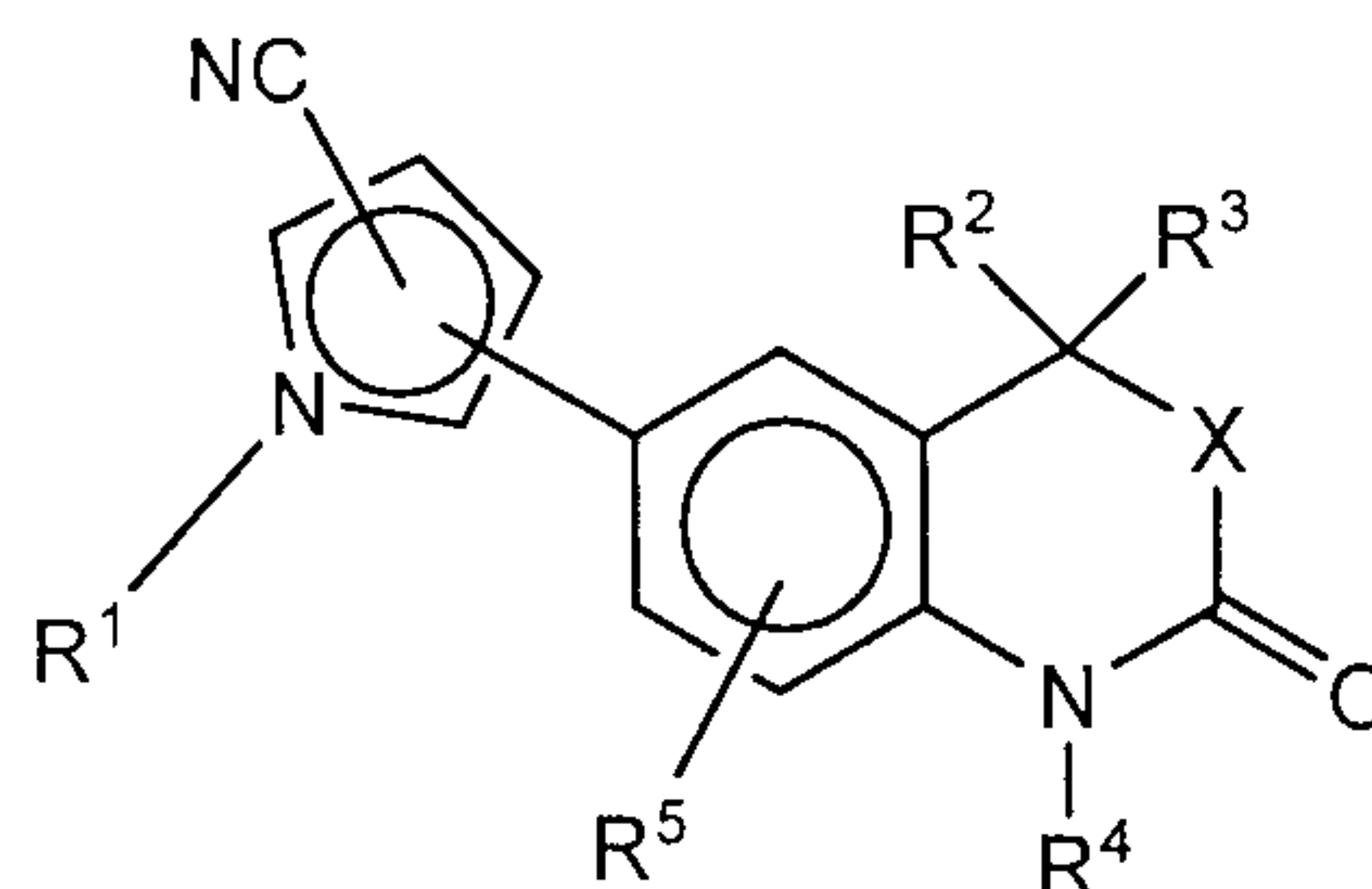
wherein rings (i)-(iii) are optionally substituted by 1 to 3 substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, C_1 to C_6 alkoxy,

substituted C₁ to C₆ alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁ to C₆ aminoalkyl, and substituted C₁ to C₆ aminoalkyl;

R¹⁰ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, NH₂, NHR¹¹, and N(R¹¹)₂; and

R¹¹ is selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, aryl, substituted aryl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, substituted C₁ to C₆ aminoalkyl, C₁ to C₆ thioalkyl, substituted C₁ to C₆ thioalkyl, and NH₂.

10. The method according to claim 7, wherein said carbonyl compound is of the structure:



wherein:

R¹ is C₁ to C₆ alkyl or substituted C₁ to C₆ alkyl;

R² and R³ are, independently, H, C₁ to C₆ alkyl, or substituted C₁ to C₆ alkyl;

or R² and R³ are fused to form a ring comprising -CH₂(CH₂)_nCH₂-,

-CH₂CH₂C(CH₃)₂CH₂CH₂-, -O(CH₂)_pCH₂-, -O(CH₂)_qO-, -CH₂CH₂OCH₂CH₂-, or -CH₂CH₂NR⁶CH₂CH₂-;

n is 1 to 5;

p is 1 to 4;

q is 1 to 4;

R⁴ is H, OH, NH₂, CN, halogen, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, or substituted C₂ to C₆ alkynyl;

R⁵ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R^6 is H or C_1 to C_6 alkyl;

X is O, S, or absent;

or a pharmaceutically acceptable salt thereof.

11. The method according to any one of claims 1 to 10, wherein said decoy agent is acetonitrile.

12. The method according to any one of claims 1 to 10, wherein said decoy agent comprises an electron withdrawing substituent.

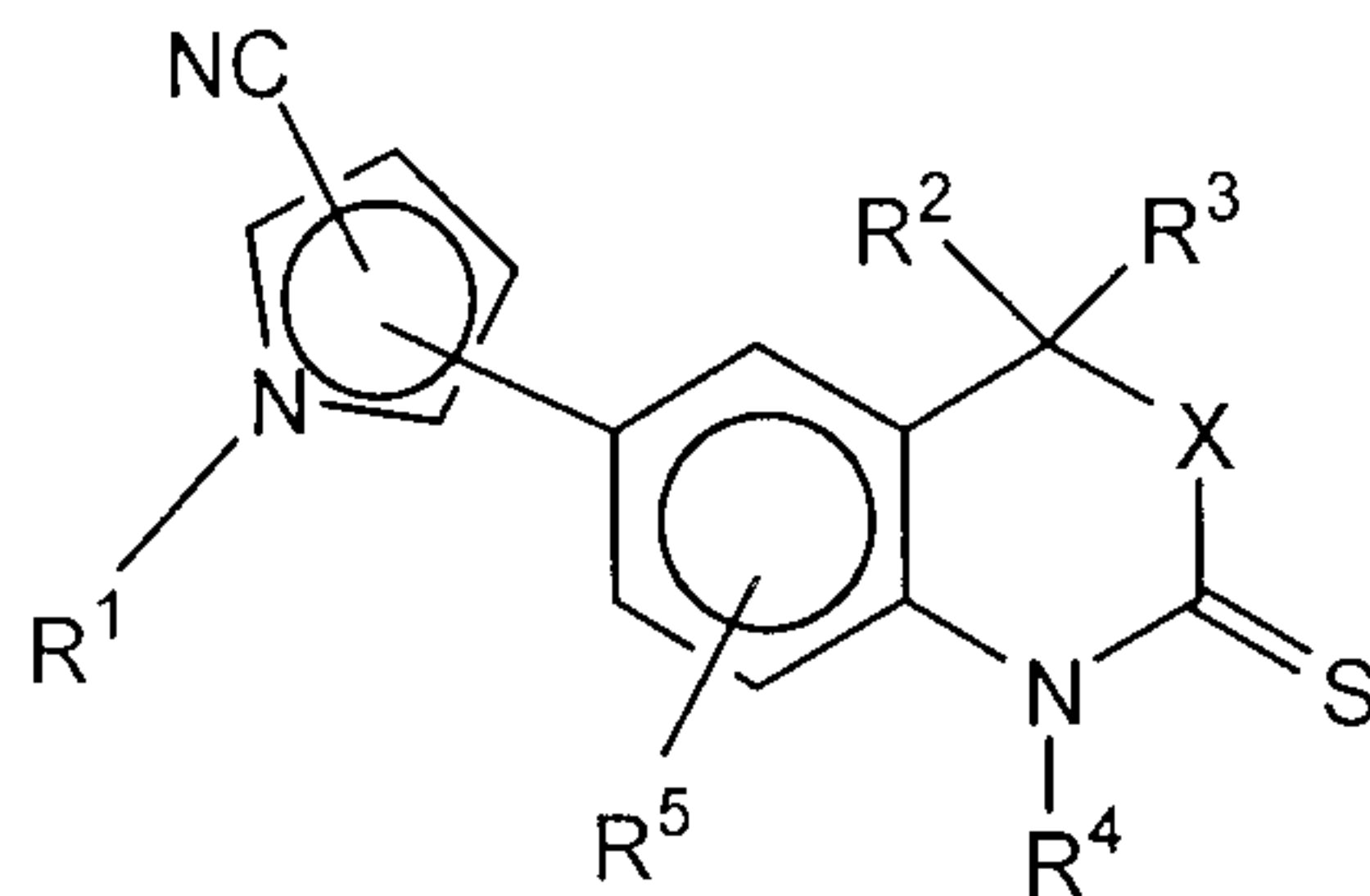
13. The method according to claim 12, wherein said decoy agent is chloroacetonitrile or trichloroacetonitrile.

14. The method according to any one of claims 1 to 10, wherein said decoy agent is an aryl nitrile selected from the group consisting of benzonitrile, p-chlorobenzonitrile, p-ethoxybenzonitrile, p-methoxybenzonitrile, o-nitrobenzonitrile, p-acetylbenzonitrile, p-methylbenzonitrile, p-fluorobenzonitrile, and 1,3-dicyanobenzene.

15. The method according to any one of claims 1 to 10, wherein said decoy agent is a heteroaryl nitrile selected from the group consisting of N-methyl-2-pyrrolecarbonitrile, 2-thiophenecarbonitrile, 2-cyanopyridine, 3-cyanopyridine and 4-cyanopyridine.

16. The method according to any one of claims 1 to 15, wherein said thionation is performed with a thionating agent selected from the group consisting of hydrogen sulfide, Lawesson's reagent, phosphorus pentasulfide, and diethyldithiophosphate.

17. The use of a decoy agent containing a nitrile group in a method for preparing a compound having the formula:



wherein:

R^1 is C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^2 and R^3 are, independently, H, C_1 to C_6 alkyl, or substituted C_1 to C_6 alkyl;

or R^2 and R^3 are fused to form a ring comprising $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$,

$-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $-\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, or

$-\text{CH}_2\text{CH}_2\text{NR}^6\text{CH}_2\text{CH}_2-$;

n is 1 to 5;

p is 1 to 4;

q is 1 to 4;

R^4 is H, OH, NH_2 , CN, halogen, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, or substituted C_2 to C_6 alkynyl;

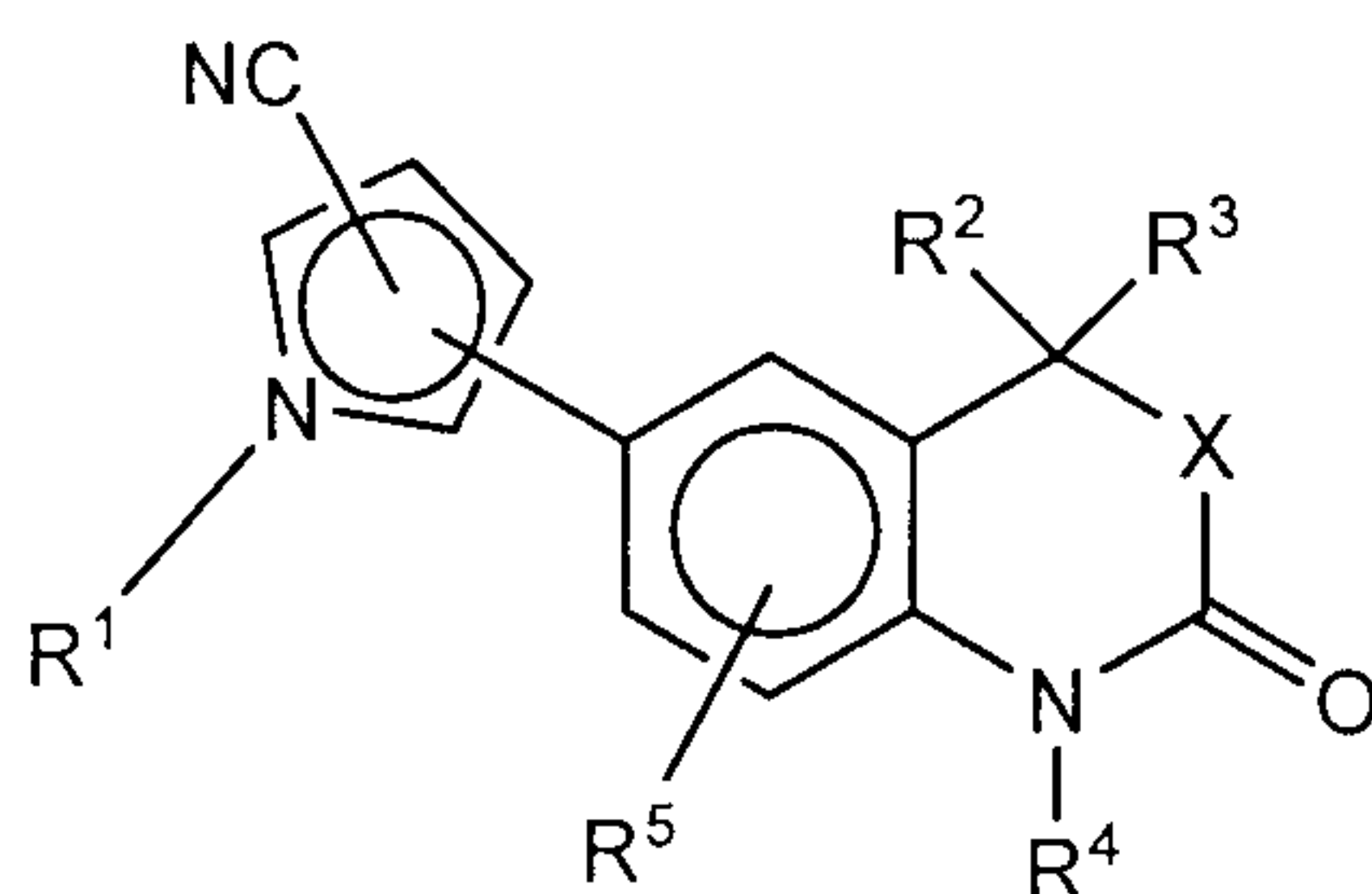
R^5 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^6 is H or C_1 to C_6 alkyl;

X is O, S, or absent;

or a pharmaceutically acceptable salt thereof;

said method comprising reacting a thionating agent with a carbonyl compound having the formula



wherein $R^1 - R^6$, n, p, q, and X are as defined above;

wherein said decoy agent prevents or reduces thionation of the one or more nitrile groups present in said carbonyl compound.

18. The use according to claim 17 wherein said thionating agent is selected from the group consisting of hydrogen sulfide, Lawesson's reagent, phosphorus pentasulfide, and diethyldithiophosphate.

19. The use according to claim 17 or 18, wherein said decoy agent is an aryl nitrile selected from the group consisting of benzonitrile, p-chlorobenzonitrile, p-ethoxybenzonitrile, p-methoxybenzonitrile, o-nitrobenzonitrile, p-acetylbenzonitrile, p-methylbenzonitrile, p-fluorobenzonitrile, and 1,3-dicyanobenzene.

20. The use according to claim 17 or 18, wherein said decoy agent is a heteroaryl nitrile selected from the group consisting of N-methyl-2-pyrrolicarbonitrile, 2-thiophenecarbonitrile, 2-cyanopyridine, 3-cyanopyridine and 4-cyanopyridine.

21. The use according to claim 17 or 18, wherein said decoy agent is an aliphatic nitrile selected from the group consisting of acetonitrile, propionitrile, butyronitrile, isobutyronitrile, chloroacetonitrile, trichloroacetonitrile and malononitrile.

22. The use according to any one of claims 17 to 21 wherein the molar ratio of said decoy agent to said carbonyl compound is greater than 1:1.

23. The use according to any one of claims 17 to 22 wherein the thionation reaction is carried out in a solvent selected from the group consisting of tetrahydrofuran, 1,2-dimethoxyethane, methylene chloride, and toluene.